

## Circulation

### AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

# 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

#### Writing Committee Members\*

Paul A. Heidenreich, MD, MS, FACC, FAHA, FHFS, Chair; Biykem Bozkurt, MD, PhD, FACC, FAHA, FHFS, Vice Chair; David Aguilar, MD, MSc, FAHAT†; Larry A. Allen, MD, MHS, FACC, FAHA, FHFSAT†; Joni J. Byunt; Monica M. Colvin, MD, MS, FAHAT†; Anita Deswal, MD, MPH, FACC, FAHA, FHFSAT‡; Mark H. Drazner, MD, MSc, FACC, FAHA, FHFSAT†; Shannon M. Dunlay, MD, MS, FAHA, FHFSAT†; Linda R. Evers, JD†; James C. Fang, MD, FACC, FAHA, FHFSAT†; Savitri E. Fedson, MD, MAT; Gregg C. Fonarow, MD, FACC, FAHA, FHFSAT§; Salim S. Hayek, MD, FACCT; Adrian F. Hernandez, MD, MHS‡; Prateeti Khazanie, MD, MPH, FHFSAT†; Michelle M. Kittleson, MD, PhD†; Christopher S. Lee, PhD, RN, FAHA, FHFSAT†; Mark S. Link, MDT; Carmelo A. Milano, MDT; Lorraine C. Nnacheta, DrPH, MPH†; Alexander T. Sandhu, MD, MST; Lynne Warner Stevenson, MD, FACC, FAHA, FHFSAT†; Orly Vardeny, PharmD, MS, FAHA, FHFSAT||; Amanda R. Vest, MBBS, MPH, FHFSAT||; Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFSAT†

**AIM:** The “2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure” replaces the “2013 ACCF/AHA Guideline for the Management of Heart Failure” and the “2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure.” The 2022 guideline is intended to provide patient-centric recommendations for clinicians to prevent, diagnose, and manage patients with heart failure.

**METHODS:** A comprehensive literature search was conducted from May 2020 to December 2020, encompassing studies, reviews, and other evidence conducted on human subjects that were published in English from MEDLINE (PubMed), EMBASE, the Cochrane Collaboration, the Agency for Healthcare Research and Quality, and other relevant databases. Additional relevant clinical trials and research studies, published through September 2021, were also considered. This guideline was harmonized with other American Heart Association/American College of Cardiology guidelines published through December 2021.

**STRUCTURE:** Heart failure remains a leading cause of morbidity and mortality globally. The 2022 heart failure guideline provides recommendations based on contemporary evidence for the treatment of these patients. The recommendations present an evidence-based approach to managing patients with heart failure, with the intent to improve quality of care and align with patients’ interests. Many recommendations from the earlier heart failure guidelines have been updated with new evidence, and new recommendations have been created when supported by published data. Value statements are provided for certain treatments with high-quality published economic analyses.

\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Representative. ‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison. §ACC/AHA Task Force on Performance Measures Representative. ||HFSA Representative.

ACC/AHA Joint Committee on Clinical Practice Guidelines Members, see page e986.

The American Heart Association requests that this document be cited as follows: Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063  
© 2022 by the American Heart Association, Inc., the American College of Cardiology Foundation, and the Heart Failure Society of America.

*Circulation* is available at [www.ahajournals.org/journal/circ](http://ahajournals.org/journal/circ)

**Key Words:** AHA Scientific Statements ■ heart failure ■ heart failure with reduced ejection fraction ■ heart failure with preserved ejection fraction ■ heart failure with mildly reduced ejection fraction ■ systolic heart failure ■ heart failure rehabilitation ■ cardiac failure ■ chronic heart failure ■ acute decompensated heart failure ■ cardiogenic shock ■ beta blockers ■ mineralocorticoid receptor antagonists ■ ACE inhibitors ■ angiotensin and neprilysin receptor antagonist ■ sacubitril valsartan ■ angiotensin receptor antagonist ■ sodium glucose co-transporter 2 ■ SGLT2 inhibitors ■ cardiac amyloidosis ■ atrial fibrillation ■ congestive heart failure ■ guideline-directed medical therapy ■ diabetes ■ cardiomyopathy ■ valvular heart disease ■ mitral regurgitation ■ cardiomyopathy in pregnancy ■ reduced ejection fraction ■ right heart pressure ■ palliative care ■ cardio-oncology ■ social determinants of health

## TABLE OF CONTENTS

Abstract .....	e895
Top 10 Take-Home Messages .....	e897
Preamble .....	e898
1. Introduction .....	e899
1.1. Methodology and Evidence Review .....	e899
1.2. Organization of the Writing Committee .....	e899
1.3. Document Review and Approval .....	e899
1.4. Scope of the Guideline .....	e899
1.5. Class of Recommendation and Level of Evidence.....	e900
1.6. Abbreviations .....	e900
2. Definition of HF .....	e901
2.1. Stages of HF .....	e901
2.2. Classification of HF by Left Ventricular Ejection Fraction (LVEF).....	e901
2.3. Diagnostic Algorithm for Classification of HF According to LVEF .....	e905
3. Epidemiology and Causes of HF.....	e906
3.1. Epidemiology of HF .....	e906
3.2. Cause of HF.....	e907
4. Initial and Serial Evaluation .....	e908
4.1. Clinical Assessment: History and Physical Examination .....	e908
4.1.1. Initial Laboratory and Electrocardiographic Testing .....	e910
4.2. Use of Biomarkers for Prevention, Initial Diagnosis, and Risk Stratification.....	e911
4.3. Genetic Evaluation and Testing.....	e912
4.4. Evaluation With Cardiac Imaging.....	e913
4.5. Invasive Evaluation .....	e915
4.6. Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring).....	e916
4.7. Exercise and Functional Capacity Testing .....	e917
4.8. Initial and Serial Evaluation: Clinical Assessment: HF Risk Scoring .....	e918
5. Stage A (Patients at Risk for HF) .....	e919
5.1. Patients at Risk for HF (Stage A: Primary Prevention).....	e919
6. Stage B (Patients With Pre-HF).....	e921
6.1. Management of Stage B: Preventing the Syndrome of Clinical HF in Patients With Pre-HF .....	e921
7. Stage C HF .....	e923

7.1. Nonpharmacological Interventions .....	e923
7.1.1. Self-Care Support in HF .....	e923
7.1.2. Dietary Sodium Restriction .....	e925
7.1.3. Management of Stage C HF: Activity, Exercise Prescription, and Cardiac Rehabilitation.....	e926
7.2. Diuretics and Decongestion Strategies in Patients With HF .....	e927
7.3. Pharmacological Treatment for HFrEF.....	e928
7.3.1. Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi.....	e928
7.3.2. Beta Blockers .....	e931
7.3.3. Mineralocorticoid Receptor Antagonists (MRAs).....	e931
7.3.4. Sodium-Glucose Cotransporter 2 Inhibitors .....	e932
7.3.5. Hydralazine and Isosorbide Dinitrate .....	e933
7.3.6. Other Drug Treatment .....	e934
7.3.7. Drugs of Unproven Value or That May Worsen HF .....	e935
7.3.8. GDMT Dosing: Sequencing and Up titration .....	e937
7.3.9. Additional Medical Therapies .....	e939
7.3.9.1. Management of Stage C HF: Ivabradine .....	e939
7.3.9.2. Pharmacological Treatment for Stage C HFrEF (Digoxin) .....	e940
7.3.9.3. Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators .....	e941
7.4. Device and Interventional Therapies for HFrEF .....	e941
7.4.1. ICDs and CRTs .....	e941
7.4.2. Other Implantable Electrical Interventions .....	e945
7.4.3. Revascularization for CAD .....	e945
7.5. Valvular Heart Disease .....	e946
7.6. Heart Failure With Mildly Reduced EF (HFmrEF) and Improved EF (HFimpHF).....	e948
7.6.1. HF With Mildly Reduced Ejection Fraction .....	e948
7.6.2. HF With Improved Ejection Fraction .....	e949

7.7.	Preserved EF (HFpEF) .....	e949
7.7.1.	HF With Preserved Ejection Fraction .....	e949
7.8.	Cardiac Amyloidosis.....	e952
7.8.1.	Diagnosis of Cardiac Amyloidosis....	e952
7.8.2.	Treatment of Cardiac Amyloidosis....	e954
8.	Stage D (Advanced) HF .....	e955
8.1.	Specialty Referral for Advanced HF.....	e955
8.2.	Nonpharmacological Management: Advanced HF .....	e956
8.3.	Inotropic Support .....	e957
8.4.	Mechanical Circulatory Support .....	e958
8.5.	Cardiac Transplantation.....	e960
9.	Patients Hospitalized With Acute Decompensated HF.....	e960
9.1.	Assessment of Patients Hospitalized With Decompensated HF .....	e960
9.2.	Maintenance or Optimization of GDMT During Hospitalization .....	e962
9.3.	Diuretics in Hospitalized Patients: Decongestion Strategy.....	e963
9.4a.	Parenteral Vasodilation Therapy in Patients Hospitalized With HF .....	e964
9.4b.	VTE Prophylaxis in Hospitalized Patients.....	e965
9.5.	Evaluation and Management of Cardiogenic Shock.....	e965
9.6.	Integration of Care: Transitions and Team-Based Approaches .....	e967
10.	Comorbidities in Patients With HF .....	e969
10.1.	Management of Comorbidities in Patients With HF .....	e969
10.2.	Management of AF in HF.....	e972
11.	Special Populations.....	e973
11.1.	Disparities and Vulnerable Populations .....	e973
11.2.	Cardio-Oncology.....	e975
11.3.	HF and Pregnancy.....	e978
12.	Quality Metrics and Reporting .....	e980
12.1.	Performance Measurement .....	e980
13.	Goals of Care .....	e980
13.1.	Palliative and Supportive Care, Shared Decision-Making, and End-of-Life .....	e980
14.	Recommendation for Patient-Reported Outcomes and Evidence Gaps and Future Research Directions .....	e986
14.1.	Patient-Reported Outcomes .....	e986
14.2.	Evidence Gaps and Future Research Directions.....	e986
References .....	e987	
Appendix 1		
Author Relationships With Industry and Other Entities (Relevant) .....	e1026	
Appendix 2		
Reviewer Relationships With Industry and Other Entities (Comprehensive) .....	e1029	

## Appendix 3

Appendix for Tables 3 and 4. Suggested Thresholds for Structural Heart Disease and Evidence of Increased Filling Pressures.....e1032

**TOP 10 TAKE-HOME MESSAGES**

1. Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i).
2. SGLT2i have a Class of Recommendation 2a in HF with mildly reduced ejection fraction (HFmrEF). Weaker recommendations (Class of Recommendation 2b) are made for ARNi, ACEi, ARB, MRA, and beta blockers in this population.
3. New recommendations for HFpEF are made for SGLT2i (Class of Recommendation 2a), MRAs (Class of Recommendation 2b), and ARNi (Class of Recommendation 2b). Several prior recommendations have been renewed including treatment of hypertension (Class of Recommendation 1), treatment of atrial fibrillation (Class of Recommendation 2a), use of ARBs (Class of Recommendation 2b), and avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (Class of Recommendation 3: No Benefit).
4. Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF >40%. These patients should continue their HFrEF treatment.
5. Value statements were created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published.
6. Amyloid heart disease has new recommendations for treatment including screening for serum and urine monoclonal light chains, bone scintigraphy, genetic sequencing, tetramer stabilizer therapy, and anticoagulation.
7. Evidence supporting increased filling pressures is important for the diagnosis of HF if the LVEF is >40%. Evidence for increased filling pressures can be obtained from noninvasive (eg, natriuretic peptide, diastolic function on imaging) or invasive testing (eg, hemodynamic measurement).
8. Patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies, and uses palliative care including palliative inotropes where consistent with the patient's goals of care.
9. Primary prevention is important for those at risk for HF (stage A) or pre-HF (stage B). Stages of

HF were revised to emphasize the new terminologies of “at risk” for HF for stage A and pre-HF for stage B.

10. Recommendations are provided for select patients with HF and iron deficiency, anemia, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease, and malignancy.

## PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations.

## Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease (CVD). The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients’ interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

## Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

## Methodology and Modernization

The ACC/AHA Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the National Academy of Medicine (formerly, the Institute of Medicine),<sup>1,2</sup> and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in

response to evolving technologies and other factors to optimally facilitate dissemination of information to health care professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them shorter and enhance “user friendliness.” Guidelines are written and presented in a modular, “knowledge chunk” format in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. In recognition of the importance of cost–value considerations, in certain guidelines, when appropriate and feasible, an assessment of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.<sup>3</sup>

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of “full revision” and “focused update” will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual<sup>4</sup> and other methodology articles.<sup>5–7</sup>

## Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

## Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online. Appendix 1 of the guideline lists writing committee members’ relevant RWI; for the purposes of full transparency, their comprehensive disclosure information is available in a Supplemental Appendix. Comprehensive disclosure information for the Joint Committee is also available online.

## Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on

all available data.<sup>4,5</sup> Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are  $\geq 1$  questions deemed of utmost clinical importance and merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked “<sup>SR</sup>”.

## Guideline-Directed Medical Therapy

The term guideline-directed medical therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

*Joshua A. Beckman, MD, MS, FAHA, FACC  
Chair, ACC/AHA Joint Committee on Clinical Practice Guidelines*

## 1. INTRODUCTION

### 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Collaboration, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from May 2020 to December 2020. Key search words included but were not limited to the following: *heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; heart failure with mildly reduced ejection fraction; systolic heart failure; heart failure rehabilitation; cardiac failure; chronic heart failure; acute decompensated heart failure; cardiogenic shock; beta blockers; mineralocorticoid receptor antagonists; ACE-inhibitors, angiotensin and neprilysin receptor antagonist; sacubitril valsartan; angiotensin receptor antagonist; Sodium glucose co-transporter 2 or SGLT2 inhibitors; cardiac amyloidosis; atrial fibrillation; congestive heart failure; guideline-directed medical therapy; HFpEF; diabetes mellitus; cardiomyopathy; cardiac amyloidosis; valvular heart disease; mitral regurgitation; cardiomyopathy in pregnancy; reduced ejection fraction; right heart pressure; palliative care.*

Additional relevant studies, published through September 2021 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. This guideline was harmonized with other ACC/AHA guidelines published through December 2021. The final evidence tables are included in the Online Data Supplement and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

### 1.2. Organization of the Writing Committee

The writing committee consisted of cardiologists, HF specialists, internists, interventionists, an electrophysiologist, surgeons, a pharmacist, an advanced nurse practitioner, and 2 lay/patient representatives. The writing committee included representatives from the ACC, AHA, and Heart Failure Society of America (HFSA). Appendix 1 of the present document lists writing committee members' relevant RWI. For the purposes of full transparency, the writing committee members' comprehensive disclosure information is available in a Supplemental Appendix.

### 1.3. Document Review and Approval

This document was reviewed by 2 official reviewers nominated by the AHA; 1 official reviewer nominated by the ACC; 2 official reviewers from the HFSA; 1 official Joint Committee on Clinical Practice Guidelines reviewer; and 32 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2). This document was approved for publication by the governing bodies of the ACC, AHA, and HFSA.

### 1.4. Scope of the Guideline

The purpose of the “2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure” (2022 HF guideline) is to provide an update and to consolidate the “2013 ACCF/AHA Guideline for the Management of Heart Failure”<sup>1</sup> for adults and the “2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure”<sup>2</sup> into a new document.

Related ACC/AHA guidelines include recommendations relevant to HF and, in such cases, the HF guideline refers to these documents. For example, the 2019 primary prevention of cardiovascular disease guideline<sup>3</sup> includes recommendations that will be useful in preventing HF, and the 2021 valvular heart disease guideline<sup>4</sup> provides recommendations for mitral valve (MV) clipping in mitral regurgitation (MR).

### Areas of focus include:

- Prevention of HF.
- Management strategies in stage C HF, including:
  - New treatment strategies in HF, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and angiotensin receptor-neprilysin inhibitors (ARNi).
  - Management of HF and atrial fibrillation (AF), including ablation of AF.
  - Management of HF and secondary MR, including MV transcatheter edge-to-edge repair.
- Specific management strategies, including:
  - Cardiac amyloidosis.
  - Cardio-oncology.
- Implantable devices.
- Left ventricular assist device (LVAD) use in stage D HF.

The intended primary target audience consists of clinicians who are involved in the care of patients with HF. Recommendations are stated in reference to the patients and their condition. The focus is to provide the most up-to-date evidence to inform the clinician during shared decision-making with the patient. Although the present document is not intended to be a procedural-based manual of recommendations that outlines the best practice for HF, there are certain practices that clinicians might use that are associated with improved clinical outcomes.

In developing the 2022 HF guideline, the writing committee reviewed previously published guidelines and related statements. Table 1 contains a list of these guidelines and statements deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

### 1.5. Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 2).<sup>1</sup>

### 1.6. Abbreviations

Abbreviation	Meaning/Phrase
ACEi	angiotensin-converting enzyme inhibitors
ACS	acute coronary syndrome
ARNi	angiotensin receptor-neprilysin inhibitors
ARB	angiotensin (II) receptor blockers
AF	atrial fibrillation
AL-CM	immunoglobulin light chain amyloid cardiomyopathy
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTRv	variant transthyretin amyloidosis
ATTRwt	wild-type transthyretin amyloidosis
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCM	cardiac contractility modulation
CHF	congestive heart failure
CKD	chronic kidney disease
CMR	cardiovascular magnetic resonance
COVID-19	coronavirus disease 2019
CPET	cardiopulmonary exercise test
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy with defibrillation
CRT-P	cardiac resynchronization therapy with pacemaker
CT	computed tomography
CVD	cardiovascular disease
CVP	central venous pressure
DOAC	direct-acting oral anticoagulants
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
FLC	free light chain
GDMT	guideline-directed medical therapy
HF	heart failure
HFimpEF	heart failure with improved ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrefEF	heart failure with reduced ejection fraction
ICD	implantable cardioverter-defibrillator
IFE	immunofixation electrophoresis
LBBB	left bundle branch block
LV	left ventricular
LVAD	left ventricular assist device
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy

Abbreviation	Meaning/Phrase
MCS	mechanical circulatory support
MI	myocardial infarction
MR	mitral regurgitation
MRA	mineralocorticoid receptor antagonist
MV	mitral valve
NSAID	nonsteroidal anti-inflammatory drug
NSVT	nonsustained ventricular tachycardia
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
QALY	quality-adjusted life year
QOL	quality of life
PA	pulmonary artery
PCWP	pulmonary capillary wedge pressure
PET	positron emission tomography
PPAR- $\gamma$	peroxisome proliferator-activated receptor gamma
PUFA	polyunsaturated fatty acid
RA	right atrial
RASS	renin-angiotensin-aldosterone system
RAASi	renin-angiotensin-aldosterone system inhibitors
RCT	randomized controlled trial
RV	right ventricular
SCD	sudden cardiac death
SGLT2i	sodium-glucose cotransporter-2 inhibitors
SPECT	single photon emission CT
$^{99m}$ Tc-PYP	technetium pyrophosphate
TEER	transcatheter mitral edge-to-edge repair
TTE	transthoracic echocardiogram
VA	ventricular arrhythmia
VF	ventricular fibrillation
VHD	valvular heart disease
VO <sub>2</sub>	oxygen consumption/oxygen uptake
VT	ventricular tachycardia

## 2. DEFINITION OF HF

### HF Description

HF is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. The writing committee recognizes that asymptomatic stages with structural heart disease or cardiomyopathies are not covered under the above definition as having HF. Such asymptomatic stages are considered at-risk for HF (stage A) or pre-HF (stage B), as explained in Section 2.1, "Stages of HF."

### 2.1. Stages of HF

The ACC/AHA stages of HF (Figure 1, Table 3) emphasize the development and progression of disease,<sup>1,2</sup> and advanced stages and progression are as-

sociated with reduced survival.<sup>3</sup> Therapeutic interventions in each stage aim to modify risk factors (stage A), treat risk and structural heart disease to prevent HF (stage B), and reduce symptoms, morbidity, and mortality (stages C and D). To address the evolving role of biomarkers and structural changes for recognition of patients who are at risk of developing HF, who are potential candidates for targeted treatment strategies for the prevention of HF, and to enhance the understanding and adoption of these classifications, the writing committee proposed the terminologies listed in Table 3 for the stages of HF. For thresholds of cardiac structural, functional changes, elevated filling pressures, and biomarker elevations, refer to Appendix 3.

### New York Heart Association (NYHA) Classification

The NYHA classification is used to characterize symptoms and functional capacity of patients with symptomatic (stage C) HF or advanced HF (stage D). It is a subjective assessment by a clinician and can change over time. Although reproducibility and validity can be limited,<sup>4,5</sup> the NYHA functional classification is an independent predictor of mortality,<sup>6,7</sup> and it is widely used in clinical practice to determine the eligibility of patients for treatment strategies. Clinicians specify NYHA classification at baseline after the initial diagnosis and after treatment through the continuum of care of a patient with HF. Although a patient with symptomatic HF (stage C) may become asymptomatic with treatment (NYHA class I), that patient will still be categorized as stage C HF. Patients with stage C HF can be classified according to the trajectory of their symptoms (Figure 2).

### 2.2. Classification of HF by Left Ventricular Ejection Fraction (LVEF)

LVEF is considered important in the classification of patients with HF because of differing prognosis and response to treatments and because most clinical trials select patients based on ejection fraction (EF). RCTs with evidence of survival benefit in patients with HF have mainly enrolled patients with HF with an LVEF  $\leq 35\%$  or  $\leq 40\%$ , often labeled HF with reduced ejection fraction (HFrEF).<sup>1</sup> In this guideline, HFrEF is defined as LVEF  $\leq 40\%$  (Table 4). HF with preserved EF (HFpEF) represents at least 50% of the population with HF, and its prevalence is increasing.<sup>2</sup> HFpEF has been variably classified as LVEF  $> 40\%$ ,  $> 45\%$ , or  $\geq 50\%$ . Because some of these patients do not have entirely normal LVEF but also do not have major reduction in systolic function, the term preserved EF has been used. In this guideline, the threshold for HFpEF is an LVEF  $\geq 50\%$  (Table 4).

**Table 1. Associated Guidelines and Statements**

Title	Organization	Publication Year (Reference)
Guidelines		
2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery <i>Hillis et al., "2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery" is now replaced and retired by the "2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization"</i> <sup>6</sup>	ACCF/AHA	2011 <sup>6</sup>
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention <i>Levine et al., "2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention," is now replaced and retired by the "2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization"</i> <sup>6</sup>	ACCF/AHA/SCAI	2011 <sup>7</sup>
2015 ACCF/AHA/SCAI Focused Update Guideline for Percutaneous Coronary Intervention	ACCF/AHA/SCAI	2016 <sup>8</sup>
2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease	ACC/AHA	2021 <sup>4</sup>
2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy	ACC/AHA	2020 <sup>9</sup>
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease	ACC/AHA	2019 <sup>3</sup>
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation	AHA/ACC/HRS	2019 <sup>10</sup>
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/AphA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults	ACC/AHA/AAPA/ABC/ACPM/AGS/AphA/ASH/ASPC/NMA/PCNA	2018 <sup>11</sup>
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure	ACC/AHA/HFSA	2017 <sup>2</sup>
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure	ACC/AHA/HFSA	2016 <sup>12</sup>
2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	ACC/AHA/AATS/PCNA/SCAI/STS	2014 <sup>13*</sup>
2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk	AHA/ACC	2014 <sup>14</sup>
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults	AHA/ACC/TOS	2014 <sup>15</sup>
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/AphA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol	AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/AphA/ASPC/NLA/PCNA	2019 <sup>16</sup>
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults	ACC/AHA	2014 <sup>17</sup>
2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk	ACC/AHA	2014 <sup>18</sup>
2013 ACCF/AHA Guideline for the Management of Heart Failure	ACCF/AHA	2013 <sup>1</sup>
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction	ACCF/AHA	2013 <sup>19</sup>
2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities	ACCF/AHA/HRS	2012 <sup>20</sup>
2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	ACCF/AHA/ACP/AATS/PCNA/SCAI/STS	2012 <sup>21</sup>
Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update	AHA	2011 <sup>22</sup>
AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update	AHA/ACCF	2011 <sup>23</sup>
2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults	ACCF/AHA	2010 <sup>24</sup>
Part 9: Post–Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care	AHA	2010 <sup>25</sup>
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	NHLBI	2003 <sup>26</sup>
Statements		
Cardiac Amyloidosis: Evolving Diagnosis and Management	AHA	2020 <sup>27</sup>
Testing of Low-Risk Patients Presenting to the Emergency Department With Chest Pain	AHA	2010 <sup>28</sup>
Primary Prevention of Cardiovascular Diseases in People With Diabetes Mellitus	AHA/ADA	2007 <sup>29</sup>
Prevention and Control of Influenza	CDC	2005 <sup>30</sup>

AATS indicates American Association for Thoracic Surgery; AACVPR, American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Associates; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; AphA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; CDC, Centers for Disease Control and Prevention; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Care Excellence; NMA, National Medical Association; NLA, National Lipid Association; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; SIHD, stable ischemic heart disease; STS, Society of Thoracic Surgeons; TOS, The Obesity Society; and WHF, World Heart Federation.

\*The full SIHD guideline is from 2012.<sup>21</sup> A focused update was published in 2014.<sup>13</sup>

**Table 2.** Applying American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)\*

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS 1 (STRONG)</b>  <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>• Is recommended</li><li>• Is indicated/useful/effective/beneficial</li><li>• Should be performed/administered/other</li><li>• Comparative-Effectiveness Phrases†:<ul style="list-style-type: none"><li>– Treatment/strategy A is recommended/indicated in preference to treatment B</li><li>– Treatment A should be chosen over treatment B</li></ul></li></ul>	<b>Benefit &gt;&gt; Risk</b>  <b>LEVEL A</b> <ul style="list-style-type: none"><li>• High-quality evidence‡ from more than 1 RCT</li><li>• Meta-analyses of high-quality RCTs</li><li>• One or more RCTs corroborated by high-quality registry studies</li></ul>
<b>CLASS 2a (MODERATE)</b>  <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>• Is reasonable</li><li>• Can be useful/effective/beneficial</li><li>• Comparative-Effectiveness Phrases†:<ul style="list-style-type: none"><li>– Treatment/strategy A is probably recommended/indicated in preference to treatment B</li><li>– It is reasonable to choose treatment A over treatment B</li></ul></li></ul>	<b>Benefit &gt;&gt; Risk</b>  <b>LEVEL B-R</b> <b>(Randomized)</b> <ul style="list-style-type: none"><li>• Moderate-quality evidence‡ from 1 or more RCTs</li><li>• Meta-analyses of moderate-quality RCTs</li></ul>
<b>CLASS 2b (WEAK)</b>  <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>• May/might be reasonable</li><li>• May/might be considered</li><li>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established</li></ul>	<b>Benefit ≥ Risk</b>  <b>LEVEL B-NR</b> <b>(Nonrandomized)</b> <ul style="list-style-type: none"><li>• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li><li>• Meta-analyses of such studies</li></ul>
<b>CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only)</b>  <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>• Is not recommended</li><li>• Is not indicated/useful/effective/beneficial</li><li>• Should not be performed/administered/other</li></ul>	<b>Benefit = Risk</b>  <b>LEVEL C-LD</b> <b>(Limited Data)</b> <ul style="list-style-type: none"><li>• Randomized or nonrandomized observational or registry studies with limitations of design or execution</li><li>• Meta-analyses of such studies</li><li>• Physiological or mechanistic studies in human subjects</li></ul>
<b>Class 3: Harm (STRONG)</b>  <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>• Potentially harmful</li><li>• Causes harm</li><li>• Associated with excess morbidity/mortality</li><li>• Should not be performed/administered/other</li></ul>	<b>Risk &gt; Benefit</b>  <b>LEVEL C-EO</b> <b>(Expert Opinion)</b> <ul style="list-style-type: none"><li>• Consensus of expert opinion based on clinical experience</li></ul>

COR and LOE are determined independently (any COR may be paired with any LOE). A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

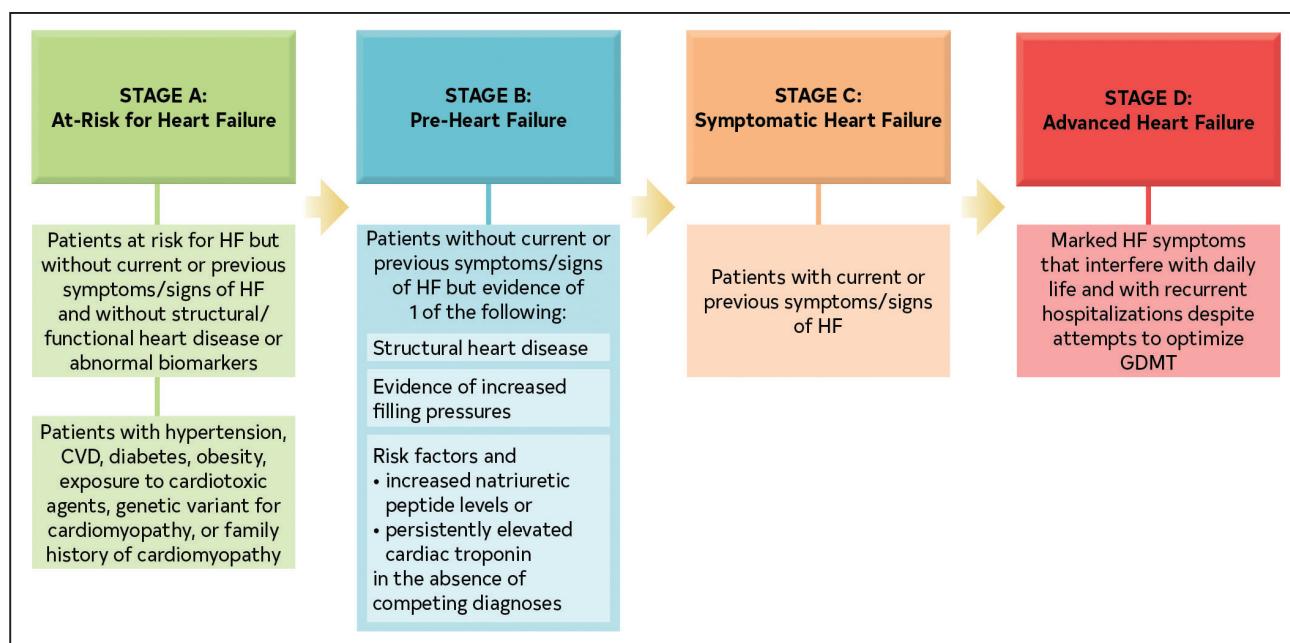
† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Patients with HF and an LVEF between the HFrEF and HFpEF range have been termed as “HF with mid-range EF,”<sup>3,4</sup> or “HF with mildly reduced EF.”<sup>4</sup> Because of LVEF being lower than normal, these patients are classified in this document as HF with mildly reduced EF (HFmrEF). Patients with HFmrEF are usually in a dynamic trajectory to improvement from HFrEF or to deterioration to HFrEF (Figure 3). Therefore, for patients whose EF falls into this mildly reduced category, 1 EF measurement at 1 time point may not be adequate, and the trajectory of LVEF over time and the cause is important to evaluate (Figure 3). Furthermore, the diagnosis of HFmrEF and HFpEF can be challenging. Although the classic clinical signs and symptoms of HF, together with EF of 41% to 49%

or ≥50%, respectively, are necessary for the diagnosis of the HFmrEF and HFpEF, the requirements for additional objective measures of cardiac dysfunction can improve the diagnostic specificity. The signs and symptoms of HF are frequently nonspecific and overlap with other clinical conditions. Elevated natriuretic peptide levels are supportive of the diagnosis, but normal levels do not exclude a diagnosis of HFmrEF or HFpEF. To improve the specificity of diagnosing HFmrEF and HFpEF, the clinical diagnosis of HF in these EF categories should be further supported by objective measures. Therefore, the writing committee proposes the addition of evidence of spontaneous (at rest) or provokable (eg, during exercise, fluid challenge) increased LV filling pressures (eg, elevated

**Figure 1. ACC/AHA Stages of HF.**

The ACC/AHA stages of HF are shown. ACC indicates American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and HF, heart failure.

natriuretic peptide, noninvasive/invasive hemodynamic measurement) to the classifications of HFM-REF and HFpEF (Table 4).

The “2013 ACCF/AHA Guideline for the Management of Heart Failure”<sup>1</sup> has used the HFpEF-improved terminology for those whose EF improved from a lower level to EF >40% under the subgrouping of patients with HFpEF. Others have proposed a

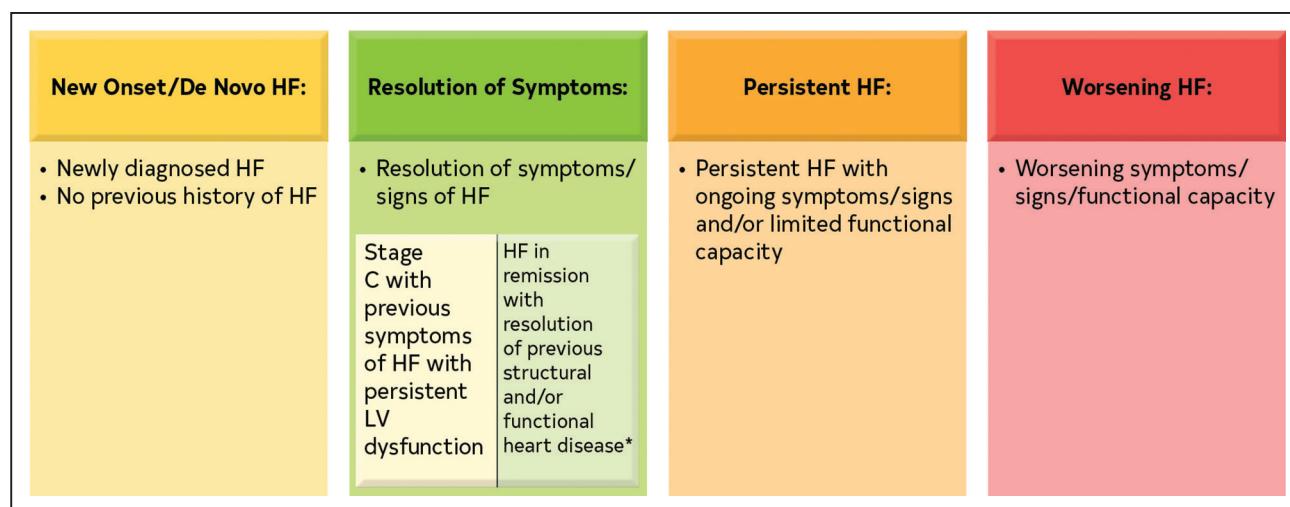
working definition of HF-recovered EF that included a baseline LVEF ≤40%, a ≥10% increase from baseline LVEF, and a second measurement of LVEF >40%.<sup>3</sup> Although associated with better outcomes, improvement in LVEF does not mean full myocardial recovery or normalization of LV function. In most patients, cardiac structural abnormalities, such as LV chamber dilatation and ventricular systolic and diastolic

**Table 3. Stages of HF**

Stages	Definition and Criteria
Stage A: At Risk for HF	At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury (eg, patients with hypertension, atherosclerotic CVD, diabetes, metabolic syndrome and obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy).
Stage B: Pre-HF	No symptoms or signs of HF and evidence of 1 of the following: <i>Structural heart disease*</i> Reduced left or right ventricular systolic function Reduced ejection fraction, reduced strain Ventricular hypertrophy Chamber enlargement Wall motion abnormalities Valvular heart disease <i>Evidence for increased filling pressures*</i> By invasive hemodynamic measurements By noninvasive imaging suggesting elevated filling pressures (eg, Doppler echocardiography) <i>Patients with risk factors and</i> <i>Increased levels of BNP*</i> or <i>Persistently elevated cardiac troponin</i> in the absence of competing diagnoses resulting in such biomarker elevations such as acute coronary syndrome, CKD, pulmonary embolus, or myopericarditis
Stage C: Symptomatic HF	Structural heart disease with current or previous symptoms of HF.
Stage D: Advanced HF	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT.

BNP indicates B-type natriuretic peptide; CKD, chronic kidney disease; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and HF, heart failure.

\*For thresholds of cardiac structural, functional changes, elevated filling pressures, and biomarker elevations, refer to Appendix 3.

**Figure 2. Trajectory of Stage C HF.**

The trajectory of stage C HF is displayed. Patients whose symptoms and signs of HF are resolved are still stage C and should be treated accordingly. If all HF symptoms, signs, and structural abnormalities resolve, the patient is considered to have HF in remission. HF indicates heart failure; and LV, left ventricular. \*Full resolution of structural and functional cardiac abnormalities is uncommon.

dysfunction, may persist. Furthermore, changes in LVEF might not be unidirectional; a patient may have improvement followed by a decrease in EF or vice versa depending on the underlying cause, duration of disease, adherence to the GDMT, or reexposure to cardiotoxicity.<sup>5</sup> Therefore, the writing committee elected not to use “recovered EF” or HFpEF, even if subsequent LVEF was >50% but, rather, “HF with improved EF” (HFimpEF) as a subgroup of HFrEF to characterize these patients (Table 4, Figure 3). Importantly, EF can decrease after withdrawal of pharmacological treatment in many patients who had improved EF to normal range with GDMT.<sup>5</sup> Trajectory of LVEF can be important, and a significant reduction in LVEF over time is a poor prognostic factor.

**Table 4. Classification of HF by LVEF**

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Please see Appendix 3 for suggested thresholds for structural heart disease and evidence of increased filling pressures.

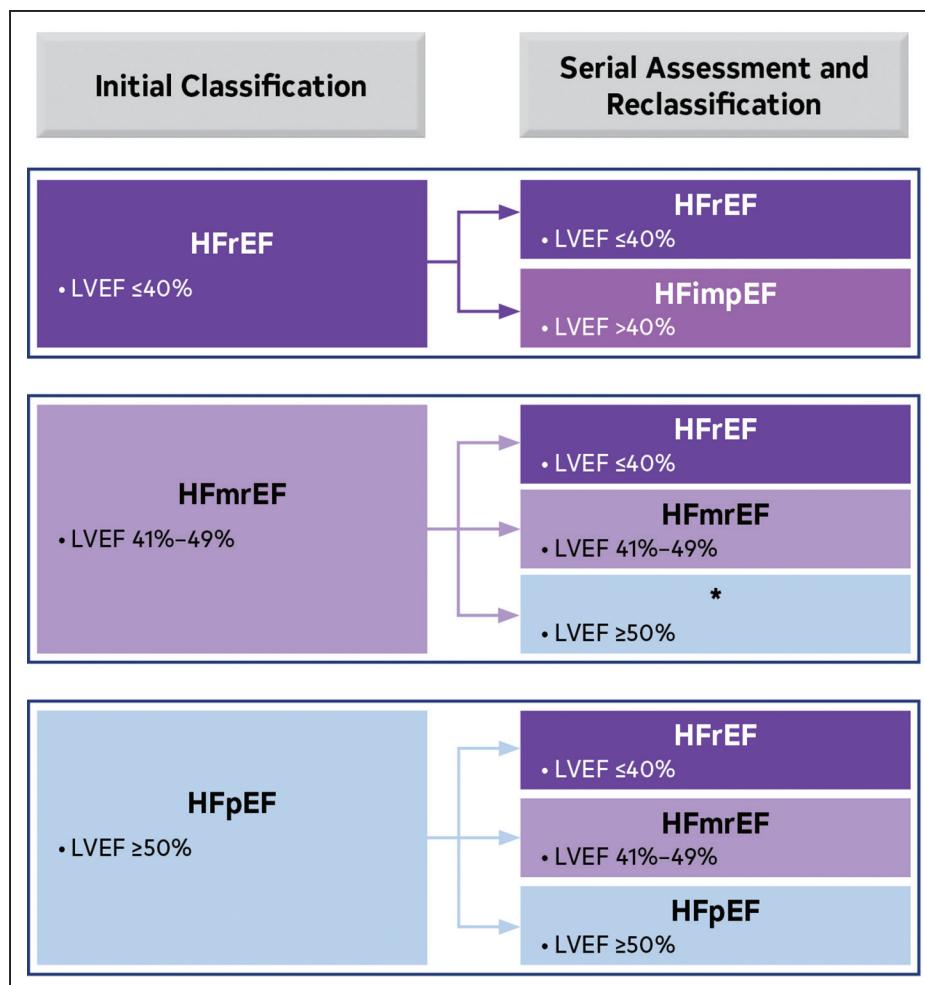
HF indicates heart failure; LV, left ventricular; and LVEF, left ventricular ejection fraction.

### 2.3. Diagnostic Algorithm for Classification of HF According to LVEF

Structural and functional alterations of the heart as the underlying cause for the clinical presentation support the diagnosis of HFmrEF and HFpEF<sup>1</sup> (Figure 4). The criteria for diagnosis of HFmrEF and HFpEF require evidence of increased LV filling pressures at rest, exercise, or other provocations. The criteria can be fulfilled with findings of elevated levels of natriuretic peptides, echocardiographic diastolic parameters such as an E/e' ≥15 or other evidence of elevated filling pressures, or invasive hemodynamic measurement at rest or exercise. Evidence of structural heart disease (eg, LV structural or functional alterations) may be used to further support the diagnosis of HFpEF. Key structural alterations are an increase in left atrial size and volume (left atrial volume index) and/or an increase in LV mass (LV mass index).

Exercise stress testing with echocardiographic evaluation of diastolic parameters can be helpful if the diagnosis remains uncertain.<sup>2,3</sup> Alternatively, or in addition, invasive hemodynamics at rest or with exercise, with assessment of filling pressures (pulmonary capillary wedge pressure or LV end diastolic pressures, pulmonary artery [PA] pressures, stroke volumes, and cardiac output) can be performed to help further establish the diagnosis.<sup>4</sup>

The diagnosis of HFpEF is often challenging. A clinical composite score to diagnose HFpEF, the H<sub>2</sub>FPEF score,<sup>5–7</sup> integrates these predictive variables: obesity, atrial fibrillation (AF), age ≥60 years, treatment with ≥2 antihypertensive medications, echocardiographic E/e' ratio >9, and echocardiographic PA systolic pressure >35 mm Hg. A weighted score based on these

**Figure 3. Classification and Trajectories of HF Based on LVEF.**

See Appendix 3 for suggested thresholds for laboratory findings. The classification for baseline and subsequent LVEF is shown. Patients with HFrEF who improve their LVEF to >40% are considered to have HFimpEF and should continue HFrEF treatment. HF indicates heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction. \*There is limited evidence to guide treatment for patients who improve their LVEF from mildly reduced (41%–49%) to ≥50%. It is unclear whether to treat these patients as HFpEF or HFmrEF.

6 variables was used to create the composite score ranging from 0 to 9. The odds of HFpEF doubled for each 1-unit score increase (odds ratio, 1.98; 95% CI: 1.74-2.30;  $P<0.0001$ ), with a c-statistic of 0.841. Scores <2 and ≥6 reflect low and high likelihood, respectively, for HFpEF. A score between 2 and 5 may require further evaluation of hemodynamics with exercise echocardiogram or cardiac catheterization to confirm or negate a diagnosis of HFpEF. The use of this H<sub>2</sub>FPEF score may help to facilitate discrimination of HFpEF from noncardiac causes of dyspnea and can assist in determination of the need for further diagnostic testing in the evaluation of patients with unexplained exertional dyspnea.<sup>6,7</sup>

The European Society of Cardiology has developed a diagnostic algorithm.<sup>8</sup> This involves a pretest that assesses for HF symptoms and signs, typical clinical demographics (obesity, hypertension, diabetes,

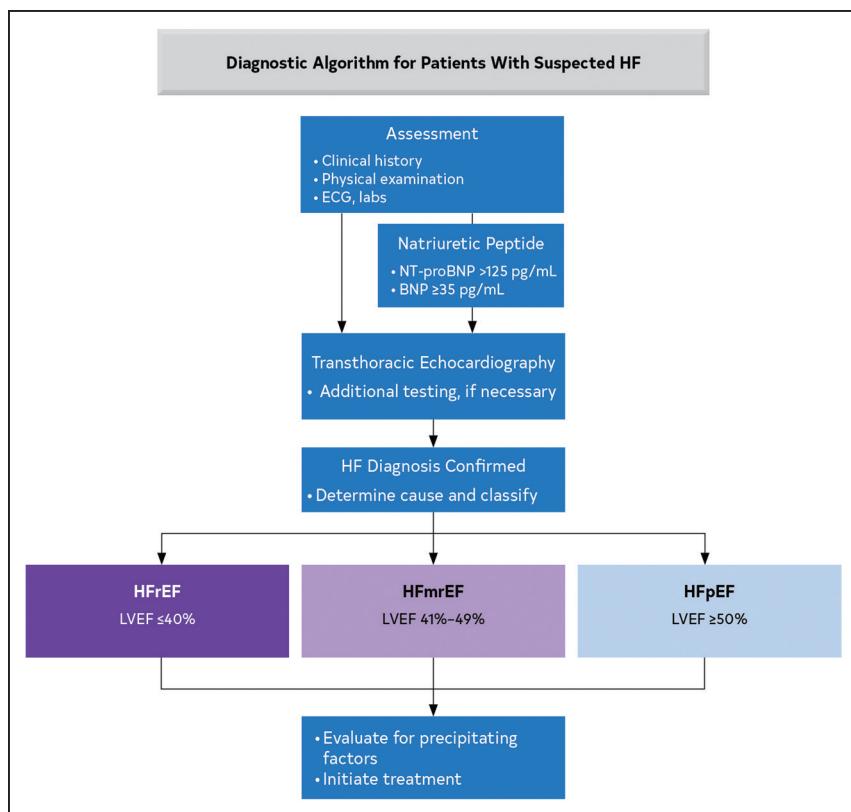
elderly, AF), and diagnostic laboratory tests, ECG, and echocardiography. In the absence of overt noncardiac causes of breathlessness, HFpEF can be suspected if there is a normal LVEF, no significant heart valve disease or cardiac ischemia, and at least 1 typical risk factor. The score used functional, morphological, and biomarker domains. The points score assigns 2 points for a major criterion or 1 point for a minor criterion within each domain, with a maximum of 2 points for each domain.

### 3. EPIDEMIOLOGY AND CAUSES OF HF

#### 3.1. Epidemiology of HF

##### Trends in Mortality and Hospitalization for HF

HF is a growing health and economic burden for the United States, in large part because of the aging popula-



**Figure 4. Diagnostic Algorithm for HF and EF-Based Classification.**

The algorithm for a diagnosis of HF and EF-based classification is shown. BNP indicates B-type natriuretic peptide; ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LV, left ventricular; and NT-proBNP, N-terminal pro-B type natriuretic peptide.

tion.<sup>1,2</sup> Beginning in 2012, the age-adjusted death rate per capita for HF increased for the first time in the United States.<sup>3</sup> A recent US evaluation found total deaths caused by HF have increased from 275 000 in 2009 to 310 000 in 2014.<sup>3</sup>

US hospitalizations for HF decreased up until 2012<sup>4</sup>; however, from 2013 to 2017, an increase in HF hospitalizations was observed. In 2017, there were 1.2 million HF hospitalizations in the United States among 924 000 patients with HF.<sup>4</sup> This represents a 26% increase in HF hospitalizations and number of patients hospitalized with HF.

Although the absolute number of patients with HF has partly grown as a result of the increasing number of older adults, the incidence of HF has decreased.<sup>5</sup> Among US Medicare beneficiaries, HF incidence declined from 36 cases per 1000 beneficiaries in 2011 to 27 cases per 1000 beneficiaries in 2014 and remained stable through 2016.<sup>5</sup> Divergent trends in the incidence of HF have been observed for those with HFrEF (decreasing incidence) and HFpEF (increasing incidence).<sup>6,7</sup> Deaths attributable to cardiomyopathies have been increasing globally because of, in part, increased recognition, diagnosis, and documentation of specific cardiomyopathies and cardiotoxicity.<sup>2</sup>

## Racial and Ethnic Disparities in Mortality and Hospitalization for HF

Racial and ethnic disparities in death resulting from HF persist, with non-Hispanic Black patients having the

highest death rate per capita.<sup>4</sup> A report examining the US population found age-adjusted mortality rate for HF to be 92 per 100 000 individuals for non-Hispanic Black patients, 87 per 100 000 for non-Hispanic White patients, and 53 per 100 000 for Hispanic patients.<sup>4</sup> Among Medicare beneficiaries, non-Hispanic Black beneficiaries had a slightly greater decrease in HF incidence (38 cases per 1000 to 26 cases per 1000,  $P=0.009$ ) than non-Hispanic White beneficiaries (36 cases per 1000 to 28 cases per 1000,  $P=0.003$ ) from 2011 to 2016.<sup>4</sup> Among patients with established HF, non-Hispanic Black patients experienced a higher rate of HF hospitalization and a lower rate of death compared with non-Hispanic White patients with HF.<sup>8–10</sup> Hispanic patients with HF have been found to have similar<sup>8</sup> or higher<sup>10</sup> HF hospitalization rates and similar<sup>10</sup> or lower<sup>8</sup> mortality rates compared with non-Hispanic White patients. Asian/Pacific Islander patients with HF have had a similar rate of hospitalization as non-Hispanic White patients but a lower rate of death.<sup>8,10</sup> These racial and ethnic disparities in outcome, for those with HF, warrant studies and health policy changes to address health inequity.

## 3.2. Cause of HF

In the United States, approximately 115 million people have hypertension, 100 million have obesity, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic CVD.<sup>1</sup> These are

**Table 5. Other Potential Nonischemic Causes of HF**

Cause	Reference
Chemotherapy and other cardiotoxic medications	23–25
Rheumatologic or autoimmune	26
Endocrine or metabolic (thyroid, acromegaly, pheochromocytoma, diabetes, obesity)	27–31
Familial cardiomyopathy or inherited and genetic heart disease	32
Heart rhythm-related (eg, tachycardia-mediated, PVCs, RV pacing)	33
Hypertension	34
Infiltrative cardiac disease (eg, amyloid, sarcoid, hemochromatosis)	21,35,36
Myocarditis (infectious, toxin or medication, immunological, hypersensitivity)	37,38
Peripartum cardiomyopathy	39
Stress cardiomyopathy (Takotsubo)	40,41
Substance abuse (eg, alcohol, cocaine, methamphetamine)	42–44

HF indicates heart failure; PVC, premature ventricular contraction; and RV, right ventricular.

known risk factors with high relative risk and population attributable risk for development of HF. Therefore, a large proportion of the US population can be categorized as being at-risk for HF or stage A HF. The common causes of HF include ischemic heart disease and myocardial infarction (MI), hypertension, and valvular heart disease (VHD). Other causes can include familial or genetic cardiomyopathies; amyloidosis; cardiotoxicity with cancer or other treatments or substance abuse such as alcohol, cocaine, or methamphetamine; tachycardia, right ventricular (RV) pacing or stress-induced cardiomyopathies; peripartum cardiomyopathy; myocarditis; autoimmune causes, sarcoidosis; iron overload, including hemochromatosis; and thyroid disease and other endocrine metabolic and nutritional causes (Table 5). Furthermore, with cardiac imaging and biomarkers, myocardial injury or cardiac maladaptive structural changes can be detected at earlier phases with a higher sensitivity, even in the absence of gross LV dysfunction or symptoms. With the coronavirus disease 2019 (COVID-19) pandemic, investigators are gaining better insights into infection and inflammation-related myocardial injury and myocarditis. With the increasing ability to detect myocardial injury and with an increasing awareness of cardiotoxicity and injury patterns including inflammation, pre-HF or stage B HF will likely continue to increase. Beyond classifications of EF and staging in HF, clinicians should seek the cause of HF because appropriate treatment may be determined by the cause (Table 5).

## 4. INITIAL AND SERIAL EVALUATION

### 4.1. Clinical Assessment: History and Physical Examination

#### Recommendations for Clinical Assessment: History and Physical Examination

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	<ul style="list-style-type: none"> <li>1. In patients with HF, vital signs and evidence of clinical congestion should be assessed at each encounter to guide overall management, including adjustment of diuretics and other medications.<sup>1–6</sup></li> </ul>
1	B-NR	<ul style="list-style-type: none"> <li>2. In patients with symptomatic HF, clinical factors indicating the presence of advanced HF should be sought via the history and physical examination.<sup>7–12</sup></li> </ul>
1	B-NR	<ul style="list-style-type: none"> <li>3. In patients with cardiomyopathy, a 3-generation family history should be obtained or updated when assessing the cause of the cardiomyopathy to identify possible inherited disease.<sup>13,14</sup></li> </ul>
1	B-NR	<ul style="list-style-type: none"> <li>4. In patients presenting with HF, a thorough history and physical examination should direct diagnostic strategies to uncover specific causes that may warrant disease-specific management.<sup>15,16</sup></li> </ul>
1	C-EO	<ul style="list-style-type: none"> <li>5. In patients presenting with HF, a thorough history and physical examination should be obtained and performed to identify cardiac and noncardiac disorders, lifestyle and behavioral factors, and social determinants of health that might cause or accelerate the development or progression of HF.</li> </ul>

### Synopsis

The history and physical examination remain a cornerstone in the assessment of patients with HF. The history and physical examination provide information about the cause of an underlying cardiomyopathy, including the possibility of an inherited cardiomyopathy as ascertained by a family history or a condition requiring disease-specific therapy like amyloid heart disease, as well as reasons why a previously stable patient developed acutely decompensated HF. A critical component of the history and physical examination is to assess for clinical congestion (ie, those signs and symptoms resulting from elevated cardiac filling pressures). Congestion is a target for medication adjustment and is associated with quality of life (QOL) and prognosis. The history and physical examination also allow for the determination of clinical clues that suggest the patient has advanced HF, which may warrant referral to an advanced HF center.

### Recommendation-Specific Supportive Text

1. Clinical congestion can be assessed by various methods, including the presence of jugular venous

distention,<sup>17</sup> orthopnea,<sup>18</sup> bendaropnea,<sup>19</sup> a square-wave response to the Valsalva maneuver,<sup>20</sup> and leg edema.<sup>6</sup> On a practical level, clinicians use extent of clinical congestion to guide titration of pharmacological treatments, including doses of diuretics. Observational studies have shown that clinical congestion is an important adverse risk factor in patients with HF.<sup>1–6,17</sup> Recently, the PARADIGM-HF (The Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) investigators showed that, in patients with chronic HFrEF, changes in markers of clinical congestion were associated with QOL as assessed by the Kansas City Cardiomyopathy Questionnaire and also provided prognostic information independently even of natriuretic peptides or the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) risk score.<sup>2</sup> These data highlight the ongoing relevance of clinical congestion ascertained by the history and physical examination.

2. Some patients with HF progress to an advanced state, a condition that can be treated with specialized interventions such as mechanical circulatory support (MCS) or cardiac transplantation. Such patients should be identified before they progress to a state of extremis, at which point they may succumb to their illness or suffer complications of an intervention as a result of their very advanced state. Several “simple clinical clues” are available to identify advanced HF and should be ascertained via a focused history and physical examination. The recognition that a patient has advanced HF will allow for earlier referral to an advanced HF center, when appropriate, as will be discussed later in this document (see Section 8, “Specialty Referral for Advanced HF”).
3. Increasingly, familial cardiomyopathy is recognized as a more accurate diagnosis in some patients previously classified as having an idiopathic dilated cardiomyopathy (DCM). A detailed family history may provide the first clue of a genetic basis. A broad array of questions includes whether family members had a weak, enlarged, or thick heart, or HF; muscular dystrophy; a pacemaker or defibrillator; were on a heart transplant list; or died unexpectedly. Periodic updating of the family history in patients with a cardiomyopathy of uncertain origin may lead to a diagnosis of familial cardiomyopathy in the event that a relative subsequently develops a cardiomyopathy or a related complication. A 3-generation family pedigree obtained by genetic health

care professionals improved the rate of detection of a familial process as compared with routine care.<sup>14</sup> Furthermore, a family history of cardiomyopathy, as determined by a 3-generation pedigree analysis, was associated with findings of gadolinium enhancement on cardiac magnetic resonance imaging (MRI) and increased major adverse cardiac events.<sup>13</sup> The possibility of an inherited cardiomyopathy provides the impetus for cascade screening of undiagnosed family members, thereby potentially avoiding preventable adverse events in affected relatives by implementation of GDMT and other management that otherwise would not be initiated.

4. Certain conditions that cause HF require disease-specific therapies. For example, in amyloid heart disease, whether on the basis of transthyretin<sup>21</sup> or light chain deposition,<sup>22</sup> there are specific treatments that otherwise would not be used in patients with HF. Hence, expeditious and accurate diagnosis of such conditions is important. Currently, important delays have been reported in diagnosing amyloid heart disease,<sup>16</sup> perhaps not unexpectedly given the wide spectrum of possible clinical presentations.<sup>15</sup> Similarly, HF attributable to sarcoidosis, hemochromatosis, hypothyroidism, hyperthyroidism, acromegaly, connective tissue disease, tachycardia-induced cardiomyopathy, or high-output HF from an arteriovenous fistula, among others, requires specific therapeutic approaches. Given that the differential diagnosis of HF is broad, the history and physical examination can provide clues to narrow the number of causes to consider and guide the diagnostic approach to identify such conditions (Table 5).
5. The history and physical examination help to identify the cause of a clinical deterioration. To determine the cause of a clinical deterioration, the clinician assesses for concurrent illness (eg, ongoing myocardial ischemia, pulmonary emboli, or systemic infection), initiation of a medication potentially detrimental in the setting of HF (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]), or the possibility of chronic RV pacing (eg, a newly implanted pacemaker or medications such as amiodarone that leads to bradycardia and resultant chronic RV pacing), nonadherence to a medication or dietary regimen, and ongoing substance abuse. In addition, an assessment of social determinants of health (eg, housing stability, food security, available transportation) should be made.

#### 4.1.1. Initial Laboratory and Electrocardiographic Testing

Recommendations for Initial Laboratory and Electrocardiographic Testing		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-NR	<ol style="list-style-type: none"> <li>For patients presenting with HF, the specific cause of HF should be explored using additional laboratory testing for appropriate management.<sup>1–8</sup></li> </ol>
1	C-EO	<ol style="list-style-type: none"> <li>For patients who are diagnosed with HF, laboratory evaluation should include complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone to optimize management.</li> </ol>
1	C-EO	<ol style="list-style-type: none"> <li>For all patients presenting with HF, a 12-lead ECG should be performed at the initial encounter to optimize management.</li> </ol>

#### Synopsis

Laboratory evaluation with complete blood count, urinalysis, serum electrolytes (including sodium, potassium, calcium, and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, iron studies (serum iron, ferritin, transferrin saturation), and thyroid-stimulating hormone level and electrocardiography is part of the standard diagnostic evaluation of a patient with HF. In addition to routine assessment, specific diagnostic testing and evaluation is often necessary to identify specific cause and other comorbidities in patients with HF.

#### Recommendation-Specific Supportive Text

1. Identifying the specific cause of HF is important, because conditions that cause HF may require disease-specific therapies. Depending on the clinical suspicion, additional diagnostic studies are usually required to diagnose specific causes (Table 6) such as ischemic cardiomyopathy, cardiac amyloidosis, sarcoidosis, hemochromatosis, infectious mechanisms (eg, HIV, COVID-19, Chagas), hypothyroidism, hyperthyroidism, acromegaly, connective tissue disorders, tachycardia-induced cardiomyopathy, Takotsubo, peripartum cardiomyopathy, cardiotoxicity with cancer therapies, or substance abuse would require specific management in addition to or beyond GDMT.<sup>1,2,9–15</sup>

**Table 6. Selected Potential Causes of Elevated Natriuretic Peptide Levels<sup>50–53</sup>**

Cardiac
HF, including RV HF syndromes
ACS
Heart muscle disease, including LVH
VHD
Pericardial disease
AF
Myocarditis
Cardiac surgery
Cardioversion
Toxic-metabolic myocardial insults, including cancer chemotherapy
Noncardiac
Advancing age
Anemia
Renal failure
Pulmonary: Obstructive sleep apnea, severe pneumonia
Pulmonary embolism, pulmonary arterial hypertension
Critical illness
Bacterial sepsis
Severe burns

ACS indicates acute coronary syndromes; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy; RV, right ventricular; and VHD, valvular heart disease.

2. Laboratory evaluation with complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, iron studies (serum iron, ferritin, transferrin saturation), and thyroid-stimulating hormone levels provides important information regarding patients' comorbidities, suitability for and adverse effects of treatments, potential causes or confounders of HF, severity and prognosis of HF, and is usually performed on initial evaluation. Pertinent laboratory tests are repeated with changes in clinical condition or treatments (eg, to monitor renal function or electrolytes with diuretics).
3. Electrocardiography is part of the routine evaluation of a patient with HF and provides important information on rhythm, heart rate, QRS morphology and duration, cause, and prognosis of HF. It is repeated when there is a clinical indication, such as a suspicion for arrhythmia, ischemia or myocardial injury, conduction, or other cardiac abnormalities.

## 4.2. Use of Biomarkers for Prevention, Initial Diagnosis, and Risk Stratification

**Recommendations for Use of Biomarkers for Prevention, Initial Diagnosis, and Risk Stratification**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients presenting with dyspnea, measurement of B-type natriuretic peptide (BNP) or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is useful to support a diagnosis or exclusion of HF. <sup>1–12</sup>
1	A	2. In patients with chronic HF, measurements of BNP or NT-proBNP levels are recommended for risk stratification. <sup>11,18–29</sup>
1	A	3. In patients hospitalized for HF, measurement of BNP or NT-proBNP levels at admission is recommended to establish prognosis. <sup>11,13–19</sup>
2a	B-R	4. In patients at risk of developing HF, BNP or NT-proBNP-based screening followed by team-based care, including a cardiovascular specialist, can be useful to prevent the development of LV dysfunction or new-onset HF. <sup>30,31</sup>
2a	B-NR	5. In patients hospitalized for HF, a predischarge BNP or NT-proBNP level can be useful to inform the trajectory of the patient and establish a postdischarge prognosis. <sup>14,17,20–29</sup>

### Synopsis

Assays for BNP and NT-proBNP are frequently used to establish the presence and severity of HF. In general, BNP and NT-proBNP levels are similar, and either can be used in patient care settings as long as their respective absolute values and cut-points are not used interchangeably.<sup>32–34</sup> Obesity is associated with lower levels of BNP and NT-proBNP thereby reducing their diagnostic sensitivity.<sup>35,36</sup> A substantial evidence base supports the use of natriuretic peptide biomarkers for excluding HF as a cause of symptoms in ambulatory and emergency department settings. Although a reduction in BNP and NT-proBNP has been associated with better outcomes, the evidence for treatment guidance using serial BNP or NT-proBNP measurements remains insufficient.<sup>37–39</sup> Lastly, a widening array of biomarkers including markers of myocardial injury, inflammation, oxidative stress, vascular dysfunction, and matrix remodeling have been shown to provide incremental prognostic information over natriuretic peptides but remain without evidence of an incremental management benefit.<sup>13,40–49</sup>

### Recommendation-Specific Supportive Text

- Measurement of BNP and NT-proBNP levels in the ambulatory setting for a suspected cardiac cause of dyspnea provides incremental diagnostic value to clinical judgment when the cause of dyspnea is unclear and the physical examination equivocal.<sup>1–9</sup> In the emergency setting, BNP and NT-proBNP

levels have higher sensitivity than specificity and may be more useful for ruling out HF than ruling in HF. Although lower levels of BNP and NT-proBNP may help exclude the presence of HF, and higher levels have high positive predictive value to diagnose HF, increases in both BNP and NT-proBNP levels have been reported in patients with various cardiac and noncardiac causes (Table 6).<sup>50–53</sup>

- and 3. Higher levels of BNP and NT-proBNP are associated with a greater risk for adverse short- and long-term outcomes in patients with HF, including all-cause and cardiovascular death and major cardiovascular events.<sup>11,13–19</sup> Studies have shown incremental prognostic value of these biomarkers to standard approaches of CVD risk assessment.<sup>11,16</sup> Not all patients may need biomarker measurement for prognostication, especially if they already have advanced HF with established poor prognosis or persistently elevated levels of biomarkers in former settings.
- The STOP-HF (St Vincent's Screening to Prevent Heart Failure) study is a large single-center trial of patients at risk of HF, defined by the presence of hypertension, diabetes, or known vascular disease but without established LV systolic dysfunction or symptomatic HF, who were randomly assigned to screening with BNP testing or usual care.<sup>31</sup> Participants in the intervention group with BNP levels  $\geq 50$  pg/mL underwent echocardiography and referral to a cardiovascular specialist.<sup>31</sup> All patients received coaching by a specialist nurse who provided education on the importance of adherence to medication and healthy lifestyle behaviors.<sup>31</sup> BNP-based screening reduced the composite endpoint of incident asymptomatic LV dysfunction with or without newly diagnosed HF. Similarly, accelerated uptitration of renin-angiotensin-aldosterone system (RAAS) antagonists and beta blockers reduced cardiac events in patients with diabetes and elevated NT-proBNP levels but without cardiac disease at baseline.<sup>30</sup> Standardized screening for HF remains challenging as a result of the heterogeneity of risk factors across different patient populations. Studies are needed to assess the cost-effectiveness and risks of such screening, as well as its impact on QOL and mortality.
- Predischarge BNP and NT-proBNP levels are strong predictors of the risk of death or hospital readmission for HF.<sup>14,17,20–29</sup> Although patients in whom levels of BNP or NT-proBNP decreased with treatment had better outcomes than those without any changes or with a biomarker rise,<sup>14,23,28,29</sup> targeting a certain threshold, value, or relative change in these biomarker levels during hospitalization has not been shown to be consistently effective in improving outcomes.<sup>37–39</sup> Patients in which GDMT

**Table 7. Examples of Factors Implicating Possible Genetic Cardiomyopathy**

Phenotypic Category	Patient or Family Member Phenotypic Finding*	Ask Specifically About Family Members* With
Cardiac morphology	Marked LV hypertrophy	Any mention of cardiomyopathy, enlarged or weak heart, HF. Document even if attributed to other causes, such as alcohol or peripartum cardiomyopathy
	LV noncompaction	
	Right ventricular thinning or fatty replacement on imaging or biopsy	
Findings on 12-lead ECG	Abnormal high or low voltage or conduction, and repolarization, altered RV forces	Long QT or Brugada syndrome
Dysrhythmias	Frequent NSVT or very frequent PVCs Sustained ventricular tachycardia or fibrillation	ICD Recurrent syncope Sudden death attributed to "massive heart attack" without known CAD Unexplained fatal event such as drowning or single-vehicle crash
	Early onset AF	"Lone" AF before age 65 y
	Early onset conduction disease	Pacemaker before age 65 y
Extracardiac features	Skeletal myopathy Neuropathy Cutaneous stigmata Other possible manifestations of systemic syndromes	Any known skeletal muscle disease, including mention of Duchenne and Becker's, Emory-Dreifuss limb-girdle dystrophy Systemic syndromes: Dysmorphic features Mental retardation Congenital deafness Neurofibromatosis Renal failure with neuropathy

AF indicates atrial fibrillation; CAD, coronary artery disease; LV, left ventricular; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; and RV, right ventricular.

\*Note that genetic cause is more likely when the person is younger at the onset of events. However, the cardiac morphology and peripheral manifestations of hereditary amyloidosis may present in later life, unlike most other inherited cardiomyopathies.

leads to a reduction in BNP and NT-proBNP levels represent a population with improved long-term outcomes compared with those with persistently elevated levels despite appropriate treatment.<sup>37–39</sup> BNP and NT-proBNP levels and their change could help guide discussions on prognosis as well as adherence to, and optimization of, GDMT.

### 4.3. Genetic Evaluation and Testing

Recommendations for Genetic Evaluation and Testing		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-NR	1. In first-degree relatives of selected patients with genetic or inherited cardiomyopathies, genetic screening and counseling are recommended to detect cardiac disease and prompt consideration of treatments to decrease HF progression and sudden death. <sup>1,2</sup>
2a	B-NR	2. In select patients with nonischemic cardiomyopathy, referral for genetic counseling and testing is reasonable to identify conditions that could guide treatment for patients and family members. <sup>3,4</sup>

### Synopsis

In patients in whom a genetic or inherited cardiomyopathy is suspected, a family history should be performed, including at least 3 generations and ideally

diagrammed as a family tree pedigree (see Section 4.1, "Clinical Assessment: History and Physical Examination"). Genetic variants have been implicated in 25% to 40% of patients with DCM with a positive family history but also in 10% to 30% of patients without a recognized family history.<sup>3,4</sup> Phenotype and family history are important for identifying patients in whom genetic testing is most likely to yield clinically actionable information (Table 7). Presentation of DCM with conduction disease or ventricular arrhythmias raises concern of sarcoidosis and arrhythmogenic cardiomyopathy, which is of particular concern because of the risk of sudden death in patients and families.<sup>5</sup> No controlled studies have shown clinical benefits of genetic testing for cardiomyopathy, but genetic testing contributes to risk stratification and has implications for treatment, currently most often for decisions regarding defibrillators for primary prevention of sudden death<sup>5</sup> and regarding exercise limitation for hypertrophic cardiomyopathy and the desmosomal variants. Consultation with a trained counselor before and after genetic testing helps patients to understand and weigh the implications of possible results for their own lives and those of family members, including possible discrimination on the basis of genetic information. Unless shown to be free of the genetic variant(s) implicated in the proband, first-degree relatives of affected probands should undergo periodic screening with echocardiography and electrocardiography.

## Recommendation-Specific Supportive Text

1. and 2. Inherited dilated, restrictive, and hypertrophic cardiomyopathies have been identified, although 1 gene variant may cause different phenotypes in the same family. The most common pathogenic variants identified are truncations in the large structural protein titin, which have been implicated in DCM<sup>3–5</sup> and also in peripartum or alcoholic cardiomyopathies; however, variants that do not cause disease are also common. Pathogenic variants in lamin A/C can be associated with conduction block and atrial arrhythmias as well as ventricular arrhythmias, which may progress more rapidly than symptoms of HF. Although previously linked with the phenotype of arrhythmogenic RV cardiomyopathy, desmosomal protein variants are now recognized to affect the left ventricle also with or without the right ventricle, and the term arrhythmogenic cardiomyopathy is now preferred for the phenotype of arrhythmias combined with DCM. Filamin-C mutations have been associated with skeletal myopathies and with isolated cardiomyopathy with ventricular arrhythmias. The identification of pathogenic variants associated with increased risk of sudden death may trigger consideration of primary prevention implantable cardioverter-defibrillators (ICDs) even in patients who have LVEF >0.35 or <3 months of guideline-recommended therapies.<sup>6</sup> Evidence of desmosomal cardiac disease carries the additional implication of advice to avoid strenuous exercise, which may accelerate ventricular remodeling.<sup>7</sup> Genetic confirmation of symptomatic Fabry's cardiomyopathy is an indication for replacement therapy with the enzyme agalsidase beta, and migalastat was recently approved for this uncommon cardiomyopathy.

## 4.4. Evaluation With Cardiac Imaging

**Recommendations for Evaluation With Cardiac Imaging**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	<ol style="list-style-type: none"> <li>In patients with suspected or new-onset HF, or those presenting with acute decompensated HF, a chest x-ray should be performed to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient's symptoms.<sup>1,2</sup></li> </ol>
1	C-LD	<ol style="list-style-type: none"> <li>In patients with suspected or newly diagnosed HF, transthoracic echocardiography (TTE) should be performed during initial evaluation to assess cardiac structure and function.<sup>3</sup></li> </ol>

Recommendations for Evaluation With Cardiac Imaging (Continued)		
COR	LOE	Recommendations
1	C-LD	<ol style="list-style-type: none"> <li>In patients with HF who have had a significant clinical change, or who have received GDMT and are being considered for invasive procedures or device therapy, repeat measurement of EF, degree of structural remodeling, and valvular function are useful to inform therapeutic interventions.<sup>4–7</sup></li> </ol>
1	C-LD	<ol style="list-style-type: none"> <li>In patients for whom echocardiography is inadequate, alternative imaging (eg, cardiac magnetic resonance [CMR], cardiac computed tomography [CT], radionuclide imaging) is recommended for assessment of LVEF.<sup>8–15</sup></li> </ol>
2a	B-NR	<ol style="list-style-type: none"> <li>In patients with HF or cardiomyopathy, CMR can be useful for diagnosis or management.<sup>16–23</sup></li> </ol>
2a	B-NR	<ol style="list-style-type: none"> <li>In patients with HF, an evaluation for possible ischemic heart disease can be useful to identify the cause and guide management.<sup>24–27</sup></li> </ol>
2b	B-NR	<ol style="list-style-type: none"> <li>In patients with HF and coronary artery disease (CAD) who are candidates for coronary revascularization, noninvasive stress imaging (stress echocardiography, single-photon emission CT [SPECT], CMR, or positron emission tomography [PET]) may be considered for detection of myocardial ischemia to help guide coronary revascularization.<sup>28–32</sup></li> </ol>
3: No Benefit	C-EO	<ol style="list-style-type: none"> <li>In patients with HF in the absence of: 1) clinical status change, 2) treatment interventions that might have had a significant effect on cardiac function, or 3) candidacy for invasive procedures or device therapy, routine repeat assessment of LV function is not indicated.</li> </ol>

## Synopsis

Cardiac imaging has a key role in the initial evaluation of individuals with suspected HF and, when indicated, in the serial assessment of patients with HF. After a complete history and physical examination, a comprehensive TTE is the most useful initial diagnostic test given the vast amount of diagnostic and prognostic information provided. The determination of LVEF is a fundamental step to classify HF and to guide evidence-based pharmacological and device-based therapy. In certain situations, the echocardiogram is unable to accurately assess cardiac structure and/or function or more information is needed to determine the cause of the cardiac dysfunction. Other imaging modalities, such as CMR, SPECT or radionuclide ventriculography, PET, or cardiac CT or invasive coronary angiography, can provide additional and complementary information to cardiac ultrasound.<sup>11</sup> In general, cardiac imaging tests, including repeat tests, are performed only when the results have a meaningful impact on clinical care.

## Recommendation-Specific Supportive Text

- The chest x-ray is a useful initial diagnostic test for the evaluation of patients presenting with signs and symptoms of HF because it assesses cardiomegaly, pulmonary venous congestion, and interstitial or alveolar edema and may reveal alternative causes, cardiopulmonary or otherwise, of the patient's symptoms.<sup>1,2</sup> Apart from congestion, other findings on chest x-ray are associated with HF only in the context of clinical presentation. Importantly, cardiomegaly may be absent in acute HF and, although cephalization, interstitial edema, and alveolar edema are modestly specific for HF, these findings are relatively insensitive.<sup>2,33</sup> Considering the limited sensitivity and specificity, the chest x-ray should not be used as the only determinant of the specific cause or presence of HF.
- TTE provides information regarding cardiac structure and function and identifies abnormalities of myocardium, heart valves, and pericardium. Echocardiography reveals structural and functional information that predicts subsequent risk.<sup>34–40</sup> Guidelines provide recommendations for quantification of cardiac structure and function, including LVEF measurements, ventricular dimensions and volumes, evaluation of chamber geometry, and regional wall motion.<sup>41</sup> RV size and function, atrial size, and all valves are evaluated for anatomic and flow abnormalities. Guidelines also provide recommendations for diastolic function and estimates of LV filling and left atrial pressure.<sup>42</sup> The tricuspid valve regurgitant gradient, coupled with inferior vena cava diameter and its response during respiration, provides estimates of systolic PA pressure and central venous pressure. Indices of myocardial deformation, such as global longitudinal strain, may identify subclinical LV systolic dysfunction, which has been associated with greater risk of developing HF or recurrent HF hospitalizations.<sup>38,43–46</sup> Given the widespread availability, lack of ionizing radiation, and wealth of provided information, echocardiography is the preferred initial imaging modality for evaluation of patients with suspected HF. Point-of-care cardiac ultrasound is an evolving tool for assessment of cardiac function and assessment of volume status and pulmonary congestion.<sup>47–52</sup>
- Serial echocardiograms to assess changes in EF, structural remodeling, and valvular function, although not recommended routinely in stable patients, are useful in various situations. In patients who have an unexplained, significant change in clinical status, echocardiography can provide important information, such as worsening ventricular or valvular function. A subset of patients may also have reverse remodeling, improvement
- in LVEF, and valvular function in response to evidence-based medical, revascularization, and device therapies, and repeat assessment of LVEF and remodeling is appropriate in those who have received treatments that might have had a significant effect on cardiac structure and function.<sup>4–7,53–59</sup> Recovery of function appears more common in those with LV systolic dysfunction occurring in the setting of adverse energetic circumstances (eg, chronic tachycardia or thyroid disease), dilated cardiomyopathies associated with immune responses (eg, peripartum cardiomyopathy, acute myocarditis, systemic inflammatory responses), or in those who have undergone revascularization or device-based therapies.<sup>60</sup> Reevaluation of EF (>40 days after MI, >90 days after revascularization, >90 days after GDMT) is useful to determine candidacy for implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT). Finally, repeat surveillance of LV function is appropriate in patients exposed to treatments that potentially damage the myocardium, such as chemotherapy.
- If TTE is unable to accurately evaluate cardiac structure and function, additional noninvasive imaging modalities are available to clarify the initial diagnosis and to provide information on cardiac structure and function. The choice between these modalities depends on availability, local expertise, patient characteristics, indication, and goal of limiting radiation exposure. CMR provides an accurate and highly reproducible assessment of cardiac volumes, mass, and EF of the left and right ventricles.<sup>8–10</sup> CMR provides high anatomic resolution of all aspects of the heart and surrounding structures and is not associated with ionizing radiation, leading to its recommended use in known or suspected congenital heart diseases.<sup>11,61</sup> Electrocardiographic-gated cardiac CT can also accurately assess ventricular size, EF, and wall motion abnormalities, but it is accompanied with ionizing radiation.<sup>13–15</sup> Radionuclide ventriculography is highly reproducible for measurement of LVEF, although it also exposes the patient to ionizing radiation.<sup>12</sup>
- CMR provides noninvasive characterization of the myocardium that may provide insights into HF cause.<sup>62</sup> Late-gadolinium enhancement, reflecting fibrosis and damaged myocardium, can identify acute and chronic MI,<sup>63,64</sup> and identify HF caused by CAD.<sup>65,66</sup> Patterns of late-gadolinium enhancement or specific T-1 and T-2 techniques can suggest specific infiltrative and inflammatory cardiomyopathies, such as myocarditis, sarcoidosis, Fabry disease, Chagas disease, noncompaction, iron overload, and amyloidosis.<sup>16,20,22,67</sup> T-1 mapping techniques allow for measurement

of interstitial space characteristics and extracellular volume fraction and provides diagnostic and prognostic information.<sup>19,21–23,68–71</sup> The presence of delayed hyperenhancement has been associated with worse outcomes and can provide risk stratification.<sup>72–77</sup> Although registry data show that CMR findings commonly impact patient care management and provide diagnostic information in patients with suspected myocarditis or cardiomyopathy,<sup>17,18</sup> a strategy of routine screening with CMR in patients with nonischemic cardiomyopathy was not shown to yield more specific HF causes than a strategy of selective CMR strategy based on echocardiographic and clinical findings in a recent trial.<sup>78</sup>

6. HF is often caused by coronary atherosclerosis,<sup>79</sup> and evaluation for ischemic heart disease can help in determining the presence of significant coronary artery disease (CAD). Noninvasive stress imaging with echocardiography or nuclear scintigraphy can be helpful in identifying patients likely to have obstructive CAD.<sup>24,25</sup> Invasive or computed tomography coronary angiography can detect and characterize extent of CAD.<sup>26,27</sup>
7. CAD is a leading cause of HF<sup>79</sup> and myocardial ischemia may contribute to new or worsening HF symptoms. Noninvasive testing (ie, stress echocardiography, SPECT, CMR, or PET) may be considered for detection of myocardial ischemia to help guide coronary revascularization decisions. Multiple nonrandomized, observational studies have reported improved survival with revascularization in patients with viable but dysfunctional myocardium.<sup>28,30–32</sup> Despite these observational data, RCTs have not shown that viability imaging improves guidance of revascularization to a reduction of adverse cardiovascular outcomes.<sup>80–82</sup> A prespecified viability substudy of the STICH (Surgical Treatment for Ischemic Heart Failure) trial showed that the presence of myocardial viability did not determine the long-term benefit from surgical revascularization in patients with ischemic cardiomyopathy.<sup>81,82</sup> Of note, a relatively small number of individuals enrolled in the STICH substudy did not have viability, which may limit the power of the study. Although these data do not support the concept of routine viability assessment before revascularization, myocardial viability is used as one of the tools to inform decisions regarding revascularization in patients with high surgical risk or with complex medical problems.
8. Repeat noninvasive imaging of cardiac structure and function for routine surveillance is rarely appropriate in the absence of a change in clinical status or treatment interventions.<sup>11,83</sup>

## 4.5. Invasive Evaluation

### Recommendations for Invasive Evaluation

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
<b>2a</b>	<b>B-NR</b>	1. In patients with HF, endomyocardial biopsy may be useful when a specific diagnosis is suspected that would influence therapy. <sup>1,2</sup>
<b>2a</b>	<b>C-EO</b>	2. In selected patients with HF with persistent or worsening symptoms, signs, diagnostic parameters, and in whom hemodynamics are uncertain, invasive hemodynamic monitoring can be useful to guide management.
<b>3: No Benefit</b>	<b>B-R</b>	3. In patients with HF, routine use of invasive hemodynamic monitoring is not recommended. <sup>3,4</sup>
<b>3: Harm</b>	<b>C-LD</b>	4. For patients undergoing routine evaluation of HF, endomyocardial biopsy should not be performed because of the risk of complications. <sup>5,6</sup>

### Synopsis

Invasive evaluation of patients with HF may provide important clinical information to determine the cause of HF and treatment options. Routine right heart catheterization does not provide sufficient information to guide treatment decisions.<sup>3,4</sup> However, hemodynamic evaluation with right heart catheterization and monitoring in the setting of acute respiratory distress, systemic hypoperfusion including cardiogenic shock, or when hemodynamics are uncertain, may guide treatment decisions. Coronary angiography may be useful in patients who are candidates for revascularization<sup>7–9</sup> (see Section 4.4, “Evaluation with Cardiac Imaging,” for recommendations). Endomyocardial biopsy may be advantageous in patients with HF in which a histological diagnosis, such as amyloidosis or myocarditis, may influence treatment decisions.<sup>1,2</sup>

### Recommendation-Specific Supportive Text

1. Endomyocardial biopsy may be useful when seeking a specific diagnosis that would influence treatment, and biopsy should thus be considered in patients with rapidly progressive clinical HF or worsening ventricular dysfunction that persists despite appropriate medical treatment. Endomyocardial biopsy should also be considered in patients suspected of having acute cardiac rejection status after heart transplantation or having myocardial infiltrative processes. A specific example is to determine treatment for light chain (AL) amyloidosis or transthyretin amyloidosis.<sup>5</sup> Additional indications for endomyocardial biopsy include patients with rapidly progressive and unexplained cardiomyopathy and those in whom active myocarditis, especially giant cell myocarditis, is being considered.<sup>1</sup>

2. Right-heart catheterization in patients in acute HF. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial found that routine use of PA catheter monitoring for patients with HF did not provide benefit.<sup>3</sup> However, invasive hemodynamic evaluation or monitoring can be useful to guide management in carefully selected patients with acute HF who have persistent symptoms despite treatment. This includes patients whose fluid status, perfusion, or systemic or pulmonary vascular resistance is uncertain whose systolic blood pressure (SBP) remains low, or is associated with symptoms, despite initial treatment; whose renal function is worsening with therapy; or who require parenteral vasoactive agents.
3. There has been no established role for routine or periodic invasive hemodynamic measurements in the management of HF. Most drugs used to treat HF are prescribed on the basis of their ability to improve symptoms or survival rather than their effect on hemodynamic variables. The initial and target doses of these drugs are generally selected on the basis of controlled trial experience rather than changes produced in cardiac output or pulmonary capillary wedge pressure.<sup>3,4</sup>
4. Patients with HF should not undergo routine endomyocardial biopsy because of the risk of complications that include perforation, cardiac tamponade, and thrombus formation, as well as limited diagnostic yield.<sup>5,6</sup>

## 4.6. Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)

**Recommendation for Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)**  
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
2b	B-R	<ol style="list-style-type: none"><li>1. In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of GDMT with optimal device therapy, the usefulness of wireless monitoring of PA pressure by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain.<sup>1-4</sup></li></ol>
<b>Value Statement: Uncertain Value (B-NR)</b>		<ol style="list-style-type: none"><li>2. In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PA pressure by an implanted hemodynamic monitor provides uncertain value.<sup>4-7</sup></li></ol>

## Synopsis

HF is a chronic condition punctuated by periods of instability. Despite close longitudinal monitoring via in-person visits, event rates remain high, affording a potential role for remote monitoring strategies to improve clinical outcomes. Strategies tested in randomized trials include an implantable PA pressure sensor (CardioMEMS), noninvasive telemonitoring, or monitoring via existing implanted electronic devices (ICDs or CRT-Ds). Results from a single randomized trial,<sup>1-3</sup> and subsequent observational studies,<sup>8-10</sup> support consideration of an implantable PA sensor in selected patients with HF to reduce the risk of HF hospitalization. In contrast, a recent trial testing a PA pressure sensor did not meet its primary endpoint.<sup>4</sup> Results from previous clinical trials do not support the alternative remote monitoring strategies (eg, noninvasive telemonitoring or remote monitoring of physiological parameters such as patient activity, thoracic impedance, heart rate) for this purpose.<sup>11-18</sup>

## Recommendation-Specific Supportive Text

1. The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure patients) trial reported a significant 28% reduction of HF-related hospitalizations after 6 months in patients randomized to an implanted PA pressure monitor compared with a control group.<sup>1</sup> Patients had to have a HF hospitalization in the previous year and be on stable doses of a beta blocker and angiotensin-converting enzyme inhibitor (ACEi) (or angiotensin (II) receptor blocker [ARB]) if tolerated. The clinical benefit persisted after longer term follow-up and was seen in both subjects with reduced<sup>3</sup> and preserved<sup>2</sup> LVEF. However, CHAMPION was a nonblinded trial, and there was differential contact of study personnel with patients in the treatment arm, raising methodological concerns about the opportunity for bias to have influenced its results.<sup>19-21</sup> In the recent GUIDE-HF (Haemodynamic-GUIDEed management of Heart Failure) study, hemodynamic-guided management of patients with NYHA class II to IV heart failure did not significantly reduce the composite endpoint rate of mortality and total HF events.<sup>4</sup> The usefulness of noninvasive telemonitoring<sup>11,12,22,23</sup> or remote monitoring of physiological parameters<sup>13-18</sup> (eg, patient activity, thoracic impedance, heart rate) via implanted electrical devices (ICDs or CRT-Ds) to improve clinical outcomes remains uncertain. Further study of these approaches is needed before they can be recommended for routine clinical care.
2. Three model-based studies<sup>5-7</sup> have evaluated the cost-effectiveness of wireless PA pressure monitoring using data from the CHAMPION-HF<sup>1</sup> study of

the CardioMEMS device. All 3 studies estimated CardioMEMS implantation and monitoring increased survival and quality-adjusted life year (QALY) while increasing costs. Primarily based on differences regarding the expected magnitude of clinical benefit, 2 analyses<sup>5,7</sup> estimated the device provided high value while the third<sup>6</sup> estimated intermediate value. These analyses had several important differences detailed in the evidence tables, including the model duration, QOL data, cost estimates, and assumptions regarding mortality. One analysis<sup>6</sup> found the economic value of CardioMEMS implantation was highly dependent on its effect on mortality and duration of treatment benefit, both of which remain unclear. Cost-effectiveness studies incorporating data from GUIDE-HF<sup>4</sup> have not been published. Additional data regarding clinical outcomes following CardioMEMS implantation will improve estimates of its economic value.

## 4.7. Exercise and Functional Capacity Testing

**Recommendations for Exercise and Functional Capacity Testing**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. In patients with HF, assessment and documentation of NYHA functional classification are recommended to determine eligibility for treatments. <sup>1-3</sup>
1	C-LD	2. In selected ambulatory patients with HF, cardiopulmonary exercise testing (CPET) is recommended to determine appropriateness of advanced treatments (eg, LVAD, heart transplant). <sup>4-8</sup>
2a	C-LD	3. In ambulatory patients with HF, performing a CPET or 6-minute walk test is reasonable to assess functional capacity. <sup>4,5,9-16</sup>
2a	C-LD	4. In ambulatory patients with unexplained dyspnea, CPET is reasonable to evaluate the cause of dyspnea. <sup>17,18</sup>

### Synopsis

Functional impairment and exercise intolerance are common in HF. CPET and the 6-minute walk test are standardized, reliable, and reproducible tests to quantify functional capacity.<sup>19-22</sup> The NYHA functional classification can be used to grade the severity of functional limitation based on patient report of symptoms experienced with activity<sup>1</sup> and is used to define candidates for certain treatments.

### Recommendation-Specific Supportive Text

- NYHA functional classification is an ordinal, categorical variable (I-IV) that is used to document functional limitation in patients with cardiac disease, including HF.<sup>1</sup> In HF, NYHA functional class I includes patients with no limitations in physical activity resulting from

their HF. NYHA class II includes patients who are comfortable at rest but have slight symptoms resulting from HF (dyspnea, fatigue, lightheadedness) with ordinary activity. NYHA class III includes patients who are comfortable at rest but have symptoms of HF with less than ordinary activity. NYHA class IV includes patients who are unable to carry out any physical activity without symptoms and have symptoms at rest. NYHA functional classification has been widely used in clinical practice, clinical trials, and clinical practice guidelines to determine candidacy for drug and device therapy. Limitations include its ability to be inconsistently assessed from 1 clinician to another, resulting in poor reproducibility.<sup>23</sup>

- Many CPET variables have been associated with prognosis in patients with HF.<sup>4,5,12,14,16,24</sup> Peak exercise oxygen consumption/oxygen uptake ( $\text{VO}_2$ ) is often used to risk stratify patients and make decisions about timing of advanced HF therapies, including heart transplantation and LVAD. In a landmark article,<sup>7</sup> investigators divided patients referred for heart transplantation into groups based on their peak  $\text{VO}_2$ .<sup>7</sup> Patients with peak  $\text{VO}_2 < 14 \text{ mL/kg/min}$  were listed for transplant, while those with higher peak  $\text{VO}_2$  values were deferred for being too well. Patients with peak  $\text{VO}_2 > 14 \text{ mL/kg/min}$  who were deferred had 1- and 2-year survival of 94% and 84%, respectively, which was similar to survival after heart transplant. As such, the authors proposed peak  $\text{VO}_2 \leq 14 \text{ mL/kg/min}$  as a cutoff to distinguish patients who may derive survival benefit from heart transplant.<sup>7</sup> Patients tolerating beta blockers may have improved survival with an equivalent  $\text{VO}_2$  compared with patients who do not tolerate beta blockers.<sup>25,26</sup> For patients on beta blockers, a peak  $\text{VO}_2 \leq 12 \text{ mL/kg/min}$  has been suggested as a more appropriate cutoff to consider cardiac transplant listing.<sup>8</sup>
- Objective assessment of exercise capacity with CPET can be useful in the clinical management of patients with HF. Although CPET remains the gold standard measure of exercise capacity, limitations to more widespread use include need for special equipment and trained personnel, which leads to lack of availability at many hospitals and clinics. Furthermore, it is not well tolerated by some patients. The 6-minute walk test is an alternative way to measure exercise capacity that is widely available and well tolerated by patients. It entails walking for 6 minutes on a measured flat course, and patients are allowed to slow down or stop if needed. A systematic review of 14 studies found that the 6-minute walk test results correlated moderately with peak  $\text{VO}_2$  levels and were a reliable and valid indicator of functional capacity in patients with HF who did not walk  $> 490 \text{ m}.$ <sup>8</sup> Distance walked in the 6-minute walk test has been associated with prognosis in HF

across multiple studies.<sup>9–13,15,16,27</sup> A cutoff of <300 m roughly correlates to patients with NYHA class III to IV symptoms and is associated with worse 3-year survival free of heart transplant (62% versus 82% for those walking ≥300 m).<sup>27</sup>

- Dyspnea is a complex symptom that can reflect abnormalities in a number of different systems and can be influenced by psychological and environmental factors. CPET involves having patients perform a treadmill (or stationary bicycle) exercise test, while also performing ventilatory gas exchange measurements.<sup>28</sup> CPET enables the comprehensive assessment of multiple physiological measures that can impact exercise capacity and contribute to dyspnea. It provides analysis of gas exchange and yields measures of oxygen uptake ( $\text{VO}_2$ ), carbon dioxide output, and ventilation. These measures can be integrated with standard exercise testing variables, such as heart rate, blood pressure, electrocardiographic findings, and symptoms to provide insights into the physiologic mechanisms underlying a patient's dyspnea. In particular, CPET can help to distinguish respiratory versus cardiac etiologies of dyspnea. If exercise capacity is diminished but cardiopulmonary responses are normal, other causes of dyspnea, such as metabolic abnormalities and deconditioning, should be considered.

## 4.8. Initial and Serial Evaluation: Clinical Assessment: HF Risk Scoring

Recommendation for Initial and Serial Evaluation: Clinical Assessment: HF Risk Scoring		
Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	LOE	Recommendation
2a	B-NR	1. In ambulatory or hospitalized patients with HF, validated multivariable risk scores can be useful to estimate subsequent risk of mortality. <sup>1–14</sup>

## Synopsis

Clinicians should routinely assess a patient's risk for an adverse outcome to guide discussions on prognosis, goals of care, and treatment decisions. Several predictive models of outcomes of patients with HF have been developed and validated using data from clinical trials, registries, and population-based cohorts. The best performing models have focused on predicting short- and long-term mortality, whereas predictive models for hospitalization or readmission for HF have generally had poor or modest discrimination. Predictive models may also assess the risk of incident HF among the general population and should be considered in the prevention of HF. In the course of standard evaluation, clinicians should routinely assess the patient's potential for adverse outcome, because accurate

**Table 8. Selected Multivariable Risk Scores to Predict Outcome in HF**

Risk Score	Reference/Link	Year Published
Chronic HF		
All Patients With Chronic HF		
Seattle Heart Failure Model	2 <a href="https://depts.washington.edu/shfm/?width=1440&amp;height=900">https://depts.washington.edu/shfm/?width=1440&amp;height=900</a> 15	2006
Heart Failure Survival Score	1	1997
MAGGIC	3 <a href="http://www.heartfailure-risk.org/">http://www.heartfailure-risk.org/</a> 16	2013
CHARM Risk Score	4	2006
CORONA Risk Score	5	2009
Specific to Chronic HFrEF		
PARADIGM-HF	6	2020
HF-ACTION	7	2012
GUIDE-IT	8	2019
Specific to Chronic HFpEF		
I-PRESERVE Score	9	2011
TOPCAT	10	2020
Acutely Decompensated HF		
ADHERE Classification and Regression Tree (CART) Model	11	2005
AHA Get With The Guidelines Score	12 <a href="https://www.mdcalc.com/gwtg-heart-failure-risk-score">https://www.mdcalc.com/gwtg-heart-failure-risk-score</a> 17	2010, 2021
EFFECT Risk Score	13 <a href="http://www.ccort.ca/Research/CHFRisk-Model.aspx">http://www.ccort.ca/Research/CHFRisk-Model.aspx</a> 18	2003, 2016
ESCAPE Risk Model and Discharge Score	14	2010

ADHERE indicates Acute Decompensated Heart Failure National Registry; AHA, American Heart Association; ARIC, Atherosclerosis Risk in Communities; CHARM, Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EFFECT, Enhanced Feedback for Effective Cardiac Treatment; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; GUIDE-ID, Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HF-ACTION, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training MAGGIC Meta-analysis Global Group in Chronic Heart Failure; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; PCP-HF, Pooled Cohort Equations to Prevent HF; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.

risk stratification may help guide therapeutic decision-making, including a more rapid transition to advanced HF therapies. Several methods objectively assess risk (Table 8), including biomarker testing, as well as various multivariable clinical risk scores, and some that include

machine learning.<sup>1–14</sup> These risk scores are for use in ambulatory, hospitalized patients, and the general population.

### Recommendation-Specific Supportive Text

1. For HF, there are several clinical models to consider that include the spectrum of HF based on EF and clinical setting. For chronic HF, the Seattle Heart Failure Model,<sup>2</sup> the Heart Failure Survival score,<sup>1</sup> and the MAGGIC score<sup>3</sup> have commonly been used to provide estimates of survival. The MAGGIC predictive model may be quite useful given its derivation and validation across multiple clinical trials and cohorts, including more recent studies. For chronic HFrEF, there are additional models that include other clinical variables, including exercise capacity<sup>7</sup> and natriuretic peptide levels.<sup>8</sup> Likewise, for chronic HFpEF there are more specific predictive models for that population derived from clinical trial data.<sup>9,10</sup> In acute HF, several clinical models may be used to predict short-term survival.<sup>11–13</sup>

## 5. STAGE A (PATIENTS AT RISK FOR HF)

### 5.1. Patients at Risk for HF (Stage A: Primary Prevention)

Recommendations for Patients at Risk for HF (Stage A: Primary Prevention)		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	A	1. In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic HF. <sup>1–9</sup>
1	A	2. In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT2i should be used to prevent hospitalizations for HF. <sup>10–12</sup>
1	B-NR	3. In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. <sup>13–21</sup>
2a	B-R	4. For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. <sup>22,23</sup>
2a	B-NR	5. In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF. <sup>24–26</sup>

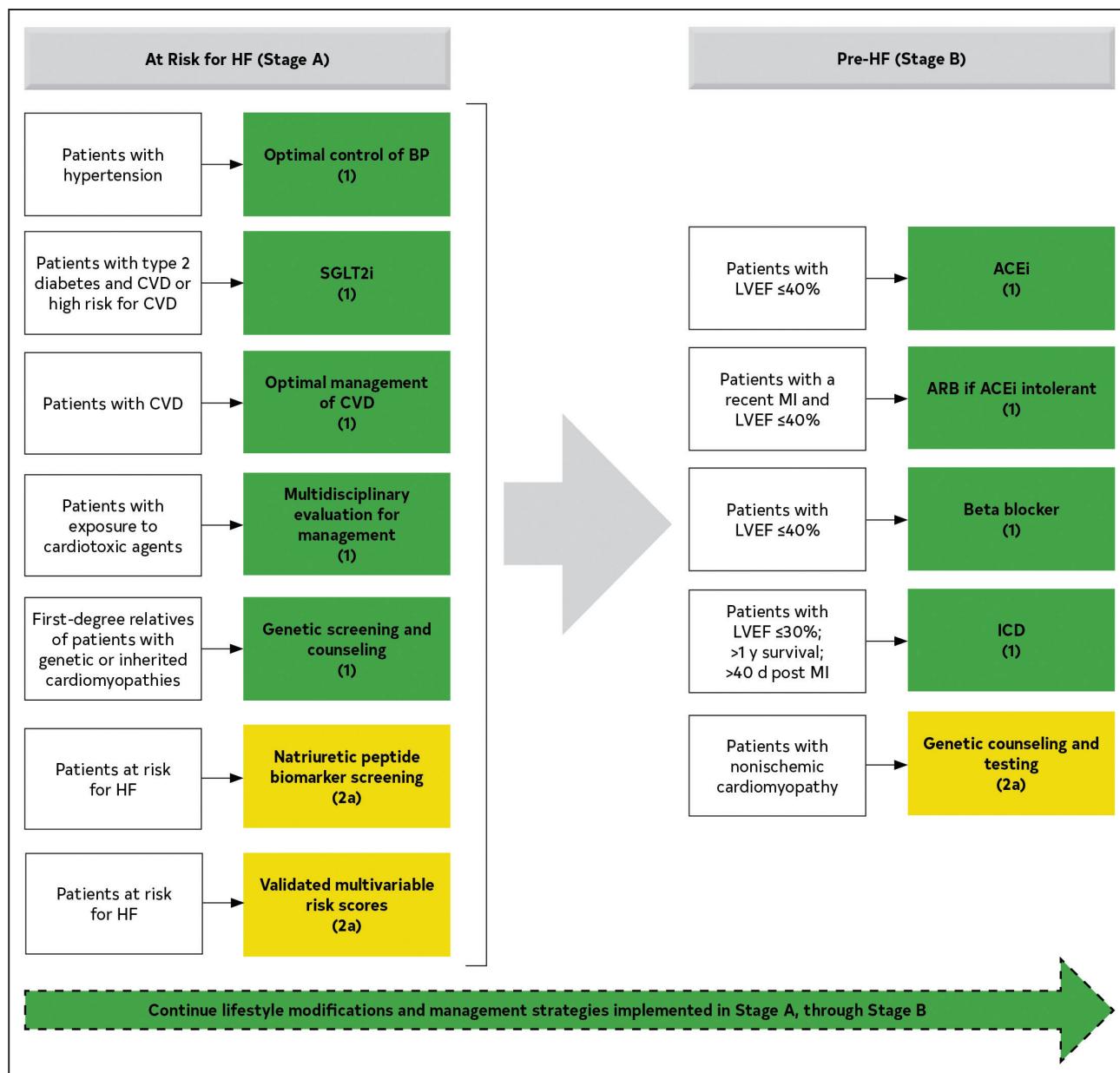
### Synopsis

Healthy lifestyle habits such as maintaining regular physical activity; normal weight, blood pressure, and blood glucose levels; healthy dietary patterns, and not smoking reduce primordial risk and have been associated with a lower lifetime risk of developing HF.<sup>13–21,27</sup> The AHA/

ACC primary prevention guidelines provide recommendations for diet, physical activity, and weight control, all of which have been associated with the risk of HF.<sup>28</sup> Blood pressure is an important risk factor for HF, and a treatment goal of <130/80 mm Hg is recommended for those with a CVD risk of ≥10%.<sup>29,30</sup> Multiple RCTs have found that patients with diabetes and CVD without HF have improved survival and reduced HF hospitalizations with SGLT2i.<sup>31</sup> Patients at risk for HF screened with BNP or NT-proBNP followed by collaborative care, diagnostic evaluation, and treatment in those with elevated levels can reduce combined rates of LV systolic dysfunction, diastolic dysfunction, and HF.<sup>22,23</sup> See Figure 5 for COR 1 and 2a for stage A (at risk for HF) and stage B (pre-HF).

### Recommendation-Specific Supportive Text

- Elevated systolic and diastolic blood pressure are major risk factors for the development of symptomatic HF.<sup>8,9,32</sup> Many trials have shown that hypertension control reduces the risk of HF.<sup>1–7</sup> Although the magnitude of benefit varies with the patient population, target blood pressure reduction, and HF criteria, effective hypertension treatment invariably reduces HF events. In the SPRINT (Systolic Blood Pressure Intervention Trial) trial, control to an SBP goal <120 mm Hg decreased incident HF by 38% and mortality by 23% compared with an SBP goal of <140 mm Hg.<sup>6,7</sup> A meta-analysis showed that blood pressure control was associated with an approximately 40% reduction in HF events.<sup>5</sup> Therefore, SBP and diastolic blood pressure should be controlled in accordance with published clinical practice guidelines.<sup>30</sup>
- Multiple RCTs in patients with type 2 diabetes and at risk for, or with established CVD or at high risk for CVD, have shown that SGLT2i prevent HF hospitalizations compared with placebo.<sup>10–12</sup> The benefit for reducing HF hospitalizations in these trials predominantly reflects primary prevention of symptomatic HF, because only approximately 10% to 14% of participants in these trials had HF at baseline. The mechanisms for the improvement in HF events have not been clearly elucidated but seem to be independent of glucose lowering. Proposed mechanisms include reductions in plasma volume, cardiac preload and afterload, alterations in cardiac metabolism, reduced arterial stiffness, and interaction with the Na<sup>+</sup>/H<sup>+</sup> exchanger.<sup>33,34</sup> SGLT2i are generally well tolerated, but these agents have not been evaluated in those with severe renal impairment (estimated glomerular filtration rate [eGFR] <25 mL/min/1.73 m<sup>2</sup>).<sup>35</sup>
- Greater adherence to healthy lifestyle habits such as regular physical activity, avoiding obesity, maintaining normal blood pressure and



**Figure 5. Recommendations (Class 1 and 2a) for Patients at Risk of HF (Stage A) and Those With Pre-HF (Stage B).**

Colors correspond to COR in Table 2. COR 1 and COR 2a for patients at risk for HF (stage A) and those with pre-HF (stage B) are shown. Management strategies implemented in patients at risk for HF (stage A) should be continued through stage B. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; COR, Class of Recommendation; CVD, cardiovascular disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

blood glucose, not smoking, and healthy dietary patterns have been associated with a lower lifetime risk of HF and greater preservation of cardiac structure.<sup>13–16,27</sup> Healthful eating patterns, particularly those that are based more on consumption of foods derived from plants, such as the Mediterranean, whole grain, plant-based diet and the DASH (Dietary Approaches to Stop Hypertension) diet, are inversely associated with incident HF and may offer some protection against HF development.<sup>17–21</sup>

4. A large-scale unblinded single-center study (STOP-HF [The St Vincent's Screening to Prevent Heart Failure])<sup>22</sup> of patients at risk of HF (identified by the presence of hypertension, diabetes, or known vascular disease) but without established LV systolic dysfunction or symptomatic HF at baseline found that screening with BNP testing and then intervening on those with levels of ≥50 pg/mL (performing echocardiography and referral to a cardiovascular specialist) reduced the composite endpoint of asymptomatic LV dysfunction (systolic

**Table 9. Selected Multivariable Risk Scores to Predict Development of Incident HF**

Risk Score	Reference	Year Published
Framingham Heart Failure Risk Score	24	1999
Health ABC Heart Failure Score	25	2008
ARIC Risk Score	26	2012
PCP-HF	29	2019

ARIC indicates Atherosclerosis Risk in Communities; HF, heart failure; and PCP-HF, Pooled Cohort Equations to Prevent HF.

or diastolic) with or without newly diagnosed HF.<sup>22</sup> Similarly, in another small, single-center RCT, accelerated uptitration of RAAS antagonists and beta blockers reduced cardiac events in patients with diabetes and elevated NT-proBNP levels but without cardiac disease at baseline.<sup>23</sup>

5. Incident HF may be predicted from different models, including those derived from diverse populations (Table 9). The PCP-HF (Pooled Cohort equations to Prevent HF) model provides race- and sex-specific 10-year risk equations from 7 community-based cohorts with at least 12 years of follow-up.<sup>29</sup> Predictors of HF included in the race- and sex-specific models were age, blood pressure (treated or untreated), fasting glucose (treated or untreated), body mass index, cholesterol, smoking status, and QRS duration. Models can be applied to the clinical setting of interest, with clinical trial models potentially less generalizable to registry- or population-based models. In addition, predictive models provide the average estimate of risk derived from a population, and individual risk may vary.<sup>36</sup> The integration of risk scores into clinical practice have shown improved outcomes. As data generation increases from electronic health records and digital sources, advanced methods with machine learning are expected to proliferate the development of risk prediction models. Machine learning models are often not externally validated, and their performance may vary based on the population and clinical setting.<sup>37</sup> Patient populations change over time, and models may need to be recalibrated periodically.

## 6. STAGE B (PATIENTS WITH PRE-HF)

### 6.1. Management of Stage B: Preventing the Syndrome of Clinical HF in Patients With Pre-HF

**Recommendations for Management of Stage B: Preventing the Syndrome of Clinical HF in Patients With Pre-HF**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients with LVEF ≤40%, ACEi should be used to prevent symptomatic HF and reduce mortality. <sup>1–4</sup>

Recommendations for Management of Stage B: Preventing the Syndrome of Clinical HF in Patients With Pre-HF (Continued)		
COR	LOE	Recommendations
1	A	2. In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. <sup>5–9</sup>
1	B-R	3. In patients with a recent MI and LVEF ≤40% who are intolerant to ACEi, ARB should be used to prevent symptomatic HF and reduce mortality. <sup>10</sup>
1	B-R	4. In patients with a recent or remote history of MI or acute coronary syndrome (ACS) and LVEF ≤40%, evidence-based beta blockers should be used to reduce mortality. <sup>11–13</sup>
1	B-R	5. In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving GDMT and have reasonable expectation of meaningful survival for >1 year, an ICD is recommended for primary prevention of sudden cardiac death (SCD) to reduce total mortality. <sup>14</sup>
1	C-LD	6. In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. <sup>12,13</sup>
3: Harm	B-R	7. In patients with LVEF <50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. <sup>15</sup>
3: Harm	C-LD	8. In patients with LVEF <50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. <sup>16,17</sup>

### Synopsis

In general, all recommendations for patients with stage A HF also apply to those with stage B HF. Stage B (pre-HF) represents a phase of clinically asymptomatic structural and functional cardiac abnormalities that increases the risk for symptomatic HF.<sup>18–21</sup> Identifying individuals with stage B HF provides an opportunity to initiate lifestyle modification and pharmacological therapy that may prevent or delay the transition to symptomatic HF (stage C/D). Several ACC/AHA clinical practice guidelines address appropriate management of patients with stage B HF (Table 10). Although multiple studies highlight the increased HF risk associated with asymptomatic LV systolic<sup>19,20,22–26</sup> and diastolic dysfunction identified by noninvasive imaging,<sup>19,26–30</sup> beneficial pharmacotherapy for asymptomatic LV systolic dysfunction, such as inhibitors of the renin-angiotensin system and beta blockers, have been predominantly observed in individuals with depressed LVEF (LVEF <35%–40%).<sup>1–4,11–13</sup> Studies of specific treatments to alter the onset of HF in the setting of asymptomatic cardiac dysfunction with preserved LVEF (eg, abnormalities of myocardial deformation or diastolic dysfunction) have been limited. Several comorbid conditions, including diabetes, obesity, and hypertension, have been associated with asymptomatic LV dysfunction<sup>27,28,30,31</sup> and with progression of asymptomatic LV dysfunction to symptomatic HF.<sup>27</sup> Accordingly, these comorbidities are controlled according to current clinical

**Table 10. Other ACC/AHA Clinical Practice Guidelines Addressing Patients With Stage B HF**

Consideration	Reference
Patients with an acute MI who have not developed HF symptoms treated in accordance with GDMT	2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction <sup>51</sup> 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes <sup>52</sup>
Coronary revascularization for patients without symptoms of HF in accordance with GDMT	2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction <sup>53</sup> (This guideline has been replaced by Lawton, 2021. <sup>54</sup> ) 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease <sup>55</sup> 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery <sup>56</sup> (This guideline has been replaced by Lawton, 2021. <sup>54</sup> )
Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation and no symptoms of HF in accordance with GDMT	2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease. <sup>57,58</sup>
Patients with congenital heart disease that may increase the risk for the development of HF	2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease <sup>59</sup>

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; GDMT, guideline-directed medical therapy; HF, heart failure; MI, myocardial infarction; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; and STS, The Society of Thoracic Surgeons.

practice guidelines. The benefits of mineralocorticoid receptor antagonists (MRA) after MI have mostly been shown in patients with symptomatic HF<sup>EF</sup>.<sup>32–34</sup>

ARNi have not been well studied in stage B HF. The PARADISE-MI (Prospective ARNi vs. ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction) study<sup>35</sup> will report the efficacy and safety of sacubitril/valsartan in patients after acute MI, with LVEF ≤40 and/or pulmonary congestion, plus an additional risk-enhancing factor, compared with ramipril.

### Recommendation-Specific Supportive Text

- ACEi have been shown to impede maladaptive remodeling after acute MI in patients with reduced LVEF.<sup>36,37</sup> In survivors of acute MI with asymptomatic LV dysfunction (LVEF <35%–40%), RCTs have shown that ACEi reduced mortality, HF hospitalizations, and progression to severe HF compared with placebo.<sup>24</sup> Similarly, in those individuals with asymptomatic LV dysfunction in the SOLVD (Studies of Left Ventricular Systolic Dysfunction) prevention trial, which included approximately 20% without ischemic heart disease, enalapril was associated with reduced HF hospitalization and mortality compared with placebo.<sup>13</sup>
- In multiple RCTs,<sup>42</sup> statins have been shown to prevent adverse CAD events in patients with an MI, ACS, and with high cardiovascular risk. These trials have also shown that statin therapy reduces the risk of incident HF.<sup>5–9</sup> A meta-analysis of 6 RCTs of >110 000 patients with an ACS showed that intensive statin therapy reduced hospitalizations for HF.<sup>5</sup> A subsequent, larger collaborative meta-analysis of up to 17 major primary and secondary prevention RCTs showed that statins reduced HF hospitalization.<sup>42</sup> These data support the use of statins to prevent symptomatic HF and cardiovascular events in patients with acute MI or ACS.
- Two major trials have compared ARB with ACEi after MI. The VALIANT (Valsartan in Acute Myocardial Infarction) trial, which included approximately 25% of patients with asymptomatic LV dysfunction, showed that the benefits of valsartan on mortality and other adverse cardiovascular outcomes were comparable to captopril.<sup>10,38</sup> In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial, losartan did not meet the noninferiority criteria for mortality compared with captopril.<sup>39</sup> It has been hypothesized that the lower dose of losartan (50 mg daily) in the OPTIMAAL trial may have contributed to the greater difference than those seen with valsartan in VALIANT.<sup>40</sup> No clinical trials have specifically evaluated ARB in patients with asymptomatic reduced LVEF in the absence of previous MI. Although ARB are alternatives for patients with ACEi-induced angioedema, caution is advised because some patients have also developed angioedema with ARB.
- Current evidence supports the use of beta blockers to improve adverse cardiac remodeling and outcomes in patients with asymptomatic reduced LVEF after MI. Among patients with a recent MI and reduced LVEF, carvedilol reduced maladaptive remodeling<sup>41</sup> and reduced mortality compared with placebo.<sup>11</sup> Among patients with asymptomatic LV systolic dysfunction in the SOLVD prevention trial (which included 80% with previous MI) and the SAVE (Survival and Ventricular Enlargement) trial, secondary analyses showed that the administration of beta blockers in addition to ACEi reduced mortality and hospitalization.<sup>12,13</sup>

5. The Framingham studies have shown a 60% increased risk of death in patients with asymptomatic low LVEF compared with those with normal LVEF, and almost half of these patients remained free of HF before their death.<sup>25</sup> MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) showed a 31% relative risk reduction in all-cause mortality in patients with post-MI with LVEF  $\leq 30\%$  receiving a prophylactic ICD compared with standard of care.<sup>14</sup> These findings provided justification for the broad adoption of ICDs for primary prevention of SCD in the post-MI setting with reduced LVEF, even in the absence of HF symptoms.
6. Although beta blockers have been shown to improve outcomes in patients with symptomatic HFrEF and in patients with reduced LVEF after MI,<sup>11</sup> few data exist regarding the use of beta blockers in asymptomatic patients with depressed LVEF without a history of MI. There is evidence to support the role of beta blockers to prevent adverse LV remodeling in asymptomatic patients with LV systolic dysfunction, including those with nonischemic cause.<sup>43</sup> Also, in a post hoc analysis of the SOLVD prevention trial, which included approximately 20% of participants with nonischemic HF cause, beta blockers were associated with a reduction in the risk of death and in death or hospitalization for symptomatic HF in those patients randomized to enalapril, a finding that was not seen in the placebo group.<sup>12</sup> Given the long-term benefits of beta blockers to reduce HF hospitalizations in patients with symptomatic HFrEF,<sup>44</sup> beta-blocker therapy is recommended to prevent symptomatic HF in patients with reduced LVEF.
7. Thiazolidinediones have been associated with fluid retention and increased rates of HF in RCTs of patients with type 2 diabetes who were predominantly free of symptomatic HF at baseline.<sup>47–49</sup> In a smaller RCT of patients with more severely symptomatic HFrEF, pioglitazone was associated with increased rates of HF hospitalization compared with placebo.<sup>50</sup> In patients with more mild symptoms (NYHA class I to II) but with depressed LVEF,<sup>15</sup> rosiglitazone was associated with more fluid-related events, including worsening edema and need for increased HF medications.<sup>15</sup> Given the evidence, thiazolidinediones should be avoided in patients with reduced LVEF.
8. Nondihydropyridine calcium channel blockers diltiazem and verapamil are myocardial depressants and generally not tolerated in HF. In previous studies of patients with HF or reduced LVEF after acute MI, diltiazem was associated with increased risk of HF,<sup>16,17</sup> although in a smaller study of patients with non-ischemic cardiomyopathy, diltiazem had no impact on mortality.<sup>45</sup> Verapamil had no impact on survival or major cardiovascular events after acute MI.<sup>46</sup> Although not specifically tested in asymptomatic

patients with low LVEF, nondihydropyridine calcium channel blockers may be harmful in this population because of their negative inotropic effects.

## 7. STAGE C HF

### 7.1. Nonpharmacological Interventions

#### 7.1.1. Self-Care Support in HF

**Recommendations for Nonpharmacological Interventions: Self-Care Support in HF**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

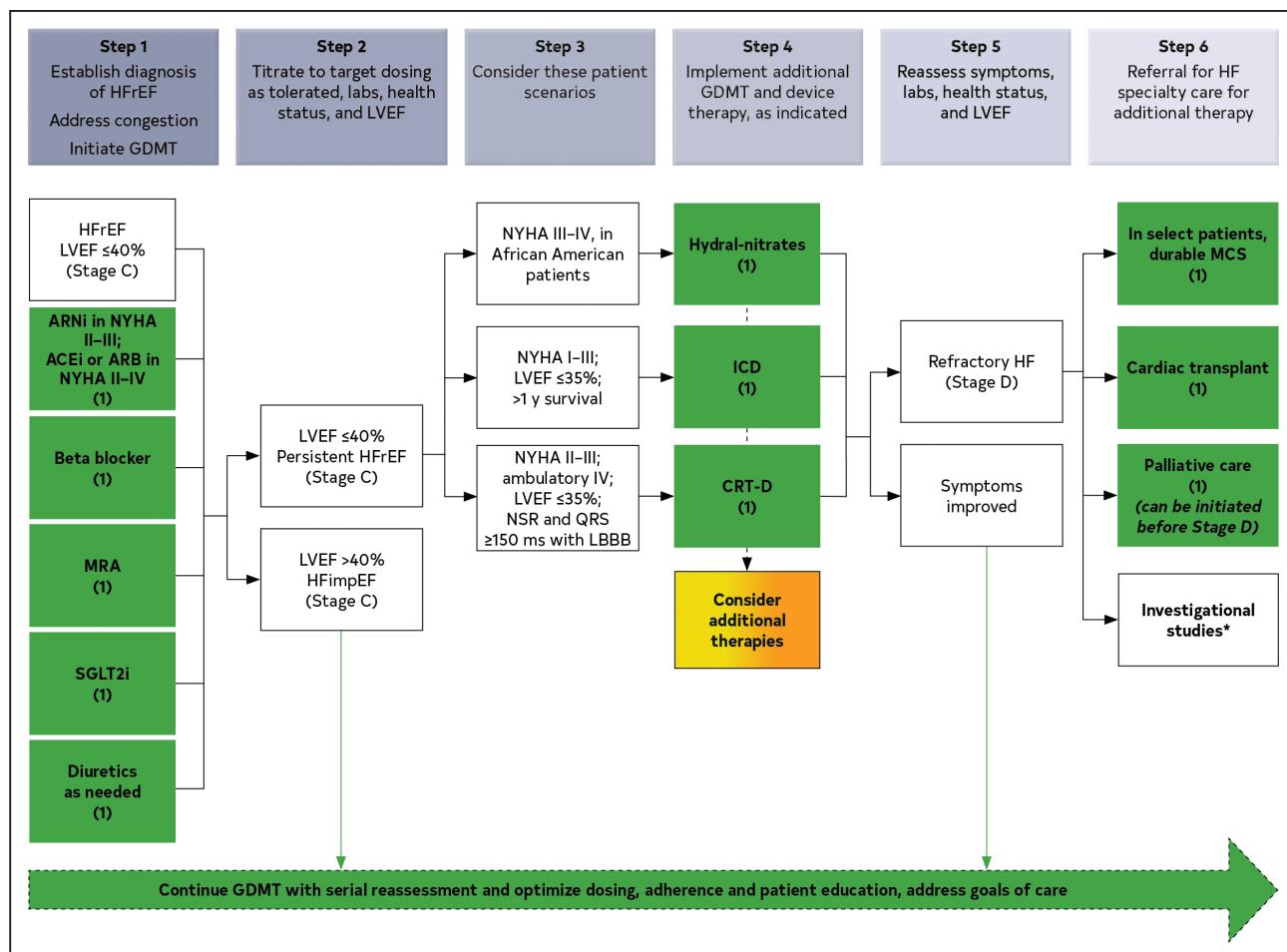
COR	LOE	Recommendations
1	A	1. Patients with HF should receive care from multidisciplinary teams to facilitate the implementation of GDMT, address potential barriers to self-care, reduce the risk of subsequent rehospitalization for HF, and improve survival. <sup>1–4</sup>
1	B-R	2. Patients with HF should receive specific education and support to facilitate HF self-care in a multidisciplinary manner. <sup>2,5–9</sup>
2a	B-NR	3. In patients with HF, vaccinating against respiratory illnesses is reasonable to reduce mortality. <sup>10–16</sup>
2a	B-NR	4. In adults with HF, screening for depression, <sup>17,18</sup> social isolation, <sup>19–22</sup> frailty, <sup>23,24</sup> and low health literacy <sup>25,26</sup> as risk factors for poor self-care is reasonable to improve management.

### Synopsis

Because of the complexity of HF management and coordination of other health and social services required, HF care is ideally provided by multidisciplinary teams<sup>27–30</sup> that include cardiologists, nurses, and pharmacists who specialize in HF as well as dieticians, mental health clinicians, social workers, primary care clinicians, and additional specialists.<sup>31–33</sup> Self-care in HF comprises treatment adherence and health maintenance behaviors.<sup>34,35</sup> Patients with HF should learn to take medications as prescribed, restrict sodium intake, stay physically active, and get vaccinations.<sup>36,37</sup> They also should understand how to monitor for signs and symptoms of worsening HF, and what to do in response to symptoms when they occur.<sup>36,37</sup> Knowledge alone is insufficient to improve self-care.<sup>38</sup> Patients with HF need time and support to gain skills and overcome barriers to effective self-care.<sup>37</sup> Measures listed as Class 1 recommendations for patients in stages A and B are recommended where appropriate for patients in stage C. GDMT, as depicted in Figure 6, should be the mainstay of pharmacological therapy for HFrEF.

### Recommendation-Specific Supportive Text

- In a meta-analysis of 30 RCTs, multidisciplinary interventions reduced hospital admission and

**Figure 6. Treatment of HFrEF Stages C and D.**

Colors correspond to COR in Table 2. Treatment recommendations for patients with HFrEF are displayed. Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; MCS, mechanical circulatory support; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; and SGLT2i, sodium-glucose cotransporter 2 inhibitor. \*Participation in investigational studies is appropriate for stage C, NYHA class II and III HF.

all-cause mortality.<sup>1</sup> In a separate meta-analysis of 22 RCTs, specialized multidisciplinary team follow-up was associated with reduced HF hospitalizations and all-cause hospitalizations.<sup>2</sup> In a recent meta-analysis of 22 RCTs, multidisciplinary interventions that included a pharmacist reduced HF hospitalizations.<sup>3</sup> In a recent Cochrane systematic review and meta-analysis of 43 RCTs, both case management (ie, active management of complex patients by case managers working in integrated care systems) and multidisciplinary interventions (ie, coordinated multidisciplinary health care interventions and communications) were shown to reduce all-cause mortality, all-cause readmission, and readmission for HF.<sup>4</sup>

2. Meta-analyses of RCTs have shown that interventions focused on improving HF self-care

significantly reduce the risk of HF-related hospitalization,<sup>2,5-8</sup> all-cause hospitalization,<sup>2,8,9</sup> and all-cause mortality,<sup>6,9</sup> as well as improve QOL.<sup>5</sup> Interventions that aim to improve self-care knowledge and skill,<sup>2,5,8</sup> and those that focus on enhancing medication adherence<sup>9</sup> or reinforce self-care with structured telephone support,<sup>6,7</sup> are effective in patients with HF. There is uncertainty whether mobile health-delivered educational interventions improve self-care in patients with HF.<sup>39</sup> In a single RCT involving rural patients with HF, an educational intervention was shown to improve knowledge and self-care<sup>40</sup> but did not significantly decrease the combined endpoint of cardiac death or HF hospitalization.<sup>41</sup> In a recent pragmatic trial, a transitional care services program that included

self-care education improved discharge preparedness, quality of transition, and QOL but did not significantly improve clinical outcomes compared with usual care.<sup>42</sup>

3. In propensity-adjusted models, influenza vaccination was associated with a significant reduction in all-cause mortality among participants in PARADIGM-HF (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure).<sup>14</sup> In adjusted models, influenza vaccination was associated with significant reductions in all-cause mortality and cardiovascular mortality<sup>12</sup> in 1 registry study and was associated with significant reductions in all-cause mortality and the composite of all-cause mortality and cardiovascular hospitalizations in another large cohort study.<sup>11</sup> In a self-controlled case series study of patients with HF, influenza vaccination was associated with a significantly lower risk of cardiovascular, respiratory, and all-cause hospitalization.<sup>43</sup> In a meta-analysis of 16 studies of patients with CVD, influenza vaccination was associated with a lower risk of all-cause, cardiovascular mortality, and major adverse cardiovascular events compared with control patients.<sup>15</sup> In the Cardiovascular Health Study, pneumococcal vaccination was associated with significant reductions in incident HF, all-cause mortality, and cardiovascular mortality.<sup>16</sup> Patients with HF are uniquely susceptible to poor outcomes in the setting of SARS-CoV-2 infection<sup>44–47</sup> and should be vaccinated against COVID-19.<sup>10</sup>
4. Many health and social factors are associated with poor HF self-care.<sup>36,37</sup> (Table 11) but have also been linked to poor clinical outcomes and fundamentally change how education and support must be delivered. Depression is a risk factor for poor self-care,<sup>40</sup> rehospitalization,<sup>17</sup> and all-cause mortality<sup>18</sup> among patients with HF. Interventions that focus on improving HF self-care have been reported to be effective among patients with moderate/severe depression with reductions in hospitalization and mortality risk.<sup>5</sup> Nonrandomized studies have provided evidence of a link between social isolation and mortality in patients with HF.<sup>19,20</sup> In a recent meta-analysis of 29 cohort studies, frailty was associated with an increased risk of all-cause mortality and hospitalization.<sup>23</sup> Frailty also has been shown to impair self-care among elderly patients with HF.<sup>24</sup> A recent meta-analysis of observational studies revealed social isolation to be common among adults with HF (ie, 37%) and associated with a 55% greater risk of HF-related rehospitalization.<sup>21</sup> Poor social support also has been shown in nonrandomized studies to be associated with lower HF self-care.<sup>22</sup> A recent meta-analysis of observational studies showed that inadequate/

marginal health literacy is common among adults with HF (ie, 24%) and associated independently with the risk of mortality and hospitalization.<sup>25</sup> Low literacy also is associated with poor HF self-care, as most interventions depend on both literacy and health literacy/numeracy.<sup>26</sup>

### 7.1.2. Dietary Sodium Restriction

Recommendation for Dietary Sodium Restriction		
COR	LOE	Recommendation
2a	C-LD	1. For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. <sup>1–6</sup>

### Synopsis

Restricting dietary sodium is a common nonpharmacological treatment for patients with HF symptomatic with congestion, but specific recommendations have been based on low-quality evidence.<sup>7</sup> Concerns about the quality of data regarding clinical benefits or harm of sodium restriction in patients with HF include the lack of current pharmacological therapy, small samples without sufficient racial and ethnic diversity, questions about the correct threshold for clinical benefit, uncertainty about which subgroups benefit most from sodium restriction,<sup>7,8</sup> and serious questions about the validity of several RCTs in this area.<sup>9–11</sup> However, there are promising pilot trials of sodium restriction in patients with HF.<sup>3,5,6</sup> The AHA currently recommends a reduction of sodium intake to <2300 mg/d for general cardiovascular health promotion<sup>12</sup>; however, there are no trials to support this level of restriction in patients with HF.<sup>13</sup> Sodium restriction can result in poor dietary quality with inadequate macronutrient and micronutrient intake.<sup>14</sup> Nutritional inadequacies have been associated with clinical instability,<sup>15–17</sup> but routine supplementation of oral iron,<sup>18</sup> thiamine,<sup>19</sup> zinc,<sup>20</sup> vitamin D,<sup>21</sup> or multivitamins has not proven beneficial.<sup>22</sup> The DASH diet is rich in antioxidants and potassium, can achieve sodium restriction without compromising nutritional adequacy when accompanied by dietary counseling,<sup>5</sup> and may be associated with reduced hospitalizations for HF.<sup>23</sup>

### Recommendation-Specific Supportive Text

1. A registered dietitian- or nurse-coached intervention with 2 to 3 g/d sodium restriction improved NYHA functional class and leg edema in patients with HFrEF.<sup>1</sup> In a nonrandomized study (>2.5 g/d versus <2.5 g/d), lower dietary sodium was associated with worse all-cause mortality in patients with HFrEF.<sup>2</sup> In small RCTs, aggressive sodium restriction (0.8 g/d) during hospitalization for acute decompensated HF has not reduced weight, congestion, diuretic use, rehospitalization, or all-cause mortality in patients with HFrEF<sup>24</sup> or in patients with HFpEF.<sup>25</sup>

**Table 11.** Potential Barriers to Effective HF Self-Care and Example Interventions

Potential Barrier	Example Screening Tools	Example Interventions
Medical Barriers		
Cognitive impairment <sup>48-50</sup>	Mini-Cog Mini-Mental State Examination (MMSE) Montreal Cognitive Assessment (MoCA)	Home health aide Home meal deliveries Adult day care Geriatric psychiatry referral Memory care support groups
Depression <sup>51,52</sup>	Hamilton Depression Rating Scale (HAM-D) Beck Depression Inventory-II (BDI-II) Patient Health Questionnaire-9 (PHQ-9)	Psychotherapy Selective serotonin reuptake inhibitors Nurse-led support
Substance use disorders <sup>53</sup>	Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)	Referral to social work services and community support partners Referral for addiction psychiatry consultation
Frailty <sup>54</sup>	Fried frailty phenotype	Cardiac rehabilitation Registered dietitian nutritionist evaluation for malnutrition
Social Barriers		
Financial burden of HF treatments <sup>55</sup>	COmprehensive Score for financial Toxicity–Functional Assessment of Chronic Illness Therapy (COST-FACIT)	PharmD referral to review prescription assistance eligibilities
Food insecurity <sup>56,57</sup>	Hunger Vital Sign, 2 items US Household Food Security Survey Module, 6 items	Determine eligibility for the Supplemental Nutrition Assistance Program (SNAP) Connect patients with community partners such as food pantries/food banks Home meal deliveries Registered dietitian nutritionist evaluation for potential malnutrition
Homelessness or housing insecurity <sup>58-60</sup>	Homelessness Screening Clinical Reminder (HSCR)	Referral to local housing services Connect patients with community housing partners
Intimate partner violence or elder abuse <sup>61,62</sup>	Humiliation, Afraid, Rape, Kick (HARK) questionnaire Partner Violence Screen (PVS) Woman Abuse Screening Tool (WAST)	Referral to social work services and community support partners
Limited English proficiency or other language barriers <sup>63</sup>	Routinely inquire in which language the patient is most comfortable conversing	Access to interpreter services covering a wide range of languages, ideally in person or, alternatively, via video platform Printed educational materials in a range of appropriate languages
Low health literacy <sup>64</sup>	Short Assessment of Health Literacy (SAHL) Rapid Estimate of Adult Literacy in Medicine—Short Form (REALM-SF) Brief Health Literacy Screen (BHLS), 3 items	Agency for Healthcare Research and Quality (AHRQ) Health Literacy Universal Precautions Toolkit Written education tools provided at sixth grade reading level or below Graphic educational documents
Social isolation or low social support <sup>65</sup>	Patient-Reported Outcomes Measurement Information System (PROMIS) Social Isolation Short Form	Determine eligibility for home care services Support group referral
Transport limitations	No validated tools currently available.	Referral to social work services Determine eligibility for insurance or state-based transportation, or reduced-cost public transportation Maximize opportunities for telehealth visits and remote monitoring

HF indicates heart failure.

A recent pilot RCT N=27) showed that providing patients with 1.5 g/d sodium meals can reduce urinary sodium and improve QOL but not improve clinical outcomes.<sup>3</sup> Another recent pilot RCT (N=38) of 1.5 versus 2.3 g/d sodium resulted in sodium intake and improvement in BNP levels and QOL in the 1.5 g/d sodium intake arm<sup>5</sup>; the full trial is due to be completed in 2022. A third pilot RCT (N=66) of home-delivered 1.5 g/d meals showed favorable but nonsignificant trends toward improvement in clinical status and readmission rates.<sup>6</sup> Moreover, results from RCTs have shown that reducing dietary sodium is difficult to achieve in patients with HF, even with prepared meals<sup>3</sup> or home visits.<sup>26</sup>

### 7.1.3. Management of Stage C HF: Activity, Exercise Prescription, and Cardiac Rehabilitation

#### Recommendations for Management of Stage C HF: Activity, Exercise Prescription, and Cardiac Rehabilitation

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. For patients with HF who are able to participate, exercise training (or regular physical activity) is recommended to improve functional status, exercise performance, and QOL. <sup>1-9</sup>
2a	B-NR	2. In patients with HF, a cardiac rehabilitation program can be useful to improve functional capacity, exercise tolerance, and health-related QOL. <sup>1,2,5,6,8</sup>

## Synopsis

Exercise training in patients with HF is safe and has numerous benefits. In a major trial of exercise and HF, exercise training was associated with a reduction in CVD mortality or hospitalizations in the exercise training group after adjustment for risk factors.<sup>1</sup> Meta-analyses show that cardiac rehabilitation improves functional capacity, exercise duration, and health-related QOL. A cardiac rehabilitation program for patients with HF usually includes a medical evaluation, education regarding the importance of medical adherence, dietary recommendations, psychosocial support, and an exercise training and physical activity counseling program. Patients with HF on optimal GDMT, who are in stable medical condition and are able to participate in an exercise program, are candidates for an exercise rehabilitation program.<sup>10,11</sup>

## Recommendation-Specific Supportive Text

1. Evidence from RCTs indicates that exercise training improves functional status, exercise performance, and QOL in patients with HFrEF and HFpEF. In HF-ACTION, the largest randomized trial with exercise training in patients with HF,<sup>1</sup> 2331 patients with LVEF  $\leq 35\%$  (NYHA class II and III) were randomized to usual care versus supervised exercise training plus usual care. There were modest reductions in all-cause mortality and hospitalization rates that did not reach significance by primary analysis but, after prespecified adjustment, were associated with reductions in cardiovascular mortality or HF hospitalizations.<sup>1</sup> Many RCTs of exercise training in HF have been conducted, but the statistical power of most was low.<sup>2-5,9-13</sup> Meta-analyses suggest that exercise training is associated with improvement in functional capacity, exercise duration, health-related QOL, and reduction in HF hospitalizations in patients with HFrEF as well as HFpEF.<sup>2-6,8,11,14,15</sup> Most studies and meta-analyses have not shown significant changes in all-cause mortality,<sup>2,12,14-22</sup> except for a few showing mortality benefit with longer follow-up.<sup>6,7</sup> Other benefits of exercise training include improved endothelial function, blunted catecholamine spillover, increased peripheral oxygen extraction, and improvement in peak oxygen consumption.<sup>2-5,8,10-12,21</sup>
2. A formal cardiac rehabilitation program usually includes a medical evaluation, education regarding the importance of medical adherence, dietary recommendations, psychosocial support, and an exercise training and physical activity counseling program. Exercise-based cardiac rehabilitation has been associated with an improvement in functional capacity, exercise tolerance, the rate of overall and HF-specific hospitalization, and improved

QOL.<sup>3,4,6,7,11,16,17</sup> In a diverse population of older patients who were hospitalized for acute decompensated HF, an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains (strength, balance, mobility, and endurance) initiated during, or early after hospitalization for HF, and continued after discharge, resulted in greater improvement in physical function than usual care.<sup>9</sup>

## 7.2. Diuretics and Decongestion Strategies in Patients With HF

**Recommendations for Diuretics and Decongestion Strategies in Patients With HF**

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	<ul style="list-style-type: none"> <li>1. In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF.<sup>1-5</sup></li> </ul>
1	B-NR	<ul style="list-style-type: none"> <li>2. For patients with HF and congestive symptoms, addition of a thiazide (eg, metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities.<sup>6</sup></li> </ul>

## Synopsis

Bumetanide, furosemide, and torsemide inhibit reabsorption of sodium or chloride at the loop of Henle, whereas thiazide and thiazide-like diuretics act in the distal convoluting tubule and potassium-sparing diuretics (eg, spironolactone) in the collecting duct.<sup>7,8</sup> Loop diuretics are the preferred diuretic agents for use in most patients with HF. Thiazide diuretics such as chlorthalidone or hydrochlorothiazide may be considered in patients with hypertension and HF and mild fluid retention. Metolazone or chlorothiazide may be added to loop diuretics in patients with refractory edema unresponsive to loop diuretics alone. Diuretics should be prescribed to patients who have evidence of congestion or fluid retention. In any patient with a history of congestion, maintenance diuretics should be considered to avoid recurrent symptoms. The treatment goal of diuretic use is to eliminate clinical evidence of fluid retention, using the lowest dose possible to maintain euolemia. With the exception of MRAs, the effects of diuretics on morbidity and mortality are uncertain.<sup>1-5</sup> As such, diuretics should not be used in isolation but always combined with other GDMT for HF that reduces hospitalizations and prolongs survival. Table 12 lists oral diuretics recommended for use in the treatment of chronic HF. Hyponatremia complicates HF management. If reversing potential causes and free water restriction do not improve hyponatremia, vasopressin antagonists may be helpful in the acute management of

**Table 12. Commonly Used Oral Diuretics in Treatment of Congestion for Chronic HF**

Drug	Initial Daily Dose	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5–1.0 mg once or twice	10 mg	4–6 h
Furosemide	20–40 mg once or twice	600 mg	6–8 h
Torsemide	10–20 mg once	200 mg	12–16 h
Thiazide diuretics			
Chlorthiazide	250–500 mg once or twice	1000 mg	6–12 h
Chlorthalidone	12.5–25 mg once	100 mg	24–72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6–12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12–24 h

HF indicates heart failure.

volume overload to decrease congestion while maintaining serum sodium.

### Recommendation-Specific Supportive Text

- Controlled trials with diuretics showed their effects to increase urinary sodium excretion, decrease physical signs of fluid retention, and improve symptoms, QOL, and exercise tolerance.<sup>1–5</sup> Recent data from the nonrandomized OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry revealed reduced 30-day all-cause mortality and hospitalization for HF with diuretic use compared with no diuretic use after hospital discharge for HF.<sup>9</sup> The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (eg, bumetanide, torsemide), potentially because of their increased oral bioavailability.<sup>10–12</sup> In outpatients with HF, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (eg, NSAIDs), or have significant impairment of renal function or perfusion.
- Diuretic resistance can be overcome in several ways, including escalation of loop diuretic dose, intravenous administration of diuretics (bolus or continuous infusion),<sup>6</sup> or combination of different diuretic classes.<sup>13–16</sup> The use of a thiazide or thiazide-like diuretic (eg, metolazone) in combination with a loop diuretic inhibits compensatory distal tubular sodium reabsorption, leading to enhanced

natriuresis. However, in a propensity-score matched analysis in patients with hospitalized HF, the addition of metolazone to loop diuretics was found to increase the risk for hypokalemia, hyponatremia, worsening renal function, and mortality, whereas use of higher doses of loop diuretics was not found to adversely affect survival.<sup>17</sup> Although randomized data comparing the 2 diuretic strategies are limited, the DOSE (Diuretic Optimization Strategies Evaluation) trial lends support for the use of high-dose intravenous loop diuretics.<sup>18</sup>

## 7.3. Pharmacological Treatment\* for HFrEF

### 7.3.1. Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

**Recommendations for Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality. <sup>1–5</sup>
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible. <sup>6–13</sup>
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality. <sup>14–18</sup>
<b>Value Statement: High Value (A)</b>		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value. <sup>19–25</sup>
1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality. <sup>1–5</sup>
<b>Value Statement: High Value (A)</b>		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value. <sup>26–29</sup>
3: Harm	B-R	7. ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi. <sup>30,31</sup>
3: Harm	C-LD	8. ARNi should not be administered to patients with any history of angioedema. <sup>32–35</sup>
3: Harm	C-LD	9. ACEi should not be administered to patients with any history of angioedema. <sup>36–39</sup>

\*See Section 7.2, “Diuretics and Decongestion Strategies in Patients with HF,” for diuretic recommendations.

### Synopsis

Inhibition of the renin-angiotensin system is recommended to reduce morbidity and mortality for patients with HFrEF, and ARNi, ACEi, or ARB are recommended as first-line therapy.<sup>1–18</sup> If patients have chronic symptomatic

HFrEF with NYHA class II or III symptoms and they tolerate an ACEi or ARB, they should be switched to an ARNi because of improvement in morbidity and mortality.<sup>1–5</sup> An ARNi is recommended as de novo treatment in hospitalized patients with acute HF before discharge given improvement in health status, reduction in the prognostic biomarker NT-proBNP, and improvement of LV remodeling parameters compared with ACEi/ARB. Although data are limited, the use of an ARNi may be efficacious as de novo treatment in patients with symptomatic chronic HFrEF to simplify management. ARB may be used as an alternative to ACEi in the setting of intolerable cough, or as alternatives to ACEi and ARNi in patients with a history of angioedema. If patients are switched from an ACEi to an ARNi or vice versa, there should be at least 36 hours between ACEi and ARNi doses.

### Recommendation-Specific Supportive Text

1. An ARNi is composed of an ARB and an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. In PARADIGM-HF (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure), an RCT that compared the first approved ARNi, sacubitril-valsartan, with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACEi or ARB, sacubitril-valsartan significantly reduced the composite endpoint of cardiovascular death or HF hospitalization by 20% relative to enalapril.<sup>1</sup> The benefit was observed to a similar extent for death and HF hospitalization and was consistent across prespecified subgroups.<sup>1</sup> Use of an ARNi is more frequently associated with symptomatic hypotension and a comparable incidence of angioedema when compared with enalapril.<sup>1</sup> Sacubitril-valsartan has been approved for patients with symptomatic HF. HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets. Trial data have included ACEi/ARB-naïve patients before ARNi initiation (53% in the PIONEER-HF [Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode] trial and 24% in the TRANSITION [Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HFrEF Patients After an Acute Decompensation Event] trial) and have shown similar efficacy and safety in treatment-naïve patients.<sup>2,3</sup> The PIONEER-HF trial showed that ARNi reduced NT-proBNP levels in patients hospitalized for acute decompensated HF without increased rates of adverse events (worsening renal function, hyperkalemia, symptomatic hypotension, angioedema) when compared with enalapril.<sup>3</sup> Additional outcome analyses suggested reduction in all-cause mortality and rehospitalization for HF but were only hypothesis-generating as exploratory study endpoints. In the open-label TRANSITION trial, patients with HFrEF hospitalized with worsening HF were randomized to start ARNi either before or after discharge.<sup>2</sup> Safety outcomes were similar for both arms, suggesting that early initiation may simplify management (rather than initiating and uptitrating ACEi first and then switching to ARNi).<sup>2</sup> ARNi should be initiated de novo in patients hospitalized with acute HFrEF before discharge in the absence of contraindications. ARNi may be initiated de novo in patients with chronic symptomatic HFrEF to simplify management, although data are limited. The PARADISE-MI (Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) trial<sup>40</sup> will provide information on whether sacubitril-valsartan will significantly reduce the rate of cardiovascular death, HF hospitalization or outpatient HF requiring treatment in patients after acute MI, with LVEF  $\leq 40\%$  and/or pulmonary congestion, and 1 of 8 additional risk-enhancing factors like AF, previous MI, diabetes, compared with the ACEi ramipril; and whether the safety and tolerability of sacubitril-valsartan was comparable to that of ramipril. Thus, at the present time, the efficacy of ARNi in patients with LV dysfunction, and HF in the early post-MI period, remains uncertain.
2. ACEi reduce morbidity and mortality in HFrEF. RCTs clearly establish the benefits of ACE inhibition in patients with mild, moderate, or severe symptoms of HF and in patients with or without CAD.<sup>6–11</sup> Data suggest that there are no differences among available ACEi in their effects on symptoms or survival.<sup>12</sup> ACEi should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials. ACEi can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium ( $>5.0$  mEq/L). If maximal doses are not tolerated, intermediate doses should be tried; abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided. Although the use of an ARNi in lieu of an ACEi for HFrEF has been found to be superior, for those patients for whom ARNi is inappropriate, continued use of an ACEi for all classes of HFrEF remains strongly advised.
3. ARB have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs.<sup>14–16</sup> Long-term treatment with ARB in patients with HFrEF produces hemodynamic,

neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system.<sup>17,18</sup> Unlike ACEi, ARB do not inhibit kininase and are associated with a much lower incidence of cough and angioedema, although kininase inhibition by ACEi may produce beneficial vasodilatory effects. Patients who are intolerant to ACEi because of cough or angioedema should be started on an ARB. ARB should be started at low doses and titrated upward, with an attempt to use doses shown to reduce the risk of cardiovascular events in clinical trials. ARB should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium ( $>5.0\text{ mEq/L}$ ). Although ARB are alternatives for patients with ACEi-induced angioedema, caution is advised because some patients have also developed angioedema with ARB. For those patients for whom an ACEi or ARNi is inappropriate, use of an ARB remains advised.

4. Several cost-effectiveness analyses consistently found that ACEi therapy provides high value for patients with chronic HF. A model-based analysis, using generic ACEi costs, found ACEi therapy was high value.<sup>19</sup> Previous analyses also found ACEi therapy was high value despite previously higher ACEi costs.<sup>19,21,22,24,25</sup> This includes a trial-based analysis of SOLVD (Studies of Left Ventricular Dysfunction) that modeled long-term outcomes.<sup>21</sup> Previous analyses included a range of clinical scenarios including asymptomatic LV dysfunction<sup>24</sup> and LV dysfunction after MI,<sup>25</sup> with ACEi therapy providing high value in each. There are limited data on the cost-effectiveness of ARBs from 2 clinical trials—a within-trial analysis of Val-HeFT (Valsartan Heart Failure Trial)<sup>23</sup> and an analysis of the ELITE (Evaluation of Losartan in the Elderly) study<sup>20</sup>—which both suggested ARB therapy is high value. The high value of ARB therapy is also supported by its similar efficacy as ACEi therapy and the low-cost generic availability for both medication classes.
5. Patients with chronic stable HFrEF who tolerate ACEi and ARB should be switched to ARNi. In patients with mild-to-moderate HF who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNi (sacubitin-valsartan; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan-sacubitin compound compared with enalapril.<sup>1</sup> Another RCT and meta-analysis showed improvement in LV remodeling parameters with ARNi compared with enalapril.<sup>4,5</sup>
6. Multiple model-based analyses evaluated the economic value of ARNi therapy compared with ACEi

therapy using the results of PARADIGM-HF.<sup>26–29,41</sup> Three high-quality analyses<sup>26,28,29</sup> consistently found costs per QALY  $<\$60\,000$ , which provides high value according to the benchmarks adopted for the current clinical practice guideline. These results were robust to the range of sacubitin-valsartan costs currently seen in care. These results were sensitive to the estimated mortality reduction and duration of treatment effectiveness. ARNi would need to maintain effectiveness beyond the PARADIGM-HF study period (mean, 27 months) to be considered high value.<sup>29</sup> If clinical benefit were limited to 27 months, ARNi would be intermediate value. One additional analysis, based on the PIONEER-HF trial, found that inpatient initiation of ARNi was also high value compared with delayed initiation postdischarge.<sup>27</sup>

7. Oral neprilysin inhibitors, used in combination with ACEi, can lead to angioedema, and concomitant use is contraindicated and should be avoided. A medication that represented a neprilysin inhibitor and an ACEi— omapatrilat—was studied in hypertension and HF, but its development was terminated because of an unacceptable incidence of angioedema.<sup>30,31</sup> and associated significant morbidity. This adverse effect was thought to occur because ACEi and neprilysin break down bradykinin, which can directly or indirectly cause angioedema.<sup>31,32</sup> An ARNi should not be administered within 36 hours of switching from or to an ACEi.
8. Omapatrilat, a neprilysin inhibitor (as well as an ACEi and aminopeptidase P inhibitor), was associated with a higher frequency of angioedema than that seen with enalapril in an RCT of patients with HFrEF.<sup>30</sup> In a very large RCT of hypertensive patients, omapatrilat was associated with a 3-fold increased risk of angioedema compared with enalapril.<sup>31</sup> Black patients and patients who smoked were particularly at risk. The high incidence of angioedema ultimately led to cessation of the clinical development of omapatrilat.<sup>33,34</sup> Because of these observations, angioedema was an exclusion criterion in the first large trial assessing ARNi therapy in patients with hypertension<sup>35</sup> and then in the large trial that showed clinical benefit of ARNi therapy in HFrEF.<sup>1</sup> The rates of angioedema were numerically higher in patients treated with ARNi than in patients treated with ACEi in PARADIGM-HF, although this difference did not reach significance.<sup>1</sup> ARNi therapy should not be administered in patients with a history of angioedema because of the concern that it will increase the risk of a recurrence of angioedema.
9. Angioedema attributable to ACEi is thought to result from defective degradation of the vasoactive peptides bradykinin, des-Arg9-BK (a metabolite

of bradykinin), and substance P.<sup>36,37</sup> ACEi should not be administered to patients with any history of angioedema, but ARB do not interfere as directly with bradykinin metabolism and have been associated with low rates of angioedema.<sup>38,39</sup>

### 7.3.2. Beta Blockers

Recommendation for Beta Blockers		
Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	LOE	Recommendation
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. <sup>1-3</sup>
<b>Value Statement:</b> <b>High Value (A)</b>		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value. <sup>4-8</sup>

### Synopsis

Treatment with beta blockers reduces the risk of death and the combined risk of death or hospitalization in patients with HFrEF.<sup>1-3</sup> In addition, this treatment can improve LVEF, lessen the symptoms of HF, and improve clinical status.<sup>1-3,9-11</sup> Clinical trials have shown that beta blockers should be prescribed to all patients when HFrEF is diagnosed, including in-hospital, unless contraindicated or not tolerated.<sup>1-3,9-11</sup> These benefits of beta blockers were observed in patients with or without CAD, and in patients with or without diabetes, older patients, as well as in women and across racial and ethnic groups but not in patients with AF.<sup>1-3,10-12</sup> Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major cardiovascular events. Beta blockers should be initiated at low doses, and every effort should be made to achieve the target doses of the beta blockers shown to be effective in major clinical trials, as tolerated<sup>1-3,9,10</sup> (see Section 7.3.8, "GDMT Dosing, Sequencing and Uptitration").

### Recommendation-Specific Supportive Text

- Three beta blockers have been shown to be effective in reducing the risk of death in patients with HFrEF: bisoprolol, sustained-release metoprolol (succinate), and carvedilol.<sup>1-3</sup> The favorable findings with these 3 agents, however, should not be considered a beta-blocker class effect in HFrEF. Other beta blockers are not included in this recommendation for use.<sup>13-15</sup> Even when asymptomatic, or when symptoms are mild or improve with other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented.<sup>16</sup> Data show that beta blockers can be safely initiated before

hospital discharge, provided patients are clinically stabilized and do not require intravenous inotropic therapy for HF.<sup>17</sup> If a contraindication or intolerance are noted, they should be documented, and the patient restarted on beta-blocker therapy in the future, so long as an absolute contraindication is not present. Even if symptoms or LVEF improve, long-term treatment with beta blockers and use of target doses should be maintained to reduce the risk of progression in LV dysfunction or major cardiovascular events.<sup>18,19</sup> Abrupt withdrawal of beta-blocker therapy can lead to clinical deterioration and should be avoided unless indicated.<sup>18</sup>

- Multiple analyses have shown the high value of beta-blocker therapy among HF patients. A model-based analysis, using generic beta-blocker costs, found beta-blocker therapy was high value.<sup>4</sup> These results were consistent with earlier model-based cost-effectiveness analyses<sup>5-7</sup> and a trial-based economic analysis of the US Carvedilol Heart Failure (CHF) Trials Program.<sup>8</sup> Each of these studies also found treatment with a beta blocker was high value despite using previously higher beta-blocker costs.

### 7.3.3. Mineralocorticoid Receptor Antagonists (MRAs)

Recommendations for Mineralocorticoid Receptor Antagonists (MRAs)		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m <sup>2</sup> and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency. <sup>1-3</sup>
<b>Value Statement:</b> <b>High Value (A)</b>		2. In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value. <sup>4-7</sup>
3: Harm	B-NR	3. In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia. <sup>8,9</sup>

### Synopsis

MRA (also known as aldosterone antagonists or anti-mineralocorticoids) show consistent improvements in all-cause mortality, HF hospitalizations, and SCD across a wide range of patients with HFrEF.<sup>1-3</sup> Patients at risk for renal dysfunction or hyperkalemia require close monitoring, and eGFR ≤30 mL/min/1.73 m<sup>2</sup> or serum potassium ≥5.0 mEq/L are contraindications to MRA initiation.<sup>10,11</sup> Because of the higher selectivity of eplerenone for the aldosterone receptor, adverse effects such as gynecomastia and vaginal bleeding

are observed less often in patients who take eplerenone than in those who take spironolactone.

## Recommendation-Specific Supportive Text

- Clinical trials taken on MRA together—RALES (Randomized Aldactone Evaluation Study)<sup>1</sup> randomized highly symptomatic patients with LVEF  $\leq 35\%$ ; EPESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)<sup>2</sup> randomized patients post-MI with LVEF  $\leq 40\%$ ; and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)<sup>3</sup> randomized patients with mild symptoms and LVEF  $\leq 30\%$ —suggest a benefit of MRA across the spectrum of HFrEF, inclusive of a wide range of etiologies and disease severities. Initiation in the ambulatory or hospital setting is appropriate.<sup>12</sup> The starting dose of spironolactone and eplerenone is 25 mg orally daily, increased to 50 mg daily orally after a month; for eGFR 31 to 49 mL/min/1.73 m<sup>2</sup>, dosing should be reduced by half. Regular checks of serum potassium levels and renal function should be performed according to clinical status, approximately 1 week, then 4 weeks, then every 6 months after initiating or intensifying MRA, with more frequent testing for clinical instability. We elected to remove the 2013 recommendation “Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated” because the new recommendation covers the spectrum of symptomatic patients with HF.
- The economic value of MRA therapy was assessed by both RCTs (RALES<sup>5</sup> and EPESUS<sup>6,7</sup>) and a model-based analysis.<sup>4</sup> The model-based analysis used generic MRA costs and found therapy was high value with a cost per QALY of under \$1000.<sup>4</sup> The earlier trial-based economic analyses of MRAs from RALES and EPESUS also found MRA therapy was high value despite using previously higher MRA costs.<sup>5–7</sup>
- Spironolactone and eplerenone are partially excreted through the kidneys, raising concerns about safety when eGFR is  $\leq 30$  mL/min/1.73 m<sup>2</sup>.<sup>10,11</sup> Spironolactone and eplerenone decrease renal potassium excretion, raising the risk of hyperkalemia, particularly when MRA is initiated at serum potassium  $\geq 5.0$  mEq/L and continued  $\geq 5.5$  mEq/L. The incidence of clinically significant hyperkalemia events was  $<1\%$  in EPESUS and EMPHASIS-HF, without a significant difference between eplerenone and placebo,<sup>2,3</sup> however, in the closely monitored setting of a RCT with enrollment

of younger patients with fewer multiple chronic conditions than seen in the general HFrEF population, safety may be overstated. Observational data have raised concerns about less favorable outcomes of MRA use for HFrEF during usual care.<sup>8,9</sup> Coadministration of MRA with ACEi or ARB mildly increases the risk of hyperkalemia. Hyperkalemia risk was lower with ARNi in patients with chronic HF in the PARADIGM-HF trial<sup>13</sup> but not different in patients with HF who were decompensated in the PIONEER-HF trial<sup>14</sup> when compared with ACEi. Diarrhea causing dehydration or loop diuretic therapy interruption, because of worsening renal function or hyperkalemia, should be a consideration for temporarily holding the MRA. The development of worsening renal function or hyperkalemia is often a reflection of acute clinical change or progressive disease, prompting careful evaluation of the entire medical regimen and other causes of hyperkalemia, in addition to holding the MRA. The efficacy of the use of potassium binders (eg, patiromer, sodium zirconium cyclosilicate) to improve outcomes by facilitating continuation of MRA is uncertain<sup>15,16</sup> and is addressed in Section 7.3.6, “Other Drug Treatment.”

### 7.3.4. Sodium-Glucose Cotransporter 2 Inhibitors

#### Recommendation for SGLT2i

Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
1	A	<ol style="list-style-type: none"> <li>In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.<sup>1,2</sup></li> </ol>
Value Statement: Intermediate Value (A)		<ol style="list-style-type: none"> <li>In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.<sup>3,4</sup></li> </ol>

### Synopsis

Several RCTs in patients with type 2 diabetes and either established CVD or high risk for CVD have shown that SGLT2i prevent HF hospitalizations compared with placebo.<sup>5–7</sup> The overall 31% reduction in HF hospitalizations was noted irrespective of the presence or absence of preexisting HF, although only 10% to 14% of participants had HF at baseline. The benefit appears independent of the glucose-lowering effects.<sup>8</sup> Therefore, several trials were launched to examine the efficacy of SGLT2i on outcomes in patients with HF, irrespective of the presence of type 2 diabetes. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial and EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) showed the benefit of SGLT2i (dapagliflozin and empagliflozin, respectively) versus placebo on outcomes (median follow-up, 16–18

months).<sup>1,2</sup> Patients enrolled had symptomatic chronic HFrEF (LVEF ≤40%, NYHA class II to IV, and elevated natriuretic peptides) and were already on GDMT. Important exclusions were eGFR <20 (EMPEROR-Reduced) or <30 mL/min/1.73 m<sup>2</sup> (DAPA-HF), type 1 diabetes, or lower SBP <95 to 100 mm Hg.

## Recommendation-Specific Supportive Text

- In the DAPA-HF and EMPEROR-Reduced trials, SGLT2i compared with placebo reduced the composite of cardiovascular death or HF hospitalization by approximately 25%.<sup>1,2,9</sup> The benefit in reduction of HF hospitalization was greater (30%) in both trials.<sup>9</sup> Risk of cardiovascular death was significantly lowered (18%) with dapagliflozin, as was risk of all-cause mortality (17%). Although no significant cardiovascular mortality benefit was observed with empagliflozin in a meta-analysis of DAPA-HF and EMPEROR-Reduced trials, SGLT2i therapy was associated with a reduction in all-cause mortality and cardiovascular death.<sup>9</sup> The benefits in both trials were seen irrespective of baseline diabetes status. Furthermore, serious renal outcomes were less frequent, and the rate of decline in eGFR was slower in patients treated with SGLT2i.<sup>1,2,9</sup> In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes And Worsening Heart Failure) trial, patients with diabetes and HF hospitalization (79%: LVEF, <50%) were enrolled before discharge or within 3 days of discharge. Sotagliflozin, a dual inhibitor of sodium-glucose co-transporters 1 and 2, reduced the combined endpoint of cardiovascular death, HF hospitalization, or urgent HF visits by 33%<sup>10</sup> but has not been approved by the US Food and Drug Administration (FDA) as of 2021. Although SGLT2i increased risk for genital infections, they were otherwise well tolerated in the trials. As the use of SGLT2i is translated into clinical practice, caution is warranted for euglycemic ketoacidosis, genital and soft tissue infections, and adjustment of diuretics, if needed, to prevent volume depletion.<sup>11</sup>
- Two model-based analyses evaluated the economic value of dapagliflozin therapy compared with usual care based on the results of the DAPA-HF trial.<sup>3,4</sup> Both analyses found costs per QALY between \$60 000 and \$90 000, which is consistent with intermediate value according to the benchmarks adopted for the current guideline. The results were most sensitive to the magnitude of cardiovascular mortality reduction, with a ≥8% reduction in cardiovascular mortality necessary for a cost per QALY below \$150 000 in 1 study.<sup>3</sup> There are a wide range of costs currently seen with dapagliflozin.

These 2 analyses estimated a cost per QALY below \$50 000 with annual dapagliflozin costs of \$3240 (43% reduction from main analysis) and \$2500 (40% reduction from main analysis), respectively.<sup>3,4</sup> A smaller reduction in drug cost would lead to a cost per QALY of under \$60 000, the threshold for high value in this guideline.

### 7.3.5. Hydralazine and Isosorbide Dinitrate

**Recommendations for Hydralazine and Isosorbide Dinitrate**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	<ol style="list-style-type: none"> <li>For patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.<sup>1,2</sup></li> </ol>
	<b>Value Statement: High Value (B-NR)</b>	<ol style="list-style-type: none"> <li>For patients self-identified as African American with NYHA class III to IV HFrEF who are receiving optimal medical therapy with ACEi or ARB, beta blockers, and MRA, the combination of hydralazine and isosorbide dinitrate provides high economic value.<sup>3</sup></li> </ol>
2b	C-LD	<ol style="list-style-type: none"> <li>In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.<sup>4,5</sup></li> </ol>

## Synopsis

Two RCTs, V-HeFT I (Vasodilator Heart Failure Trial) and A-HeFT (African-American Heart Failure Trial), established benefit of the combination of hydralazine-isosorbide dinitrate in self-identified African Americans.<sup>2,4</sup> A-HeFT was terminated early because of evidence of remarkable benefit, but the result is vulnerable to a small number of events and the exigencies of early cessation of RCTs.<sup>2</sup> The benefit in both trials was seen only at doses achieved in those trials that are higher than doses typically used in clinical practice and with short-acting nitrate therapy.<sup>2,4</sup> Uptake of this regimen has been modest as a result of the complexity of the medical regimen and the array of drug-related adverse effects.<sup>5</sup> Even when prescribed, there is marked underusage based on very low prescription refill rates. Race-based medical therapy remains a challenging issue, as well, with ongoing research now focused on biological hypotheses, particularly absence of European ancestry, which may be associated with responsiveness to this combination. There are insufficient data to guide the use of hydralazine-isosorbide dinitrate with ARNi. In patients with HFrEF who cannot receive first-line agents such as ARNi, ACEi, or ARB, referral to a HF specialist can provide guidance for further management because the use of hydralazine and isosorbide dinitrate in these patients is uncertain.

## Recommendation-Specific Supportive Text

- In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality in patients with HF treated with digoxin and diuretics but not an ACEi or beta blocker.<sup>4</sup> However, in 2 other trials that compared the vasodilator combination with an ACEi, the ACEi produced more favorable effects on survival.<sup>5,7</sup> A post hoc retrospective analysis of these vasodilator trials showed particular efficacy of isosorbide dinitrate and hydralazine in the African American cohort.<sup>1</sup> In a subsequent trial, which was limited to patients self-identified as African American, the addition of a fixed-dose combination of hydralazine and isosorbide dinitrate to standard therapy with an ACEi or ARB, a beta blocker, and MRA offered significant benefit.<sup>2</sup> Thus, the combination of hydralazine and isosorbide dinitrate is appropriate for African Americans with HFrEF who remain symptomatic despite concomitant use of ACEi (or ARB), beta blockers, and MRA. There are insufficient data for concomitant use with ARNi.
- The economic value of hydralazine and isosorbide nitrate therapy was assessed by the A-HeFT trial.<sup>3</sup> This analysis found hydralazine and isosorbide dinitrate increased survival and reduced health care costs over the 12.8-month trial. Extrapolating beyond the trial, the analysis found hydralazine and isosorbide dinitrate remained high value over a lifetime with a cost per life-year <\$60 000 despite conservative assumptions regarding the durability of therapy effectiveness and previously higher hydralazine and isosorbide dinitrate costs.
- It is unclear if a benefit of hydralazine-isosorbide dinitrate (suggested in a trial before the use of ACEi)<sup>4</sup> exists for non–African Americans with HFrEF. Despite the lack of data with the vasodilator combination in patients who are intolerant of ACEi or ARB, especially those with renal insufficiency, the combined use of hydralazine and isosorbide dinitrate might be considered as a therapeutic option in such patients. Although the potential benefit is unknown and has not been shown in recent observational datasets,<sup>5</sup> in V-HeFT I, the use of hydralazine and isosorbide dinitrate reduced mortality in patients with HF treated with digoxin and diuretics, compared with placebo.<sup>4</sup> If patients are unable to tolerate first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance, hypotension, or renal insufficiency, referral to a HF specialist can provide guidance for further management, and the use of hydralazine and isosorbide dinitrate in these patients might be considered.

## 7.3.6. Other Drug Treatment

### Recommendations for Other Drug Treatment

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
<b>2b</b>	<b>B-R</b>	<ol style="list-style-type: none"><li>In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid (PUFA) supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations.<sup>1-4</sup></li></ol>
<b>2b</b>	<b>B-R</b>	<ol style="list-style-type: none"><li>In patients with HF who experience hyperkalemia (serum potassium level <math>\geq</math>5.5 mEq/L) while taking a renin-angiotensin-aldosterone system inhibitor (RAASi), the effectiveness of potassium binders (patiromer, sodium zirconium cyclosilicate) to improve outcomes by facilitating continuation of RAASi therapy is uncertain.<sup>5,6</sup></li></ol>
<b>3: No Benefit</b>	<b>B-R</b>	<ol style="list-style-type: none"><li>In patients with chronic HFrEF without a specific indication (eg, venous thromboembolism [VTE], AF, a previous thromboembolic event, or a cardioembolic source), anticoagulation is not recommended.<sup>7-9</sup></li></ol>

## Synopsis

Trials in prevention of CVD, including HF, showed that omega-3 PUFA supplementation results in a 10% to 20% risk reduction in fatal and nonfatal cardiovascular events when used with other evidence-based therapies.<sup>2,3,10</sup> Hyperkalemia is common in HF and can lead to arrhythmias and underuse of GDMT.<sup>11,12</sup> Two newer gastrointestinal potassium-binding agents—patiromer and sodium zirconium cyclosilicate—have been shown to lower potassium levels and enable treatment with a RAASi in patients with HF.<sup>5,6,13</sup>

## Recommendation-Specific Supportive Text

- Supplementation with omega-3 PUFA has been evaluated as an adjunctive therapy for CVD and HF.<sup>14</sup> The GISSI-HF (Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure) trial showed a reduction in death among post-MI patients taking 1 g of omega-3 PUFA (850–882 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1.2).<sup>10</sup> A post hoc subgroup analysis revealed that this reduction in mortality and SCD was concentrated in the approximately 2000 patients with reduced LVEF.<sup>10</sup> The GISSI-HF investigators randomized symptomatic patients with HF to 1 g daily of omega-3 PUFA (850–882 mg of EPA-DHA) or placebo. Death from any cause was reduced from 29% with placebo to 27% in those treated with omega-3 PUFA.<sup>2</sup> The outcome of death or admission to hospital for a cardiovascular event was also significantly reduced. The REDUCE-IT trial randomized patients with established CVD

or diabetes with risk factors to 2 g of icosapent ethyl (a highly purified EPA) twice daily or placebo and showed a reduced risk for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina.<sup>3</sup> In reported studies, omega-3 PUFA therapy has been well tolerated. Recent studies have reported that in patients with cardiovascular risk treated with omega-3 fatty acid, there may be a dose-related risk of AF.<sup>3,15,16</sup>

2. Hyperkalemia is common in HF as a result of the syndrome itself, comorbidities (diabetes, CKD), and use of RAASi, and can increase the risk for ventricular arrhythmias and mortality.<sup>11</sup> Hyperkalemia results in dose reductions or discontinuation of RAASi, compromising their cardio-renal benefit in HF.<sup>12</sup> Two newer gastrointestinal potassium binders—patiromer (RLY5016) and sodium zirconium cyclosilicate (SZC)—remove potassium by exchanging cations (calcium for patiromer, and sodium and hydrogen for SZC), leading to increased fecal excretion. Both agents have been FDA approved for treatment of hyperkalemia for patients receiving RAASi. In the PEARL-HF (Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder in patients with chronic heart failure) trial, patiromer led to lower potassium levels, less hyperkalemia, and a higher proportion of patients able to increase spironolactone dose to 50 mg daily compared with placebo.<sup>5</sup> The HARMONIZE (Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance) trial included 94 patients (out of 258 total) with HF (87 of whom entered the double-blind phase).<sup>6,13</sup> The SZC groups achieved lower potassium levels overall compared with placebo, and a higher proportion maintained normokalemia (potassium levels, <5.1 mEq/L). Whether patiromer or SZC improve clinical outcomes is under investigation. Adverse effects for the newer potassium binders include hypomagnesemia (for patiromer) and edema (for SZC).
3. In several retrospective analyses, the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs.<sup>17–19</sup> The use of warfarin was associated with a reduction in major cardiovascular events and death in patients with HF in some studies but not in others.<sup>20–22</sup> An RCT that compared the outcome of patients with HFrEF assigned to aspirin, warfarin, or clopidogrel found that no therapy was superior.<sup>7</sup> Another trial that compared aspirin with warfarin in patients with reduced LVEF, sinus rhythm, and no cardioembolic source showed no difference in either the primary outcome of death, stroke, or intracerebral hemorrhage, and no

difference in the combined outcome of death, ischemic stroke, intracerebral hemorrhage, MI, or HF hospitalization.<sup>8</sup> There was a significant increase in major bleeding with warfarin. A trial of rivaroxaban in patients with HFrEF, CAD, and normal sinus rhythm showed no difference in mortality, MI, and stroke compared with placebo.<sup>9</sup> Therefore, there is no evidence of benefit for anticoagulation in HF patients without a specific indication (eg, VTE, AF, a previous thromboembolic event, or a cardioembolic source).

### 7.3.7. Drugs of Unproven Value or That May Worsen HF

Recommendations for Drugs of Unproven Value or Drugs That May Worsen HF		
COR	LOE	Recommendations
<b>3: No Benefit</b>	<b>A</b>	1. In patients with HFrEF, dihydropyridine calcium channel-blocking drugs are not recommended treatment for HF. <sup>1,2</sup>
<b>3: No Benefit</b>	<b>B-R</b>	2. In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. <sup>3–9</sup>
<b>3: Harm</b>	<b>A</b>	3. In patients with HFrEF, nondihydropyridine calcium channel-blocking drugs are not recommended. <sup>10–13</sup>
<b>3: Harm</b>	<b>A</b>	4. In patients with HFrEF, class IC antiarrhythmic medications and dronedarone may increase the risk of mortality. <sup>14–16</sup>
<b>3: Harm</b>	<b>A</b>	5. In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. <sup>17–21</sup>
<b>3: Harm</b>	<b>B-R</b>	6. In patients with type 2 diabetes and high cardiovascular risk, the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin and alogliptin increase the risk of HF hospitalization and should be avoided in patients with HF. <sup>22–24</sup>
<b>3: Harm</b>	<b>B-NR</b>	7. In patients with HFrEF, NSAIDs worsen HF symptoms and should be avoided or withdrawn whenever possible. <sup>25–28</sup>

### Synopsis

Although there is strong evidence for benefit with selected medications for HFrEF as outlined in Section 7.3, “Pharmacological Treatment for HF With Reduced Ejection Fraction (HFrEF),” there remain several classes of medications that have either unproven value or potential for harm (Table 13). These recommendations are not exhaustive but focus on the most relevant and commonly encountered medications in the management of patients with HFrEF: calcium channel blockers; antiarrhythmic agents; NSAIDs; medications for treatment of type 2 diabetes including thiazolidinediones and DPP-4 inhibitors; and vitamins, hormones, and nutritional supplements.

**Table 13. Selected Prescription Medications That May Cause or Exacerbate HF**

Drug or Therapeutic Class	Associated With HF		Magnitude of HF Induction or Precipitation	LOE for HF Induction or Precipitation	Possible Mechanism(s)	Onset
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction				
COX, nonselective inhibitors (NSAIDs)		X	Major	B	Prostaglandin inhibition leading to sodium and water retention, increased systemic vascular resistance, and blunted response to diuretics	Immediate
COX, selective inhibitors (COX-2 inhibitors)		X	Major	B		
Thiazolidinediones		X	Major	A	Possible calcium channel blockade	Intermediate
Saxagliptin		X	Major	A	Unknown	Intermediate to delayed
Alogliptin		X	Major	A		
Flecainide		X	Major	A	Negative inotrope, proarrhythmic effects	Immediate to intermediate
Disopyramide		X	Major	B		
Sotalol		X	Major	A	Proarrhythmic properties, beta blockade	Immediate to intermediate
Dronedarone		X	Major	A	Negative inotrope	
<b>Alpha-1 blockers</b>						
Doxazosin		X	Moderate	B	Beta-1-receptor stimulation with increases in renin and aldosterone	Intermediate to delayed
Diltiazem		X	Major	B	Negative inotope	Immediate to intermediate
Verapamil		X	Major	B		
Nifedipine		X	Moderate	C		

COX indicates cyclo-oxygenase; HF, heart failure; LOE, Level of Evidence; and NSAID, nonsteroidal anti-inflammatory drug.

Adapted from Page RL 2nd et al.<sup>57</sup> Copyright 2016 American Heart Association Inc.

## Recommendation-Specific Supportive Text

- Second-generation dihydropyridine calcium channel blockers, including amlodipine and felodipine, have greater selectivity for calcium channels in vascular smooth muscle cells and less myocardial depressant activity. By reducing peripheral vasoconstriction and LV afterload, calcium channel blockers were thought to have a potential role in the management of chronic HF. The PRAISE-1 (Prospective Randomized Amlodipine Survival Evaluation-1) study showed a reduction in mortality in the subgroup of patients with nonischemic cardiomyopathy who received amlodipine.<sup>1</sup> However, in the PRAISE-2 (Prospective Randomized Amlodipine Survival Evaluation 2) trial, which enrolled only patients with nonischemic cardiomyopathy, no survival benefit was observed, indicating the limitations of conclusions derived from subgroup analyses.<sup>29</sup> However, dihydropyridine calcium channel blockers may be used for treatment of hypertension in patients who have elevated blood pressure despite optimization of GDMT.
- Many nutritional supplements and hormonal therapies have been proposed for the treatment of HF.<sup>3-9,30,31</sup> Ultimately, most studies are limited by small sample sizes, surrogate endpoints, or

nonrandomized design.<sup>32,33</sup> In addition, adverse effects and drug-nutraceutical interactions remain unresolved. There is a lack of evidence of benefit from vitamin D,<sup>3-5</sup> thiamine,<sup>34-36</sup> carnitine,<sup>37</sup> and taurine<sup>38,39</sup> and potential harm from vitamin E.<sup>6,7</sup> The largest RCT of coenzyme Q10—Q-SYMBIO (Coenzyme Q10 as adjunctive treatment of chronic heart failure with focus on SYMptoms, Blomarker status [Brain-Natriuretic Peptide], and long-term Outcome [hospitalisations/mortality])—showed no changes in NYHA functional classification at 16 weeks, although the incidence of major adverse cardiovascular events at 2 years was significantly reduced (hazard ratio, 0.50; 95% CI, 0.32–0.80;  $P=0.003$ ).<sup>8</sup> Despite these findings, concerns about slow recruitment in this trial have tempered enthusiasm for coenzyme Q10 supplementation in clinical practice.<sup>9,31</sup> Hormonal therapies have been proposed for the treatment of HF, but trials have shown a neutral effect of testosterone,<sup>40,41</sup> growth hormone,<sup>30,42</sup> and thyroid hormone<sup>43-45</sup> in HF outcomes.

- Nondihydropyridine calcium channel blockers—diltiazem and verapamil—are myocardial depressants and generally not well tolerated in HF. Verapamil had no impact of survival or major cardiac events post-MI, including in those patients with HFrEF after acute MI.<sup>10</sup> In patients with nonischemic

- cardiomyopathy, diltiazem had no impact on mortality<sup>13</sup> but, in HFrEF after acute MI, diltiazem was associated with a higher risk of recurrent HF.<sup>11,12</sup>
4. In the CAST (Cardiac Arrhythmia Suppression) trial, patients with asymptomatic ventricular arrhythmias post-MI on the class IC antiarrhythmics encainide or flecainide had increased mortality.<sup>14</sup> The applicability of CAST to patients without recent MI or to other class I antiarrhythmic drugs is uncertain, but class IC antiarrhythmic agents are generally avoided in patients with structural heart disease. In ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease Study), for the class III antiarrhythmic dronedarone, patients with HFrEF who were hospitalized had increased mortality.<sup>16</sup> In the SWORD (Survival With ORal D-sotalol) trial of the class III antiarrhythmic sotalol, patients with HF post-MI had increased mortality.<sup>15</sup> However, SWORD was published in 1996, and whether sotalol would be harmful in the current era of GDMT and ICDs is uncertain; sotalol may be used for refractory atrial-ventricular arrhythmias with close monitoring for decompensation. Amiodarone<sup>46,47</sup> and dofetilide<sup>48,49</sup> are the only antiarrhythmic agents with neutral effects on mortality in clinical trials of patients with HFrEF. Class IA antiarrhythmic agents such as quinidine and class IB agents such as mexiletine have not been studied and may be indicated for the management of refractory ventricular arrhythmias in the context of the individual patient's risk benefit calculus and in conjunction with electrophysiology consultation.
  5. Thiazolidinediones increase insulin sensitivity by activating nuclear peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ). Expressed in virtually all tissues, PPAR- $\gamma$  also regulates sodium reabsorption in the collecting ducts of the kidney. In observational cohort studies,<sup>17</sup> meta-analysis,<sup>18</sup> and clinical trials,<sup>19–21</sup> thiazolidinediones have been associated with increased incidence of fluid retention and HF events in those patients with<sup>19,21</sup> or without<sup>18,20</sup> a previous history of HF.
  6. DPP-4 is a cell-surface enzyme that deactivates several peptides include glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1. DPP-4 inhibitors affect glucose regulation through multiple mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake. The impact of DPP-4 inhibitors on cardiovascular outcomes in patients with diabetes and high cardiovascular risk has been assessed in multiple RCTs. Saxagliptin increased the risk of hospitalization for HF<sup>22</sup> as did alogliptin in a post hoc analysis

including only patients with no HF history,<sup>23,50</sup> but sitagliptin<sup>51,52</sup> and linagliptin<sup>53–55</sup> did not; these findings may have been a result of baseline differences in the use of metformin, thiazolidinediones, and insulin, which also affect HF risk. The FDA recommends discontinuation specifically of saxagliptin and alogliptin in patients who develop HF<sup>56</sup> and whether the risk of worsening HF is a class effect of DPP-4 inhibitors is unclear.

7. NSAIDs inhibit the synthesis of renal prostaglandins, which mediate vasodilation in the kidneys and directly inhibit sodium resorption in the thick ascending loop of Henle and collecting tubule. Hence, NSAIDs can cause sodium and water retention and blunt the effects of diuretics. Several observational cohort studies have revealed increased morbidity and mortality in patients with HF using either nonselective or selective NSAIDs.<sup>25–28</sup>

### 7.3.8. GDMT Dosing: Sequencing and Uptitration

**Recommendations for GDMT Dosing: Sequencing and Uptitration**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	<ol style="list-style-type: none"> <li>In patients with HFrEF, titration of guideline-directed medication dosing to achieve target doses showed to be efficacious in RCTs is recommended, to reduce cardiovascular mortality and HF hospitalizations, unless not well tolerated.<sup>1–10</sup></li> </ol>
2a	C-EO	<ol style="list-style-type: none"> <li>In patients with HFrEF, titration and optimization of guideline-directed medications as frequently as every 1 to 2 weeks depending on the patient's symptoms, vital signs, and laboratory findings can be useful to optimize management.</li> </ol>

### Synopsis

Clinical trials of ACEi, ARB, ARNi, beta blockers, and most other HFrEF medications had therapy initiated at low dose by trial protocol.<sup>1–9,11–14</sup> If the initial dose was tolerated, the protocol would then direct the uptitration of medication dose over time to a specified target dose (Table 14), unless not well tolerated. Even if symptoms improved or other indicators of response were shown at lower doses, the medication dose would still be increased to the trial-defined target doses. Because these target doses were the ones that established the efficacy and safety of these medications in HFrEF and serve as the basis of the guideline recommendations (Table 15), use of these target doses is recommended, if tolerated.<sup>1–9,11–14</sup> Use of all 4 drug classes has been estimated to reduce all-cause mortality by 73% compared with no treatment.<sup>15</sup>

If the target dose cannot be achieved or is not well tolerated, then the highest tolerated dose is recommended.

**Table 14. Drugs Commonly Used for HFrEF (Stage C HF)**

Drug	Initial Daily Dose(s)	Target Doses(s)	Mean Doses Achieved in Clinical Trials	References
<b>ACEi</b>				
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	122.7 mg total daily	19
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg total daily	3
Fosinopril	5–10 mg once daily	40 mg once daily	NA	...
Lisinopril	2.5–5 mg once daily	20–40 mg once daily	32.5–35.0 mg total daily	17
Perindopril	2 mg once daily	8–16 mg once daily	NA	...
Quinapril	5 mg twice daily	20 mg twice daily	NA	...
Ramipril	1.25–2.5 mg once daily	10 mg once daily	NA	...
Trandolapril	1 mg once daily	4 mg once daily	NA	...
<b>ARB</b>				
Candesartan	4–8 mg once daily	32 mg once daily	24 mg total daily	20
Losartan	25–50 mg once daily	50–150 mg once daily	129 mg total daily	18
Valsartan	20–40 mg once daily	160 mg twice daily	254 mg total daily	21
<b>ARNi</b>				
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily	182 mg sacubitril and 193 mg valsartan total daily	22
<b>Beta blockers</b>				
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg total daily	1
Carvedilol	3.125 mg twice daily	25–50 mg twice daily	37 mg total daily	23
Carvedilol CR	10 mg once daily	80 mg once daily	NA	...
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily	159 mg total daily	11
<b>Mineralocorticoid receptor antagonists</b>				
Spironolactone	12.5–25 mg once daily	25–50 mg once daily	26 mg total daily	6
Eplerenone	25 mg once daily	50 mg once daily	42.6 mg total daily	13
<b>SGLT2i</b>				
Dapagliflozin	10 mg once daily	10 mg once daily	9.8 mg total daily	8
Empagliflozin	10 mg once daily	10 mg once daily	NR	9
<b>Isosorbide dinitrate and hydralazine</b>				
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily	40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily	90 mg isosorbide dinitrate and ~175 mg hydralazine total daily	10
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate and 25–50 mg hydralazine 3–4 times daily	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses	NA	24
<b>I<sub>f</sub> Channel inhibitor</b>				
Ivabradine	5 mg twice daily	7.5 mg twice daily	12.8 total daily	25–27
<b>Soluble guanylate cyclase stimulator</b>				
Vericiguat	2.5 mg once daily	10 mg once daily	9.2 mg total daily	28
<b>Cardiac glycoside</b>				
Digoxin	0.125–0.25 mg daily (modified according to monogram)	Individualized variable dose to achieve serum digoxin concentration 0.5–<0.9 ng/mL	NA	29,30

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NR, not reported; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

There are no direct data showing that use of lower doses of HFrEF medications among patients, where higher target doses could be tolerated, would produce the same or simi-

lar degree of clinical benefit. In trials that have evaluated dose response for outcomes, composite event rates were lower with target doses compared with lower dose.<sup>16–18</sup>

**Table 15. Benefits of Evidence-Based Therapies for Patients With HFrEF<sup>3–6,8,10–14,23,31–42</sup>**

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All-Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNi†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NNT, number needed to treat; RCT, randomized controlled trial; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

\*Median duration follow-up in the respective clinical trial.

†Benefit of ARNi therapy incremental to that achieved with ACEi therapy. For the other medications shown, the benefits are based on comparisons to placebo control.

‡Benefit of hydralazine-nitrate therapy was limited to African American patients in this trial.

## Recommendation-Specific Supportive Text

1. The use of these specific medications for HFrEF should involve initiation at low-starting doses, uptitration at specified intervals as tolerated, and achieving-maintaining the target doses shown to be effective in major clinical trials. Every effort should be made by clinicians to achieve and maintain the clinical trial-defined target doses (Table 13) of guideline-directed medications, as long as they are well tolerated by the patient. Patients should be monitored for changes in heart rate, blood pressure, electrolytes, renal function, and symptoms during this uptitration period. Planned uptitration of a HF medication should be delayed until any adverse effects observed with lower doses have resolved. When such a strategy is used for dose titration, most patients (approximately 70%–85%) enrolled in clinical trials who received these medications were able to tolerate short-, intermediate-, and long-term treatment with these agents and achieve and maintain the trial defined target dose.<sup>1–9,11–14</sup> Repeated attempts at uptitration can result in optimization, even if initial attempts may fail. In patients with HFrEF, beta blockers provide dose-dependent improvements in LVEF, reduction in HF hospitalizations, and reduction in all-cause mortality.<sup>17</sup> Trials of lower versus higher dose of ACEi and ARB have shown lower risk of cardiovascular death or HF hospitalization with higher doses, with similar safety and tolerability.<sup>17,18</sup>
2. Initiation and titration should be individualized and optimized without delay according to patient's symptoms, vital signs, functional status, tolerance, renal function, electrolytes, comorbidities, specific

cause of HF, and ability of follow-up. In patients with HFrEF, simultaneous initiation or sequencing, and order of guideline-directed medications are usually individualized according to patient's symptoms, vital signs, functional status, tolerance, renal function, electrolytes, comorbidities, specific cause of HF, and ability of follow-up, and does not necessarily need to be done according to the sequence of trial publications and should not be delayed.

### 7.3.9. Additional Medical Therapies

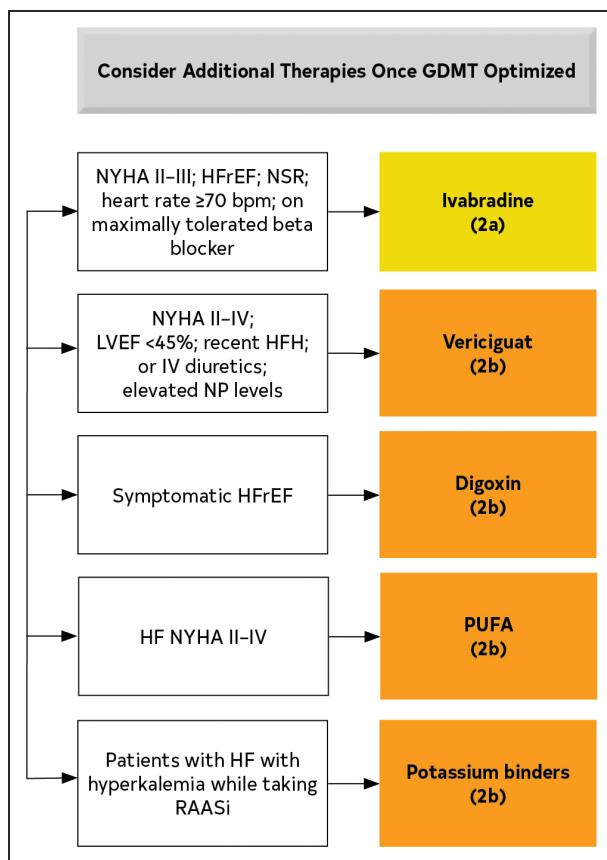
#### 7.3.9.1. Management of Stage C HF: Ivabradine

**Recommendation for the Management of Stage C HF: Ivabradine**  
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
<b>2a</b>	<b>B-R</b>	<p>1. For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.<sup>1,2</sup></p>

### Synopsis

Heart rate is a strong predictor of cardiovascular outcomes in the general population and in patients with CVD, including HF. The SHIFT (Ivabradine and Outcomes in Chronic Heart Failure) trial tested the hypothesis that reducing heart rate in patients with HF improves cardiovascular outcomes.<sup>1</sup> SHIFT demonstrated the efficacy of ivabradine, a sinoatrial node modulator that selectively inhibits the  $I_f$  current, in reducing the composite endpoint of cardiovascular death or HF hospitalization in patients with HF. See Figure 7 for a summary of additional medical therapy recommendations.

**Figure 7. Additional Medical Therapies for Patients With HFrEF.**

Colors correspond to COR in Table 2. Recommendations for additional medical therapies that may be considered for patients with HF are shown. GDMT indicates guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; MV, mitral valve; MR, mitral regurgitation; NP, natriuretic peptide; NSR, normal sinus rhythm; NYHA, New York Heart Association; and RAASi, renin-angiotensin-aldosterone system inhibitors.

### Recommendation-Specific Supportive Text

- Although the primary outcome in SHIFT was a composite of hospitalization and cardiovascular death, the greatest benefit was a reduction in HF hospitalization. SHIFT included patients with HFrEF and LVEF  $\leq 35\%$  who were in sinus rhythm with a resting heart rate of  $\geq 70$  bpm. Participants were predominantly NYHA class II and III. Participants had been hospitalized for HF in the preceding 12 months and were on stable GDMT for 4 weeks before initiation of ivabradine therapy.<sup>1-4</sup> The target of ivabradine is heart rate, and the benefit of ivabradine results from a reduction in heart rate. However, only 25% of patients studied in SHIFT were on optimal doses of beta-blocker therapy. Given the well-proven mortality benefits of beta-blocker therapy, these agents should be initiated and uptitrated to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation.<sup>5,6</sup>

### 7.3.9.2. Pharmacological Treatment for Stage C HFrEF: Digoxin

Recommendation for the Pharmacological Treatment for Stage C HFrEF: Digoxin

Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
2b	B-R	1. In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF. <sup>1,2</sup>

### Synopsis

To date, there has been only 1 large-scale, RCT of digoxin in patients with HF.<sup>1</sup> This trial, which predated current GDMT, primarily enrolled patients with NYHA class II to III HF and showed that treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization. The trial also found no significant effect on health-related QOL in a subset of the trial patients.<sup>3</sup> The effect of digoxin on hospitalizations has been supported by retrospective analyses and meta-analyses.<sup>2,4-6</sup> Additionally, observational studies and retrospective analyses have shown improvement in symptoms and exercise tolerance in mild to moderate HF; however, they have mostly shown either lack of mortality benefit or increased mortality associated with digoxin.<sup>7</sup> The benefit in patients on current GDMT is unclear because most trials preceded current GDMT. Thus, use of digoxin requires caution in patients with HF and is reserved for those who remain symptomatic despite optimization of GDMT.

### Recommendation-Specific Supportive Text

- Digoxin is usually initiated at a low dose because higher doses are rarely required in the management of HF and are potentially detrimental. Two retrospective analyses of large-scale clinical trials have shown a linear relationship between mortality and digoxin serum concentration in patients with AF and at risk for stroke, including those with HF, and in patients with HF. The risk of death was independently associated with serum digoxin concentration, with a significantly higher risk observed in those with concentrations  $\geq 1.2$  ng/mL and  $\geq 1.6$  ng/mL.<sup>8,9</sup> The benefit of digoxin in patients with HF remains controversial. GDMT is expected to be optimized before considering the addition of digoxin. Clinical worsening after withdrawal of digoxin has been shown.<sup>10</sup> Therapy with digoxin may either be continued in the absence of a contraindication or discontinued with caution.<sup>11</sup> Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used initially if the patient is  $>70$  years of

age, has impaired renal function, or has a low lean body mass. Higher doses (eg, digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF.

### 7.3.9.3. Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators

#### Recommendation for Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators

Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. <sup>1</sup>

### Synopsis

In patients with progression of HFrEF despite GDMT, there may be a role for novel therapeutic agents. Oral soluble guanylyl cyclase stimulator (eg, vericiguat) directly binds and stimulates sGC and increases cGMP production. cGMP has several potentially beneficial effects in patients with HF, including vasodilation, improvement in endothelial function, as well as decrease in fibrosis and remodeling of the heart.<sup>2-7</sup> The VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial randomized 5050 higher-risk patients with worsening HFrEF to vericiguat versus placebo.<sup>1</sup>

### Recommendation-Specific Supportive Text

- Patients with HFrEF in the VICTORIA trial had LVEF <45%, NYHA class II to IV, were on GDMT, with elevated natriuretic peptides (BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL if in sinus rhythm; higher cutoffs with AF), and recent HF worsening (hospitalized within 6 months or recently received intravenous diuretic therapy without hospitalization). Patients on long-acting nitrates, with SBP <100 mm Hg, or eGFR <15 mL/min/1.73 m<sup>2</sup> were excluded.<sup>1</sup> Over a median follow-up of 10.8 months, the primary outcome, cardiovascular death or HF hospitalization, occurred in 35.5% with vericiguat compared with 38.5% with placebo (HR, 0.90; *P*=0.019). All-cause mortality occurred in 20.3% in the vericiguat group and 21.2% in the placebo group (HR, 0.95; 95% CI, 0.84-1.07; *P*=0.38) and composite of any-cause death or HF hospitalization was also lower in the vericiguat group versus placebo group (HR, 0.90; 95% CI, 0.83-0.98; *P*=0.02). The relative risk reduction of 10% in the primary outcome was lower than expected, even in

a higher risk population. Although not statistically significant, symptomatic hypotension (9.1% versus 7.9%; *P*=0.12) and syncope (4.0% versus 3.5%; *P*=0.30) were numerically higher in the vericiguat group versus placebo. There was heterogeneity by subgroup analysis, and patients in the highest quartile of NT-proBNP subgroup (NT proBNP level >5314 pg/mL) did not have benefit from vericiguat when compared with placebo.

## 7.4. Device and Interventional Therapies for HFrEF

### 7.4.1. ICDs and CRTs

#### Recommendations for ICDs and CRTs

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	<ol style="list-style-type: none"> <li>In patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF ≤35% and NYHA class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for &gt;1 year, ICD therapy is recommended for primary prevention of SCD to reduce total mortality.<sup>1-9</sup></li> </ol>
<b>Value Statement: High Value (A)</b>		<ol style="list-style-type: none"> <li>2. A transvenous ICD provides high economic value in the primary prevention of SCD particularly when the patient's risk of death caused by ventricular arrhythmia is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status.<sup>10-15</sup></li> </ol>
1	B-R	<ol style="list-style-type: none"> <li>3. In patients at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for &gt;1 year, ICD therapy is recommended for primary prevention of SCD to reduce total mortality.<sup>6</sup></li> </ol>
1	B-R	<ol style="list-style-type: none"> <li>4. For patients who have LVEF ≤35%, sinus rhythm, left bundle branch block (LBBB) with a QRS duration ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT, CRT is indicated to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.<sup>16-21</sup></li> </ol>
<b>Value Statement: High Value (B-NR)</b>		<ol style="list-style-type: none"> <li>5. For patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration of ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT, CRT implantation provides high economic value.<sup>22-27</sup></li> </ol>
2a	B-R	<ol style="list-style-type: none"> <li>6. For patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration ≥150 ms, and NYHA class II, III, or ambulatory class IV symptoms on GDMT, CRT can be useful to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.<sup>16-21,28-33</sup></li> </ol>
2a	B-R	<ol style="list-style-type: none"> <li>7. In patients with high-degree or complete heart block and LVEF of 36% to 50%, CRT is reasonable to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.<sup>34,35</sup></li> </ol>

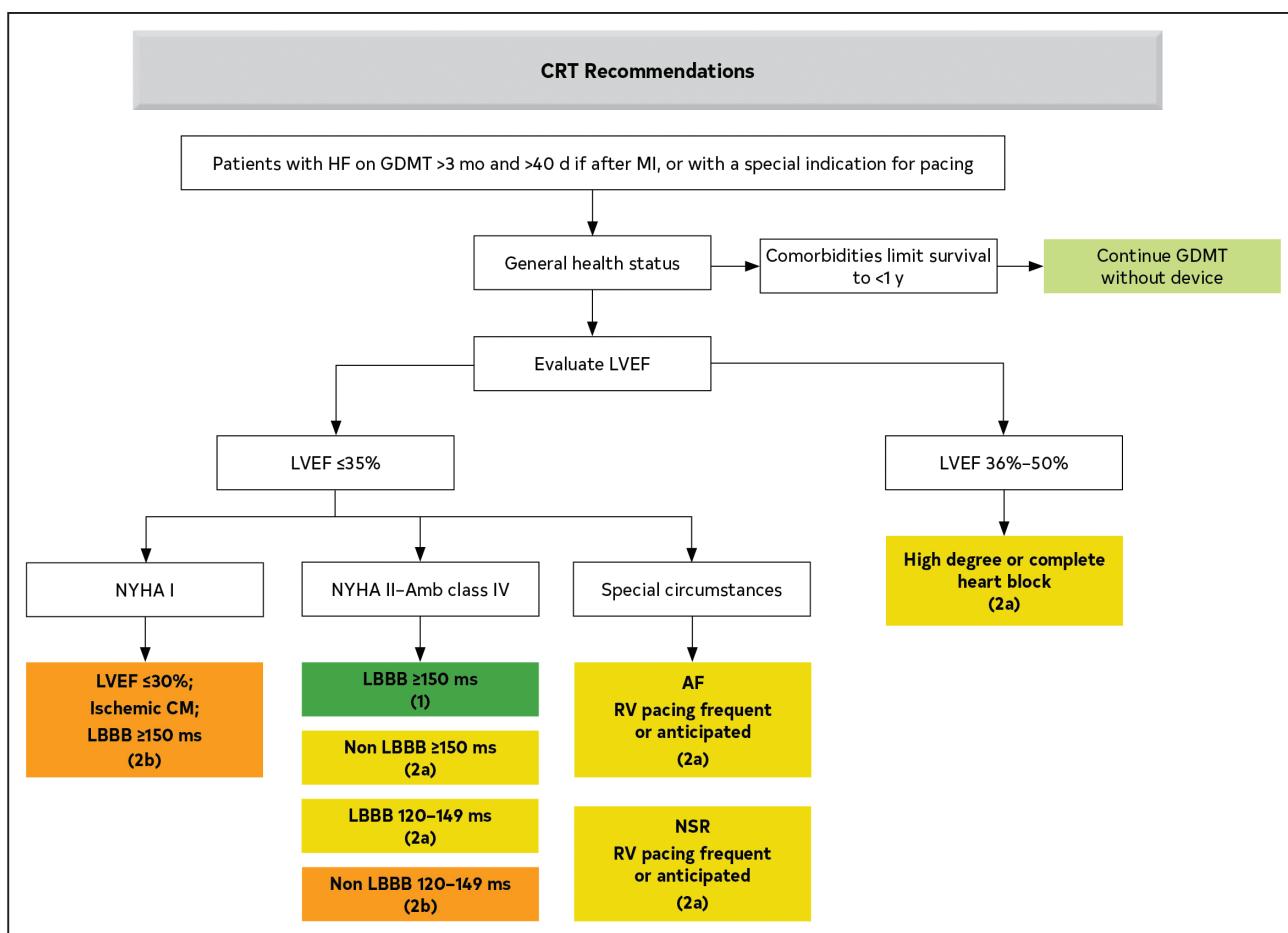
Recommendations for ICDs and CRTs (Continued)		
COR	LOE	Recommendations
<b>2a</b>	<b>B-NR</b>	8. For patients who have LVEF $\leq 35\%$ , sinus rhythm, LBBB with a QRS duration of 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT, CRT can be useful to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL. <sup>16-21,28-33</sup>
<b>2a</b>	<b>B-NR</b>	9. In patients with AF and LVEF $\leq 35\%$ on GDMT, CRT can be useful to reduce total mortality, improve symptoms and QOL, and increase LVEF, if: a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) atrioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT. <sup>16-21,28-33</sup>
<b>2a</b>	<b>B-NR</b>	10. For patients on GDMT who have LVEF $\leq 35\%$ and are undergoing placement of a new or replacement device implantation with anticipated requirement for significant ( $>40\%$ ) ventricular pacing, CRT can be useful to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL. <sup>16-21,28-33</sup>
<b>2a</b>	<b>B-NR</b>	11. In patients with genetic arrhythmogenic cardiomyopathy with high-risk features of sudden death, with EF $\leq 45\%$ , implantation of ICD is reasonable to decrease sudden death. <sup>36,37</sup>
<b>2b</b>	<b>B-NR</b>	12. For patients who have LVEF $\leq 35\%$ , sinus rhythm, a non-LBBB pattern with QRS duration of 120 to 149 ms, and NYHA class III or ambulatory class IV on GDMT, CRT may be considered to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL. <sup>16-21,28-33</sup>
<b>2b</b>	<b>B-NR</b>	13. For patients who have LVEF $\leq 30\%$ , ischemic cause of HF, sinus rhythm, LBBB with a QRS duration $\geq 150$ ms, and NYHA class I symptoms on GDMT, CRT may be considered to reduce hospitalizations and improve symptoms and QOL. <sup>16-21,28-33</sup>
<b>3: No Benefit</b>	<b>B-R</b>	14. In patients with QRS duration $< 120$ ms, CRT is not recommended. <sup>36-41</sup>
<b>3: No Benefit</b>	<b>B-NR</b>	15. For patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration $< 150$ ms, CRT is not recommended. <sup>16-21,28-33</sup>
<b>3: No Benefit</b>	<b>C-LD</b>	16. For patients whose comorbidities or frailty limit survival with good functional capacity to $< 1$ year, ICD and cardiac resynchronization therapy with defibrillation (CRT-D) are not indicated. <sup>1-9,16-21</sup>

## Synopsis

RCTs have informed the decisions regarding cardiac implantable devices (ICDs and CRTs) over the past 20 years. In fact, the seminal RCTs for ICDs and CRTs are unlikely to be repeated. Subgroup analyses of these trials have also informed decisions, but these were not the primary endpoints of these studies and thus should be interpreted with caution. GDMT is optimized before ICD and CRT implantation to assess whether the LVEF improves. Figures 8 and 9 summarize device and interventional therapy recommendations.

## Recommendation-Specific Supportive Text

- ICDs were first assessed in patients who had been resuscitated from a cardiac arrest. In AVID (Antiarrhythmics versus Implantable Defibrillators trial), CASH (Cardiac Arrest Study Hamburg), and CIDS (Canadian Implantable Defibrillator StudyS), benefit was observed in those who were randomized to ICDs.<sup>1-3</sup> Extension of benefit was then shown in other patient populations that were at perceived risk of SCD. In the first MADIT (Multicenter Automated Defibrillator Implantation Trial) trial, patients with previous MI, LVEF  $\leq 35\%$  with nonsustained VT had a mortality benefit with ICD.<sup>4</sup> Similar populations in MUSTT (Multicenter UnSustained Tachycardia Trial) also showed benefit.<sup>5</sup> In MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II), patients with no arrhythmia qualifier but with previous MIs and LVEF  $\leq 30\%$  derived benefit from ICD.<sup>6</sup> The DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) study included only non-ischemic patients with LVEF  $\leq 35\%$  and frequent premature ventricular contractions (PVCs) or non-sustained ventricular tachycardia (VT).<sup>7</sup> There was a trend to mortality benefit, but it ultimately did not achieve significance. In SCD-HEFT (Sudden Cardiac Death in Heart Failure Trial), patients with ischemic and nonischemic cardiomyopathy, LVEF  $\leq 35\%$ , and HF class II to III showed benefit with an ICD compared with either amiodarone or placebo.<sup>8</sup> More recently, the DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial enrolled patients with nonischemic cardiomyopathy and LVEF  $\leq 35\%$  to ICD or standard care.<sup>9</sup> There was no reduction in the primary endpoint of total mortality, but there was a reduction in SCD risk. In the DANISH trial, 58% of patients in each limb received CRT, possibly mitigating the benefit of an ICD.
- Economic outcomes of ICD implantation for primary prevention of SCD were assessed in 3 RCTs (MADIT-I,<sup>13</sup> MADIT-II,<sup>15</sup> and SCD-HeFT,<sup>12</sup> 1 observational study,<sup>10</sup> and 3 simulation models,<sup>11,14,42</sup> all of which had generally consistent results. All studies reported increased survival and life expectancy and higher lifetime costs of medical care with an ICD than without an ICD. The incremental cost-effectiveness ratios were generally  $< \$60\,000$  per year of life added by an ICD, which provides high value according to the benchmarks adopted for the current guideline. The value provided by an ICD was consistently high when life expectancy was projected to increase by  $> 1.4$  years.<sup>14</sup> In contrast, when survival was not increased by ICD implantation, as in the coronary artery bypass graft (CABG) Patch trial,<sup>43</sup> the ICD did not provide value, because



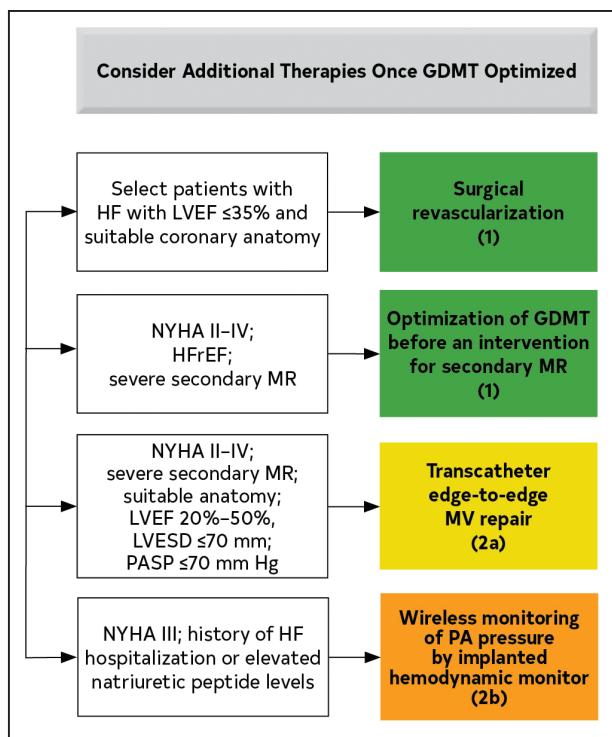
**Figure 8. Algorithm for CRT Indications in Patients With Cardiomyopathy or HFrEF.**

Colors correspond to COR in Table 2. Recommendations for cardiac resynchronization therapy (CRT) are displayed. AF indicates atrial fibrillation; Amb, ambulatory; CM, cardiomyopathy; GDMT, guideline-directed medical therapy; HB, heart block; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NSR, normal sinus rhythm; NYHA, New York Heart Association; and RV, right ventricular.

the higher costs were unaccompanied by a gain in life expectancy.<sup>14</sup>

3. The MADIT-II trial randomized patients with previous MI and LVEF <30%, without any limitation of HF class, to ICDs or not.<sup>6</sup> Thirty-seven percent of the patients were in class I congestive heart failure (CHF). Mortality was reduced with an ICD.
4. Most of the relevant data for the guidelines of CRT in HF come from seminal trials published from 2002 to 2010. The first of these was the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial, which took patients with LVEF ≤35%, moderate to severe HF, and QRS duration ≥130 ms.<sup>16</sup> There was a benefit in the 6-minute walk test, QOL, functional HF classification, and LVEF. The COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial, which enrolled NYHA class III to IV patients with QRS ≥120 ms, included 3 arms: GDMT, CRT-D, and CRT pacemaker (CRT-P).<sup>17</sup> The primary endpoint of death or hospitalization was decreased

with CRT-P and CRT-D. The CARE-HF (Cardiac Resynchronization Heart Failure) trial included a similar group with NYHA class III to IV, LVEF ≤35%, QRS >120 ms, and showed a significant reduction in primary and endpoint of death or hospitalization.<sup>18</sup> In the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial, patients with NYHA class I to II and LVEF ≤40% were randomized to CRT-D on for 1 year and CRT-D off for 1 year or vice versa.<sup>19</sup> A HF composite endpoint was less common when CRT was activated. MADIT-CRT enrolled NYHA class I and II HF with LVEF ≤30% and QRS ≥130 ms and compared CRT-D with ICD.<sup>20</sup> The primary endpoint of death or HF was reduced by CRT-D. The RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure) trial randomized patients with NYHA class II to III HF, LVEF ≤30%, QRS >120 ms, or paced QRS ≥200 ms and compared CRT-D with ICD.<sup>21</sup> Again, there was a reduction in the primary endpoint of death or HF hospitalization.

**Figure 9. Additional Device Therapies.**

Colors correspond to COR in Table 2. Recommendations for additional nonpharmaceutical interventions that may be considered for patients with HF are shown. GDMT indicates guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; MV, mitral valve; MR, mitral regurgitation; NP, natriuretic peptide; NSR, normal sinus rhythm; NYHA, New York Heart Association; and PASP, pulmonary artery systolic pressure.

5. The economic value of CRT has been evaluated by 3 RCTs (COMPANION,<sup>22</sup> MADIT-CRT,<sup>26</sup> and REVERSE<sup>23</sup>), 2 model-based analyses,<sup>25,27</sup> and 1 observational study.<sup>24</sup> These analyses consistently found CRT increased survival and QOL in addition to increasing health care costs. However, the economic value of CRT likely varies as a result of the shown variation in treatment effect.<sup>26</sup> Among populations with larger expected mortality reduction and improvement in QOL, such as patients with a LBBB with QRS duration >150 ms, the cost per QALY is <\$60 000.<sup>22,26,27</sup> Among other populations expected to have smaller treatment benefit, the economic value is more uncertain. However, a model-based analysis of patients with NYHA class I to II found the incremental cost-effectiveness ratio remained <\$150 000 per QALY with even small reductions in all-cause mortality.<sup>27</sup> Therefore, CRT likely provides at least intermediate value for patients with other guideline-indicated recommendations in which CRT is expected to reduce mortality.
6. Subgroup analysis of the previously mentioned trials has informed us of the predictors of benefit,

including longer QRS duration, and LBBB versus non-LBBB.<sup>28</sup> The most benefit was gained with wider QRS durations and with LBBB. This was true in COMPANION, CARE-HF, MADIT-CRT, REVERSE, and RAFT.<sup>17,29-32</sup> A QRS duration >150 ms was also a predictor of response, and in those with non-LBBB, a prolonged PR predicted benefit in MADIT-CRT but not in REVERSE.<sup>33</sup>

7. Extension of benefit to those with LVEF between 35% and 50% has been seen. In the BLOCK-HF (Biventricular versus Right Ventricular Pacing in Heart Failure) trial, patients with NYHA class I to III HF, LVEF ≤50%, and atrioventricular block randomized to RV pacing or CRT, there was benefit to CRT in reduction in the primary outcome of death, urgent HF visit, or 15% increase in LV end systolic volume.<sup>34</sup>
8. In the previously mentioned CRT trials, there was some benefit for those with LBBB and QRS durations between 120 and 149, but not as much benefit as those with LBBB ≥150 ms.<sup>17,28-32</sup>
9. Several trials have included patients with AF. In the MUSTIC AF (Multisite Stimulation in Cardiomyopathies),<sup>44</sup> RAFT,<sup>45</sup> and the SPARE (Spanish Atrial Fibrillation and Resynchronization)<sup>46</sup> trials, there were benefits in patients with AF, while in COMPANION,<sup>47</sup> AF attenuated the benefit of CRT. In the PAVE (Post AV Nodal Ablation Evaluation) study, patients with NYHA class II to III, mean LVEF of 46%, and AF undergoing atrioventricular node ablation, CRT improved the 6-minute walk test and LVEF compared with those who were RV paced.<sup>35</sup>
10. In patients in whom there is an expected high burden of ventricular pacing, especially if >40%, CRT may be used to reduce mortality, reduce hospitalizations, and improve symptoms and QOL.<sup>35,48</sup>
11. Identification of specific arrhythmogenic genetic variants such as *LMNA/C*, desmosomal proteins, phospholamban, and Filamin-C carry implications for implantation of ICDs for primary prevention of sudden death even in patients who have LVEF >35%, or <3 months of GDMT. Most patients with *LMNA/C* cardiomyopathy will progress to cardiac transplantation, sometimes precipitated by refractory arrhythmias more than by pump failure.<sup>36-38,49</sup>
12. Subgroup analysis of the CRT RCTs has shown that patients with LVEFs ≤35%, non-LBBB, and QRS duration of 120 to 149 ms and NYHA class III to ambulatory class IV did not derive as much benefit as those with LBBB ≥120 ms.<sup>17,28-32</sup>
13. The MADIT-CRT trial included NYHA class I (and class II) patients with ischemic heart disease, LVEF ≤30%, and QRS >130 ms.<sup>39</sup> Patients with non-ischemic cardiomyopathy were enrolled if they had NYHA class II HF.

14. Extension of benefit to patients with narrow QRS has been attempted but has generally failed. In the RETHINOQ (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) trial, patients with QRS duration <130 ms were randomized to CRT or not.<sup>40</sup> There was no benefit from CRT, but subgroup analysis showed there was a benefit with QRS durations between 120 and 130 ms. In the ECHO-CRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial, patients with NYHA class III to IV HF, LVEF ≤35% and a QRS duration ≤130 ms, and mechanical dysynchrony on echocardiography underwent randomization to CRT.<sup>50</sup> There was no benefit to CRT in this trial. And in the LESSER-EARTH (Evaluation of Resynchronization Therapy for Heart Failure) trial, patients with severe LV dysfunction and QRS <120 ms derived no benefit from CRT.<sup>51</sup> The NARROW-CRT (Narrow QRS Ischemic Patients Treated With Cardiac Resynchronization Therapy) was the only trial that showed a benefit in a clinical composite score in patients with an indication for an ICD and QRS <120 ms.<sup>52</sup>
15. Subgroup analysis of the CRT trials has shown no benefit for those with LVEF ≤35%, non-LBBB 120 to 149, and NYHA class I-II HF.<sup>17,28-32</sup>
16. The 1-year survival is a standard inclusion for ICD and CRT trials.<sup>1-9,16-21</sup>

#### 7.4.2. Other Implantable Electrical Interventions

Autonomic nervous system modulation is intriguing as a treatment for HFrEF because of the heightened sympathetic response and decreased parasympathetic response in HF.<sup>1</sup> Trials of device stimulation of the vagus nerve, spinal cord, and baroreceptors have had mixed responses.<sup>2</sup> An implantable device that electrically stimulates the baroreceptors of the carotid artery has been approved by the FDA for the improvement of symptoms in patients with advanced HF who are unsuited for treatment with other HF devices including CRT. In a prospective, multicenter, RCT with a total of 408 patients with current or recent NYHA class III HF, LVEF ≤35%, baroreceptor stimulation was associated with improvements in QOL, exercise capacity, and NT-proBNP levels.<sup>3</sup> To date, there are no mortality or hospitalization rates results available with this device. Although early trials of vagus nerve stimulation were positive, the largest and latest trial did not show a reduction in mortality and HF hospitalizations.<sup>4</sup> Multisite LV pacing studies initially were promising.<sup>5,6</sup> However, more recent data have not confirmed benefit, and the larger phase 2 trial was terminated early for low probability of benefit.<sup>7</sup> His bundle and left bundle pacing are attractive because they use the intrinsic conduction system. In observational data, there does appear to be a benefit over RV pacing<sup>8</sup>; however, comparisons to CRT are limited.<sup>9,10</sup> Cardiac contractility modulation

(CCM), a device-based therapy that involves applying relatively high-voltage, long-duration electric signals to the RV septal wall during the absolute myocardial refractory period, has been associated with augmentation of LV contractile performance. CCM is FDA-approved for patients with NYHA class III with LVEF of 25% to 45% who are not candidates for CRT. Four RCTs have shown benefits in exercise capacity and QOL but, as of yet, no benefits in death or hospitalizations.<sup>11-14</sup> Most patients in these trials were class III CHF.<sup>3</sup>

#### 7.4.3. Revascularization for CAD

##### Recommendation for Revascularization for CAD

Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
1	B-R	1. In selected patients with HF, reduced EF (EF ≤35%), and suitable coronary anatomy, surgical revascularization plus GDMT is beneficial to improve symptoms, cardiovascular hospitalizations, and long-term all-cause mortality. <sup>1-8</sup>

#### Synopsis

CAD is commonly associated with HF, necessitating revascularization in selected patients with angina or HF symptoms. Data from the STICH Trial showed that, compared with optimal medical management alone, CABG surgery plus GDMT did not reduce the primary endpoint of all-cause mortality at a median of 56 months; however, at 10 years' follow-up, CABG+GDMT resulted in significant reductions in all-cause mortality, cardiovascular mortality, and death from any cause or cardiovascular hospitalization in patients with LVEF ≤35% and ischemic cardiomyopathy.<sup>7,8</sup> Furthermore, a retrospective analysis showed significant reductions in first and recurrent all-cause, cardiovascular, and HF hospitalizations at 10 years in patients receiving CABG+ optimal medical therapy compared with optimal medical therapy alone.<sup>2</sup> Similar benefits from percutaneous coronary intervention revascularization, in this cohort, have not yet been shown in an RCT, although the REVIVED-BCIS2 (Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure) trial, which compares percutaneous coronary intervention with medical therapy in a similar population, is ongoing.<sup>9</sup> Recent data continue to show a benefit of CABG over percutaneous coronary intervention in patients with diabetes, CAD, and LV dysfunction and in patients with left main CAD and moderate or severe LV dysfunction.<sup>4,6,10</sup> Figure 9 summarizes revascularization and additional device therapy recommendations.

#### Recommendation-Specific Supportive Text

1. CABG has been shown to improve outcomes in patients with left main or left main equivalent

disease and HF.<sup>1,4,10–14</sup> Long-term follow-up shows a reduction in all-cause, cardiovascular, and HF hospitalizations and in all-cause and cardiovascular mortality in patients with LV dysfunction who receive CABG and GDMT compared with GDMT alone.<sup>27</sup> The long-term survival benefit is greater in those with more advanced ischemic cardiomyopathy (lower EF or 3-vessel disease) and diminishes with increasing age.<sup>5,7</sup> CABG also improves QOL compared with GDMT alone.<sup>3</sup> An RCT of CABG combined with surgical ventricular remodeling compared with CABG alone did not show a reduction in death or hospitalization, or improvement in symptoms with surgical ventricular remodeling.<sup>15</sup> Surgical ventricular remodeling performed at the time of CABG may be useful in patients with intractable HF, large thrombus, or persistent arrhythmias resulting from well-defined aneurysm or scar, if other therapies are ineffective or contraindicated.<sup>15,16</sup>

## 7.5. Valvular Heart Disease

**Recommendations for Valvular Heart Disease**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-R	1. In patients with HF, VHD should be managed in a multidisciplinary manner in accordance with clinical practice guidelines for VHD to prevent worsening of HF and adverse clinical outcomes. <sup>1–11</sup>
1	C-LD	2. In patients with chronic severe secondary MR and HFrEF, optimization of GDMT is recommended before any intervention for secondary MR related to LV dysfunction. <sup>3–5,12–14</sup>

### Synopsis

GDMT applies to all patients with HFrEF, irrespective of the presence of VHD. Significant valve disease warrants evaluation by a multidisciplinary team with expertise in VHD, and management should proceed in accordance with the VHD guidelines.<sup>15</sup>

### Mitral Regurgitation

Optimization of GDMT can improve secondary MR associated with LV dysfunction and obviate the need for intervention.<sup>14,16,17</sup> Therefore, optimizing GDMT and reassessing MR before MV interventions are important. Patients with persistent severe secondary MR despite GDMT may benefit from either surgical or transcatheter repair, depending on clinical scenario. Thus, patient-centric conversation with a multidisciplinary cardiovascular team that includes a cardiologist with expertise in HF is essential when considering MV intervention.<sup>15</sup> Two RCTs of transcatheter mitral valve edge-to-edge repair (TEER) in patients with HFrEF and severe secondary MR have been performed. The COAPT trial showed significant reduction in HF and all-cause mor-

tality in patients treated with TEER and GDMT compared with GDMT alone, while MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) showed no benefit of TEER over GDMT in reducing death or hospitalization.<sup>6</sup> Specifically, transcatheter edge-to-edge MV repair has been shown to be beneficial in patients with persistent symptoms despite GDMT, appropriate anatomy on transesophageal echocardiography and with LVEF between 20% and 50%, LVESD  $\leq$ 70 mm, and pulmonary artery systolic pressure  $\leq$ 70 mm Hg<sup>6</sup> (Figure 10). Optimal management of secondary MR may depend on the degree of MR relative to LV remodeling.<sup>4,5,14,18–22</sup> Disproportionate MR (MR out of proportion to LV remodeling) may respond better to procedural interventions that reduce MR, such as CRT, TEER, and MV surgery. Proportionate MR may respond to measures that reverse LV remodeling and reduce LV volumes, such as GDMT and CRT.

### Aortic Stenosis

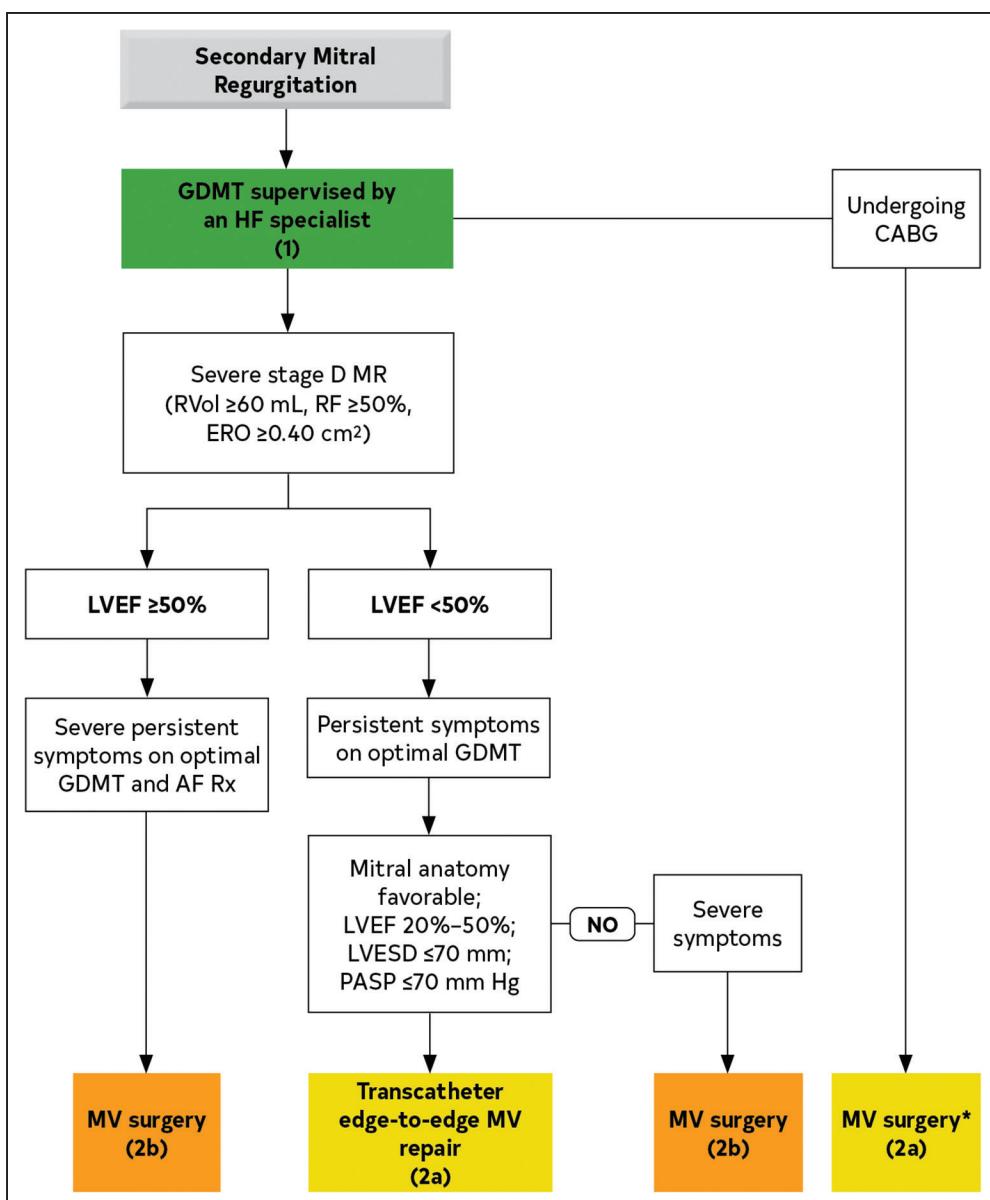
In patients with symptomatic aortic stenosis, transcatheter and surgical aortic valve repair can improve survival, symptoms, and LV function.<sup>15</sup> However, the choice of transcatheter aortic valve implantation versus surgical aortic valve replacement is based on shared decision-making, indications, and assessment of the risk-benefit profile.<sup>23,24</sup> The benefit of GDMT in nonsevere aortic stenosis and HFrEF is being evaluated in the TAVR UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure) trial.<sup>25</sup> GDMT is usually continued in conjunction with clinical surveillance and imaging in patients with nonsevere aortic stenosis and reduced EF.

### Tricuspid Regurgitation

The severity of secondary tricuspid regurgitation may be dynamic, depending on RV function and pulmonary hypertension, and management entails focusing on underlying causes, such as pulmonary hypertension, RV failure, and HFrEF. Referral to the multidisciplinary team for consideration of intervention might be helpful in patients with refractory tricuspid regurgitation.

### Recommendation-Specific Supportive Text

1. VHD is a significant cause of HF. In patients with HF, management of VHD should be performed by a multidisciplinary team with expertise in HF and VHD, in accordance with the VHD guidelines.<sup>15</sup> Cardiologists with expertise in the management of HF are integral to the multidisciplinary team and to guiding the optimization of GDMT in patients with HF and coexisting valve disease. Severe aortic stenosis, aortic regurgitation, MR, and tricuspid regurgitation are associated with adverse outcomes and require timely assessment, optimization of medical

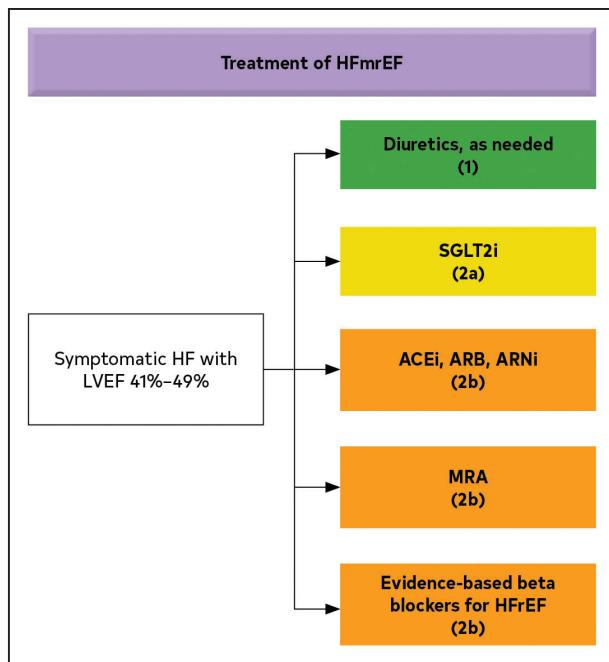
**Figure 10. Treatment Approach in Secondary Mitral Regurgitation.**

Colors correspond to Table 2. AF indicates atrial fibrillation; CABG, coronary artery bypass graft; ERO, effective regurgitant orifice; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, medication. \*Chordal-sparing MV replacement may be reasonable to choose over downsized annuloplasty repair. Adapted from Otto CM, et al.<sup>15</sup> Copyright 2021 American College of Cardiology Foundation and American Heart Association, Inc.

therapies, and consideration of surgical or transcatheter interventions accordingly to prevent worsening of HF and other adverse outcomes.<sup>1-10,12-20,22-35</sup>

2. GDMT, including RAAS inhibition, beta blockers, and biventricular pacing, improves MR and LV dimensions in patients with HFrEF and secondary MR, particularly MR that is proportionate to LV dilatation.<sup>1-5,12,13,17</sup> In a small RCT, sacubitril-valsartan resulted in a significant reduction in effective regurgitant area and in regurgitant volume when compared with valsartan. The COAPT trial showed a mortality benefit with TEER in patients with

severe secondary MR, LVEF between 20% and 50%, LV end-systolic diameter  $\leq$ 70 mm, PA systolic pressure  $\leq$ 70 mm Hg, and persistent symptoms (NYHA class II to IV) while on optimal GDMT,<sup>28</sup> and these criteria apply when considering TEER. A cardiologist with expertise in the management of HF is integral to shared decision-making for valve intervention and should guide optimization of GDMT to ensure that medical options for HF and secondary MR have been effectively applied for an appropriate time period and exhausted before considering intervention.



**Figure 11. Recommendations for Patients With Mildly Reduced LVEF (41%–49%).**

Colors correspond to COR in Table 2. Medication recommendations for HFmrEF are displayed. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

## 7.6. Heart Failure With Mildly Reduced EF (HFmrEF) and Improved EF (HFimpHF)

### 7.6.1. HF With Mildly Reduced Ejection Fraction

**Recommendations for HF With Mildly Reduced Ejection Fraction**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
<b>2a</b>	<b>B-R</b>	1. In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. <sup>1</sup>
<b>2b</b>	<b>B-NR</b>	2. Among patients with current or previous symptomatic HFmrEF (LVEF, 41%–49%), use of evidence-based beta blockers for HFrEF, ARNi, ACEi, or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. <sup>2–9</sup>

### Synopsis

There are no prospective RCTs for patients specifically with HFmrEF (LVEF, 41%–49%). All data for HFmrEF are from post hoc or subsets of analyses from previous HF trials with patients now classified as HFmrEF. LVEF is a spectrum, and among patients with LVEF 41% to 49%, patients with LVEF on the lower end of this spectrum ap-

pear to respond to medical therapies similarly to patients with HFrEF. Thus, it may be reasonable to treat these patients with GDMT used for treatment of HFrEF. Patients with HFmrEF should have repeat evaluation of LVEF to determine the trajectory of their disease process. Future prospective studies are needed to further clarify treatment recommendations for patients with HFmrEF. Figure 11 summarizes COR 1, 2a, and 2b for HFmrEF.

### Recommendation-Specific Supportive Text

1. EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) showed a significant benefit of the SGLT2i, empagliflozin, in patients with symptomatic HF, with LVEF >40% and elevated natriuretic peptides.<sup>1</sup> The 21% reduction in the primary composite endpoint of time to HF hospitalization or cardiovascular death was driven mostly by a significant 29% reduction in time to HF hospitalization (nonsignificant lower cardiovascular death [HR, 0.91; 95% CI, 0.76–1.0]), with no benefit on all-cause mortality. Empagliflozin also resulted in a significant reduction in total HF hospitalizations, decrease in the slope of the eGFR decline, and a modest improvement in QOL at 52 weeks. Of note, the benefit was similar irrespective of the presence or absence of diabetes at baseline. In a subgroup of 1983 patients with LVEF 41% to 49% in EMPEROR-Preserved, empagliflozin, a SGLT2i, reduced the risk of the primary composite endpoint of cardiovascular death or hospitalization for HF.<sup>1</sup> Although the benefit in the primary endpoint did not have a significant interaction by LVEF subgroups (41%–49%, 50%–<60%, and >60%),<sup>1</sup> in a subgroup analysis by EF, there was a signal for lower benefit on the primary composite endpoint, first and recurrent hospitalizations for HF at higher LVEFs >62.5%.<sup>10</sup>
2. Post hoc and subsets of analyses of HFrEF trials that included HFmrEF (LVEF 41%–49%) have suggested benefit from use of GDMT for HFrEF (ie, beta blockers, ARNi, ACEi or ARB, and spironolactone).<sup>2,3,5–8</sup> The BBmeta-HF (Beta-blockers in Heart Failure Collaborative Group) performed a meta-analysis of 11 HF trials; in a subgroup of 575 patients with LVEF 40% to 49% in sinus rhythm, beta blockers reduced the primary outcome of all-cause and cardiovascular mortality.<sup>2</sup> A subgroup analysis of the PARAGON-HF (Prospective Comparison of ARNi with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial for patients with LVEF 45% to 57% (lower range of EFs in the trial) suggested benefit of sacubitril-valsartan versus valsartan alone (rate ratio, 0.78; 95% CI, 0.64–0.95).<sup>3</sup> In a subgroup of 1322 patients with LVEF 41% to 49% in a post hoc analysis of pooled data from the

CHARM (Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity) trials, candesartan reduced risk of cardiovascular death and HF hospitalization, the risk of first HF hospitalization, and the risk of recurrent HF hospitalization.<sup>5</sup> In a subgroup of 520 patients with LVEF 44% to 49% in a post hoc analysis of TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), spironolactone reduced the risk of the primary composite endpoint of cardiovascular death, HF hospitalization, or resuscitated sudden death, which was mostly caused by a reduction in cardiovascular mortality with spironolactone and among patients enrolled in North and South America.<sup>6</sup> Spironolactone is preferred among HFmrEF patients with poorly controlled hypertension given previous evidence supporting its use for blood pressure management.<sup>1</sup> Continuation of GDMT for patients with improved HFrEF and HFmrEF is important to reduce risk of recrudescent HF.<sup>4</sup> Meta-analyses report diverse findings with neurohormonal antagonism in patients with HFmrEF, specifying benefit in certain subgroups, underlining the heterogeneity of this phenotype.<sup>29</sup> Patients with HFmrEF should have repeat evaluation of LVEF to determine the trajectory of their disease process and should undergo testing as clinically indicated to diagnose conditions warranting disease-specific therapy (eg, CAD, sarcoidosis, amyloidosis).

### 7.6.2. HF With Improved Ejection Fraction

Recommendation for HF With Improved Ejection Fraction		
Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	LOE	Recommendation
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. <sup>1</sup>

### Synopsis

Although GDMT can result in improvement in symptoms, functional capacity, LVEF, and reverse remodeling in patients with HFrEF,<sup>2</sup> in most patients, LV function and structural abnormalities do not fully normalize, and symptoms and biomarker abnormalities may persist or reoccur. Many patients deemed to have recovered from HF with resolution of symptoms and improvement of LVEF and natriuretic peptide levels will relapse after withdrawal of GDMT.<sup>1</sup> Resolution of symptoms and improvement in cardiac function and biomarkers after treatment does not reflect full and sustained recovery but, rather, remission, which requires treatment to be maintained.<sup>3</sup> Stage C HF patients are defined as patients with structural heart disease with previous or current symptoms of HF. In those patients who do not improve (ie, patients who remain

symptomatic or with LV dysfunction), GDMT should not only be continued but also optimized.

## Recommendation-Specific Supportive Text

1. In an open-label RCT,<sup>1</sup> phased withdrawal of HF medications in patients with previous DCM—who were now asymptomatic, whose LVEF had improved from <40% to ≥50%, whose left ventricular end-diastolic volume (LVEDV) had normalized, and who had an NT-proBNP concentration <250 ng/L—resulted in relapse of cardiomyopathy and HF in 40% of the patients within 6 months. Relapse was defined by at least 1 of these: 1) a reduction in LVEF by >10% and <50%; 2) an increase in LVEDV by >10% and to higher than the normal range; 3) a 2-fold rise in NT-proBNP concentration and to >400 ng/L; or 4) clinical evidence of HF. Treatment was withdrawn successfully in only 50% of patients.<sup>1</sup> Secondary analyses showed worsening Kansas City Cardiomyopathy Questionnaire scores, a substantial reduction in LVEF, and nonsignificant increases in NT-proBNP and LV volumes with withdrawal of HF medications.

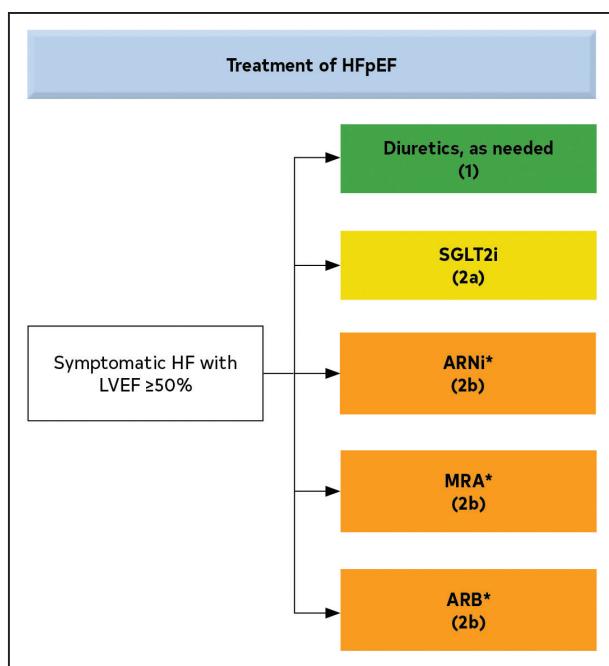
## 7.7. Preserved EF (HFpEF)

### 7.7.1. HF With Preserved Ejection Fraction

**Recommendations for HF With Preserved Ejection Fraction\***  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. <sup>1–3</sup>
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. <sup>4</sup>
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. <sup>5–7</sup>
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. <sup>8,9</sup>
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. <sup>10,11</sup>
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective. <sup>12,13</sup>

\*See Section 7.2, “Diuretics and Decongestion Strategies in Patients with HF” and Section 10.2, “Management of Atrial Fibrillation (AF) in HF” for recommendations for use of diuretics and management of AF in HF.



**Figure 12. Recommendations for Patients With Preserved LVEF ( $\geq 50\%$ ).**

Colors correspond to COR in Table 2. Medication recommendations for HFrEF are displayed. ARB indicates angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

\*Greater benefit in patients with LVEF closer to 50%.

### Synopsis

HFrEF (LVEF  $\geq 50\%$ ) is highly prevalent, accounting for up to 50% of all patients with HF, and is associated with significant morbidity and mortality.<sup>14</sup> HFrEF is a heterogeneous disorder, contributed to by comorbidities that include hypertension, diabetes, obesity, CAD, CKD, and specific causes such as cardiac amyloidosis.<sup>15–17</sup> Clinical trials have used variable definitions of HFrEF (eg, LVEF  $\geq 40\%$ , 45%, or 50%, and the varying need for accompanying evidence of structural heart disease or elevated levels of natriuretic peptides).<sup>18</sup> Until recently, clinical trials had been generally disappointing, with no benefit on mortality and marginal benefits on HF hospitalizations.<sup>5,8,11,19,20</sup> Currently, recommended management is that used for HF in general with use of diuretics to reduce congestion and improve symptoms (see Section 7.1.1 for recommendations for nonpharmacological management and Section 7.2 for recommendations for diuretics), identification and treatment of specific causes such as amyloidosis, and management of contributing comorbidities such as hypertension, CAD, and AF (see Section 10.2 for recommendations on management of AF). Figure 12 summarizes COR 1, 2a, and 2b for HFrEF.

### Recommendation-Specific Supportive Text

1. The role of blood pressure control is well established for the prevention of HF, as well as for reduction of other cardiovascular events and HF mortality in patients without prevalent baseline HF.<sup>1–3,21–24</sup> The SPRINT (Systolic Blood Pressure Intervention) trial and meta-analyses established that more intensive blood pressure control in patients with high cardiovascular risk significantly reduces HF and other cardiovascular outcomes.<sup>2,3,25</sup> In recent clinical practice guidelines for hypertension, blood pressure targets in HFrEF are extrapolated from those for treatment of patients with hypertension in general.<sup>26</sup> However, the optimal blood pressure goal and antihypertensive regimens are not known for patients with HFrEF. RAAS antagonists including ACEi, ARB, MRA, and possibly ARNi, could be first-line agents given experience with their use in HFrEF trials.<sup>8,10,16,20,27,28</sup> Beta blockers may be used to treat hypertension in patients with a history of MI,<sup>27</sup> symptomatic CAD, or AF with rapid ventricular response. These effects need to be balanced with the potential contribution of chronotropic incompetence to exercise intolerance in some patients.<sup>29</sup>
2. EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) showed a significant benefit of the SGLT2i, empagliflozin, in symptomatic patients with HF with LVEF  $>40\%$  and elevated natriuretic peptides.<sup>30</sup> The 21% reduction in the primary composite endpoint of time to HF hospitalization or cardiovascular death was driven mostly by a significant 29% reduction in time to HF hospitalization (nonsignificant lower cardiovascular death [HR, 0.91; 95% CI, 0.76–1.0]), with no benefit on all-cause mortality. Empagliflozin also resulted in a significant reduction in total HF hospitalizations, decrease in the slope of the eGFR decline, and a modest improvement in QOL at 52 weeks. Of note, the benefit was similar irrespective of the presence or absence of diabetes at baseline. Although the benefit in the primary endpoint did not have a significant interaction by LVEF subgroups (<50%, 50%–<60%, and >60%),<sup>30</sup> in a subgroup analysis by EF, there was a signal for lower benefit on the primary composite endpoint, first and recurrent HF hospitalizations at higher LVEFs  $>62.5\%.$ <sup>31</sup>
3. Large, randomized clinical trial data are unavailable to specifically guide therapy in patients with HFrEF and AF. Currently, the comprehensive care of AF can be extrapolated from the clinical practice guidelines for AF, with individualization of strategies for rate or rhythm control in patients with HFrEF (see also Section 10.2, “Management of Atrial

Fibrillation (AF) in HF<sup>31</sup> for HF specific recommendations for AF). Although beta blockers and nondihydropyridine calcium channel blockers are often considered as first-line agents for heart rate control in patients with HFpEF, a recent smaller open-label trial, RATE-AF in elderly patients with AF and symptoms of HF (most with preserved LVEF), compared the use of the beta blocker, bisoprolol, to digoxin.<sup>32</sup> At 6 months, the primary endpoint of QOL was similar between the 2 groups. However, several secondary QOL endpoints, functional capacity, and reduction in NT-proBNP favored digoxin at 12 months. There was a similar heart rate reduction in both groups. Of note, more adverse events such as higher rates of dizziness, lethargy, and hypotension occurred with beta blockers than digoxin. The comprehensive care of AF is beyond the scope of these guidelines. AF-specific care recommendations can be found in separate ACC/AHA clinical practice guidelines.<sup>33,34</sup>

4. MRAs improve diastolic function in patients with HFpEF.<sup>35</sup> The TOPCAT trial investigated the effects of spironolactone in patients with HFpEF. The small reduction (HR, 0.89) in the composite of death, aborted cardiac death, and HF hospitalization was not statistically significant, although HF hospitalization was reduced (HR, 0.83); adverse effects of hyperkalemia and increasing creatinine levels were more common in the treatment group.<sup>5</sup> A post hoc analysis<sup>6</sup> showed efficacy in the Americas (HR 0.83) but not in Russia-Georgia (HR 1.10). A sample of the Russia-Georgia population in the active treatment arm had nondetectable levels of a spironolactone metabolite. Post hoc analyses have limitations, but they suggest a possibility of benefit in appropriately selected patients with symptomatic HFpEF (LVEF  $\geq$ 45%, elevated BNP level or HF admission within 1 year, eGFR  $>30$  mL/min/1.73 m<sup>2</sup>, creatinine  $<2.5$  mg/dL, and potassium  $<5.0$  mEq/L). Furthermore, another post hoc analysis suggested that the potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum.<sup>7</sup> Careful monitoring of potassium, renal function, and diuretic dosing at initiation and follow-up are key to minimizing the risk of hyperkalemia and worsening renal function.
5. Although RAAS inhibition strategies have been successful in the treatment of HFrEF, and RAAS activation is suggested in HFpEF,<sup>36,37</sup> clinical trials with RAAS inhibition have not shown much benefit in patients HFpEF. In the CHARM-Preserved (Candesartan in patients with chronic HF and preserved left-ventricular ejection fraction) trial, patients with LVEF  $>40\%$  were randomized to an ARB, candesartan, or to placebo.<sup>38</sup> The primary endpoint (cardiovascular death or

HF hospitalization) was not significantly different between the 2 groups (HR, 0.89; 95% CI, 0.77–1.03,  $P=0.118$ ; covariate-adjusted HR, 0.86;  $P=0.051$ ). Cardiovascular mortality was identical in the 2 groups; HF hospitalizations were lower in the candesartan arm, with borderline statistical significance on the covariate-adjusted analysis only (HR, 0.84; 95% CI, 0.70–1.00;  $P=0.047$ ; unadjusted  $P=0.072$ ). The number of individuals hospitalized for HF (reported by the investigator) was lower in the candesartan group than placebo (230 versus 279;  $P=0.017$ ). A post hoc analysis of the CHARM trials showed that improvement in outcomes with candesartan was greater at the lower end of the LVEF spectrum.<sup>39</sup> In a meta-analysis of 7694 patients with HFpEF in 4 trials evaluating ARB, there was no signal for benefit on cardiovascular mortality (HR, 1.02), all-cause mortality (HR, 1.02), or HF hospitalization (HR, 0.92; 95% CI, 0.83–1.02).<sup>40,41</sup>

6. In the PARAMOUNT-HF (Prospective Comparison of ARNi With ARB on Management of Heart Failure With Preserved Ejection Fraction) trial, a phase II RCT in patients with HFpEF (LVEF  $\geq$ 45%), sacubitril-valsartan resulted in a lower level of NT-proBNP after 12 weeks of treatment compared with the ARB, valsartan.<sup>42</sup> In the PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction) trial, in 4822 patients with HFpEF (LVEF  $\geq$ 45%, HF admission within 9 months or elevated natriuretic peptide levels, and eGFR  $\geq$ 30 mL/min/m<sup>2</sup>), sacubitril-valsartan compared with valsartan did not achieve a significant reduction in the primary composite endpoint of cardiovascular death or total (first and recurrent) HF hospitalizations (rate ratio, 0.87; 95% CI, 0.75–1.01;  $P=0.06$ ).<sup>10</sup> Given the primary outcome was not met, other analyses are exploratory. There was no benefit of sacubitril-valsartan on cardiovascular death (HR, 0.95) or total mortality (HR, 0.97). There was a signal of benefit for the ARNi for HF hospitalizations (rate ratio, 0.85; 95% CI, 0.72–1.00;  $P=0.056$ ). The occurrence of hyperkalemia and the composite outcome of decline in renal function favored sacubitril-valsartan, but it was associated with a higher incidence of hypotension and angioedema. In pre-specified subgroup analyses, a differential effect by LVEF and sex was noted. A benefit of sacubitril-valsartan compared with valsartan was observed in patients with LVEF below the median (45%–57%; rate ratio, 0.78; 95% CI, 0.64–0.95), and in women (rate ratio, 0.73; 95% CI, 0.59–0.90).<sup>10,43,44</sup>
7. Nitrate therapy can reduce pulmonary congestion and improve exercise tolerance in patients

with HFrEF. However, the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) trial<sup>45</sup> randomized 110 patients with EF ≥50% on stable HF therapy, not including nitrates, and with activity limited by dyspnea, fatigue, or chest pain, to either isosorbide mononitrate or placebo and found no beneficial effects on activity levels, QOL, exercise tolerance, or NT-proBNP levels. Although the routine use of nitrates in patients with HFpEF does not appear beneficial, patients with HFpEF and symptomatic CAD may still receive symptomatic relief with nitrates. Phosphodiesterase-5 inhibition augments the nitric oxide system by upregulating cGMP activity. The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial<sup>13</sup> randomized 216 patients with EF ≥50% on stable HF therapy and with reduced exercise tolerance (peak observed VO<sub>2</sub> <60% of predicted) to phosphodiesterase-5 inhibition with sildenafil or placebo. This study did not show improvement in oxygen consumption or exercise tolerance.

## 7.8. Cardiac Amyloidosis

### 7.8.1. Diagnosis of Cardiac Amyloidosis

**Recommendations for Diagnosis of Cardiac Amyloidosis**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	<ol style="list-style-type: none"> <li>Patients for whom there is a clinical suspicion for cardiac amyloidosis*<sup>1–5</sup> should have screening for serum and urine monoclonal light chains with serum and urine immunofixation electrophoresis and serum free light chains.<sup>6</sup></li> </ol>
1	B-NR	<ol style="list-style-type: none"> <li>In patients with high clinical suspicion for cardiac amyloidosis, without evidence of serum or urine monoclonal light chains, bone scintigraphy should be performed to confirm the presence of transthyretin cardiac amyloidosis.<sup>7</sup></li> </ol>
1	B-NR	<ol style="list-style-type: none"> <li>In patients for whom a diagnosis of transthyretin cardiac amyloidosis is made, genetic testing with <i>TTR</i> gene sequencing is recommended to differentiate hereditary variant from wild-type transthyretin cardiac amyloidosis.<sup>8</sup></li> </ol>

\*LV wall thickness ≥14 mm in conjunction with fatigue, dyspnea, or edema, especially in the context of discordance between wall thickness on echocardiogram and QRS voltage on ECG, and in the context of aortic stenosis, HFpEF, carpal tunnel syndrome, spinal stenosis, and autonomic or sensory polyneuropathy.

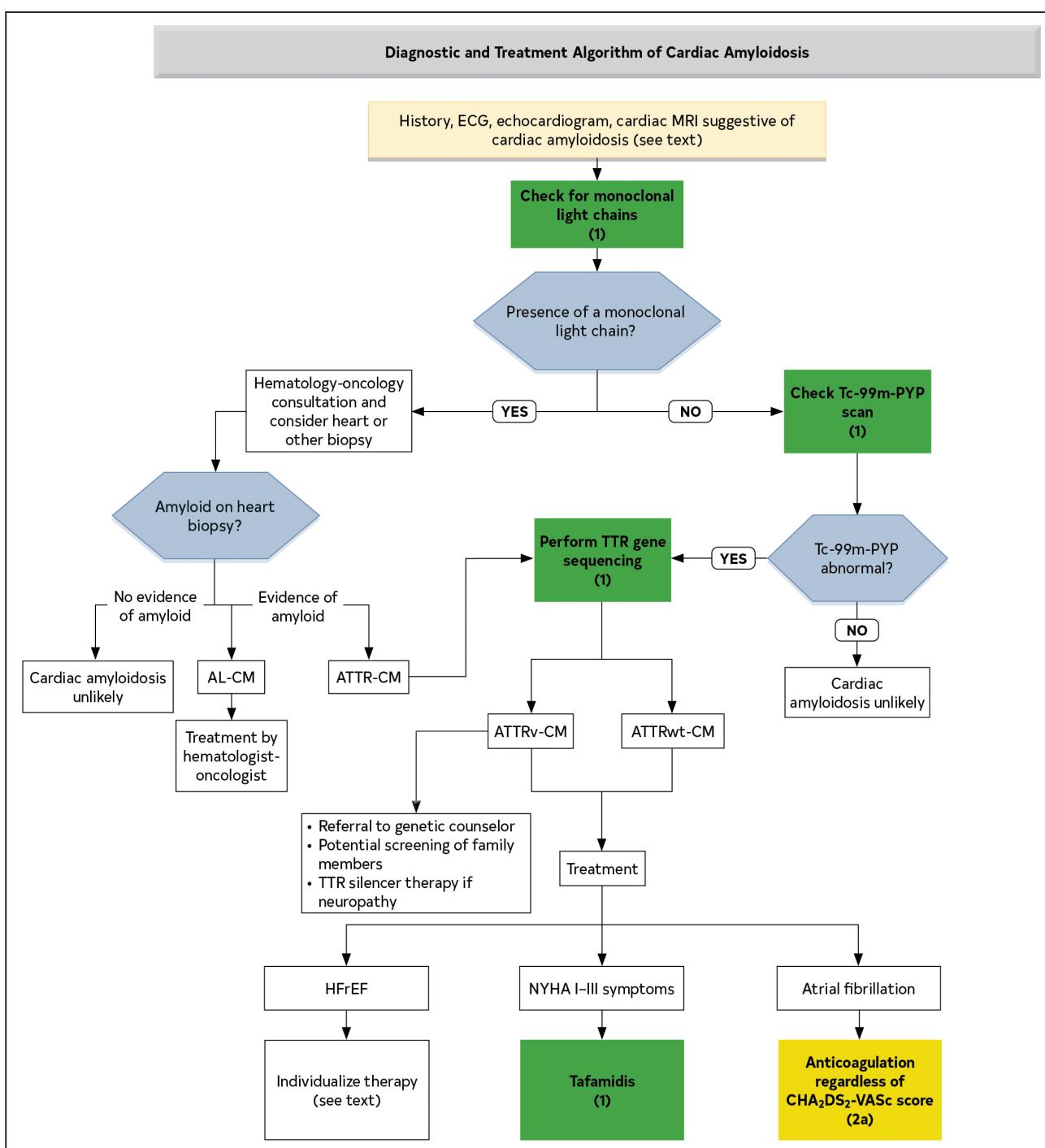
### Synopsis

Cardiac amyloidosis is a restrictive cardiomyopathy with extracellular myocardial protein deposition, most commonly monoclonal immunoglobulin light chains (amyloid

cardiomyopathy [AL-CM]) or transthyretin amyloidosis (ATTR-CM). ATTR can be caused by pathogenic variants in the transthyretin gene *TTR* (variant transthyretin amyloidosis, ATTRv) or wild-type transthyretin (wild-type transthyretin amyloidosis, ATTRwt). A diagnostic approach is outlined in Figure 13.<sup>9</sup>

### Recommendation-Specific Supportive Text

- Diagnosis of ATTR-CM requires a high index of suspicion. LV thickening (wall thickness ≥14 mm) along with fatigue, dyspnea, or edema should trigger consideration of ATTR-CM, especially with discordance between wall thickness on echocardiogram and QRS voltage on ECG,<sup>10</sup> or other findings such as apical sparing of LV longitudinal strain impairment on echocardiography and diffuse late-gadolinium enhancement on cardiac MRI. ATTR-CM is prevalent in severe aortic stenosis,<sup>1</sup> HFpEF,<sup>2</sup> carpal tunnel syndrome,<sup>3</sup> lumbar spinal stenosis,<sup>4</sup> and autonomic or sensory polyneuropathy.<sup>5</sup> Practically, screening for the presence of a monoclonal light chain and technetium pyrophosphate (<sup>99m</sup>Tc-PYP) scan can be ordered at the same time for convenience, but the results of the <sup>99m</sup>Tc-PYP scan are interpreted only on the context of a negative monoclonal light chain screen. <sup>99m</sup>Tc-PYP scans may be positive even in AL amyloidosis<sup>7</sup> and, thus, a bone scintigraphy scan alone, without concomitant testing for light chains, cannot distinguish ATTR-CM from AL-CM. Serum free light chain (FLC) concentration and serum and urine immunofixation electrophoresis (IFE) are assessed to rule out AL-CM. IFE is preferred because serum plasma electrophoresis and urine plasma electrophoresis are less sensitive. Together, measurement of serum IFE, urine IFE, and serum FLC is >99% sensitive for AL amyloidosis.<sup>6,11</sup>
- The use of <sup>99m</sup>Tc bone-avid compounds for bone scintigraphy allows for noninvasive diagnosis of ATTR-CM.<sup>7</sup> <sup>99m</sup>Tc compounds include PYP, 3,3-diphosphono-1,2-propanodicarboxylic acid, and hydromethylene diphosphonate, and PYP is used in the United States. In the absence of a light-chain abnormality, the <sup>99m</sup>Tc-PYP scan is diagnostic of ATTR-CM if there is grade 2/3 cardiac uptake or an H/CL ratio of >1.5. In fact, the presence of grade 2/3 cardiac uptake in the absence of a monoclonal protein in serum or urine has a very high specificity and positive predictive value for ATTR-CM.<sup>7</sup> SPECT is assessed in all positive scans to confirm that uptake represents myocardial retention of the tracer and not blood pool or rib uptake signal.<sup>12</sup>

**Figure 13. Diagnostic and Treatment of Transthyretin Cardiac Amyloidosis Algorithm.**

Colors correspond to COR in Table 2. AF indicates atrial fibrillation; AL-CM, amyloid cardiomyopathy; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; ECG, electrocardiogram; H/CL, heart to contralateral chest; HFrEF, heart failure with reduced ejection fraction; IFE, immunofixation electrophoresis; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PYP, pyrophosphate; Tc, technetium; and TTR, transthyretin.

3. If ATTR-CM is identified, then genetic sequencing of the *TTR* gene will determine if the patient has a pathological variant (ATTRv) or wild-type (ATTRwt) disease.<sup>12</sup> Differentiating ATTRv from ATTRwt is important because confirmation

of ATTRv would trigger genetic counseling and potential screening of family members and therapies, inotersen and patisiran, which are presently approved only for ATTRv with polyneuropathy.<sup>13,14</sup>

## 7.8.2. Treatment of Cardiac Amyloidosis

Recommendations for Treatment of Cardiac Amyloidosis		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-R	<p>1. In select patients with wild-type or variant transthyretin cardiac amyloidosis and NYHA class I to III HF symptoms, transthyretin tetramer stabilizer therapy (tafamidis) is indicated to reduce cardiovascular morbidity and mortality.<sup>1</sup></p>
<b>Value Statement: Low Value (B-NR)</b>		<p>2. At 2020 list prices, tafamidis provides low economic value (&gt;\$180 000 per QALY gained) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis.<sup>2</sup></p>
2a	C-LD	<p>3. In patients with cardiac amyloidosis and AF, anticoagulation is reasonable to reduce the risk of stroke regardless of the CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) score.<sup>3,4</sup></p>

## Synopsis

For patients with ATTR-CM and EF ≤40%, GDMT may be poorly tolerated. The vasodilating effects of ARNi, ACEi, and ARB may exacerbate hypotension, especially with amyloid-associated autonomic dysfunction. Beta blockers may worsen HF symptoms as patients with ATTR-CM rely on heart rate response to maintain cardiac output. The benefit of ICDs in ATTR-CM has not been studied in randomized trials, and a case-control study showed unclear benefit.<sup>5</sup> CRT has not been studied in ATTR-CM with HFrEF. Disease-modifying therapies include TTR silencers (disrupt hepatic synthesis via mRNA inhibition/degradation: inotersen and patisiran), TTR stabilizers (prevent misfolding/deposition: diflunisal and tafamidis), and TTR disruptors (target tissue clearance: doxycycline, taurooursodeoxycholic acid [TUDCA], and epigallocatechin-3-gallate [EGCG] in green tea). Light chain cardiac amyloidosis is managed by hematology-oncology specialists and beyond the scope of cardiologists, but diagnosis is often made by cardiologists when cardiac amyloid becomes manifest (Figure 13). AL amyloidosis is treatable, and patients with AL amyloidosis with cardiac involvement should promptly be referred to hematology-oncology for timely treatment. Inotersen and patisiran are associated with slower progression of amyloidosis-related polyneuropathy in ATTRv-CM.<sup>6,7</sup> There are ongoing trials of the impact of inotersen and patisiran and newer generation mRNA inhibitors-degraders on cardiovascular morbidity or mortality. There is limited benefit of diflunisal,<sup>8</sup> doxycycline plus TUDCA,<sup>9,10</sup> and EGCG,<sup>11</sup> on surrogate endpoints such as LV mass, but the impact of these agents on cardiovascular morbidity and mortality has not been assessed. Evaluation and management of autonomic dysfunction, volume status, and arrhythmia are important.

## Recommendation-Specific Supportive Text

1. Tafamidis is currently the only therapy to improve cardiovascular outcomes in ATTR-CM.<sup>1</sup> Tafamidis binds the thyroxin-binding site of TTR. In the ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) clinical trial, a randomized trial of patients with ATTRwt-CM or ATTRv-CM and NYHA class I to III symptoms, tafamidis had lower all-cause mortality (29.5% versus 42.9%) and lower cardiovascular-related hospitalization (0.48 versus 0.70 per year) after 30 months.<sup>1</sup> There was a higher rate of cardiovascular-related hospitalizations in patients with NYHA class III HF, potentially attributable to longer survival during a more severe period of disease. Given that tafamidis prevents but does not reverse amyloid deposition, tafamidis is expected to have greater benefit when administered early in the disease course. As the survival curves separate after 18 months, patients for whom noncardiac disease is not expected to limit survival should be selected. Benefit has not been observed in patients with class IV symptoms, severe aortic stenosis, or impaired renal function (eGFR <25 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> body surface area). Tafamidis is available in 2 formulations: tafamidis meglumine is available in 20-mg capsules; and the FDA-approved dose is 80 mg (4 capsules) once daily. Tafamidis is also available in 61-mg capsules; the FDA-approved dose for this new formulation is 61 mg once daily.
2. One model-based analyses used the results of the ATTR-ACT study<sup>1</sup> to evaluate the cost-effectiveness of chronic tafamidis compared with no amyloidosis-specific therapy among patients with wild-type or variant transthyretin amyloidosis and NYHA class I to III HF.<sup>2</sup> With assumptions that tafamidis remained effective beyond the clinical trial duration, they estimated tafamidis increased average survival by 1.97 years and QALY by 1.29. Despite these large clinical benefits, tafamidis (with an annual cost of \$225 000) had an incremental cost-effectiveness ratio >\$180 000 per QALY gained, the benchmark used by this guideline for low value. The cost of tafamidis would need to decrease by approximately 80% for it to be intermediate value with a cost per QALY <\$180 000.
3. Intracardiac thrombosis occurs in approximately one-third of patients with cardiac amyloidosis, in some cases in the absence of diagnosed AF<sup>3,4,12</sup> and regardless of CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>13</sup> The use of anticoagulation reduced the risk of intracardiac thrombi in a retrospective study.<sup>4</sup> The choice of direct oral anticoagulants (DOAC)

**Table 16. ESC Definition of Advanced HF**

All these criteria must be present despite optimal guideline-directed treatment:
1. Severe and persistent symptoms of HF (NYHA class III [advanced] or IV)
2. Severe cardiac dysfunction defined by ≥1 of these:
LVEF ≤30%
Isolated RV failure
Nonoperable severe valve abnormalities
Nonoperable severe congenital heart disease
EF ≥40%, elevated natriuretic peptide levels and evidence of significant diastolic dysfunction
3. Hospitalizations or unplanned visits in the past 12 mo for episodes of:
Congestion requiring high-dose intravenous diuretics or diuretic combinations
Low output requiring inotropes or vasoactive medications
Malignant arrhythmias
4. Severe impairment of exercise capacity with inability to exercise or low 6-minute walk test distance (<300 m) or peak VO <sub>2</sub> (<12–14 mL/kg/min) estimated to be of cardiac origin
Criteria 1 and 4 can be met in patients with cardiac dysfunction (as described in criterion 2) but who also have substantial limitations as a result of other conditions (eg, severe pulmonary disease, noncardiac cirrhosis, renal disease). The therapeutic options for these patients may be more limited.

EF indicates ejection fraction; ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular; and VO<sub>2</sub>, oxygen consumption/oxygen uptake.

Adapted with permission from Crespo-Leiro et al.<sup>1</sup>

versus warfarin has not been studied in patients with ATTR, nor has the role of left atrial appendage closure devices. The risk of anticoagulation on bleeding risk in patients with ATTR-CM and AF has not been established. However, although patients with AL amyloidosis may have acquired hemostatic abnormalities, including coagulation factor deficiencies, hyperfibrinolysis, and platelet dysfunction, TTR amyloidosis is not associated with hemostatic defects.

## 8. STAGE D (ADVANCED) HF

### 8.1. Specialty Referral for Advanced HF

Recommendation for Specialty Referral for Advanced HF		
COR	LOE	Recommendation
1	C-LD	1. In patients with advanced HF, when consistent with the patient's goals of care, timely referral for HF specialty care is recommended to review HF management and assess suitability for advanced HF therapies (eg, LVAD, cardiac transplantation, palliative care, and palliative inotropes). <sup>1–6</sup>

### Synopsis

A subset of patients with chronic HF will continue to progress and develop persistently severe symptoms despite maximum GDMT. Several terms have been

used to describe this population, including "end-stage," "advanced," and "refractory" HF. In 2018, the European Society of Cardiology updated its definition of advanced HF (Table 16), which now includes 4 distinct criteria.<sup>1</sup> The revised definition focuses on refractory symptoms rather than cardiac function and more clearly acknowledges that advanced HF can occur in patients without severely reduced EF, including those with isolated RV dysfunction, uncorrectable valvular or congenital heart disease, and in patients with preserved and mildly reduced EF.<sup>1,3</sup> The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) has developed 7 profiles that further stratify patients with advanced HF (Table 17).<sup>7</sup>

Determining that HF and not a concomitant pulmonary disorder is the basis of dyspnea is important. Severely symptomatic patients presenting with a new diagnosis of HF can often improve substantially if they are initially stabilized. Patients should also be evaluated for nonadherence to medications.<sup>8–11</sup> Finally, a careful review of medical management should be conducted to verify that all therapies likely to improve clinical status have been considered.

### Recommendation-Specific Supportive Text

1. Clinical indicators of advanced HF that should trigger possible referral to an advanced HF specialist are shown in Table 18.<sup>1,2,12–14</sup> Timely referral for review and consideration of advanced HF therapies is crucial to achieve optimal patient outcomes.<sup>15–17</sup> Acronyms such as I-Need-Help...

I, Intravenous inotropes

N, New York Heart Association (NYHA) class IIIB to IV or persistently elevated natriuretic peptides

E, End-organ dysfunction

E, EF ≤35%

D, Defibrillator shocks

H, Hospitalizations >1

E, Edema despite escalating diuretics

L, Low systolic BP ≤90, high heart rate

P, Prognostic medication; progressive intolerance or down-titration of GDMT

...have been developed to assist in decision-making for referral to advanced HF.<sup>18</sup> Indications and contraindications to durable mechanical support are listed in Table 19. After patients develop end-organ dysfunction or cardiogenic shock, they may no longer qualify for advanced therapies.<sup>19,20</sup> A complete assessment of the patient is not required before referral, because comprehensive, multidisciplinary assessment of cardiac disease and comorbid conditions is routinely performed when evaluating patients for advanced therapies.<sup>19,20</sup> Decisions around evaluation and use of advanced therapies should be informed by the patient's values, goals, and preferences. Discussion with

**Table 17. INTERMACS Profiles**

Profile*	Profile Description	Features
1	Critical cardiogenic shock	Life-threatening hypotension and rapidly escalating inotropic/pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels.
2	Progressive decline	"Dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Can also apply to a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions cannot be maintained because of tachyarrhythmias, clinical ischemia, or other intolerance.
3	Stable but inotope dependent	Clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal).
4	Resting symptoms on oral therapy at home	Patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living (dressing or bathing). He or she may have orthopnea, shortness of breath during dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites, or severe lower extremity edema.
5	Exertion intolerant	Patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound.
6	Exertion limited	Patient who is comfortable at rest without evidence of fluid overload but who is able to do some mild activity. Activities of daily living are comfortable, and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes or with any meaningful physical exertion.
7	Advanced NYHA class III	Patient who is clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

ICD indicates implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and NYHA, New York Heart Association.

Adapted from Stevenson et al,<sup>7</sup> with permission from the International Society for Heart and Lung Transplantation.

\*Modifier options: Profiles 3 to 6 can be modified for patients with recurrent decompensations leading to frequent (generally at least 2 in past 3 mo or 3 in past 6 mo) emergency department visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Profile 3 can be modified in this manner if the patient is usually at home. If a Profile 7 patient meets the modification of frequent hospitalizations, the patient should be moved to Profile 6 or worse. Other modifier options include arrhythmia, which should be used in the presence of recurrent ventricular tachyarrhythmias contributing to the overall clinical course (eg, frequent ICD shocks or requirement of external defibrillation, usually more than twice weekly); or temporary circulatory support for hospitalized patients Profiles 1 to 3.

HF specialists and other members of the multidisciplinary team may help ensure that the patient has adequate information to make an informed decision.

## 8.2. Nonpharmacological Management: Advanced HF

Recommendation for Nonpharmacological Management: Advanced HF		
COR	LOE	Recommendation
2b	C-LD	1. For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. <sup>1-4</sup>

### Synopsis

Hyponatremia and diuretic-refractory congestion is common in advanced HF and is associated with poor clinical<sup>5,6</sup> and patient-reported outcomes.<sup>7</sup> Moreover, improvement in hyponatremia has been shown to improve clinical outcomes.<sup>8,9</sup> Fluid restriction is commonly prescribed for patients with hyponatremia in acute HF but only improves hyponatremia modestly.<sup>1</sup> Although restricting fluid is a common recommendation for patients with HF, evidence in this area is of low quality,<sup>10</sup> and many studies have not included patients with advanced HF specifically. Moreover, fluid restric-

tion has limited-to-no effect on clinical outcomes or diuretic use.<sup>4</sup> Although HF nutritional counseling typically focuses on restricting sodium and fluid, patients with advanced HF have the greatest risk of developing cachexia or malnutrition.<sup>11</sup> Hence, dietary restrictions and recommendation should be both evidence-based and comprehensive.

### Recommendation-Specific Supportive Text

- In a registry study of hyponatremia in acute decompensated HF, fluid restriction only improved hyponatremia marginally.<sup>1</sup> A registered dietitian-guided fluid and sodium restriction intervention improved NYHA functional classification and leg edema in patients with HFrEF who were not in stage D HF,<sup>2</sup> and fluid restriction improved QOL in a pilot RCT of patients with HFrEF and HFpEF (NYHA class I to IV).<sup>3</sup> In a meta-analysis of RCTs on fluid restriction in HF in general, restricted fluid intake compared with free fluid consumption did not result in reduced hospitalization or mortality rates, changes in thirst, the duration of intravenous diuretic use, serum creatinine, or serum sodium levels.<sup>4</sup> The validity of a previous trial supporting clinical benefits of fluid restriction in HF is in serious question.<sup>12</sup>

**Table 18. Clinical Indicators of Advanced HF<sup>1,2,12,13,23–37</sup>**

Repeated hospitalizations or emergency department visits for HF in the past 12 mo.
Need for intravenous inotropic therapy.
Persistent NYHA functional class III to IV symptoms despite therapy.
Severely reduced exercise capacity (peak VO <sub>2</sub> <14 mL/kg/min or <50% predicted, 6-min walk test distance <300 m, or inability to walk 1 block on level ground because of dyspnea or fatigue).
Intolerance to RAASi because of hypotension or worsening renal function.
Intolerance to beta blockers as a result of worsening HF or hypotension.
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d or use of supplemental metolazone therapy.
Refractory clinical congestion.
Progressive deterioration in renal or hepatic function.
Worsening right HF or secondary pulmonary hypertension.
Frequent SBP ≤90 mm Hg.
Cardiac cachexia.
Persistent hyponatremia (serum sodium, <134 mEq/L).
Refractory or recurrent ventricular arrhythmias; frequent ICD shocks.
Increased predicted 1-year mortality (eg, >20%) according to HF survival models (eg, MAGGIC, <sup>21</sup> SHFM <sup>22</sup> ).

HF indicates heart failure; ICD, implantable cardioverter-defibrillator; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure; SHFM, Seattle Heart Failure model; and VO<sub>2</sub>, oxygen consumption/oxygen uptake.

### 8.3. Inotropic Support

Recommendations for Inotropic Support		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
<b>2a</b>	<b>B-NR</b>	1. In patients with advanced (stage D) HF refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation, continuous intravenous inotropic support is reasonable as “bridge therapy.” <sup>1–4</sup>
<b>2b</b>	<b>B-NR</b>	2. In select patients with stage D HF, despite optimal GDMT and device therapy who are ineligible for either MCS or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. <sup>5–7</sup>
<b>3: Harm</b>	<b>B-R</b>	3. In patients with HF, long-term use of either continuous or intermittent intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. <sup>5,6,8–11</sup>

### Synopsis

Despite improving hemodynamic compromise, positive inotropic agents have not shown improved survival in patients with HF in either the hospital or the outpatient setting.<sup>6</sup> Regardless of their mechanism of action (eg, inhibition of phosphodiesterase, stimulation of adrenergic

**Table 19. Indications and Contraindications to Durable Mechanical Support<sup>37</sup>**

Indications (combination of these):
Frequent hospitalizations for HF
NYHA class IIIb to IV functional limitations despite maximal therapy
Intolerance of neurohormonal antagonists
Increasing diuretic requirement
Symptomatic despite CRT
Inotrope dependence
Low peak VO <sub>2</sub> (<14–16)
End-organ dysfunction attributable to low cardiac output
Contraindications:
Absolute
Irreversible hepatic disease
Irreversible renal disease
Irreversible neurological disease
Medical nonadherence
Severe psychosocial limitations
Relative
Age >80 y for destination therapy
Obesity or malnutrition
Musculoskeletal disease that impairs rehabilitation
Active systemic infection or prolonged intubation
Untreated malignancy
Severe PVD
Active substance abuse
Impaired cognitive function
Unmanaged psychiatric disorder
Lack of social support

CRT indicates cardiac resynchronization therapy; HF, heart failure; NYHA, New York Heart Association; VO<sub>2</sub>, oxygen consumption; and PVD, peripheral vascular disease.

or dopaminergic receptors, calcium sensitization), parenteral inotropes remain an option to help the subset of patients with HF who are refractory to other therapies and are suffering consequences from end-organ hypoperfusion. In hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly low cardiac index, short-term, continuous intravenous inotropic support may be reasonable to maintain systemic perfusion and preserve end-organ performance.<sup>8,11,12</sup> There continues to be lack of robust evidence to suggest the clear benefit of 1 inotrope over another.<sup>13</sup> To minimize adverse effects, lower doses of parenteral inotropic drugs are preferred, although the development of tachyphylaxis should be acknowledged, and the choice of agent may need to be changed during longer periods of support. Similarly, the ongoing need for inotropic support and the possibility of discontinuation should be regularly assessed. Table 20 compares commonly used inotropes.

**Table 20.** Intravenous Inotropic Agents Used in the Management of HF

Inotropic Agent	Dose (mcg/kg)		Drug Kinetics and Metabolism	Effects					Adverse Effects	Special Considerations	
	Bolus	Infusion (/min)		CO	HR	SVR	PVR				
Adrenergic agonists											
Dopamine	NA	5–10	$t_{1/2}$ : 2–20 min	↑	↑	↔	↔	T, HA, N, tissue necrosis	Caution: MAO-I		
	NA	10–15	R, H, P	↑	↑	↑	↔				
Dobutamine	NA	2.5–20	$t_{1/2}$ : 2–3 min H	↑	↑	↔	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; Cl: sulfite allergy		
PDE 3 inhibitor											
Milrinone	NR	0.125–0.75	$t_{1/2}$ : 2.5 h H	↑	↑	↓	↓	T, ↓BP		Accumulation may occur in setting of renal failure; monitor kidney function and LFTs	
Vasopressors											
Epinephrine	NR	5–15 mcg/min	$t_{1/2}$ : 2–3 min	↑	↑	↑(↓)	↔	HA, T	Caution: MAO-I		
		15–20 mcg/min	$t_{1/2}$ : 2–3 min	↑	↑↑	↑↑	↔	HA, T			
Norepinephrine	NR	0.5–30 mcg/min	$t_{1/2}$ : 2.5 min	↔	↑	↑↑	↔	↓ HR, tissue necrosis	Caution: MAO-I		

BP indicates blood pressure; CI, contraindication; CO, cardiac output; F, fever; H, hepatic; HA, headache; HF, heart failure; HR, heart rate; LFT, liver function test; MAO-I, monoamine oxidase inhibitor; N, nausea; NA, not applicable; NR, not recommended; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; T, tachyarrhythmias; and  $t_{1/2}$ , elimination half-life.

Up arrow means increase. Side arrow means no change. Down arrow means decrease. Up/down arrow means either increase or decrease.

## Recommendation-Specific Supportive Text

- More prolonged use of inotropes as “bridge” therapy for those awaiting either heart transplantation or MCS may have benefit in reducing pulmonary hypertension and maintaining end-organ perfusion beyond initial stabilization of patients.<sup>1–4</sup>
- The use of inotropes for palliation does carry with it risks for arrhythmias and catheter-related infections, although the presence of an ICD does decrease the mortality associated with arrhythmias. This risk should be shared with patients if there is planned use of inotropes in a patient without an ICD, or in whom the preference is to deactivate the ICD for palliative purposes. The rate of inappropriate shocks for sinus tachycardia is relatively low, and the concomitant use of beta blockers may help in these patients. Patients may elect to have their shocking devices deactivated, especially if they receive numerous shocks.<sup>14,15</sup>
- With the currently available inotropic agents, the benefit of hemodynamic support and stabilization may be compromised by increased myocardial oxygen demand and increased arrhythmic burden. As newer agents are developed, more options may not have these known risks. There are investigational inotropic agents that may provide more options for the management of patients with HF and represent different classes of agents.<sup>16</sup>

## 8.4. Mechanical Circulatory Support

**Recommendations for Mechanical Circulatory Support**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	<p>1. In select patients with advanced HFrEF with NYHA class IV symptoms who are deemed to be dependent on continuous intravenous inotropes or temporary MCS, durable LVAD implantation is effective to improve functional status, QOL, and survival.<sup>1–18</sup></p>
2a	B-R	<p>2. In select patients with advanced HFrEF who have NYHA class IV symptoms despite GDMT, durable MCS can be beneficial to improve symptoms, improve functional class, and reduce mortality.<sup>2,4,7,10,12–17,19</sup></p>
Value Statement: Uncertain Value (B-NR)		<p>3. In patients with advanced HFrEF who have NYHA class IV symptoms despite GDMT, durable MCS devices provide low to intermediate economic value based on current costs and outcomes.<sup>20–24</sup></p>
2a	B-NR	<p>4. In patients with advanced HFrEF and hemodynamic compromise and shock, temporary MCS, including percutaneous and extracorporeal ventricular assist devices, are reasonable as a “bridge to recovery” or “bridge to decision.”<sup>25–29</sup></p>

## Synopsis

MCS is a therapeutic option for patients with advanced HFrEF to prolong life and improve functional capacity. Over the past 10 years, evolution and refinement of temporary and durable options has continued. MCS is differentiated by the implant location, approach, flow characteristics,

pump mechanisms, and ventricle(s) supported. It can be effective for short-term support (hours to days) and for long-term management (months to years). There are anatomic and physiologic criteria that make durable MCS inappropriate for some patients; it is most appropriate for those with HFrEF and a dilated ventricle. With any form of MCS, the device will eventually be turned off, whether at the time of explant for transplantation or recovery, or to stop support in a patient who either no longer wishes to continue support, or in whom the continued functioning of an MCS prevents their death from other causes, such as a catastrophic neurologic event, or metastatic malignancy.<sup>30</sup> This topic should be addressed a priori with patients before discussions about MCS. Particularly with temporary devices, the potential need to either discontinue or to escalate support should be addressed at time of implantation.

### Recommendation-Specific Supportive Text

1. Durable LVADs should be considered in selected patients with NYHA class IV symptoms who are deemed dependent on IV inotropes or temporary MCS. The magnitude of the survival benefit for durable LVAD support in advanced NYHA class IV patients has progressively improved, with a 2-year survival >80% in recent trials with newer generation LVADs, which approaches the early survival after cardiac transplantation.<sup>2</sup> The 2020 INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) report showed that 87.6% of recent durable LVAD recipients were categorized as INTERMACS 1 to 3 before their implant surgery.<sup>10</sup> It also showed improved mean survival, >4 years for the destination LVAD cohort, and >5 years for bridge-to-transplant patients. Durable LVAD support has also achieved impressive functional improvement and QOL improvement in multiple trials,<sup>2,7,31</sup> although patients remain tethered to external electrical power supplies via a percutaneous lead can limit this improvement. Most patients require rehospitalization within the first year post-implant. These factors emphasize the need for a thorough evaluation and patient education before the decision to proceed with the treatment. Appropriate patient selection benefits from review by a multidisciplinary team that typically includes an HF cardiologist, surgeon, social worker, nurse, pharmacist, dietitian, and a palliative medicine specialist.
2. Durable MCS should be considered in patients with NYHA class IV symptoms despite optimal medical therapy or those deemed dependent on IV inotropes. Destination therapy MCS provides considerable survival advantage in addition to improvement in functional status and health-related QOL.<sup>1,7,12,32,33</sup> There is no clear 1-risk model to assess patient risk for complications, but factors such as elevated central venous pressure, pulmonary hypertension, and coagulopathy have been linked to poorer outcomes.<sup>15,34–36</sup> In patients who are unable to tolerate anticoagulation after repeated challenges, implantation of a durable MCS is associated with excess morbidity; incidents of pump thrombosis, hemolysis, and ischemic neurologic events have been linked to subtherapeutic international normalized ratios.<sup>37–41</sup> In addition, implantation of MCS in patients with INTERMACS profile of 1 has been associated with poorer outcome, while those ambulatory patients with profiles 5 to 7 might be too well to have large significant benefit, depending on their symptom burden.<sup>19</sup> For patients who are initially considered to be transplant ineligible because of pulmonary hypertension, obesity, overall frailty, or other reasons, MCS can provide time to reverse or modify these conditions.<sup>35,42–44</sup> Continuing and uptitrating GDMT in patients with durable MCS is recommended.<sup>45</sup>
3. Multiple studies evaluated the cost-effectiveness of ventricular assist device implantation for advanced HF between 2012 and 2017.<sup>20,21,23</sup> They consistently found device implantation was of low economic value, with incremental cost-effectiveness ratios of \$200 000 per QALY gained compared with medical therapy alone among patients who potentially underwent subsequent heart transplant and those who were ineligible for heart transplant. In these studies, costs after implantation remained high given high rates of complication and rehospitalization. However, these studies used earlier estimates of post-implant outcomes and complication-related costs that have generally improved over time with better care and newer devices.<sup>46–48</sup> Additionally, limited recent data suggest improvement in health care costs and intermediate economic value with LVAD among patients with advanced HF who are either eligible or ineligible for subsequent heart transplant.<sup>22,24</sup> The improvement may result from lower complication rates, increased survival, lower implant costs, and higher estimated QOL. However, given the conflicting data and limited analyses of contemporary data, the current value of LVAD therapy is uncertain.
4. Temporary MCS can help stabilize patients and allow time for decisions about the appropriateness of transitions to definitive management, such as durable MCS as a bridge or destination therapy, stabilization until cardiac transplantation or, in the case of improvement and recovery, suitability for device removal.<sup>45</sup> These patients often present in cardiogenic shock that cannot be managed solely with IV inotropes and in whom other organ function is at risk. Temporary MCS is also appropriate for

use to allow patients to engage in decision-making for durable MCS or transplantation and for determination of recovery of neurologic status.

## 8.5. Cardiac Transplantation

Recommendation for Cardiac Transplantation		
COR	LOE	Recommendation
1	C-LD	<ol style="list-style-type: none"> <li>For selected patients with advanced HF despite GDMT, cardiac transplantation is indicated to improve survival and QOL.<sup>1–3</sup></li> </ol>
<b>Value Statement:</b> <b>Intermediate Value</b> <b>(C-LD)</b>		<ol style="list-style-type: none"> <li>In patients with stage D (advanced) HF despite GDMT, cardiac transplantation provides intermediate economic value.<sup>4</sup></li> </ol>

### Synopsis

The evidence that cardiac transplantation provides a mortality and morbidity benefit to selected patients with stage D HF (refractory, advanced) is derived from observational cohorts. Datasets from the International Society for Heart and Lung Transplantation<sup>1</sup> and United Network of Organ Sharing<sup>2</sup> document the median survival of adult transplant recipients to be now >12 years; the median survival of patients with stage D HF without advanced therapies is <2 years. For comparison, the risk of death becomes greater than survival between 3 and 4 years on an LVAD, regardless of implant strategy (eg, bridge-to-transplant, bridge-to-decision, destination therapy).<sup>3</sup> Improvements in pre- and posttransplant management have also increased more patients to be eligible for transplant, and treated rejection rates in the first year after transplantation are now <15%.<sup>1</sup> Minimizing waitlist mortality while maximizing posttransplant outcomes continues to be a priority in heart transplantation and was addressed with the recent changes in donor allocation policy instituted in 2018.<sup>5</sup> Several analyses<sup>6–11</sup> have confirmed a decrease in waitlist mortality as well as an increase in the use of temporary circulatory support devices, graft ischemic times, and distances between donor and recipient hospitals. The impact on posttransplant survival remains uncertain. Multiorgan transplantation remains uncommon and reserved for highly selected candidates. In 2018, 7% of all heart transplants involved another organ, in addition to the heart.<sup>1</sup>

### Recommendation-Specific Supportive Text

- Cardiac transplantation is the established treatment for eligible patients with stage D HF refractory to GDMT, device, and surgical optimization. The survival of adult recipients who received a transplantation between 2011 and 2013 at 1, 3, and 5 years is 90.3%, 84.7%, and 79.6%, respectively.<sup>2</sup> Conditional survival now approaches 15

years.<sup>1</sup> Cardiac transplantation also improves functional status and health-related QOL.<sup>12–15</sup> Good outcomes can be achieved in patients not only with HF that is primarily cardiovascular in origin, including reversible pulmonary hypertension,<sup>16</sup> congenital heart disease,<sup>17</sup> and hypertrophic cardiomyopathy,<sup>18</sup> but also in patients with systemic conditions complicated by HF, such as muscular dystrophy,<sup>19</sup> sarcoidosis,<sup>20</sup> and amyloidosis.<sup>21</sup> CPET can refine candidate prognosis and selection.<sup>22–28</sup> Appropriate patient selection should include integration of comorbidity burden, caretaker status, and goals of care. The listing criteria, evaluation, and management of patients undergoing cardiac transplantation are described by the International Society for Heart and Lung Transplantation.<sup>29</sup> The United Network of Organ Sharing Heart Transplant Allocation Policy was revised in 2018 with a broader geographic sharing policy and a 6-tiered system to better prioritize more unstable patients and minimize waitlist mortality.<sup>5–11</sup>

- One study evaluated the cost-effectiveness of heart transplantation compared with medical therapy among patients with inotrope-dependent advanced HF.<sup>30</sup> This analysis found transplantation was of intermediate value. The results were similar across a broad range of patient age, waitlist duration, and monthly mortality risk with medical therapy.

## 9. PATIENTS HOSPITALIZED WITH ACUTE DECOMPENSATED HF

### 9.1. Assessment of Patients Hospitalized With Decompensated HF

Recommendations for Assessment of Patients Hospitalized With Decompensated HF		
COR	LOE	Recommendations
1	C-LD	<ol style="list-style-type: none"> <li>In patients hospitalized with HF, severity of congestion and adequacy of perfusion should be assessed to guide triage and initial therapy.<sup>1–5</sup></li> </ol>
1	C-LD	<ol style="list-style-type: none"> <li>In patients hospitalized with HF, the common precipitating factors and the overall patient trajectory should be assessed to guide appropriate therapy.<sup>5,6</sup></li> </ol>
Goals for Optimization and Continuation of GDMT		
1	C-LD	<ol style="list-style-type: none"> <li>For patients admitted with HF, treatment should address reversible factors, establish optimal volume status, and advance GDMT toward targets for outpatient therapy.<sup>6</sup></li> </ol>

### Synopsis

Initial triage includes clinical assessment of the hemodynamic profile for severity of congestion and adequa-

**Table 21. Common Factors Precipitating HF Hospitalization With Acute Decompensated HF**

ACS
Uncontrolled hypertension
AF and other arrhythmias
Additional cardiac disease (eg, endocarditis)
Acute infections (eg, pneumonia, urinary tract)
Nonadherence with medication regimen or dietary intake
Anemia
Hyper- or hypothyroidism
Medications that increase sodium retention (eg, NSAID)
Medications with negative inotropic effect (eg, verapamil)

ACS indicates acute coronary syndrome; AF, atrial fibrillation; HF, heart failure; and NSAID, nonsteroidal anti-inflammatory drug.<sup>12</sup>

cy of perfusion.<sup>1–5</sup> The diagnosis of cardiogenic shock warrants consideration of recommendations in Section 9.5, “Evaluation and Management of Cardiogenic Shock,” but any concern for worsening hypoperfusion should also trigger involvement of the multidisciplinary team for hemodynamic assessment and intervention. Initial triage includes recognition of patients with ACS for whom urgent revascularization may be indicated. In the absence of ischemic disease, recent onset with accelerating hemodynamic decompensation may represent inflammatory heart disease, particularly when accompanied by conduction block or ventricular arrhythmias.<sup>7,8</sup> However, most HF hospitalizations for decompensation are not truly “acute” but follow a gradual increase of cardiac filling pressures on preexisting structural heart disease, often with precipitating factors that can be identified<sup>3,6</sup> (Table 21). Some patients present with pulmonary edema and severe hypertension, which require urgent treatment to reduce blood pressure, more commonly in patients with preserved LVEF. Patients require assessment and management of ischemia, arrhythmia and other precipitating factors and comorbidities. The presenting profile, reversible factors, appropriate workup for the cause of HF including ischemic and nonischemic causes, comorbidities, and potential for GDMT titration inform the plan of care to optimize the disease trajectory.<sup>5</sup>

### Recommendation-Specific Supportive Text

1. and 2. Most patients admitted with HF have clinical evidence of congestion without apparent hypoperfusion.<sup>1–5,9,10</sup> Although elevations of right- and left-sided cardiac filling pressures are usually proportional in decompensation of chronic HF with low EF, up to 1 in 4 patients have a mismatch between right- and left-sided filling pressures.<sup>9–11</sup> Disproportionate elevation

of right-sided pressures, particularly with TR, hinders effective decongestion. Disproportionate elevation of left-sided filling pressures may be underrecognized as the cause of dyspnea in the absence of jugular venous distention and edema. Elevated natriuretic peptides can help identify HF in the urgent care setting but with less utility in certain situations, including decreased sensitivity with obesity and HFpEF and decreased specificity in the setting of sepsis. Resting hypoperfusion is often underappreciated in patients with chronic HF but can be suspected from narrow pulse pressure and cool extremities<sup>1,9</sup> and by intolerance to neurohormonal antagonists. Elevated serum lactate levels may indicate hypoperfusion and impending cardiogenic shock.<sup>12</sup> When initial clinical assessment does not suggest congestion or hypoperfusion, symptoms of HF may be a result of transient ischemia, arrhythmias, or noncardiac disease such as chronic pulmonary disease or pneumonia, and more focused hemodynamic assessment may be warranted. Assessment of arrhythmia, device profiles such as percent LV pacing versus RV pacing in patients with CRT, and device therapy and shocks in patients with ICD can provide important information.

3. Hospitalization for HF is a sentinel event that signals worse prognosis and the need to restore hemodynamic compensation but also provides key opportunities to redirect the disease trajectory. During the HF hospitalization, the approach to management should include and address precipitating factors, comorbidities, and previous limitations to ongoing disease management related to social determinants of health.<sup>1</sup> Patients require assessment and management of ischemia, arrhythmia, and other precipitating factors and comorbidities. The presenting profile, reversible factors, appropriate work-up for cause of HF including ischemic and nonischemic causes, comorbidities, disease trajectory, and goals of care should be addressed. Establishment of optimal volume status is a major goal, and patients with residual congestion merit careful consideration for further intervention before and after discharge, because they face higher risk for rehospitalization and death.<sup>2–5</sup> The disease trajectory for patients hospitalized with reduced EF is markedly improved by optimization of recommended medical therapies, which should be initiated or increased toward target doses once the efficacy of diuresis has been shown.<sup>13,14</sup>

## 9.2. Maintenance or Optimization of GDMT During Hospitalization

### Recommendations for Maintenance or Optimization of GDMT During Hospitalization

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	B-NR	1. In patients with HFrEF requiring hospitalization, preexisting GDMT should be continued and optimized to improve outcomes, unless contraindicated. <sup>1–5</sup>
1	B-NR	2. In patients experiencing mild decrease of renal function or asymptomatic reduction of blood pressure during HF hospitalization, diuresis and other GDMT should not routinely be discontinued. <sup>6–11</sup>
1	B-NR	3. In patients with HFrEF, GDMT should be initiated during hospitalization after clinical stability is achieved. <sup>2,3,5,12–18</sup>
1	B-NR	4. In patients with HFrEF, if discontinuation of GDMT is necessary during hospitalization, it should be reinitiated and further optimized as soon as possible. <sup>19–22</sup>

### Synopsis

Hospitalization for HFrEF is a critical opportunity to continue, initiate, and further optimize GDMT.<sup>23–25</sup> Continuation of oral GDMT during hospitalization for HF has been shown in registries to lower risk of postdischarge death and readmission compared with discontinuation.<sup>1–5</sup> Initiation of oral GDMT during hospitalization for HF is associated with numerous clinical outcome benefits.<sup>2,5,12,16,17</sup> Based on data from the CHAMP-HF (Change the Management of Patients with Heart Failure) registry, however, only 73%, 66%, and 33% of eligible patients with HFrEF were prescribed ACEi-ARB-ARNi, beta blockers, and MRA therapy, respectively.<sup>19</sup> Furthermore, based on information obtained from claims data, roughly 42% of patients are not prescribed any GDMT within 30 days postindex hospitalization,<sup>20</sup> and 45% are prescribed either no oral GDMT or monotherapy within 1-year post-hospitalization.<sup>21</sup> In the management of patients with HFrEF in the community, very few receive target doses of oral GDMT.<sup>6</sup> Moreover, most patients with HFrEF have no changes made to oral GDMT over 12 months,<sup>21</sup> despite being discharged on suboptimal doses or no GDMT.<sup>22</sup> It cannot be assumed that oral GDMT will be initiated or optimized after hospitalization for HFrEF.

### Recommendation-Specific Supportive Text

1. In OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure), discontinuation of beta blockers was associated with a higher risk for mortality compared with those continued on beta blockers.<sup>1</sup> In a meta-analysis of observational and trial data, discontinuation of beta blockers in hospitalized patients with HFrEF also was associated with a higher risk of in-hospital mortality, short-term mortality, and the combined endpoint of short-term rehospitalization or mortality.<sup>4</sup> Withholding or reducing beta-blocker therapy should be considered in patients with marked volume overload or marginal low cardiac output. In the Get With The Guidelines-Heart Failure (GWTG-HF) registry, withdrawal of ACEi-ARB among patients hospitalized with HFrEF was associated with higher rates of postdischarge mortality and readmission.<sup>2</sup> In the COACH (Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure) study, continuation of spironolactone among hospitalized patients with HFrEF was associated with lower 30-day mortality and HF rehospitalization.<sup>3</sup> From the ARIC (Atherosclerosis Risk in Communities) study, discontinuation of any oral GDMT among patients hospitalized with HFrEF was associated with higher mortality risk.<sup>5</sup> Oral GDMT should not be withheld for mild or transient reductions in blood pressure<sup>6–9</sup> or mild deteriorations in renal function.<sup>10,11</sup> True contraindications are rare, such as advanced degree atrioventricular block for beta blockers in the absence of pacemakers; cardiogenic shock that may preclude use of certain medications until resolution of shock state; or angioedema for ACEi or ARNi.
2. In CHAMP-HF, very few patients with HF and SBP <110 mm Hg received target doses of beta blockers (17.5%) ACEi-ARB (6.2 %), or ARNi (1.8%).<sup>6</sup> In PARADIGM-HF, patients with HF and lower SBP on sacubitril-valsartan had the same tolerance and relative benefit over enalapril compared with patients with higher SBP.<sup>7</sup> From the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial, nebivolol had equivalent tolerance and benefits irrespective of SBP.<sup>8</sup> In Val-HeFT (Valsartan Heart Failure Trial), decreases in SBP did not offset the beneficial effects of valsartan on HF morbidity.<sup>9</sup> In patients with HF on oral GDMT, small to moderate worsening of renal function (defined as ≥20% decrease in eGFR in that study) was not associated with AKI.<sup>10</sup> Moreover, it has been shown that spironolactone and beta blockers might be protective in patients with HF and worsening renal function.<sup>11</sup>
3. In OPTIMIZE-HF, discharge use of carvedilol was associated with a reduction in 60- to 90-day mortality and composite risk of mortality

or rehospitalization compared with no carvedilol use.<sup>12,13</sup> Discharge use of beta blockers is also associated with lower 30-day all-cause mortality and 4-year all-cause mortality/all-cause readmission.<sup>14</sup> Caution should be used when initiating beta blockers in patients who have required inotropes during hospitalization. In GWTG-HF, initiation of ACEi-ARB in patients hospitalized with HFrEF reduced 30-day and 1-year mortality.<sup>2</sup> Among patients hospitalized with HFrEF, initiation of ACEi-ARB also is associated with lower risk of 30-day all-cause readmission and all-cause mortality.<sup>15</sup> In a claims study, initiation of MRA therapy at hospital discharge was associated with improved HF readmission but not mortality or cardiovascular readmission among older adults hospitalized with HFrEF.<sup>16</sup> In COACH, initiating spironolactone among patients hospitalized with HFrEF was associated with lower 30-day mortality and HF rehospitalization.<sup>3</sup> In the PIONEER-HF trial, ARNi use was associated with reduced NT-proBNP levels in patients hospitalized for acute decompensated HF without increased rates of adverse events (worsening renal function, hyperkalemia, symptomatic hypotension, angioedema) when compared with enalapril.<sup>18</sup> In the ARIC study, initiation of any oral GDMT was associated with reduced 1-year mortality among patients hospitalized with HFrEF.<sup>5</sup> In SOLOIST-WHF, initiation of sotagliflozin before or shortly after discharge reduced cardiovascular mortality and hospitalization.<sup>17</sup>

- Nearly half (46%) of patients with HFrEF have no changes made to oral GDMT in the 12 months after hospitalization despite many being discharged on suboptimal doses.<sup>21</sup> From claims-based studies, 42% of patients with HFrEF are not prescribed any GDMT within 30 days post-index hospitalization,<sup>20</sup> and 45% are prescribed either no oral GDMT or monotherapy within 1-year post-index hospitalization.<sup>21</sup> From CHAMP-HF, initiation or dose increases of beta blockers, ACEi-ARB-ARNi, and MRA occur in ≤10% of patients with HFrEF within 1 year of hospitalization.<sup>22</sup> Very few eligible patients with HFrEF receive target doses of beta blockers (18.7%), ACEi-ARB (10.8%), or ARNi (2.0%).<sup>6</sup> Less than 1% of patients with HFrEF are on target doses of ACEi-ARB-ARNi, beta blockers, and MRA within 12 months of an index hospitalization.<sup>22</sup> For patients with HFrEF, there is a graded improvement in the risk of death or rehospitalization with monotherapy, dual therapy, and triple therapy compared with no GDMT after an index hospitalization in Medicare claims data.<sup>21</sup>

### 9.3. Diuretics in Hospitalized Patients: Decongestion Strategy

Recommendations for Diuretics in Hospitalized Patients: Decongestion Strategy		
COR	LOE	Recommendations
1	B-NR	<ol style="list-style-type: none"> <li>Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to improve symptoms and reduce morbidity.<sup>1</sup></li> </ol>
1	B-NR	<ol style="list-style-type: none"> <li>For patients hospitalized with HF, therapy with diuretics and other guideline-directed medications should be titrated with a goal to resolve clinical evidence of congestion to reduce symptoms and rehospitalizations.<sup>1–6</sup></li> </ol>
1	B-NR	<ol style="list-style-type: none"> <li>For patients requiring diuretic treatment during hospitalization for HF, the discharge regimen should include a plan for adjustment of diuretics to decrease rehospitalizations.<sup>7</sup></li> </ol>
2a	B-NR	<ol style="list-style-type: none"> <li>In patients hospitalized with HF when diuresis is inadequate to relieve symptoms and signs of congestion, it is reasonable to intensify the diuretic regimen using either: a. higher doses of intravenous loop diuretics;<sup>1,3</sup> or b. addition of a second diuretic.<sup>3</sup></li> </ol>

### Synopsis

Intravenous loop diuretic therapy provides the most rapid and effective treatment for signs and symptoms of congestion leading to hospitalization for HF. Titration to achieve effective diuresis may require doubling of initial doses, adding a thiazide diuretic, or adding an MRA that has diuretic effects in addition to its cardiovascular benefits. A major goal of therapy is resolution of the signs and symptoms of congestion before discharge, as persistent congestion scored at discharge has been associated with higher rates of rehospitalizations and mortality. Most patients who have required intravenous diuretic therapy during hospitalization for HF will require prescription of loop diuretics at discharge to decrease recurrence of symptoms and hospitalization.

### Recommendation-Specific Supportive Text

- Diuretic therapy with oral furosemide was the cornerstone of HF therapy for >20 years before construction of the modern bases of evidence for HF therapies. The pivotal RCTs showing benefit in ambulatory HFrEF have been conducted on the background of diuretic therapy to treat and prevent recurrence of fluid retention. An RCT compared intravenous diuretic doses and infusion to bolus dosing during hospitalization for HF but without a placebo arm.<sup>1</sup> Protocols for recent trials of other medications in patients hospitalized with HF have all included intravenous diuretic therapy

- as background therapy.<sup>1–6,8,9</sup> There are no RCTs for hospitalized patients comparing intravenous loop diuretics to placebo, for which equipoise is considered unlikely.<sup>10</sup>
2. Monitoring HF treatment includes careful measurement of fluid intake and output, vital signs, standing body weight at the same time each day, and clinical signs and symptoms of congestion and hypoperfusion. Daily laboratory tests during active medication adjustment include serum electrolytes, urea nitrogen, and creatinine concentrations. Signs and symptoms of congestion have been specified as inclusion criteria in recent trials of patients hospitalized for HF, in which resolution of these signs and symptoms has been defined as a goal to be achieved by hospital discharge,<sup>1–6,8,9</sup> as it has in the recent HF hospitalization pathway consensus document.<sup>11</sup> Evidence of persistent congestion at discharge has been reported in 25% to 50% of patients,<sup>4,5,12</sup> who have higher rates of mortality and readmission and are more likely to have elevated right atrial pressures, TR, and renal dysfunction. Diuresis should not be discontinued prematurely because of small changes in serum creatinine,<sup>13,14</sup> because elevations in the range of 0.3 mg/dL do not predict worse outcomes except when patients are discharged with persistent congestion. Decongestion often requires not only diuresis but also adjustment of other guideline-directed therapies, because elevated volume status and vasoconstriction can contribute to elevated filling pressures.
  3. After discharge, ACEi-ARB, MRAs, and beta blockers all may decrease recurrent congestion leading to hospitalization in HFrEF. Despite these therapies, most patients with recent HF hospitalization require continued use of diuretics after discharge to prevent recurrent fluid retention and hospitalization, as shown in a recent large observational analysis.<sup>7</sup> Increases in diuretic doses are frequently required early after discharge even in patients on all other currently recommended therapies for HFrEF.<sup>8</sup> It is unknown how increased penetration of therapy with ARNi and SGLT2i will, in the future, affect the dosing of diuretics after discharge with HFrEF.
  4. Titration of diuretics has been described in multiple recent trials of patients hospitalized with HF, often initiated with at least 2 times the daily home diuretic dose (mg to mg) administered intravenously.<sup>1</sup> Escalating attempts to achieve net diuresis include serial doubling of intravenous loop diuretic doses, which can be done by bolus or infusion, and sequential nephron blockade with addition of a thiazide diuretic, as detailed specifically in the protocol for the diuretic arms of the CARRESS and ROSE trials.<sup>3,9</sup> In the DOSE (Diuretic Optimization Strategies Evaluation) trial, there were no significant differences in patients' global assessment of

symptoms or in the change in renal function when diuretic therapy was administered by bolus, compared with continuous infusion or at a high dose compared with a low dose. Patients in the low-dose group were more likely to require a 50% increase in the dose at 48 hours than were those in the high-dose group, and all treatment groups had higher doses of diuretics compared with baseline preadmission doses, underlining the necessity to intensify and individualize diuretic regimen.<sup>1</sup> MRAs have mild diuretic properties and addition of MRAs can help with diuresis in addition to significant cardiovascular benefits in patients with HF. Addition of low-dose dopamine to diuretic therapy in the setting of reduced eGFR did not improve outcomes in a study that included patients with all EFs, but a subset analysis showed increased urine output and weight loss in patients with LVEF <0.40,<sup>9</sup> with significant interaction of effect with LVEF. Bedside ultrafiltration initiated early after admission increased fluid loss, with decreased rehospitalizations in some studies when compared with use of diuretics without systematic escalation,<sup>15,16</sup> and was also associated with adverse events related to the intravenous catheters required.<sup>3</sup> Many aspects of ultrafiltration including patient selection, fluid removal rates, venous access, prevention of therapy-related complications, and cost require further investigation.

#### 9.4a. Parenteral Vasodilation Therapy in Patients Hospitalized With HF

Recommendation for Parenteral Vasodilation Therapy in Patients Hospitalized With HF		
Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	LOE	Recommendation
2b	B-NR	1. In patients who are admitted with decompensated HF, in the absence of systemic hypotension, intravenous nitroglycerin or nitroprusside may be considered as an adjuvant to diuretic therapy for relief of dyspnea. <sup>1,2</sup>

#### Synopsis

Vasodilators can be used in acute HF to acutely relieve symptoms of pulmonary congestion in selected patients. Although they may mitigate dyspnea and relieve pulmonary congestion, their benefits have not been shown to have durable effects for either rehospitalization or mortality benefit. In select patients who present with signs of hypoperfusion such as worsening renal function, even in the absence of hypotension, other escalation of care may need to be considered (see Section 8.3, "Inotropic Support," and Section 9.5, "Evaluation and Management of Cardiogenic Shock").

## Recommendation-Specific Supportive Text

1. The role for directed vasodilators in acute decompensated HF remains uncertain. Part of the rationale for their use is targeting pulmonary congestion, while trying to avoid some potential adverse consequences of loop diuretics. Patients with hypertension, coronary ischemia, or significant MR may be suitable candidates for the use of intravenous nitroglycerin. However, tachyphylaxis may develop within 24 hours, and up to 20% of those with HF may develop resistance to even high doses.<sup>3,4</sup> Because of sodium nitroprusside's potential for producing marked hypotension, invasive hemodynamic blood pressure monitoring (eg, an arterial line) is typically required, and nitroprusside is usually used in the intensive care setting; longer infusions of the drug have been associated, albeit rarely, with thiocyanate and cyanide toxicity, particularly in the setting of renal insufficiency and significant hepatic disease. Nitroprusside is potentially of value in severely congested patients with hypertension or severe MV regurgitation complicating LV dysfunction.<sup>5</sup> Overall, there are no data that suggest that intravenous vasodilators improve outcomes in the patient hospitalized with HF; as such, use of intravenous vasodilators is limited to the relief of dyspnea in the hospitalized HF patient with intact or high blood pressure.<sup>6,7</sup>

### 9.4b. VTE Prophylaxis in Hospitalized Patients

Recommendation for VTE Prophylaxis in Hospitalized Patients		
Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	LOE	Recommendation
1	B-R	1. In patients hospitalized with HF, prophylaxis for VTE is recommended to prevent venous thromboembolic disease. <sup>1-3</sup>

#### Synopsis

HF has long been recognized as affording additional risk for venous thromboembolic disease. When patients are hospitalized for decompensated HF, or when patients with chronic stable HF are hospitalized for other reasons, they are at increased risk for venous thromboembolic disease. The risk may be associated with higher HF symptom burden.<sup>4</sup> This risk may extend for up to 2 years after hospitalization but is greatest in the first 30 days.<sup>5,6</sup> The use of anticoagulation with subcutaneous low-molecular-weight heparin, unfractionated heparin, fondaparinux, or approved DOAC are used for the prevention of clinically symptomatic deep vein thrombosis and pulmonary embolism.<sup>7,8</sup>

## Recommendation-Specific Supporting Text

1. Trials using available antithrombotic drugs often were not limited to patients with HF but included

patients with acute illnesses, severe respiratory diseases, or simply a broad spectrum of hospitalized medical patients.<sup>9-12</sup> All included trials excluded patients perceived to have an elevated risk of bleeding complications or of toxicity from the specific agent tested (eg, enoxaparin in patients with compromised renal function). In some trials, aspirin was allowed but not controlled for as a confounding variable. Despite the increased risk for the development of VTE in the 30 days after hospitalization, the data for extending prophylaxis to the immediate post-hospital period have shown decreased development of VTE but were associated with increased bleeding events and overall do not appear to provide additional benefit.<sup>2,3,11</sup> For patients admitted specifically for decompensated HF and with adequate renal function (creatinine clearance, >30 mL/min), randomized trials suggest that enoxaparin 40 mg subcutaneously once daily,<sup>1,13</sup> unfractionated heparin 5000 units subcutaneously every 8 or 12 hours,<sup>14-17</sup> or rivaroxaban 10 mg once daily<sup>11</sup> will radiographically reduce demonstrable venous thrombosis. Effects on mortality or clinically significant pulmonary embolism rates are unclear. For obese patients, a higher dose of enoxaparin 60 mg once daily achieved target range of thromboprophylaxis without increased bleeding.<sup>12</sup>

### 9.5. Evaluation and Management of Cardiogenic Shock

Recommendations for Evaluation and Management of Cardiogenic Shock		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-NR	1. In patients with cardiogenic shock, intravenous inotropic support should be used to maintain systemic perfusion and preserve end-organ performance. <sup>1-8</sup>
2a	B-NR	2. In patients with cardiogenic shock, temporary MCS is reasonable when end-organ function cannot be maintained by pharmacologic means to support cardiac function. <sup>9-17</sup>
2a	B-NR	3. In patients with cardiogenic shock, management by a multidisciplinary team experienced in shock is reasonable. <sup>17-22</sup>
2b	B-NR	4. In patients presenting with cardiogenic shock, placement of a PA line may be considered to define hemodynamic subsets and appropriate management strategies. <sup>23-27</sup>
2b	C-LD	5. For patients who are not rapidly responding to initial shock measures, triage to centers that can provide temporary MCS may be considered to optimize management. <sup>17-22</sup>

#### Synopsis

Cardiogenic shock is a commonly encountered clinical challenge with a high mortality and is characterized by

**Table 22. Suggested Shock Clinical Criteria<sup>29</sup>**

SBP <90 mm Hg for >30 min:
a. Or mean BP <60 mm Hg for >30 min
b. Or requirement of vasopressors to maintain systolic BP ≥90 mm Hg or mean BP ≥60 mm Hg
Hypoperfusion defined by:
c. Decreased mentation
d. Cold extremities, livedo reticularis
e. Urine output <30 mL/h
f. Lactate >2 mmol/L

BP indicates blood pressure; and SBP, systolic blood pressure.

\*Systolic BP and hypoperfusion criteria need to be met for the shock diagnosis.

a critical reduction in cardiac output manifest by end-organ dysfunction.<sup>28</sup> Hypotension (eg, SBP <90 mm Hg) is the primary clinical manifestation of shock but is not sufficient for the diagnosis. Additionally, end-organ hypoperfusion should be present as a consequence of cardiac dysfunction (Tables 22, 23, 24).<sup>29</sup> Causes can be broadly separated into acute decompensations of chronic HF, acute myocardial dysfunction without precedent HF, and survivors of cardiac arrest. In the case of acute MI, urgent revascularization is paramount. The approach to cardiogenic shock should include its early

**Table 23. Suggested Shock Hemodynamic Criteria<sup>29</sup>**

1. SBP <90 mm Hg or mean BP <60 mm Hg
2. Cardiac index <2.2 L/min/m <sup>2</sup>
3. Pulmonary capillary wedge pressure >15 mm Hg
4. Other hemodynamic considerations
a. Cardiac power output ([CO x MAP]/451) <0.6 W
b. Shock index (HR/systolic BP) >1.0
c. RV shock
i. Pulmonary artery pulse index [(PASP-PADP)/CVP] <1.0
ii. CVP >15 mm Hg
iii. CVP-PCW >0.6

BP indicates blood pressure; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCW, pulmonary capillary wedge; RV, right ventricular; and SBP, systolic blood pressure.

\*Diagnosis of shock requires ≥1 criteria to be present along with cardiac index <2.0 L/min/m<sup>2</sup> and SBP <90 mm Hg.

recognition, invasive hemodynamic assessment when there is insufficient clinical improvement to initial measures and providing appropriate pharmacological and MCS to optimize end-organ perfusion and prevent metabolic complications. The evidence that supports the use of specific pharmacologic therapies and the nature of temporary MCS is primarily gleaned from observational retrospective datasets. Only a few randomized trials have been conducted to assess the most appropriate circulatory support device, and they have been limited by small

**Table 24. Society for Cardiovascular Angiography and Interventions (SCAI) Cardiogenic Shock Criteria<sup>29</sup>**

Stage	Bedside Findings	Selected Laboratory Markers	Hemodynamics
A: At risk			
Normotensive	Normal venous pressure	Normal renal function	SBP >100 mm Hg
Normal perfusion	Clear lungs	Normal lactate	Hemodynamics: Normal
Cause for risk for shock such as large myocardial infarction or HF	Warm extremities		
	Strong palpable pulses		
	Normal mentation		
B: Beginning shock ("pre-shock")			
Hypotension	Elevated venous pressure	Preserved renal function	SBP <90 mm Hg, MAP <60 mm Hg, or >30 mm Hg decrease from baseline SBP
Normal perfusion	Rales present	Normal lactate	HR >100 bpm
	Warm extremities	Elevated BNP	Hemodynamics: CI ≥ 2.2 L/min/m <sup>2</sup>
	Strong pulses		
	Normal mentation		
C: Classic cardiogenic shock			
Hypotension	Elevated venous pressure	Impaired renal function	SBP <90 mm Hg; MAP <60 mm Hg; >30 mm Hg from baseline SBP despite drugs and temporary MCS
Hypoperfusion	Rales present	Increased lactate	HR >100 bpm
	Cold, ashen, livedo	Elevated BNP	Hemodynamics: CI ≤ 2.2 L/min/m <sup>2</sup> ; PCW >15 mm Hg; CPO <0.6 W; PAPi <2.0; CVP-PCW >1.0
	Weak or nonpalpable pulses	Increased LFTs	
	Altered mentation	Acidosis	
	Decreased urine output		
	Respiratory distress		
D: Deteriorating			
Worsening hypotension	Same as stage C	Persistent or worsening values of stage C	Escalating use of pressors or MCS to maintain SBP and end-organ perfusion in setting of stage C hemodynamics
Worsening hypoperfusion			
E: Extremis			
Refractory hypotension	Cardiac arrest	Worsening values of stage C laboratories	SBP only with resuscitation
Refractory hypoperfusion	CPR		PEA
			Recurrent VT/VF

BNP indicates brain natriuretic peptide; CI, cardiac index; CPO, cardiac power output; CPR, cardiopulmonary resuscitation; CVP, central venous pressure; HR, heart rate; LFT, liver function test; MAP, mean arterial blood pressure; MCS, mechanical circulatory support; PAPi, pulmonary artery pulsatility index; PCW, pulmonary capillary wedge pressures; PEA, pulseless electrical activity; SBP, systolic blood pressure; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Adapted from Baran D et al,<sup>29</sup> with permission from Wiley Periodicals, Inc.

sample size, the inherent open-label study design, short follow-up, and surrogate endpoints.

## Recommendation-Specific Supportive Text

- Intravenous inotropic support can increase cardiac output and improve hemodynamics in patients presenting with cardiogenic shock. Despite their ubiquitous use for initial management of cardiogenic shock, there are few prospective data and a paucity of randomized trials to guide their use.<sup>1–8</sup> However, their broad availability, ease of administration, and clinician familiarity favor such agents as the first therapeutic consideration when signs of organ hypoperfusion persist despite empiric volume replacement and vasopressors. There is a lack of robust evidence to suggest the clear benefit of one inotropic agent over another in cardiogenic shock.<sup>30</sup> In general, the choice of a specific inotropic agent is guided by blood pressure, concurrent arrhythmias, and availability of drug.
- Despite the lack of direct comparative data, the use of short-term MCS has dramatically increased.<sup>9–16,31,32</sup> The hemodynamic benefits of the specific devices vary, and few head-to-head randomized comparisons exist.<sup>33–39</sup> Randomized clinical trials are underway that will address the risks and benefits of one modality over another. Vascular, bleeding, and neurologic complications are common to MCS devices, and the risk of such complications should generally be considered in the calculation to proceed with such support.<sup>40</sup> As much as possible, an understanding of a patient's wishes, overall prognosis and trajectory, and assessment of therapeutic risk should precede the use of invasive temporary MCS.
- Team-based cardiogenic shock management provides the opportunity for various clinicians to provide their perspective and input to the patient's management.<sup>17–22</sup> The escalation of either pharmacological and mechanical therapies should be considered in the context of multidisciplinary teams of HF and critical care specialists, interventional cardiologists, and cardiac surgeons. Such teams should also be capable of providing appropriate palliative care. Most documented experiences have suggested outcomes improve after shock teams are instituted.<sup>17–22</sup> In 1 such experience, the use of a shock team was associated with improved 30-day all-cause mortality (HR, 0.61; 95% CI, 0.41–0.93) and reduced in-hospital mortality (61.0% vs. 47.9%;  $P=0.041$ ).<sup>19</sup>
- If time allows, escalation to MCS should be guided by invasively obtained hemodynamic data (eg, PA catheterization). Several observational experiences have associated PA catheterization use with improved outcomes, particularly in conjunction with short-term MCS.<sup>23–27,41</sup> PA catheterization may also be useful when there is diagnostic uncertainty as to the cause of hypotension or end-organ dysfunction, particularly when a patient in shock is not responding to empiric initial shock measures.<sup>42</sup>
- Transfer to centers capable of providing such support should be considered early in the assessment of a patient with cardiogenic shock and a trajectory of worsening end-organ malperfusion.<sup>17–22,43</sup> The treatment of shock should be recognized as a temporizing strategy to support end-organ perfusion and blood pressure until the cause of the cardiac failure has either been treated (eg, revascularization in ST-elevation MI) or recovery (eg, myocarditis) or a definitive solution to the cardiac failure can be accomplished (eg, durable LVAD or transplant). In many cases, pharmacological or MCS can provide sufficient time to address the appropriateness of more definitive therapies (eg, bridge-to-decision) with the patient, family, and the multidisciplinary shock team.

## 9.6. Integration of Care: Transitions and Team-Based Approaches

Recommendations for Integration of Care: Transitions and Team-Based Approaches		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-R	<ol style="list-style-type: none"> <li>In patients with high-risk HF, particularly those with recurrent hospitalizations for HFrEF, referral to multidisciplinary HF disease management programs is recommended to reduce the risk of hospitalization.<sup>1–4</sup></li> </ol>
1	B-NR	<ol style="list-style-type: none"> <li>In patients hospitalized with worsening HF, patient-centered discharge instructions with a clear plan for transitional care should be provided before hospital discharge.<sup>5,6</sup></li> </ol>
2a	B-NR	<ol style="list-style-type: none"> <li>In patients hospitalized with worsening HF, participation in systems that allow benchmarking to performance measures is reasonable to increase use of evidence-based therapy, and to improve quality of care.<sup>7–10</sup></li> </ol>
2a	B-NR	<ol style="list-style-type: none"> <li>In patients being discharged after hospitalization for worsening HF, an early follow-up, generally within 7 days of hospital discharge, is reasonable to optimize care and reduce rehospitalization.<sup>11,12</sup></li> </ol>

## Synopsis

For patients with HF, the transition from inpatient to outpatient care can be an especially vulnerable period because of the progressive nature of the disease state, complex medical regimens, the large number of comorbid conditions, and the multiple clinicians who may be

**Table 25. Important Components of a Transitional Care Plan**

A transitional care plan, communicated with the patient and their outpatient clinicians before hospital discharge, should clearly outline plans for:
Addressing any precipitating causes of worsening HF identified in the hospital;
Adjusting diuretics based on volume status (including weight) and electrolytes;
Coordination of safety laboratory checks (eg, electrolytes after initiation or intensification of GDMT);
Further changes to optimize GDMT, including: Plans for resuming medications held in the hospital; Plans for initiating new medications; Plans for titration of GDMT to goal doses as tolerated;
Reinforcing HF education and assessing compliance with medical therapy and lifestyle modifications, including dietary restrictions and physical activity;
Addressing high-risk characteristics that may be associated with poor post-discharge clinical outcomes, such as: Comorbid conditions (eg, renal dysfunction, pulmonary disease, diabetes, mental health, and substance use disorders); Limitations in psychosocial support; Impaired health literacy, cognitive impairment;
Additional surgical or device therapy, referral to cardiac rehabilitation in the future, where appropriate;
Referral to palliative care specialists and/or enrollment in hospice in selected patients.

GDMT indicates guideline-directed medical therapy; and HF, heart failure.

involved. Patients are at highest risk for decompensation requiring readmission in the days and weeks post-hospital discharge.<sup>13</sup> Optimal transitions of care can decrease avoidable readmissions and improve patient satisfaction.<sup>14</sup> Multidisciplinary systems of care that promote improved communication between health care professionals, systematic use and monitoring of GDMT, medication reconciliation, and consistent documentation are examples of patient safety standards that should be ensured for all patients with HF transitioning out of the hospital.

### Recommendation-Specific Supportive Text

1. HF disease management programs can help to organize the patient's care across settings. Potential team members may include cardiologists, primary care clinicians, HF nurses, pharmacists, dieticians, social workers, and community health workers. A Cochrane systematic review of 47 RCTs of disease management interventions after hospital discharge found that interventions that use case management (case manager or nurse coordinates care for high-risk patients) or multidisciplinary approach may decrease all-cause mortality and rehospitalization.<sup>3</sup> Disease management programs may comprise education, self-management, medication optimization, device management, weight monitoring, exercise and dietary advice, facilitated access to care during episodes of decompensation, and social and psychological support.<sup>14</sup> Disease

management programs coordinated by HF specialists, including HF nurses, may be best suited for patients with HFrEF; however, there are far fewer data on the effectiveness of disease management programs in patients with HFpEF.<sup>2</sup>

2. Although hospitalizations for worsening HF are often characterized by rapid changes in medical, surgical, and device therapy to optimize a patient's clinical status, the patient's journey with achieving optimal HF care continues beyond hospital discharge. Written discharge instructions or educational material given to the patient, family members, or caregiver during the hospital stay or at discharge to home should address all of these: activity level, diet, discharge medications, follow-up appointment, weight monitoring, cardiac rehabilitation, and what to do if symptoms worsen.<sup>14</sup> Thorough discharge planning that includes special emphasis on ensuring adherence to an evidence-based medication regimen is associated with improved patient outcomes.<sup>15,16</sup> Details of the hospital course and the transitional plan of care, with special attention to changes in medications and new medical diagnoses, must be transmitted in a timely and clearly understandable form to all of the patient's clinicians who will be delivering follow-up care (Table 25). Any changes in prognosis that will require appropriate care coordination and follow-up post-discharge should be noted.
3. Systems of care designed to support patients with HF as they move through the continuum of care can improve outcomes.<sup>7,14,17,18</sup> Real-time feedback on performance measure benchmarks can improve use of evidence-based therapy and quality of care.<sup>8</sup> Quality improvement programs designed to increase the prescription of appropriate discharge medications can increase GDMT prescription at discharge and decrease readmissions and mortality.<sup>9</sup> Electronic point-of-care reminders to prescribe GDMT in patients with HFrEF can improve use.<sup>10,19</sup> Leveraging transparent health care analytics platforms for benchmarking and performance improvement may be helpful. There are ongoing studies to determine the most effective strategies to improve evidence-based care.<sup>20</sup>
4. Early outpatient follow-up, a central element of transitional care, varies significantly across US hospitals.<sup>11</sup> Early postdischarge follow-up may help minimize gaps in understanding of changes to the care plan or knowledge of test results and has been associated with a lower risk of subsequent rehospitalization.<sup>11,12</sup> Transition of care interventions have often bundled timely clinical follow-up with other interventions, making it challenging to isolate any unique intervention effects.<sup>21</sup> A structured contact with the patient within 7 days of hospital

**Table 26.** Most Common Co-Occurring Chronic Conditions Among Medicare Beneficiaries With HF (N=4 947 918), 2011

Beneficiaries Age ≥65 y (n=4 376 150)*			Beneficiaries Age <65 y (n=571 768)†		
	n	%		n	%
Hypertension	3 685 373	84.2	Hypertension	4 612 35	80.7
Ischemic heart disease	3 145 718	71.9	Ischemic heart disease	3 658 89	64.0
Hyperlipidemia	2 623 601	60.0	Diabetes	3 386 87	59.2
Anemia	2 200 674	50.3	Hyperlipidemia	3 254 98	56.9
Diabetes	2 027 875	46.3	Anemia	2 841 02	49.7
Arthritis	1 901 447	43.5	CKD	2 570 15	45.0
CKD	1 851 812	42.3	Depression	2 070 82	36.2
COPD	1 311 118	30.0	Arthritis	2 019 64	35.3
AF	1 247 748	28.5	COPD	1 910 16	33.4
Alzheimer's disease or dementia	1 207 704	27.6	Asthma	888 16	15.5

Data source: Centers for Medicare & Medicaid Services administrative claims data, January 2011 to December 2011, from the Chronic Condition Warehouse (CCW), ccwdata.org.<sup>50</sup>

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and HF, heart failure.

\*Mean No. of conditions is 6.1; median is 6.

†Mean No. of conditions is 5.5; median is 5.

discharge is a desired goal. Although historically this has been an in-person visit, telemedicine is being increasingly used for chronic management. A pragmatic randomized trial found that an initial telephone visit with a nurse or pharmacist to guide follow-up may reduce the need for in-person visits if they are constrained.<sup>22</sup> Overall, the timing and method of delivery (in-person clinic versus virtual visit by video or telephone) should be individualized based on patient risk and available care delivery options. Clinical risk prediction tools may help to identify patients at highest risk of postdischarge adverse outcomes.<sup>23–25</sup>

## 10. COMORBIDITIES IN PATIENTS WITH HF

### 10.1. Management of Comorbidities in Patients With HF

#### Recommendations for the Management of Comorbidities in Patients With HF

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

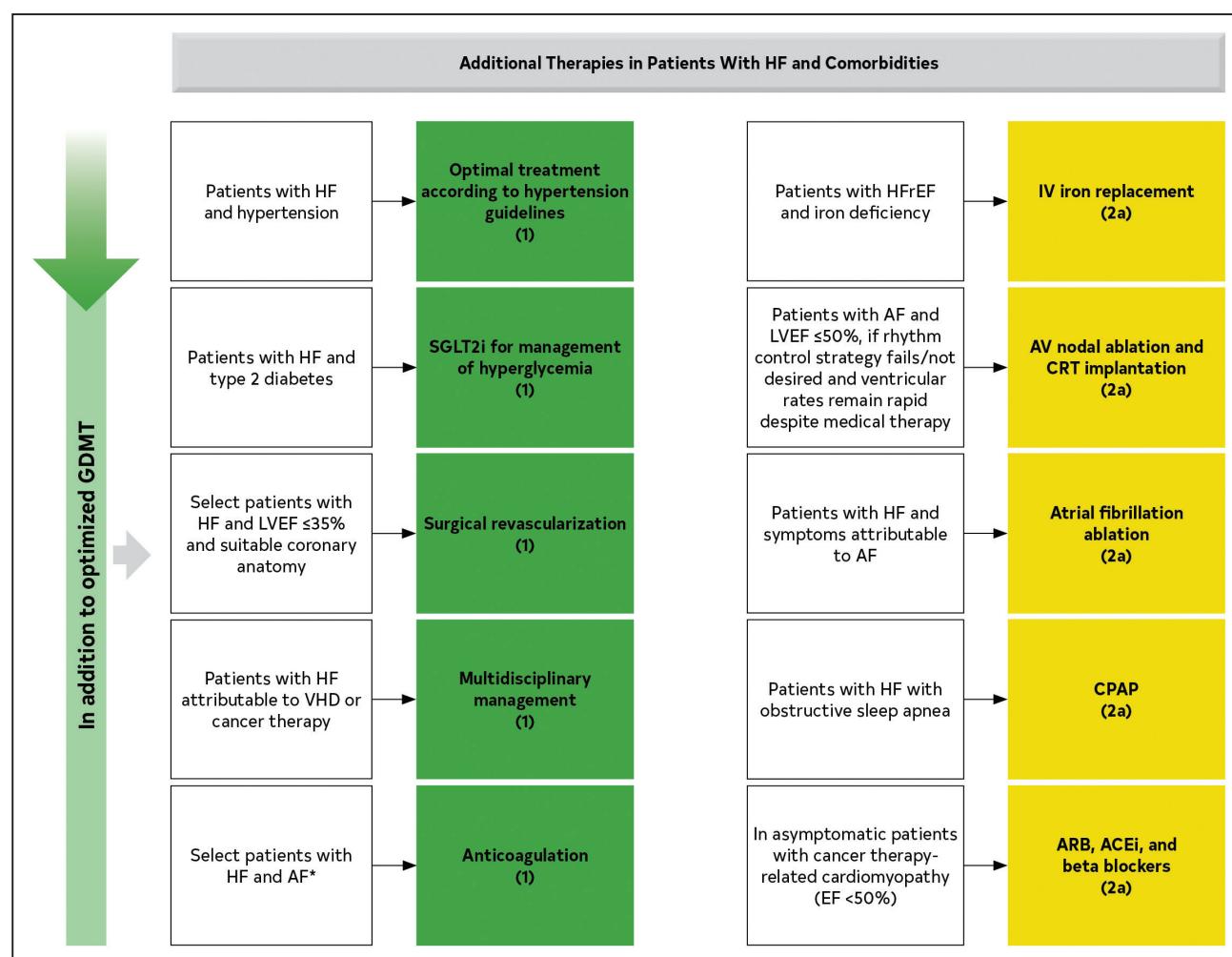
COR	LOE	Recommendations
<b>Management of Anemia or Iron Deficiency</b>		
2a	B-R	1. In patients with HFrEF and iron deficiency with or without anemia, intravenous iron replacement is reasonable to improve functional status and QOL. <sup>1–4</sup>
3: Harm	B-R	2. In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality. <sup>5,6</sup>
<b>Management of Hypertension</b>		
1	C-LD	3. In patients with HFrEF and hypertension, uptitration of GDMT to the maximally tolerated target dose is recommended. <sup>7,8</sup>

#### Recommendations for the Management of Comorbidities in Patients With HF (Continued)

COR	LOE	Recommendations
<b>Management of Sleep Disorders</b>		
2a	C-LD	4. In patients with HF and suspicion of sleep-disordered breathing, a formal sleep assessment is reasonable to confirm the diagnosis and differentiate between obstructive and central sleep apnea. <sup>9,10</sup>
2a	B-R	5. In patients with HF and obstructive sleep apnea, continuous positive airway pressure may be reasonable to improve sleep quality and decrease daytime sleepiness. <sup>9,11–13</sup>
3: Harm	B-R	6. In patients with NYHA class II to IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm. <sup>11,12</sup>
<b>Management of Diabetes</b>		
1	A	7. In patients with HF and type 2 diabetes, the use of SGLT2i is recommended for the management of hyperglycemia and to reduce HF-related morbidity and mortality. <sup>14–17</sup>

### Synopsis

Multimorbidity is common in patients with HF, with >85% of patients having ≥2 additional chronic conditions.<sup>18,19</sup> Hypertension, ischemic heart disease, diabetes, anemia, CKD, morbid obesity, frailty, and malnutrition are among the most common comorbid conditions in patients with HF (Table 26). These chronic conditions complicate the management of HF and have a significant impact on its prognosis. How to generate specific recommendations addressing many of these conditions in the setting of HF is challenging given the current state of the evidence. For example, although depression is common in patients with HF and strongly impacts QOL and mortality, conventional therapies such as antidepressants have not been effective in



**Figure 14. Recommendations for Treatment of Patients With HF and Selected Comorbidities.**

Colors correspond to COR in Table 2. Recommendations for treatment of patients with HF and select comorbidities are displayed. ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AV, atrioventricular; CHA<sub>2</sub>DS<sub>2</sub>-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category; CPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor; and VHD, valvular heart disease. \*Patients with chronic HF with permanent-persistent-paroxysmal AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of ≥2 (for men) and ≥3 (for women).

improving outcomes.<sup>20–22</sup> CKD and HF are closely intertwined in pathophysiology and have a complex and bidirectional relationship.<sup>23</sup> Renal dysfunction increases the risk of toxicities of HF therapies and impairs response to diuretics.<sup>23</sup> The effectiveness of GDMT in patients with HF and concomitant kidney disease is uncertain, because data for treatment outcomes in this patient population are sparse.<sup>24</sup> Recommendations surrounding the management of anemia, hypertension, diabetes, and sleep disorders that are attributable to the presence of evolving evidence for specific treatment strategies in HF are discussed next. Other comorbidities not addressed in the recommendations are, of course, also important and warrant attention but, because of lack of large-scale trial data, are not addressed as specific recommendations. Figure 14 summarizes COR 1 and 2a for management of select HF comorbidities.

## Recommendation-Specific Supportive Text

### Anemia

1. Routine baseline assessment of all patients with HF includes an evaluation for anemia. Anemia is independently associated with HF disease severity and mortality,<sup>25</sup> and iron deficiency appears to be uniquely associated with reduced exercise capacity.<sup>26</sup> Iron deficiency is usually defined as ferritin level <100 µg/L or 100 to 300 µg/L, if the transferrin saturation is <20%. Intravenous repletion of iron has been shown to improve exercise capacity and QOL.<sup>1–3,27</sup> The FAIR-HF (Ferric Carboxymaltose Assessment in Patients With Iron Deficiency and Chronic Heart Failure) trial showed significant improvement in NYHA classification,

the 6-minute walk test, and QOL of 459 outpatients with chronic HF who received weekly intravenous ferric carboxymaltose until iron repletion.<sup>1</sup> The improvement was independent of the presence of anemia. These findings were confirmed in 2 more recent trials.<sup>2,3</sup> The IRONOUT HF (Iron Repletion Effects on Oxygen Uptake in Heart Failure) trial, however, showed no such improvement with oral iron supplementation.<sup>28</sup> This is attributed to the poor absorption of oral iron and inadequacy of oral iron to replete the iron stores in patients with HF. Therefore, oral iron is not adequate to treat iron deficiency anemia in patients with HF. Although these trials were underpowered to detect reductions in hard clinical endpoints, 2 meta-analyses have suggested intravenous iron is associated with a reduction in cardiovascular death and hospitalizations.<sup>27,29</sup> Most recently, the AFFIRM-AHF multicenter trial, which included 1132 patients with EF <50% hospitalized for HF, showed a decrease in hospitalization for HF with intravenous ferric carboxymaltose compared to placebo (RR, 0.74; 95% CI, 0.58–0.94) but no reduction in cardiovascular death.<sup>4</sup>

2. Anemia in patients with HF is associated with impaired erythropoietin production, with low levels found to be associated with worse long-term outcomes.<sup>30,31</sup> Although small studies examining the use of erythropoietin-stimulating agents for the treatment of anemia in patients with HF have suggested a trend toward improvement in functional capacity and reduction in hospitalization, a high-quality randomized trial of darbepoetin alpha in 2278 patients showed no benefit and an increase in thrombotic events, including stroke.<sup>5,6,32</sup> A meta-analysis of 13 trials supports these findings.<sup>6</sup> Accordingly, erythropoietin-stimulating agent therapy is not recommended for the treatment of anemia in patients with HF.

## Hypertension

3. Clinical trials assessing the impact of goal blood pressure reduction on outcomes in patients with HFrEF and concomitant hypertension are lacking. The optimal blood pressure goal and antihypertensive regimen are not known. Antihypertensive therapy is associated with a decrease in the risk of incident HF in the general population,<sup>33,34</sup> notably with the more stringent SBP target <120 mm Hg.<sup>35</sup> However, low blood pressure, not as a part of an antihypertensive treatment, has been associated with poor outcomes in patients with HFrEF.<sup>7,8</sup> This observation may reflect the association between low cardiac output and low blood pressure, rather than the effects of treatment for hypertension.

Nevertheless, hypertension in patients with HFrEF represents an opportunity to maximize GDMT to goal blood pressures defined by the ACC/AHA hypertension guidelines.<sup>36</sup>

## Sleep Disorders

4. In patients with HF, daytime sleepiness—typically a feature of obstructive sleep apnea—may not reflect the degree of underlying sleep-disordered breathing.<sup>37</sup> Hence, the decision to refer a patient for a sleep study should be based on clinical judgment. Because the treatment of obstructive sleep apnea and central sleep apnea differ, and because obstructive sleep apnea and central sleep apnea can co-occur,<sup>9,11,12</sup> sleep studies can inform clinical decision-making in patients with HF.
5. In patients with HF and central sleep apnea, continuous positive airway pressure is associated with better sleep quality and nocturnal oxygenation<sup>9</sup> but has not been shown to affect survival.<sup>38</sup> In adults with HFrEF and sleep-disordered breathing, meta-analyses of RCTs have shown that positive airway pressure therapy results in a moderate reduction in BNP<sup>39</sup> and improvement in blood pressure and LVEF.<sup>40</sup>
6. Adaptive servo-ventilation was associated with increased mortality in 2 RCTs involving patients with HFrEF and central sleep apnea.<sup>11,12</sup> Meta-analyses have supported these results.<sup>41,42</sup> The weight of evidence does not support the use of adaptive servo-ventilation for central sleep apnea in HFrEF.

## Diabetes

7. The American Diabetes Association guidelines recommend the use of SGLT2i as first-line agent for the treatment of hyperglycemia in patients with diabetes with HF or at high risk of HF.<sup>43</sup> SGLT2i are the first class of glucose-lowering agents to receive approval from the FDA for the treatment of HFrEF. Treatment of patients with type 2 diabetes with SGLT2i, including canagliflozin, dapagliflozin, empagliflozin, and sotagliflozin, is associated with a reduction in major adverse cardiovascular events, including hospitalization for HF and cardiovascular death.<sup>44</sup> The mechanisms underlying the improvement in cardiovascular outcomes attributed to SGLT2i are, however, unknown but appear to be only partially related to the glucosuric effect.<sup>45</sup> Two RCTs totaling 8474 patients with NYHA class II, III, or IV HF and EF ≤40%—DAPA-HF assessing dapagliflozin and EMPEROR-Reduced assessing empagliflozin—showed significant reductions in the relative risk of all-cause death (13%), cardiovascular

death (14%), hospitalization for HF (26%), and renal outcomes (38%) with SGLT2i treatment.<sup>14–17</sup> Benefits were consistent across age, sex, and in patients with or without diabetes. Whether dapagliflozin or empagliflozin improves outcomes specifically in patients with HFpEF is being studied.<sup>46,47</sup> The SOLOIST-WHF trial extends the benefits of SGLT2i to patients with diabetes and acutely decompensated HF.<sup>48</sup> Patients on SGLT2i should be closely monitored for potential risks, including severe genitourinary infections and, less commonly, diabetic ketoacidosis.<sup>49</sup>

## 10.2. Management of AF in HF

Recommendations for Management of AF in HF		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	A	<ul style="list-style-type: none"> <li>1. Patients with chronic HF with permanent-persistent-paroxysmal AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥2 (for men) and ≥3 (for women) should receive chronic anticoagulant therapy.<sup>1–5</sup></li> </ul>
1	A	<ul style="list-style-type: none"> <li>2. For patients with chronic HF with permanent-persistent-paroxysmal AF, DOAC is recommended over warfarin in eligible patients.<sup>2–10</sup></li> </ul>
2a	B-R	<ul style="list-style-type: none"> <li>3. For patients with HF and symptoms caused by AF, AF ablation is reasonable to improve symptoms and QOL.<sup>11–14</sup></li> </ul>
2a	B-R	<ul style="list-style-type: none"> <li>4. For patients with AF and LVEF ≤50%, if a rhythm control strategy fails or is not desired, and ventricular rates remain rapid despite medical therapy, atrioventricular nodal ablation with implantation of a CRT device is reasonable.<sup>15–22</sup></li> </ul>
2a	B-NR	<ul style="list-style-type: none"> <li>5. For patients with chronic HF and permanent-persistent-paroxysmal AF, chronic anticoagulant therapy is reasonable for men and women without additional risk factors.<sup>23–26</sup></li> </ul>

### Synopsis

The interplay between AF and HF is complex. It is clear that AF may worsen HF but also that HF increases the risk of AF. Data from randomized trials support the use of anticoagulation among those with HF and AF but not in patients with HF without AF. Anticoagulation may be accomplished with DOAC or with warfarin when favored because of other indications, cost or drug-drug interactions (the DOAC are generally preferred). The choice between rate or rhythm control strategy reflects both patient symptoms and the likelihood of better ventricular function with sinus rhythm. RCTs of rhythm control with antiarrhythmic agents versus rate control have not shown a benefit of rhythm control. More recent RCTs with ablation show that ablation may be preferable to antiarrhythmic drugs for a rhythm control strategy. Patients thought to have a cardiomyopathy resulting from rapid AF despite attempts at rate control should be aggressively treated to maintain sinus rhythm and, if that is not successful,

atrioventricular nodal ablation with placement of a CRT device can be considered. Patients with HF, and difficult to control rates, may benefit from atrioventricular node ablation and implantation of a permanent pacemaker if other rate and rhythm control measures fail. If their LVEF is >50%, there is no current evidence that CRT is beneficial compared with RV pacing.<sup>15,21</sup>

### Recommendation-Specific Supportive Text

1. The efficacy of long-term warfarin for the prevention of stroke in patients with AF is well established; randomized trials have shown reduced embolic rates and mortality. The AHA/ACC/Heart Rhythm Society guidelines for AF recommend use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (history of hypertension, age ≥75 [doubled weight], diabetes mellitus, previous stroke or transient ischemic attack or thromboembolism [doubled weight], vascular disease, age 65 to 74 years, sex category) to assess patient risk for adverse outcomes before initiating anticoagulation therapy.<sup>1,27,28</sup> Regardless of whether patients receive rhythm or rate control, anticoagulation is recommended for patients with HF and AF for stroke prevention with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥2 (for men) and ≥3 (for women).<sup>2–5</sup>
2. Trials of DOAC have compared the efficacy and safety with warfarin therapy rather than placebo. Several DOAC are available, including the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and the direct thrombin inhibitor dabigatran.<sup>2–5</sup> These drugs do not need routine anticoagulation monitoring or dose adjustment. The fixed dosing together with fewer interactions may simplify patient management, particularly with the polypharmacy commonly seen in HF, but cost for some patients can be prohibitive when not covered by insurance. These drugs have a potential for an improved benefit-risk profile compared with warfarin, which may increase their use in practice, especially in those at increased bleeding risk.<sup>6–9</sup> In a meta-analysis of 4 trials examining efficacy and safety of DOAC in patients with and without HF, DOAC more effectively reduced the rate of stroke or systemic embolism, major bleeding, and intracranial bleeding compared with warfarin, with no treatment heterogeneity by HF status.<sup>10</sup>
3. The 2 largest RCTs of AF ablation in HF showed a benefit in hospitalizations and mortality with ablation.<sup>11,12</sup> although other smaller trials did not. In the AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device) trial, 203 patients with persistent AF, LVEF <40%, and NYHA class II to III HF, ablation improved the likelihood of maintaining

normal sinus rhythm at 24 months compared with amiodarone and, in addition, had a 45% decrease in hospitalization and decrease in mortality (8% vs. 18%).<sup>11</sup> The CASTLE AF (Catheter Ablation for Atrial Fibrillation with Heart Failure) trial randomized 363 patients with paroxysmal or persistent AF, LVEF <35%, NYHA class II to IV HF, and ICD to ablation versus standard medical care.<sup>12</sup> The composite endpoint of death or rehospitalization was lower in ablation (28.5%) compared with standard care (44.6%). In addition, there was a lower mortality in the ablation group. In a meta-analysis of 11 RCTs comparing rhythm versus rate control, patients undergoing catheter ablation had improved survival (49% relative risk reduction) and reduced hospitalizations (56% relative risk reduction).<sup>13</sup>

4. If a rhythm control strategy fails or is undesired, and ventricular rates remain rapid despite medical therapy after all other options are exhausted, atrioventricular nodal ablation with implantation of a CRT device can be considered as a treatment option. Ablate and pace is an old strategy for difficult to rate control AF. Early studies with RV pacing showed benefit.<sup>15,16</sup> However, when RV pacing was compared with cardiac resynchronization in more recent trials, especially in those with reduced LVEFs, CRT generally produced more benefit than RV pacing.<sup>17–21</sup> The PAVE (Left Ventricular-Based Cardiac Stimulation post AV Nodal Ablation Evaluation) and the BLOCK-HF (Biventricular versus Right Ventricular Pacing in Patients with AV block) trials included patients with LVEF >35%, with mean EF 46%<sup>22</sup> in PAVE and 40% in BLOCK-HF (enrolled ≤50%). In both of these trials, patients undergoing CRT had improved outcomes.
5. HF is a hypercoagulable state and serves as an independent risk factor for stroke, systemic embolism, and mortality in the setting of AF.<sup>23,24</sup> There are compelling data to support the use of anticoagulation in most patients with HF and concomitant AF, barring contraindications. In patients with HF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, those with AF had a 3-fold higher risk compared with individuals without concomitant AF.<sup>25</sup> In a post hoc analysis of 2 contemporary HF trials, paroxysmal and new onset AF were associated with a greater risk for hospitalization caused by HF or stroke.<sup>26</sup> In a recent registry study, the risk of stroke was particularly higher in the initial period after diagnosis of HF among patients with prevalent AF.<sup>29</sup> Because HF is a risk factor, additional risk factors may not be required to support the use of anticoagulation in patients with HF, and the decision to anticoagulate can be individualized according to risk versus benefit.

## 11. SPECIAL POPULATIONS

### 11.1. Disparities and Vulnerable Populations\*

**Recommendations for Disparities and Vulnerable Populations**  
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. In vulnerable patient populations at risk for health disparities, HF risk assessments and multidisciplinary management strategies should target both known risks for CVD and social determinants of health, as a means toward elimination of disparate HF outcomes. <sup>1–6</sup>
1	C-LD	2. Evidence of health disparities should be monitored and addressed at the clinical practice and the health care system levels. <sup>7–13</sup>

\*This section crosslinks to Section 7.1.1, “Stage C Nonpharmacological Interventions and Self-Care Support in HF,” where screening and interventions for social determinants of health are now addressed.

### Synopsis

There are important differences in HF incidence, risk factors, clinical care needs, and outcomes between specific patient populations<sup>2,3,14,15</sup> (Table 27). It is essential that HF clinicians be aware of the biological factors, social determinants of health, and implicit biases that impact the burden of disease, clinical decision-making, and effective delivery of GDMT.<sup>9,16–18</sup> Women generally present with HF later in life, with more comorbidities and lower patient-reported health status than men.<sup>10,19</sup> Survival for women with HF is generally more favorable,<sup>20</sup> although access to specialty care may be lower.<sup>21–24</sup> The highest incident of HF is consistently observed in self-identified Black patients.<sup>25,26</sup> HF hospitalization and mortality rates for Black patients are also higher than for White patients, with the gap increasing over time for young men.<sup>2,4,27</sup> These differences are driven mostly by social circumstances; a biological premise or genetic explanation for disease or disease severity should not be inferred by race or ethnicity.<sup>28</sup> Older patients with HF are especially vulnerable to polypharmacy, multimorbidity, cognitive decline, and frailty.<sup>29,30</sup> Important strategies to remove biases within health care professionals and systems impacting minority and socioeconomically disadvantaged patient populations include implicit bias training, recruiting a diverse workforce, and promoting broad access to HF care.<sup>28,31–35</sup>

### Recommendation-Specific Supportive Text

1. Hypertension is significantly more prevalent in Black patients, compared with White patients, populations in the United States, with a younger age of onset and greater attributable cardiovascular risks.<sup>36,37</sup> An estimated 50000 to 350000 immigrants to the United States from Mexico and Central America may have asymptomatic *Trypanosoma*

**Table 27.** Risk of HF and Outcomes in Special Populations

Vulnerable Population	Risk of HF	HF Outcomes
Women	The lifetime risk of HF is equivalent between sexes, but HFpEF risk is higher in women—in FHS participants with new-onset HF, odds of HFpEF (EF >45%) are 2.8-fold higher in women than in men. <sup>66</sup> Sex-specific differences in the predictive value of cardiac biomarkers for incident HF. <sup>67</sup> Nontraditional cardiovascular risk factors, including anxiety, depression, caregiver stress, and low household income may contribute more toward incident heart disease in women than men. <sup>68</sup>	Overall, more favorable survival with HF than men. In the OPTIMIZE-HF registry, women with acute HF had a lower 1-y mortality (HR, 0.93; 95% CI, 0.89–0.97), although women are more likely not to receive optimal GDMT. <sup>20,69–71</sup> Lower patient-reported quality of life for women with HFrEF, compared with men. <sup>10,71</sup> Greater transplant waitlist mortality for women but equivalent survival after heart transplantation or LVAD implantation. <sup>24,52</sup>
Older adults	Per FHS, at 40 y of age, the lifetime risk of incident HF is 20% for both sexes; at 80 y of age, the risk remains 20% for men and women despite the shorter life expectancy. <sup>72</sup> LVEF is preserved in at least two-thirds of older adults with the diagnosis of HF. <sup>73</sup>	Among 1233 patients with HF aged ≥80 y, 40% mortality during mean 27-mo follow-up; survival associated with prescription of GDMT. <sup>74</sup>
Lower socioeconomic status populations	Among 27 078 White and Black adults of low income (70% earned <\$15 000/y) participating from 2002–2009 in the Southern Community Cohort Study, a 1 interquartile increase in neighborhood deprivation index was associated with a 12% increase in risk of HF (adjusted HR, 1.12; 95% CI, 1.07–1.18). <sup>46</sup>	Age-adjusted 1999–2018 HF mortality (deaths/100 000; mean and 95% CI) was higher with increasing quartiles of ADI, which is based on 17 indicators of employment, poverty, and education: Quartile 1, 20.0 (19.4–20.5); Quartile 2, 23.3 (22.6–24.0); Quartile 3, 26.4 (25.5–27.3); Quartile 4, 33.1 (31.8–34.4). <sup>6</sup>
Black populations	In MESA, patients of Black race had highest risk of incident HF (4.6/1000 person-years) and highest proportion of nonischemic incident HF. <sup>26</sup> Higher prevalence of HF risk factors including hypertension, obesity, and diabetes, compared with White populations. <sup>75</sup>	CDC data show race-based differences in HF mortality over time: Black men had a 1.16-fold versus 1.43-fold higher age-adjusted HF-related CVD death rate compared with White men in 1999 versus 2017; Black women had a 1.35-fold versus 1.54-fold higher age-adjusted HF-related CVD death rate compared with White women in 1999 versus 2017. <sup>27</sup> Gap in outcomes is more pronounced among younger adults (35–64 y of age) versus older adults (65–84 y of age); age-adjusted HF-related CVD death rates were 2.60-fold and 2.97-fold higher in young Black versus White men and women, respectively. <sup>27</sup> Higher rates of hospitalization <sup>3</sup> and mortality among patients with HFpEF. <sup>76</sup> Lower 5-year survival after heart transplant. <sup>77–79</sup>
Hispanic populations	MESA study showed higher HF incidence in Hispanic compared with non-Hispanic White groups (3.5 versus 2.4 per 1000 person-years) but lower than for African Americans (4.6/1000 person-years). <sup>72,80</sup>	Despite higher rates of hospitalization for HF compared with non-Hispanic Whites, Hispanic patients with HF have shown lower short-term mortality rates. <sup>81</sup> In GWTG, Hispanic patients with HFpEF had lower mortality (OR, 0.50; 95% CI, 0.31–0.81) than non-Hispanic Whites, but this was not the case for Hispanic patients with HFrEF (OR, 0.94; 95% CI, 0.62–1.43). <sup>82</sup> Lower risk of developing AF in the setting of HF, compared with White patients. <sup>83</sup>
Asian and Pacific Islander populations	Limited population-specific data for Asian and Pacific Islander subgroups in the United States. <sup>84,85</sup>	High rates of preventable HF hospitalization observed in some Asian and Pacific Islander populations. <sup>13</sup> Lower mortality rates from HF for Asian subgroups when listed as the primary cause of death, compared with non-Hispanic White groups. <sup>86</sup>
Native American and Alaskan Native populations	Limited population-specific data, with cardiovascular risk factor trends best characterized by the Strong Heart Study and Strong Heart Family Study, demonstrating high rates of hypertension and diabetes. <sup>11,87</sup>	Limited data suggest HF mortality rates in American Indians and Alaska Natives are similar to those in White populations. <sup>88</sup>

CDC indicates Centers for Disease Control and Prevention; CVD, cardiovascular disease; FHS, Framingham Heart Study; GDMT, guideline-directed medical therapy; GWTG, Get With The Guidelines registry; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MESA, Multi-Ethnic Study of Atherosclerosis; OPTIMIZE-HF, Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure; and OR, odds ratio.

cruzi, with 20% progressing to Chagas cardiomyopathy.<sup>38</sup> Diabetes is highly prevalent in Southeast Asian and Pacific Islander populations and more strongly associated with poor HF outcomes.<sup>39,40</sup> Among patients with established HF, social and medical vulnerabilities can impede successful

delivery of GDMT and are associated with poorer outcomes.<sup>5,41</sup> Among older adults, low income, social isolation, and lack of caregiver support increase HF mortality and low QOL.<sup>9,18,42</sup> Nursing home residents, and elderly inpatients with acute HF, are at risk of inadequate GDMT prescription,

although interventions in nursing facilities can improve care delivery for HF.<sup>30,43–45</sup> Lower socio-economic status is associated with HF incidence and HF mortality.<sup>6,46,47</sup> Homelessness,<sup>48</sup> substance use, food insecurity, and lack of transportation each represent potential barriers to optimal disease management.<sup>49</sup> Case management and social work services are essential to the comprehensive multidisciplinary HF team approach for coordinating complex medical, psychiatric, and social needs across multiple sectors.

- Health care system factors are a potential source of disparate HF care delivery and outcomes. Women are less likely to receive discharge instructions for HF,<sup>50</sup> less likely to be referred to specialty care,<sup>21,22</sup> and less likely to receive a heart transplantation,<sup>51–54</sup> compared with men. Patients with HF of Black race have been identified as less likely to receive care from a cardiologist during an ICU admission for HF<sup>55</sup> have less access to specialized inpatient HF care,<sup>12</sup> and may be vulnerable to clinician biases during evaluation for advanced HF therapies.<sup>11,53</sup> Hispanic patients are disproportionately noninsured in the United States,<sup>56</sup> may experience language barriers to quality care,<sup>7,57</sup> and also have less access to specialized inpatient HF care.<sup>12</sup> Native American and Alaskan Native populations experience particular challenges in specialty care access because Indian Health Service facilities are often small and rural.<sup>11</sup> Engaging patients in medical care within culturally tailored environments has proven successful.<sup>58,59</sup> HF written educational materials for patients and caregivers should be delivered at or below the sixth grade reading level.<sup>60</sup> Workplace interventions that improve cultural competency and address implicit biases are increasingly available. Many aspects of GDMT have been inadequately studied by population subgroups, largely as a result of clinical trial underrepresentation.<sup>61–65</sup>

## 11.2. Cardio-Oncology

Recommendations for Cardio-Oncology		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-NR	1. In patients who develop cancer therapy-related cardiomyopathy or HF, a multidisciplinary discussion involving the patient about the risk-benefit ratio of cancer therapy interruption, discontinuation, or continuation is recommended to improve management. <sup>1,2</sup>
2a	B-NR	2. In asymptomatic patients with cancer therapy-related cardiomyopathy (EF <50%), ARB, ACEi, and beta blockers are reasonable to prevent progression to HF and improve cardiac function. <sup>2–4</sup>

Recommendations for Cardio-Oncology (Continued)		
COR	LOE	Recommendations
2a	B-NR	3. In patients with cardiovascular risk factors or known cardiac disease being considered for potentially cardiotoxic anticancer therapies, pretherapy evaluation of cardiac function is reasonable to establish baseline cardiac function and guide the choice of cancer therapy. <sup>2,5–16</sup>
2a	B-NR	4. In patients with cardiovascular risk factors or known cardiac disease receiving potentially cardiotoxic anticancer therapies, monitoring of cardiac function is reasonable for the early identification of drug-induced cardiomyopathy. <sup>2,4,6,8</sup>
2b	B-R	5. In patients at risk of cancer therapy-related cardiomyopathy, initiation of beta blockers and ACEi/ARB for the primary prevention of drug-induced cardiomyopathy is of uncertain benefit. <sup>17–28</sup>
2b	C-LD	6. In patients being considered for potentially cardiotoxic therapies, serial measurement of cardiac troponin might be reasonable for further risk stratification. <sup>29–32</sup>

## Synopsis

Advances in cancer therapy and an aging population have led to a growing number of cancer patients with comorbid CVD receiving treatment for cancer.<sup>33,34</sup> Cardiovascular complications of cancer therapy, notably cardiomyopathy and HF, can result in significant morbidity and interruption of treatment, impacting both short- and long-term survival.<sup>35,36</sup> Because drug development in cancer therapeutics grows at an exponential pace, establishing a unified framework for the management of cancer therapy-related cardiomyopathy—commonly defined as a decrease in LVEF of at least 10% to <50%—is necessary to mitigate the cardiovascular risks of established novel therapies. Cardio-oncology is the practice of precancer therapy cardiovascular risk stratification, prevention, early detection, and treatment of cardiovascular complications.<sup>36,37</sup> The evidence from which guideline recommendations in cardio-oncology have emerged has been based on studies of anthracycline and trastuzumab-induced cardiomyopathy. Cancer therapy-related cardiomyopathy is, however, a heterogeneous disease, with a wide range of presentations—from asymptomatic LV dysfunction to cardiogenic shock—and drug-dependent pathophysiologic mechanisms that are often poorly understood. Until sufficient high-quality, drug-specific evidence and cost-effectiveness analyses for screening and monitoring are available, these recommendations are applicable across potentially cardiotoxic therapies (Table 28).

## Recommendation-Specific Supportive Text

- HF secondary to cancer therapy-related cardiomyopathy is associated with significantly worse

**Table 28. Cancer Therapies Known to Be Associated With Cardiomyopathy**

Class	Agent(s)	Cardiac Function Monitoring Often Performed in Clinical Practice	
		Pretherapy	Serial
Anthracyclines <sup>55–57</sup>	Doxorubicin, epirubicin	X	X
Alkylating agents <sup>58–60</sup>	Cyclophosphamide, ifosfamide, melphalan	X	
Antimicrotubule agents. <sup>51,62</sup>	Docetaxel		
Antimetabolites <sup>63–72</sup>	Fluorouracil, capecitabine, fludarabine, decitabine		
Anti-HER2 agents <sup>73–76</sup>	Trastuzumab, pertuzumab	X	X
Monoclonal antibodies <sup>77</sup>	Rituximab		
Tyrosine-kinase inhibitors <sup>78–100</sup>	Dabrafenib, dasatinib, lapatinib, pazopanib, ponatinib, sorafenib, trametinib, sunitinib, vandetanib, imatinib, vandetanib		
Immune checkpoint inhibitors <sup>39,40,101</sup>	Nivolumab, ipilimumab, pembrolizumab		
Protease inhibitors <sup>102–106</sup>	Bortezomib, carfilzomib		
Endocrine therapy <sup>107–111</sup>	Goserelin, leuprolide, flutamide, bicalutamide, nilutamide		
Chimeric antigen receptor T-cell therapy. <sup>112,113</sup>	Tisagenlecleucel, axicabtagene ciloleucel	X	
Hematopoietic stem cell transplantation <sup>744,114–119</sup>	Hematopoietic stem cell transplantation	X	
Radiation <sup>744,114–119</sup>	Chest		

outcomes.<sup>1,2,38</sup> Patients who develop HF while receiving potentially cardiotoxic therapies should have these therapies discontinued while a diagnostic workup is undertaken to ascertain the cause of HF and initiate GDMT. The complex decision to resume, modify, or permanently discontinue therapy by the primary oncologist should be done in a patient-centered approach in concert with a cardiovascular specialist in cardio-oncology. Factors impacting the decision include the severity of cancer therapy-related cardiomyopathy and the response to neurohormonal blockade, the offending agent's specific mechanism of injury, the patient's comorbid conditions and cancer-related prognosis and, lastly, the availability of alternative noncardiotoxic treatment options. However, the clinical significance of asymptomatic cancer therapy-related cardiomyopathy that is identified on routine monitoring is less clear. This is most apparent in patients receiving trastuzumab in whom asymptomatic decreases in LVEF can occur in >10% of patients yet result in a high recovery rate and low rate of discontinuation of therapy.<sup>1,2</sup> Accordingly, trastuzumab is often continued in patients deemed low risk while neurohormonal blockade is initiated. Conversely, patients diagnosed with immune checkpoint-related myocarditis typically have the offending agents discontinued indefinitely, given the associated high mortality.<sup>39,40</sup>

2. Studying the effectiveness of neurohormonal therapies specifically in patients with the *CTRC* gene is challenging given the relative infrequency of events, heterogeneity of offending agents, the poorly understood pathophysiology, and the

overlap with comorbid CVD. Available data in patients with anthracycline and trastuzumab-induced cardiomyopathy suggest beta blockers and ACEi are effective in improving LV dysfunction.<sup>2–4</sup> Given the dearth of data specific to cancer therapy-related cardiomyopathy for other GDMT, their use should align with the HFrEF management guidelines. Initiation and uptitration of standard HF therapies remains the mainstay of treatment in patients with cancer therapy-related cardiomyopathy or LVEF <50%, with close monitoring of cardiac function to guide discussions with oncology on the resumption of, or choice of, subsequent cancer therapies.<sup>2</sup>

3. Pretherapy quantification of LVEF in patients receiving potentially cardiotoxic cancer therapies serves 4 purposes: 1) pretherapy risk stratification and diagnosis of preexisting cardiomyopathy, 2) establish a reference baseline to which reevaluations can be compared, 3) initiate cardioprotective medications before cancer therapy, and 4) guide choice of cancer therapy. Echocardiography is recommended as the first-line modality for LVEF assessment given its availability, safety, relatively low cost, and its ability to provide structural and functional information beyond LVEF.<sup>2,5–16,41–47</sup> The risk of cancer therapy-related cardiomyopathy varies greatly across cancer therapies and is modified by pre-existing cardiovascular risk factors (Table 29). Pretherapy LVEF is a strong predictor of major adverse cardiovascular events in patients receiving potentially cardiotoxic therapies.<sup>2,5–10,42–47</sup> The clinical use and cost-effectiveness of systematic screening in all patients, however, is unclear.<sup>11–16</sup>

**Table 29. Risk Factors for Cancer Therapy-Related Cardiomyopathy**

Age ≥60 y
Black race
CAD
Hypertension
Diabetes
Preexisting cardiomyopathy
Previous exposure to anthracyclines
Previous chest radiation
Elevated troponin pretherapy

CAD indicates coronary artery disease.

Patients with cancer and preexisting cardiovascular risk factors are at significantly higher risk of cancer therapy-related cardiomyopathy, representing a population in which pretherapy evaluation would have a significantly higher yield.<sup>2,5–10,42–47</sup>

- The purpose of serial monitoring of LVEF in patients receiving potentially cardiotoxic anticancer agents is to identify subclinical cardiac injury, initiate cardioprotective agents, and consider temporary or permanent interruption of the offending agent.<sup>2,4,6,8,48</sup> The practice of LVEF monitoring has mostly been implemented in patients receiving anthracyclines, trastuzumab, or both (Table 28). In a study of 2625 patients receiving anthracyclines for breast cancer or lymphoma who underwent serial LVEF monitoring, cancer therapy-related cardiomyopathy occurred in 9% of patients, of whom 81% had mild symptoms (NYHA class I to II).<sup>4</sup> Beta blockers and ACEi-ARB were initiated in all patients, with 86% having at least partial recovery of LVEF.<sup>4</sup> Patients with recovered LVEF had a lower incidence of cardiac events than those that did not.<sup>4</sup> The clinical significance of an asymptomatic decrease in LVEF and the optimal frequency and duration of monitoring is less clear and likely depend on patient risk, the anticancer agent used, and its cumulative dose. Although a one-size-fits-all approach to monitoring for cancer therapy-related cardiomyopathy may be easier to implement systematically, it may not be the most cost-effective. Until additional data are available, limiting the monitoring to patients at higher risk of cancer therapy-related cardiomyopathy (Table 29) is a reasonable strategy.
- Whether the preemptive use of ACEi-ARB, spironolactone, or selected beta blockers such as carvedilol and nebivolol is effective in reducing the risk of cancer therapy-related cardiomyopathy

has been investigated in a number of small clinic trials, with conflicting findings.<sup>17–27,49</sup> The most supportive of this practice is a study that randomized 114 patients receiving high-dose chemotherapy and having a posttreatment troponin rise >0.07 ng/mL to enalapril or placebo.<sup>20</sup> None of the patients in the enalapril arm met the primary endpoint (>10% decrease in LVEF to below 50%), while 43% of patients in the standard of care group had a significant decrease in LVEF.<sup>20</sup> Although other studies have shown similar findings, the magnitude of the difference in LVEF between arms was often small (<5%) and of questionable clinical significance.<sup>19,22</sup> Not all studies have replicated these findings.<sup>18,21,24,26</sup> Most importantly, none of the studies have assessed whether preemptive use of HF therapies in patients at risk for cancer therapy-related cardiomyopathy improves clinical outcomes, such as mortality or hospitalization for HF. Additional studies are needed to define the appropriate criteria and patient population in whom to initiate medical therapies for the primary prevention of cancer therapy-related cardiomyopathy.

- Cardiovascular biomarkers, notably troponin, have been studied for cardiovascular risk stratification in patients undergoing potentially cardiotoxic therapies.<sup>29–32</sup> A study of 452 patients with breast cancer showed that an elevated pretreatment level (>14 ng/L) was associated with a 4-fold increase in the risk of cancer therapy-related cardiomyopathy.<sup>32</sup> Other smaller studies have found no advantage in measuring troponin or natriuretic peptides pretherapy.<sup>50–53</sup> Overall, these biomarker studies were observational and small in sample size and number of events.<sup>54</sup> Serial biomarkers may be more useful in risk stratification. For example, in a study of 703 patients receiving anthracyclines, an increase in troponin within 72 hours of chemotherapy and 1 month after the completion of treatment course were associated with a greater risk of cancer therapy-related cardiomyopathy.<sup>29</sup> The clinical use of measuring biomarkers was assessed in 1 trial in which 114 patients with posttreatment increase in troponin to >0.07 ng/mL were randomized to enalapril or standard of care.<sup>20</sup> None of the patients in the enalapril group had a decrease in LVEF, compared with 43% in the standard of care group.<sup>20</sup> Data for the use of natriuretic peptides are limited. In practice, biomarkers could provide rapid risk stratification in patients for which echocardiographic findings are equivocal and help determine whether symptoms are cardiovascular in origin.

## 11.3. HF and Pregnancy

Recommendations for HF and Pregnancy		
COR	LOE	Recommendations
<b>1</b>	<b>C-LD</b>	1. In women with a history of HF or cardiomyopathy, including previous peripartum cardiomyopathy, patient-centered counseling regarding contraception and the risks of cardiovascular deterioration during pregnancy should be provided. <sup>1–8</sup>
<b>2b</b>	<b>C-LD</b>	2. In women with acute HF caused by peripartum cardiomyopathy and LVEF <30%, anticoagulation may be reasonable at diagnosis, until 6 to 8 weeks postpartum, although the efficacy and safety are uncertain. <sup>9–12</sup>
<b>3: Harm</b>	<b>C-LD</b>	3. In women with HF or cardiomyopathy who are pregnant or currently planning for pregnancy, ACEi, ARB, ARNi, MRA, SGLT2i, ivabradine, and vericiguat should not be administered because of significant risks of fetal harm. <sup>13–15</sup>

### Synopsis

HF may complicate pregnancy either secondary to an existing prepregnancy cardiomyopathy, or as a result of peripartum cardiomyopathy.<sup>16–18</sup> Peripartum cardiomyopathy is defined as systolic dysfunction, typically LVEF <45%, often with LV dilation, occurring in late pregnancy or early postpartum with no other identifiable cardiomyopathy cause.<sup>14,19–21</sup> Peripartum cardiomyopathy occurs globally,<sup>22,23</sup> with the highest incidences in Nigeria, Haiti, and South Africa. Incidence in the United States is 1 in 1000 to 8000 deliveries and has risen over time.<sup>24,25</sup> Peripartum cardiomyopathy risk factors include maternal age >30 years, African ancestry, multiparity, multigestation, preeclampsia/eclampsia, anemia, diabetes, obesity, and prolonged tocolysis.<sup>22,23,26–30</sup> A genetic contribution is recognized,<sup>31–33</sup> particularly titan gene mutations.<sup>34,35</sup> Most women present with HF within 1 month postpartum; cardiogenic shock, arrhythmias, or venous-arterial thromboembolism are all possible. Treatment includes GDMT adjusted for pregnancy or breastfeeding status and anticoagulation consideration<sup>16</sup>; identification of a pathogenic 16-kDa prolactin led to trials of the dopamine-agonist bromocriptine.<sup>36–41</sup> Patient-centered multidisciplinary planning is essential, including early institution of mechanical support for shock<sup>42</sup> (Table 30). Prognosis is related to initial LVEF, LV thrombosis, RV involvement, preeclampsia, geographic region, and race.<sup>743–48</sup> LV recovery and survival is generally favorable in developed countries<sup>11,25,49</sup>; a 100-patient US registry showed 93% transplant/LVAD-free 1-year survival.<sup>46</sup>

### Recommendation-Specific Supportive Text

- Pregnancy is generally well-tolerated in women with cardiomyopathy and NYHA class I prepregnancy. However, clinical deterioration can occur, so pre-pregnancy counseling and shared decision-making

are essential.<sup>1,3,50</sup> Among women with non-peripartum cardiomyopathy, major cardiovascular events occurred in 39% (United States) and 35% (Canada) of pregnancies, with 1% and 7% mortality, respectively.<sup>51,52</sup> Previous cardiac events, NYHA class III to IV, or LVEF <40% markedly increased maternal and fetal risks.<sup>51–55</sup> The ROPAC (Registry of Pregnancy and Cardiac disease) study describes pregnancy outcomes for 1321 women with structural heart disease: Women with prepregnancy or peripartum cardiomyopathy had the highest mortality rate (2.4%).<sup>2,22</sup> ROPAC was used to validate the modified WHO risk classification<sup>56</sup>; the ZAHARA I (Zwangerschap bij Aangeboren Hartafwijkingen I) and CARPREG II (CARdiac disease in PREGnancy) scores also support shared decision-making.<sup>51,57,58</sup> Subsequent pregnancies for women with previous peripartum cardiomyopathy have been associated with further decreases in LV function, maternal death, and adverse fetal outcomes.<sup>43,58</sup> The strongest prognostic determinant is LVEF <50% before a subsequent pregnancy.<sup>6–8</sup> An international systematic review that included 93 subsequent pregnancies with persistent LV dysfunction reported 48% further LVEF deterioration, 49% HF symptoms, and 16% mortality, whereas among 98 with recovered LV function presubsequent pregnancy, these rates were 27%, 32%, and 0%, respectively.<sup>5</sup>

- Pregnancy is a hypercoagulable state even in the absence of cardiovascular complications. In the setting of acute HF, particularly when there is LV blood stasis because of severely reduced systolic function, the risk of intracardiac thrombus formation is significant. The incidence of intracardiac thrombi during acute HF caused by peripartum cardiomyopathy has been reported to be around 16% to 17%.<sup>9,10</sup> with 9% thromboembolic events in 2 separate cohorts<sup>11,12</sup> Women with an intracardiac thrombus or a thromboembolic event receive anticoagulation as per standard of care. Women with severely depressed LVEF (<30%) in the setting of acute HF caused by peripartum cardiomyopathy can be considered for anticoagulation, especially in the first 6 to 8 weeks postpartum, when hypercoagulability is most pronounced. If bromocriptine is used for postpartum women with severe acute HF caused by peripartum cardiomyopathy and LVEF <35%, it should be accompanied by at least prophylactic-dosed anticoagulation, because of the potential association with thromboembolic events.<sup>6</sup> However, the efficacy and safety of bromocriptine for acute peripartum cardiomyopathy treatment currently remains uncertain, and further randomized placebo-controlled trials are required to define the role of this therapy, particularly in the setting of contemporary HF GDMT and cardiogenic shock management.

**Table 30.** HF Management Strategies Across the Pregnancy Continuum

	Preconception	During Pregnancy	Postpartum
Nonpharmacological strategies	<p>Preconception genetic counseling and testing for potentially heritable cardiac conditions.</p> <p>Use of pregnancy cardiovascular risk tools,<sup>51,56-58</sup> and echocardiography for myocardial structure and function assessment, to provide information that facilitates informed counseling.</p> <p>For women planning a pregnancy, provide personalized counseling that promotes the autonomy and goals of the patient (and her partner, as applicable), the patient's ability for self-care and risk awareness, and ensures adequate psychosocial support for decision-making.<sup>3</sup></p> <p>For women not currently planning a pregnancy but who might conceive, discuss HF-specific considerations regarding pregnancy and refer to gynecology or primary care for contraceptive counseling.</p>	<p>Close maternal monitoring for HF signs or symptoms or other cardiovascular instability by cardiology and obstetric and maternal-fetal medicine teams; close fetal monitoring by the obstetric and maternal-fetal medicine teams.</p> <p>Consideration of routine echocardiographic screening in the third trimester for reassessment of myocardial structure and function before labor; echocardiography for any significant changes in HF symptoms or signs during pregnancy, or if HF medications are reduced or discontinued.<sup>18</sup></p> <p>BNP or NT-proBNP monitoring during pregnancy may have some value for prediction of cardiovascular events.<sup>73,74</sup></p> <p>Close maternal monitoring by obstetrics and maternal-fetal medicine teams for preeclampsia, which has shared risk factors and pathogenesis with PPCM.<sup>47,75</sup></p> <p>For women presenting with decompensated HF or cardiogenic shock, hemodynamic monitoring and MCS, as appropriate, within a multidisciplinary collaborative approach that supports prompt decision-making about the timing and mechanism of delivery.</p>	<p>Multidisciplinary recommendations from obstetrics and neonatology and pediatrics teams and shared decision-making regarding the maternal and neonatal risks and benefits of breastfeeding.</p> <p>For women presenting with decompensated HF or cardiogenic shock, HF management should include hemodynamic monitoring and mechanical circulatory support as appropriate</p>
Pharmacological strategies	<p>Review of all current medications.</p> <p>For women planning pregnancy imminently, modification of HF pharmacotherapy including discontinuation of any ACEi, ARB, ARNi, MRA, or SGLT2i or ivabradine medications; within a construct of multidisciplinary shared decision-making, continuation of a beta blocker (most commonly metoprolol), hydralazine, and nitrates; adjustment of diuretic dosing to minimize the risk of placental hypoperfusion.<sup>13-15</sup></p> <p>Ideally, repeat echocardiography approximately 3 mo after preconception HF medication adjustments to ensure stability of myocardial structure and function before conception.</p>	<p>Close monitoring of maternal blood pressure, heart rate, and volume status, with adjustment of the modified HF regimen as appropriate to avoid hypotension (systemic vasodilation peaks in the second trimester) and placental hypoperfusion.</p> <p>For women with HF or cardiomyopathy presenting during pregnancy without preconception counseling and assessment, urgent discontinuation of any GDMT pharmacotherapies with fetal toxicities; within a construct of multidisciplinary shared decision-making, continuation of a beta blocker (most commonly metoprolol succinate), hydralazine, and nitrates; adjustment of diuretic dosing to minimize the risk of placental hypoperfusion.</p>	<p>For women with acute HF caused by PPCM and LVEF &lt;30%, consideration of anticoagulation until 6–8 wk postpartum, although the efficacy and safety remain uncertain at this time.</p> <p>For postpartum women with severe acute HF caused by PPCM and LVEF &lt;35%, in GDMT pharmacotherapy and prophylactic anticoagulation, to improve LVEF recovery<sup>6,31,36,41,76</sup>; the efficacy and safety of bromocriptine for acute PPCM treatment remains uncertain at this time, particularly in the setting of contemporary HF GDMT and cardiogenic shock management.*</p> <p>For women who choose to breastfeed, review medications with neonatology and pediatrics teams for neonatal safety during lactation, ideally with pharmacist consultation if available.</p> <p>Within a construct of multidisciplinary shared decision-making, medications that may be appropriate during breastfeeding include ACEi (enalapril or captopril preferred, monitor neonatal weight), beta blockers (metoprolol preferred, monitor neonatal heart rate).<sup>15</sup></p> <p>Diuretics can suppress lactation, but with neonatal follow-up the use of furosemide may be appropriate.<sup>15</sup></p>
Multidisciplinary care beyond the cardiology team	Consultation with genetics, gynecology, and maternal-fetal medicine teams, as appropriate to the outcome of shared decision-making.	<p>Multidisciplinary management with obstetrics and maternal-fetal medicine teams during pregnancy.</p> <p>For women with decompensated HF or evidence of hemodynamic instability antepartum, delivery planning will include obstetrics and maternal-fetal medicine, anesthesia, and neonatology teams.</p>	<p>Multidisciplinary management with obstetrics, maternal-fetal medicine, neonatology, and pediatrics teams, especially for multidisciplinary recommendations regarding lactation.</p> <p>Consultation with gynecology team for ongoing contraceptive planning.</p>

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BNP, B-natriuretic peptide; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PPCM, peripartum cardiomyopathy; RCT, randomized controlled trial; RV, right ventricular; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

\*An initial open-label pilot RCT in South Africa suggested addition of bromocriptine to GDMT was associated with greater LVEF improvement and a lower rate of the composite endpoint at 6 mo.<sup>37</sup> Among 96 women with acute PPCM in a Burkina Faso RCT, 4 wk of bromocriptine was associated with LVEF recovery and lower mortality (16.6% versus 29.1%;  $P<0.001$ ).<sup>39</sup> A multicenter German study randomized 63 patients to 1 versus 8 wk of bromocriptine (no placebo, as deemed unethical),<sup>38</sup> with LVEF recovery  $\geq 50\%$  in 52% and 68% of the 1- and 8-wk groups, respectively, and no deaths. A substudy also showed high rates of RV recovery.<sup>41</sup> Two retrospective cohorts (Germany, Canada) and a multicenter cohort of subsequent pregnancies also suggested greater LVEF recovery with bromocriptine.<sup>31,38,40</sup> Bromocriptine may currently be most justified in women with LVEF  $<25\%$  or cardiogenic shock. The downsides of prohibiting breastfeeding should be considered. Bromocriptine should be accompanied by at least prophylactic-dosed anticoagulation, because of potential hypercoagulability.<sup>38</sup> The European Society of Cardiology endorses "BOARD" (Bromocriptine, Oral HF therapy, Anticoagulation, vasoRelaxing agents, Diuretics) for acute PPCM management.<sup>13,14</sup>

3. In 2015, the FDA adopted the Pregnancy and Lactation Labeling Rule, which retired the previous pregnancy risk categories A through X and, instead, assigned a descriptive risk summary to aid medication counseling for pregnant and breastfeeding women. ACEi and ARB are associated with second- and third-trimester renal and tubular dysplasia, oligohydramnios, fetal growth restriction, ossification disorders of the skull, lung hypoplasia, contractures, large joints, anemia, and intrauterine fetal death and are, therefore, strictly contraindicated.<sup>59–61</sup> There are no specific data for ARNi or ivabradine. For spironolactone, there is sufficient information regarding dose-dependent feminization of male rabbit and rat offspring to raise concern<sup>62</sup>; data are limited for eplerenone. HFrEF medications considered acceptable during pregnancy,<sup>15</sup> within a construct of multidisciplinary shared decision-making regarding benefits and potential risks, are furosemide, beta blockers (most commonly metoprolol),<sup>63–65</sup> hydralazine, and nitrates.<sup>13,14,19</sup> Women with peripartum cardiomyopathy were historically counseled against breastfeeding because of metabolic demands and prolactin stimulation, but breastfeeding may even be associated with LV recovery.<sup>66–70</sup> Postpartum women who breastfeed can start ACEi (enalapril or captopril preferred), and metoprolol remains the preferred beta blocker.<sup>66,71</sup> The National Library of Medicine hosts LactMed (<https://www.ncbi.nlm.nih.gov/books/NBK501922/>).<sup>72</sup>

## 12. QUALITY METRICS AND REPORTING

### 12.1. Performance Measurement

Recommendations for Performance Measurement		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-NR	1. Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for patients with HF. <sup>1–7</sup>
2a	B-NR	2. Participation in quality improvement programs, including patient registries that provide benchmark feedback on nationally endorsed, clinical practice guideline-based quality and performance measures can be beneficial in improving the quality of care for patients with HF. <sup>1,2,5,6</sup>

### Synopsis

The ACC/AHA Task Force on Performance Measures (Task Force) distinguishes quality measures from performance measures. Performance measures are selected from the most important ACC/AHA clinical practice guideline recommendations with the strongest evidence. These measures are suitable for public reporting or pay for performance. Quality measures are those metrics that may be useful for local quality improvement but do not

reach the performance measure standard. Performance measures of the ACC/AHA focus on process of care measures that measure the quality of care by the clinician, facility, and health system. Patient registries that track such measures can provide feedback to participants, which may help with improvement in quality.

### Recommendation-Specific Supportive Text

1. The current ACC/AHA performance and quality measures (based on the 2013 ACC/AHA HF guideline and the 2017 ACC/AHA/HFSA guideline supplement) are displayed in Table 31.<sup>8</sup> The performance measures are derived from the most definitive guideline recommendations (ie, NYHA class I and class III recommendations). Observational data suggest that hospitals that receive feedback on their HF care improve over time.<sup>1–7</sup>
2. Hospitals that perform well on medication-related performance measures have better HF mortality rates than hospitals with poorer performance.<sup>3,4</sup> Other observational data suggest that hospitals that participate in registries have better process of care and outcomes compared with hospitals that do not participate.<sup>5,6</sup> Randomized studies of audit and feedback of performance, in many different patient groups, have, in general, showed improvement in care.<sup>7</sup> However, public reporting of HF measures in Ontario, Canada, did not clearly improve care during a randomized trial.<sup>9</sup>

## 13. GOALS OF CARE

### 13.1. Palliative and Supportive Care, Shared Decision-Making, and End-of-Life

Recommendations for Palliative and Supportive Care, Shared Decision-Making, and End-of-Life		
Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	C-LD	1. For all patients with HF, palliative and supportive care—including high-quality communication, conveyance of prognosis, clarifying goals of care, shared decision-making, symptom management, and caregiver support—should be provided to improve QOL and relieve suffering. <sup>1</sup>
1	C-LD	2. For patients with HF being considered for, or treated with, life-extending therapies, the option for discontinuation should be anticipated and discussed through the continuum of care, including at the time of initiation, and reassessed with changing medical conditions and shifting goals of care. <sup>2,3</sup>
2a	B-R	3. For patients with HF—particularly stage D HF patients being evaluated for advanced therapies, patients requiring inotropic support or temporary mechanical support, patients experiencing uncontrolled symptoms, major medical decisions, or multimorbidity, frailty, and cognitive impairment—specialist palliative care consultation can be useful to improve QOL and relieve suffering. <sup>4–6</sup>

**Table 31.** ACC/AHA 2020 HF Clinical Performance, Quality, and Structural Measures<sup>8</sup>

Measure No.	Measure Title	Care Setting	Attribution	Measure Domain
PM-1	LVEF assessment	Outpatient	Individual practitioner Facility	Diagnostic
PM-2	Symptom and activity assessment	Outpatient	Individual practitioner Facility	Monitoring
PM-3	Symptom management	Outpatient	Individual practitioner Facility	Treatment
PM-4	Beta-blocker therapy for HFrEF	Outpatient Inpatient	Individual practitioner Facility	Treatment
PM-5	ACEi, ARB, or ARNi therapy for HFrEF	Outpatient Inpatient	Individual practitioner Facility	Treatment
PM-6	ARNi therapy for HFrEF	Outpatient Inpatient	Individual practitioner Facility	Treatment
PM-7	Dose of beta blocker therapy for HFrEF	Outpatient	Individual practitioner Facility	Treatment
PM-8	Dose of ACEi, ARB, or ARNi therapy for HFrEF	Outpatient	Individual practitioner Facility	Treatment
PM-9	MRA therapy for HFrEF	Outpatient Inpatient	Individual practitioner Facility	Treatment
PM-10	Laboratory monitoring in new MRA therapy	Outpatient Inpatient	Individual practitioner Facility	Monitoring
PM-11	Hydralazine and isosorbide dinitrate therapy for HFrEF in those patients self-identified as Black or African American	Outpatient Inpatient	Individual practitioner Facility	Treatment
PM-12	Counseling regarding ICD placement for patients with HFrEF on GDMT	Outpatient	Individual practitioner Facility	Treatment
PM-13	CRT implantation for patients with HFrEF on GDMT	Outpatient	Individual practitioner Facility	Treatment
QM-1	Patient self-care education	Outpatient	Individual practitioner Facility	Self-care
QM-2	Measurement of patient-reported outcome-health status	Outpatient	Individual practitioner Facility	Monitoring
QM-3	Sustained or improved health status in HF	Outpatient	Individual practitioner Facility	Outcome
QM-4	Post-discharge appointment for patients with HF	Inpatient	Individual practitioner, facility	Treatment
SM-1	HF registry participation	Outpatient Inpatient	Facility	Structure
Rehabilitation PMs Related to HF (From the 2018 ACC/AHA performance measures for cardiac rehabilitation <sup>10</sup> )				
Rehab PM-2	Exercise training referral for HF from inpatient setting	Inpatient	Facility	Process
Rehab PM-4	Exercise training referral for HF from outpatient setting	Outpatient	Individual practitioner Facility	Process

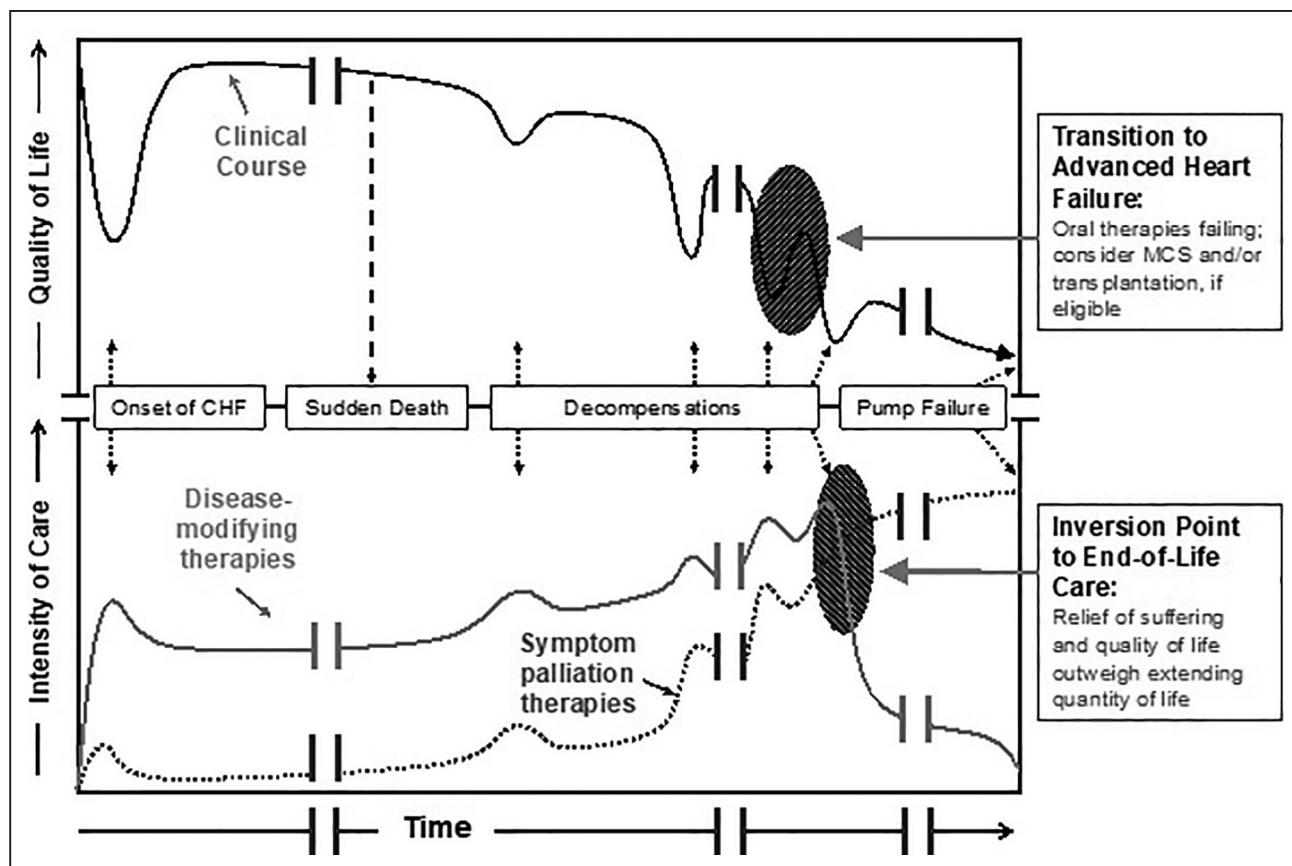
ACEi indicates angiotensin-converting enzyme inhibitor; ACC, American College of Cardiology; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PM, performance measure; QM, quality measure; and SM, structural measure.

#### Recommendations for Palliative and Supportive Care, Shared Decision-Making, and End-of-Life (Continued)

COR	LOE	Recommendations
2a	C-LD	4. For patients with HF, execution of advance care directives can be useful to improve documentation of treatment preferences, delivery of patient-centered care, and dying in preferred place. <sup>7</sup>
2a	C-LD	5. In patients with advanced HF with expected survival <6 months, timely referral to hospice can be useful to improve QOL. <sup>8</sup>

#### Synopsis

Palliative care—defined as patient- and family-centered care that optimizes health-related QOL by anticipating, preventing, and treating suffering—should be integrated into the care of all patients with HF.<sup>9</sup> Palliative care includes high-quality communication, estimation of prognosis, anticipatory guidance, addressing uncertainty; shared decision-making about medically reasonable treatment options; advance care planning; attention to physical, emotional, spiritual, and



**Figure 15. A Depiction of the Clinical Course of HF With Associated Types and Intensities of Available Therapies Over Time.<sup>12</sup>**

CHF indicates congestive heart failure; HF, heart failure; and MCS, mechanical circulatory support. Adapted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.<sup>13</sup> Readers are encouraged to read the entire article for the correct context at <https://www.atsjournals.org/doi/abs/10.1164/rccm.200605-587ST>. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations. Adapted with permission from the World Health Organization.<sup>14</sup> Copyright 1990 World Health Organization.

psychological distress; relief of suffering; and inclusion of family caregivers in patient care and attention to their needs during bereavement.<sup>10</sup> Other supportive needs include home and case management assistance, transportation, and care coordination.<sup>11</sup> Palliative and supportive care has a role across the stages of HF, starting early in the course of illness, intensifying in end-stage disease, and extending into caregiver bereavement (Figure 15).<sup>12</sup> Many palliative care needs can and should be addressed by the patient's interdisciplinary care team (primary palliative care), including clarifying their core values, health outcome goals, and therapeutic preferences.<sup>1</sup> Specialty palliative care clinicians (secondary palliative care) may be consulted to collaboratively care for patients and their families with more challenging needs.<sup>7</sup> Barriers to the receipt of palliative care include reluctance of health care professionals to address death and dying and a propensity for patients and caregivers to equate palliation and hospice as hastening death.<sup>15</sup>

### Recommendation-Specific Supportive Text

1. Palliative and supportive approaches to the care of patients with HF is inherent to their overall care and should be incorporated throughout the course of illness by all health care professionals.<sup>9</sup> The application of the principles embraced have been shown to improve various processes of care and patient outcomes (Table 32). Palliative and supportive care discussions do not imply that a formal palliative care consultation is needed for each patient but that team members should integrate palliative and supportive considerations into routine care.
2. As overall illness progresses, major decisions are increasingly made regarding the initiation, continued use, and discontinuation of potentially life-sustaining therapies, including intravenous inotropes, ICDs, MCS, and renal replacement therapy. Dependence on, and deactivation of, potentially life-sustaining therapies should be anticipated and

**Table 32. Palliative and Supportive Care Domains to Improve Processes of Care and Patient Outcomes**

Palliative and Supportive Domains of Care	What Palliative Care Adds to Overall HF Management
High-quality communication	Central to palliative care approaches are communication and patient-caregiver engagement techniques. <sup>16</sup>
Conveyance of prognosis	Palliative care specifically addresses patient and caregiver understanding of disease, treatment, and prognosis. Research suggests that patients tend to overestimate their survival <sup>17</sup> and overestimate the potential benefits of treatment. <sup>18</sup> Objective risk models can calibrate expectations, but discussion of uncertainty should accompany prognostic conversations, often summarized as “hope for the best, plan for the worst.”
Clarifying goals of care	Management of patients with HF as their disease becomes end-stage and death seems near includes decisions about when to discontinue treatments designed primarily to prolong life (eg, ICD, hospitalization, tube feeding), decisions on when to initiate treatments to reduce pain and suffering that may hasten death (eg, narcotics), and decisions about the location of death, home services, and hospice care. Exploring patients' expressed preferences, values, needs, concerns, means and desires through clinician-led discussion can clarify values-treatment concordance and improve medical decision-making. <sup>12</sup>
Shared decision-making	Shared decision-making is a process by which patients and clinicians work together to make optimal health care decisions from medically reasonable options that align with what matters most to patients. Shared decision-making requires: unbiased medical evidence about the risks, benefits, and burdens of each alternative, including no intervention; clinician expertise in communication and tailoring that evidence for individual patients; and patient goals and informed preferences. <sup>12</sup>
Symptom management	Dyspnea, fatigue, pain, nausea, depression, anxiety, and other symptoms of HF refractory to cardiovascular therapies can be partially remediated through palliative and supportive approaches in addition to GDMT. <sup>5</sup>
Caregiver support	Care of the patient with heart failure should extend to their loved ones, including beyond their death, to offer support to families and help them cope with loss.

GDMT indicates guideline-directed medical therapy; HF, heart failure; and ICD, implantable cardioverter-defibrillator.

discussed at the time of initiation and reconsidered serially with changing medical realities and evolving goals of care.<sup>12</sup> Patients have a right to decline or withdraw care at any time, consistent with the principle of respect for autonomy.<sup>19</sup> Failure to proactively address topics such as deactivation of ICD and LVAD therapies can lead to suffering at the end of life.<sup>23</sup>

3. Although a range of clinicians caring for patients with HF are able to manage many palliative care needs, formal palliative care consultation may be particularly helpful for patients with these: 1) refractory symptoms; 2) major medical decisions (eg, in the United States, inclusion of a palliative care specialist on the team is mandatory for payment from Medicare for LVAD implantation); and 3) multimorbidity, frailty, or cognitive impairment (multiple validated frailty and cognitive measures are available). A growing body of evidence supports the inclusion of specialty palliative care into the management of patients diagnosed with a range of advanced diseases,<sup>20</sup> including HF. An interdisciplinary palliative care intervention in patients with advanced HF showed greater benefits in QOL, anxiety, depression, and spiritual well-being compared with usual care alone (PAL-HF [Palliative Care in Heart Failure]).<sup>4</sup> However, other trials have been mixed,<sup>5,6</sup> and many negative,<sup>21-23</sup> such that formal palliative care interventions should be tailored to patient and caregiver wants and needs.

4. Advance care planning is a process that supports understanding and sharing of patients' personal values, life goals, and preferences regarding future medical care. Key domains include discussing patients' values, documenting plans for medical treatments, designating a surrogate decision maker, and revisiting this process over time.<sup>24</sup> Familiarity with local and state laws is needed relating to advance care planning, decisions regarding life-sustaining treatments, and evolving treatments with legal ramifications, especially when caring for vulnerable populations.<sup>19</sup> Few patients with HF have formally defined their care goals and designated a surrogate decision maker.<sup>25</sup>
5. Hospice is a specific model of subspecialty palliative care that is offered to patients with a terminal disease who are at the end of life when curative or life-prolonging therapy is no longer the focus of treatment.<sup>10</sup> Historically, hospice use has been low among patients dying with HF and, among those engaging in hospice, the duration of time in hospice was short, suggesting late referral. Low hospice referral rates and high-intensity care at end of life often reflects health care professional biases and limitations in models of care rather than patient values.<sup>26</sup> This appears to be changing in the United States, where CDC data from 2003 to 2017 on US site of death show that the proportion of cardiovascular deaths related to HF occurring in hospice facilities rose from 0.2% to 8.2% and deaths at home rose from 20.6% to 30.7%.<sup>27</sup>

**Table 33. Evidence Gaps and Future Research Directions**

Definition
Consensus on specific classifications of HFrEF, HFpEF, HFmrEF, and HFimpEF or whether a 2-category definition of HFrEF and HF with normal EF, or an additional category of HFimpEF is needed separately for HFpEF; and whether these approaches can be uniformly applied to clinical trials and practice.
Definitions, detection, and management of myocarditis and myocardial injury, especially in the context of rapidly evolving concepts, such as COVID-19 infection and cardiotoxicity.
Definition and classification of cardiomyopathies.
Screening
Cost-effectiveness of different strategies to screen for HF.
Prediction of higher risk for HF among patients with traditional risk factors (eg, which patients with diabetes would be at a higher risk HF, warranting preventive treatment for HF).
Diagnostics and monitoring
Individualized treatment targeting specific causes.
Advanced role of precision medicine with incorporation of genetic, personalized, and individualized factors in medical management of HF.
High-value methods to use biomarkers in the optimization of medical therapy.
Ability to use integrated systems biology models, including biomarkers, molecular markers, omics, diagnostic modalities, and genetic variables for diagnosis, prognosis, and targeting therapies.
Ability to monitor and adjust therapy to individual changes over time.
Nonmedical strategies
Efficacy and safety of specific dietary interventions, sodium restriction, and fluid restriction to prevent and treat HF.
Efficacy and safety of cardiac rehabilitation in patients with HFpEF and HFmrEF.
Medical therapies
Effective management strategies for patients with HFpEF.
Evidence for specific treatment strategies for HFmrEF.
Research on causes and targeted therapies for cardiomyopathies such as peripartum cardiomyopathy.
Treatment of asymptomatic LV dysfunction to prevent transition to symptomatic HF.
Therapies targeting different phenotypes of HF; patients with advanced HF, persistent congestion, patients with profiles excluded from clinical trials such as those with advanced kidney failure or hypotension.
Studies on targets for optimal decongestion; treatment and prevention of cardiorenal syndrome and diuretic resistance.
Diagnostic and management strategies of RV failure.
Efficacy and safety of hydralazine isosorbide in non–African American patients with HF and also in African American patients on GDMT including SGLT2i and ARNi.
Efficacy and safety of vericiguat in patients with HFrEF and markedly elevated natriuretic peptide levels.
Efficacy and safety of omecamtiv mecarbil in patients with stage D (advanced HF) HFrEF.
Additional efficacy and safety of SGLT2i therapies in patients with HFpEF or patients with HFmrEF, efficacy and safety of combined SGLT2i and SGLT1i in HFrEF, HFmrEF, or HFpEF.
Additional efficacy and safety of SGLT2i studies in hospitalized patients with acute decompensated HF with and without diabetes.
Efficacy and safety of nonsteroidal, selective MRA in patients with HF.
Efficacy and safety of ARNi in pre-HF stage (stage B).
Effective management strategies for combined post- and precapillary pulmonary hypertension.
Novel treatments for ATTR cardiomyopathy.
Treatment strategies targeting downstream processes such as fibrosis, cardiac metabolism or contractile performance in dilated cardiomyopathies and HFpEF.
Comparative effectiveness and safety of different initiation and titration of GDMT at the same time or in different sequences, optimal strategies for sequencing and titration of therapies for HFrEF and HFpEF.
Studies on prediction of patient response; studies on how to incorporate patient preferences.
Efficacy and safety of optimal BP target in patients with established HF and hypertension.
Optimal BP target while optimizing GDMT in patients with HFrEF and HFpEF.
Appropriate management of electrolyte abnormalities in HF (eg, hyperkalemia or hypokalemia).
Role of potassium binders in optimization of GDMT and clinical outcomes in patients with HF.
Efficacy and safety of pirenzipine and other targeted treatment strategies for maladaptive fibrosis in patients with HFpEF.
AF risk in patients treated with PUFA for patients at risk for HF or with HF.

(Continued)

**Table 33. Continued**

Device management and advanced therapies
Optimal and timely selection of candidates for percutaneous interventions, MCS, or cardiac transplantation.
Interventional approaches to recurrent, life-threatening ventricular tachyarrhythmias.
Comparative effectiveness of His-bundle pacing or multisite pacing to prevent progression of HF.
Safety and efficacy of cardiac contractility modulation, vagal nerve stimulation, autonomic modulation, and renal denervation in patients with HF.
Safety and efficacy of splanchnic nerve ablation splanchnic nerve ablation to reduce splanchnic vasoconstriction and volume redistribution in HF.
Safety and efficacy of interatrial shunt, pericardectomy, baroreceptor and neuromodulation, and renal denervation in HFrEF.
Safety and efficacy of percutaneous or surgical interventions for tricuspid regurgitation.
Clinical outcomes
Impact of therapies in patient-reported outcomes, including symptoms and QOL.
Studies addressing patient goals about care and care intensity as it intersects with disease trajectory.
Real-world evidence data to characterize generalization of therapies in HF populations who may not have been represented in trials.
Systems of care and social determinants of health
Implementation studies on how to develop a structured approach to patient participation in informed decision-making and goal setting through the continuum of HF care.
Implementation science for adoption and optimization of GDMT by clinicians on how to initiate multiple or sequenced GDMT, how to integrate these into learning health systems and networks, and how to increase patient education and adherence.
Pragmatic studies on multidisciplinary new care models (eg, cardiac teams for structural and valve management, shock teams, cardiometabolic clinics, telemedicine, digital health, cardiac rehabilitation at home or postdischarge, and palliative care).
Studies on strategies to eliminate structural racism, disparities, and health inequities in HF care.
Studies addressing evidence gaps in women, racial, and ethnic populations.
Management strategies for palliative care.
Identification of factors that lead to unwarranted variations in HF care.
Identify characteristics of systems of care (eg, disciplines and staffing, electronic health records, and models of care) that optimize GDMT before and after the discharge of hospitalized patients.
Comorbidities
Further studies on rhythm control versus ablation in AF.
Appropriate patient selection in evolving percutaneous approaches in VHD (eg, timing and appropriate patient selection for TAVI, Mitraclip, tricuspid valve interventions).
Effective and safe treatment options in CKD, sleep-disordered breathing, chronic lung disease, diabetes, depression, cognitive disorders, and iron deficiency.
Efficacy and safety of transvenous stimulation of the phrenic nerve or role of nocturnal supplemental oxygen for treatment of central sleep apnea in patients with HF.
Efficacy and safety of weight loss management and treatment strategies in patients with HF and obesity.
Efficacy and safety of nutritional and food supplementation in patients with HF and frailty and malnutrition.
Efficacy and safety of GDMT in end-stage renal disease or in patients with eGFR <30 mL/min/1.73 m <sup>2</sup> .
Future/novel strategies
Pharmacological therapies targeting novel pathways and endophenotypes.
New device therapies, including percutaneous and durable mechanical support devices.
Invasive (eg, pulmonary artery pressure monitoring catheter) or noninvasive remote monitoring.
Studies on telehealth, digital health, apps, wearables technology, and artificial intelligence.
Role of enrichment trials, adaptive trials, umbrella trials, basket trials, and machine learning-based trials.
Therapies targeting multiple cardiovascular, cardiometabolic, renovascular, and pathobiological mechanisms.
Novel dissemination and implementation techniques to identify patients with HF (eg, natural language processing of electronic health records and automated analysis of cardiac imaging data) and to test and monitor proven interventions.

AF indicates atrial fibrillation; ARNi, angiotensin receptor-neprilysin inhibitor; ATTR, transthyretin amyloidosis; BP, blood pressure; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; PUFA, polyunsaturated fatty acid; QOL, quality of life; RV, right ventricular; SGLT1i, sodium-glucose cotransporter-1 inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; TAVI, transcatheter aortic valve implantation; and VHD, valvular heart disease.

## 14. RECOMMENDATION FOR PATIENT-REPORTED OUTCOMES AND EVIDENCE GAPS AND FUTURE RESEARCH DIRECTIONS

### 14.1. Patient-Reported Outcomes

Recommendation for Patient-Reported Outcomes		
COR	LOE	Recommendation
<b>2a</b>	<b>C-LD</b>	1. In patients with HF, standardized assessment of patient-reported health status using a validated questionnaire can be useful to provide incremental information for patient functional status, symptom burden, and prognosis. <sup>1-19</sup>

#### Synopsis

Health status encapsulates symptoms, functional status, and health-related QOL. Understanding health status is important for treatment decisions and counseling. Clinicians traditionally evaluate health status based on the clinical interview and exam, summarizing it as the NYHA functional classification. Additionally, patient-reported health status can be ascertained using standardized questionnaires, such as the Kansas City Cardiomyopathy Questionnaire or the Minnesota Living with Heart Failure Questionnaire. Previous studies found discordance between patient-reported health status and clinician assessment using NYHA classification.<sup>20,21</sup> Patient-reported health status may have higher reliability and better sensitivity for clinical changes than NYHA classification and is moderately correlated with CPET and the 6-minute walk test.<sup>1-8</sup> Patient-reported health status is an independent predictor of hospitalization and mortality.<sup>9-19</sup> There are minimal data regarding the effect of incorporating patient-reported health status assessment into routine care. However, these assessments provide valuable incremental information beyond the standard evaluation. Increasing the patient's voice in clinical assessment and decision-making is important in its own right. Additionally, there is substantial variation in risk-adjusted health status across practices.<sup>22</sup> Future efforts should focus on expanding the use of patient-reported health status in routine care while researching its implementation and impact.

#### Recommendation-Specific Supportive Text

- Standardized patient-reported health status questionnaires provide reliable measures of health status correlated to other functional status measures<sup>1-8</sup> and independently associated with clinical outcomes.<sup>9-19</sup> HF-specific health status assessments (eg, Kansas City Cardiomyopathy Questionnaire, Minnesota Living with Heart Failure Questionnaire, PROMIS-Plus-HF [Patient-Reported Outcomes Measurement Information System-Plus-Heart Failure]) are preferable because they are more sensitive to changes in

disease status and more responsive to HF therapy than generic health status measures.<sup>1</sup> Although select clinics have successfully implemented patient-reported health status in clinical practice,<sup>23</sup> there are minimal data regarding the impact of such efforts. However, there are potential advantages to routine assessment. First, better understanding of symptom burden and prognosis may improve the quality of treatment decisions and, subsequently, QOL. Health status can be improved via guideline-recommended therapies.<sup>24-31</sup> Although some therapies are recommended for mortality benefit, symptom assessment can identify patients needing additional interventions (eg, diuretic escalation). Second, routine assessment can facilitate population health management by identifying high-risk patients needing closer monitoring or referral to specialized centers. Third, patient-reported health status assessment increases the patient's role, which can motivate initiation and uptitration of medical therapy. However, routine assessment of patient-reported status increases the burden of data collection for patients and health systems and underscores the need for future studies evaluating the impact of assessment.

### 14.2. Evidence Gaps and Future Research Directions

Significant gaps exist despite evolving evidence and treatment strategies in patients with HF. Table 33 provides selected, common issues that should be addressed in future clinical research.

#### ACC/AHA JOINT COMMITTEE MEMBERS

Joshua A. Beckman, MD, MS, FAHA, FACC, Chair; Patrick T. O'Gara, MD, MACC, FAHA, Immediate Past Chair\*; Sana M. Al-Khatib, MD, MHS, FACC, FAHA\*; Anastasia L. Armbruster, PharmD, FACC; Kim K. Birtcher, PharmD, MS, AACC\*; Joaquin E. Cigarroa, MD, FACC\*; Lisa de las Fuentes, MD, MS, FAHA; Anita Deswal, MD, MPH, FACC, FAHA; Dave L. Dixon, PharmD, FACC\*; Lee A. Fleisher, MD, FACC, FAHA\*; Federico Gentile, MD, FACC\*; Zachary D. Goldberger, MD, FACC, FAHA\*; Bulent Gorenek, MD, FACC; Norrisa Haynes, MD, MPH; Adrian F. Hernandez, MD, MHS; Mark A. Hlatky, MD, FACC, FAHA\*; José A. Joglar, MD, FACC, FAHA; W. Schuyler Jones, MD, FACC; Joseph E. Marine, MD, FACC\*; Daniel B. Mark, MD, MPH, FACC, FAHA; Debabrata Mukherjee, MD, FACC, FAHA; Latha P. Palaniappan, MD, MS, FACC, FAHA; Mariann R. Piano, RN, PhD, FAHA; Tanveer Rab, MD, FACC; Erica S. Spatz, MD, MS, FACC; Jacqueline E. Tamis-Holland, MD, FAHA, FACC; Duminda N. Wijeysundera, MD, PhD\*; Y. Joseph Woo, MD, FACC, FAHA

\*Former Task Force member; current member during the writing effort.

## PRESIDENTS AND STAFF

### American College of Cardiology

Dipti N. Itchhaporia, MD, FACC, President  
 Cathleen C. Gates, Chief Executive Officer  
 MaryAnne Elma, MPH, Senior Director, Enterprise Content and Digital Strategy  
 Grace D. Ronan, Team Leader, Clinical Policy Publications  
 Timothy W. Schutt, MA, Clinical Practice Guidelines Analyst

### American College of Cardiology/American Heart Association

Thomas S.D. Getchius, Director, Guideline Strategy and Operations  
 Abdul R. Abdullah, MD, Director, Guideline Science and Methodology

### American Heart Association

Donald M. Lloyd-Jones, MD, ScM, FAHA, President  
 Nancy Brown, Chief Executive Officer  
 Mariell Jessup, MD, FAHA, Chief Science and Medical Officer  
 Radhika Rajgopal Singh, PhD, Senior Vice President, Office of Science and Medicine  
 Paul St. Laurent, DNP, RN, Senior Science and Medicine Advisor, Office of Science, Medicine and Health  
 Jody Hundley, Production and Operations Manager, Scientific Publications, Office of Science Operations

## ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Heart Association Science Advisory and Coordinating Committee, the American College of Cardiology Science and Quality Committee, and the Heart Failure Society of America Executive Committee in December 2021 and the American Heart Association Executive Committee in January 2022.

Supplemental materials are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001063>

This article has been copublished in the *Journal of the American College of Cardiology* and the *Journal of Cardiac Failure*.

Copies: This document is available on the websites of the American Heart Association ([professional.heart.org](https://professional.heart.org)), the American College of Cardiology ([www.acc.org](https://www.acc.org)), and the Heart Failure Society of America ([www.hfsa.org](https://www.hfsa.org)). A copy of the document is also available at <https://professional.heart.org/statements> by selecting the "Guidelines & Statements" button. To purchase additional reprints, call 215-356-2721 or email [Meredith.Edelman@wolterskluwer.com](mailto:Meredith.Edelman@wolterskluwer.com).

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the "Guidelines & Statements" drop-down menu near the top of the webpage, then click "Publication Development".

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the "Copyright Permissions Request Form" appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

## REFERENCES

### PREAMBLE

- Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (US). *Clinical Practice Guidelines We Can Trust*. National Academies Press; 2011.
- Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (US). *Finding What Works in Health Care: Standards for Systematic Reviews*. National Academies Press; 2011.
- Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–2345.
- ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association; 2010. Accessed June 3, 2020. <https://www.acc.org/Guidelines/About-Guidelines-and-Clinical-Documents/Methodology> and [https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology\\_manual\\_and\\_policies\\_ucm\\_319826.pdf](https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology_manual_and_policies_ucm_319826.pdf)
- Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;133:1426–1428.
- Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. *Circulation*. 2014;130:1662–1667.
- Levine GN, O'Gara PT, Beckman JA, et al. Recent innovations, modifications, and evolution of ACC/AHA clinical practice guidelines: an update for our constituencies: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e879–e886.

### 1.4. Scope of the Guideline

- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646.
- Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e72–e227.
- Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e18–e114.
- Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *Circulation*. 2011;124:e652–e735.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651.
- Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients

- with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the Management of ST-elevation myocardial infarction. *Circulation*. 2016;133:1135–1147.
9. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142:e558–e631.
  10. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019;140:e125–e151.
  11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
  12. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2016;134:e282–e293.
  13. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767.
  14. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(suppl 2):S76–S99.
  15. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(suppl 2):s102–s138.
  16. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143.
  17. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(suppl 2):S1–S45.
  18. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(suppl 2):S49–S73.
  19. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
  20. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2012;126:1784–1800.
  21. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471.
  23. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124:2458–2473.
  24. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:e584–e636.
  25. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S768–S786.
  26. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.
  27. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e7–e22.
  28. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756–1776.
  29. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;115:114–126.
  30. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). Accessed March 24, 2021. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm>

## 1.5. Class of Recommendation and Level of Evidence

1. ACCF/AHA Task Force on Practice Guidelines. *Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines*. American College of Cardiology and American Heart Association; 2010. Accessed June 3, 2020. [https://www.acc.org/Guidelines/About-Guidelines-and-Clinical-Documents/Methodology\\_and\\_Policies\\_ucm\\_319826.pdf](https://www.acc.org/Guidelines/About-Guidelines-and-Clinical-Documents/Methodology_and_Policies_ucm_319826.pdf) and [https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology\\_manual\\_and\\_policies\\_ucm\\_319826.pdf](https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology_manual_and_policies_ucm_319826.pdf)

## 2.1. Stages of HF

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327.
2. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479.
3. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation*. 2007;115:1563–1570.
4. Goldman L, Hashimoto B, Cook EF, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation*. 1981;64:1227–1234.
5. Caraballo C, Desai NR, Mulder H, et al. Clinical implications of the New York Heart Association classification. *J Am Heart Assoc*. 2019;8:e014240.
6. Madsen BK, Hansen JF, Stokholm KH, et al. Chronic congestive heart failure: description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. *Eur Heart J*. 1994;15:303–310.
7. Ahmed A, Aronow WS, Fleg JL. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *Am Heart J*. 2006;151:444–450.

## 2.2. Classification of HF by Left Ventricular Ejection Fraction (LVEF)

- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327.
- Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14:591–602.
- Wilcox JE, Fang JC, Margulies KB, et al. Heart failure with recovered left ventricular ejection fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2020;76:719–734.
- Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail*. 2021;27:387–413.
- Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393:61–73.

## 2.3. Diagnostic Algorithm for Classification of HF According to LVEF

- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Eng Ed)*. 2016;69:1167.
- Erdei T, Smiseth OA, Marino P, et al. A systematic review of diastolic stress tests in heart failure with preserved ejection fraction, with proposals from the EU-FP7 MEDIA study group. *Eur J Heart Fail*. 2014;16:1345–1361.
- Donal E, Lund LH, Oger E, et al. Value of exercise echocardiography in heart failure with preserved ejection fraction: a substudy from the KaRen study. *Eur Heart J Cardiovasc Imaging*. 2016;17:106–113.
- Borlaug BA, Nishimura RA, Sorajja P, et al. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588–595.
- Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138:861–870.
- Sepehrvand N, Alemanyehu W, Dyck GJB, et al. External validation of the H2F-PEF model in diagnosing patients with heart failure and preserved ejection fraction. *Circulation*. 2019;139:2377–2379.
- Selvaraj S, Myhre PL, Vaduganathan M, et al. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. *J Am Coll Cardiol HF*. 2020;8:640–653.
- Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297–3317.

## 3.1. Epidemiology of HF

- Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606–619.
- Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743.
- Ni H, Xu J. Recent trends in heart failure-related mortality: United States, 2000–2014. NCHS Data Brief; 2015;1–8.
- Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;6:952–956.
- Khera R, Kondamudi N, Zhong L, et al. Temporal trends in heart failure incidence among Medicare beneficiaries across risk factor strata, 2011 to 2016. *JAMA Netw Open*. 2020;3:e2022190.
- Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *J Am Coll Cardiol HF*. 2018;6:678–685.
- Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14:591–602.

- Savitz ST, Leong T, Sung SH, et al. Contemporary reevaluation of race and ethnicity with outcomes in heart failure. *J Am Heart Assoc*. 2021;10:e016601.
- Rathore SS, Foody JM, Wang Y, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. *JAMA*. 2003;289:2517–2524.
- Vivo RP, Krim SR, Liang L, et al. Short- and long-term rehospitalization and mortality for heart failure in 4 racial/ethnic populations. *J Am Heart Assoc*. 2014;3:e001134.

## 3.2. Cause of HF

- Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743.

## 4.1. Clinical Assessment: History and Physical Examination

- Ambrosy AP, Pang P, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J*. 2013;34:835–843.
- Selvaraj S, Claggett B, Pozzi A, et al. Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. *Circulation*. 2019;140:1369–1379.
- Selvaraj S, Claggett B, Shah SJ, et al. Utility of the cardiovascular physical examination and impact of spironolactone in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12:e006125.
- Caldentey G, Khairy P, Roy D, et al. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: insights from the AF-CHF trial (atrial fibrillation and chronic heart failure). *J Am Coll Cardiol HF*. 2014;2:15–23.
- Simonavicius J, Sanders van-Wijk S, Rickenbacher P, et al. Prognostic significance of longitudinal clinical congestion pattern in chronic heart failure: insights from TIME-CHF Trial. *Am J Med*. 2019;132:e679–e692.
- Fudim M, Parikh KS, Dunning A, et al. Relation of volume overload to clinical outcomes in acute heart failure (from ASCEND-HF). *Am J Cardiol*. 2018;122:1506–1512.
- Anker SD, Negassa A, Coats AJ, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet*. 2003;361:1077–1083.
- Eshaghian S, Horwitz TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol*. 2006;97:1759–1764.
- Gorodeski EZ, Chu E, Reese JR, et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail*. 2009;2:320–324.
- Kittleson M, Hurwitz S, Shah MR, et al. Development of circulatory-renal limitations to angiotensin-converting enzyme inhibitors identifies patients with severe heart failure and early mortality. *J Am Coll Cardiol*. 2003;41:2029–2035.
- Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med*. 2008;359:1009–1017.
- Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*. 2007;154:260–266.
- Marume K, Noguchi T, Tateishi E, et al. Prognosis and clinical characteristics of dilated cardiomyopathy with family history via pedigree analysis. *Circ J*. 2020;84:1284–1293.
- Waddell-Smith KE, Donoghue T, Oates S, et al. Inpatient detection of cardiac-inherited disease: the impact of improving family history taking. *Open Heart*. 2016;3:e000329.
- González-López E, Gagliardi C, Dominguez F, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J*. 2017;38:1895–1904.
- Lousada I, Comenzo RL, Landau H, et al. Light chain amyloidosis: patient experience survey from the Amyloidosis Research Consortium. *Adv Ther*. 2015;32:920–928.

17. Drazner MH, Rame JE, Stevenson L, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med.* 2001;345:574–581.
18. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. *Circ Heart Fail.* 2008;1:170–177.
19. Thibodeau JT, Turer AT, Gualano SK, et al. Characterization of a novel symptom of advanced heart failure: borborema. *J Am Coll Cardiol HF.* 2014;2:24–31.
20. Feilker GM, Cuculich PS, Gheorghiade M. The Valsalva maneuver: a bedside "biomarker" for heart failure. *Am J Med.* 2006;119:117–122.
21. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation.* 2020;142:e7–e22.
22. Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. *Blood.* 2020;136:2620–2627.
23. Alexandre J, Cautela J, Ederly S, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European Cardio-Oncology Guidelines. *J Am Heart Assoc.* 2020;9:e018403.
24. Chang HM, Moudgil R, Scarabelli T, et al. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. *J Am Coll Cardiol.* 2017;70:2536–2551.
25. Chang HM, Okwusa TM, Scarabelli T, et al. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. *J Am Coll Cardiol.* 2017;70:2552–2565.
26. Prasad M, Hermann J, Gabriel SE, et al. Cardiorheumatology: cardiac involvement in systemic rheumatic disease. *Nat Rev Cardiol.* 2015;12:168–176.
27. Jabbar A, Pingitore A, Pearce S, et al. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol.* 2017;14:39–55.
28. Kenny HC, Abel ED. Heart failure in type 2 diabetes mellitus. *Circ Res.* 2019;124:121–141.
29. Zhang R, Gupta D, Albert SG. Pheochromocytoma as a reversible cause of cardiomyopathy: analysis and review of the literature. *Int J Cardiol.* 2017;249:319–323.
30. Colao A, Grasso LFS, Di Somma C, et al. Acromegaly and heart failure. *Heart Fail Clin.* 2019;15:399–408.
31. Horwitz TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis.* 2018;61:151–156.
32. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline. *J Card Fail.* 2018;24:281–302.
33. Huizar JF, Ellenbogen KA, Tan A, et al. Arrhythmia-induced cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;73:2328–2344.
34. Drazner MH. The progression of hypertensive heart disease. *Circulation.* 2011;123:327–334.
35. Kouranos V, Sharma R. Cardiac sarcoidosis: state-of-the-art review. *Heart.* 2021;107:1591–1599.
36. Muchtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res.* 2017;121:819–837.
37. Tschope C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol.* 2021;18:169–193.
38. Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. *Circulation.* 2018;138:e169–e209.
39. Davis MB, Arany Z, McNamara D, et al. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:207–221.
40. Napp LC, Bauersachs J. Takotsubo syndrome: between evidence, myths, and misunderstandings. *Herz.* 2020;45:252–266.
41. Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of Takotsubo syndrome. *Circulation.* 2017;135:2426–2441.
42. Ware JS, Amor-Salamanca A, Tayal U, et al. Genetic etiology for alcohol-induced cardiac toxicity. *J Am Coll Cardiol.* 2018;71:2293–2302.
43. Arenas DJ, Beltran S, Zhou S, et al. Cocaine, cardiomyopathy, and heart failure: a systematic review and meta-analysis. *Sci Rep.* 2020;10:19795.
44. Reddy PKV, Ng TMH, Oh EE, et al. Clinical characteristics and management of methamphetamine-associated cardiomyopathy: state-of-the-art review. *J Am Heart Assoc.* 2020;9:e016704.

#### 4.1.1. Initial Laboratory and Electrocardiographic Testing

- Cardiale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation.* 2015;131:1981–1988.
- Cardiale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation.* 2004;109:2749–2754.
- Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J.* 2017;38:2879–2887.
- Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol.* 2016;68:161–172.
- Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation.* 2016;133:2404–2412.
- Brown EE, Lee YZJ, Halushka MK, et al. Genetic testing improves identification of transthyretin amyloid (ATTR) subtype in cardiac amyloidosis. *Am J Cardiol.* 2017;24:92–95.
- Crawford TC, Okada DR, Magruder JT, et al. A contemporary analysis of heart transplantation and bridge-to-transplant mechanical circulatory support outcomes in cardiac sarcoidosis. *J Card Fail.* 2018;24:384–391.
- Wu RS, Gupta S, Brown RN, et al. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. *J Heart Lung Transplant.* 2010;29:432–438.
- Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation.* 2020;142:e7–e22.
- Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation.* 2016;134:e579–e646.
- Hendren NS, Drazner MH, Bozkurt B, et al. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation.* 2020;141:1903–1914.
- Kouranos V, Sharma R. Cardiac sarcoidosis: state-of-the-art review. *Heart.* 2021;107:1591–1599.
- Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. *Circulation.* 2018;138:e169–e209.
- Tschope C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol.* 2021;18:169–193.
- Davis MB, Arany Z, McNamara D, et al. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:207–221.

#### 4.2. Use of Biomarkers for Prevention, Initial Diagnosis, and Risk Stratification

- Richards AM, Doughty R, Nicholls MG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. *J Am Coll Cardiol.* 2001;37:1781–1787.
- Tang WH, Girod JP, Lee MJ, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation.* 2003;108:2964–2966.
- Zaphirou A, Robb S, Murray-Thomas T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail.* 2005;7:537–541.
- Son CS, Kim YN, Kim HS, et al. Decision-making model for early diagnosis of congestive heart failure using rough set and decision tree approaches. *J Biomed Inform.* 2012;45:999–1008.
- Kelder JC, Cramer MJ, van Wijngaarden J, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation.* 2011;124:2865–2873.
- Booth RA, Hill SA, Don-Wauchope A, et al. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. *Heart Fail Rev.* 2014;19:439–451.
- Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol.* 2001;37:379–385.

8. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet*. 1994;343:440–444.
9. Maisel AS, Krishnasamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161–167.
10. Januzzi JL Jr, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. *Am J Cardiol*. 2008;101:29–38.
11. Santaguida PL, Don-Wauchope AC, Ali U, et al. Incremental value of natriuretic peptide measurement in acute decompensated heart failure (ADHF): a systematic review. *Heart Fail Rev*. 2014;19:507–519.
12. Hill SA, Booth RA, Santaguida PL, et al. Use of BNP and NT-proBNP for the diagnosis of heart failure in the emergency department: a systematic review of the evidence. *Heart Fail Rev*. 2014;19:421–438.
13. van Kimmenade RR, Januzzi JL Jr, Ellinor PT, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. *J Am Coll Cardiol*. 2006;48:1217–1224.
14. Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;110:2168–2174.
15. Cheng V, Kazanegra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol*. 2001;37:386–391.
16. Fonarow GC, Peacock WF, Phillips CO, et al. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:1943–1950.
17. Logeart D, Thabut G, Jourdain P, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol*. 2004;43:635–641.
18. Maisel A, Hollander JE, Guss D, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol*. 2004;44:1328–1333.
19. Zairis MN, Tsiaousis GZ, Georgilas AT, et al. Multimarker strategy for the prediction of 31 days cardiac death in patients with acutely decompensated chronic heart failure. *Int J Cardiol*. 2010;141:284–290.
20. Dhaliwal AS, Deswal A, Pritchett A, et al. Reduction in BNP levels with treatment of decompensated heart failure and future clinical events. *J Card Fail*. 2009;15:293–299.
21. O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol*. 2010;55:872–878.
22. O'Brien RJ, Squire IB, Demme B, et al. Pre-discharge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. *Eur J Heart Fail*. 2003;5:499–506.
23. Cohen-Solal A, Logeart D, Huang B, et al. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. *J Am Coll Cardiol*. 2009;53:2343–2348.
24. Salah K, Kok WE, Eurlings LW, et al. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLlaboration on Acute decompeNsated Heart Failure: ELAN-HF Score. *Heart*. 2014;100:115–125.
25. Flint KM, Allen LA, Pham M, et al. B-type natriuretic peptide predicts 30-day readmission for heart failure but not readmission for other causes. *J Am Heart Assoc*. 2014;3:e000806.
26. Kociol RD, Horton JR, Fonarow GC, et al. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. *Circ Heart Fail*. 2011;4:628–636.
27. Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. *Circ Heart Fail*. 2013;6:240–245.
28. Verdiani V, Ognibene A, Rutigli MS, et al. NT-ProBNP reduction percentage during hospital stay predicts long-term mortality and readmission in heart failure patients. *J Cardiovasc Med (Hagerstown)*. 2008;9:694–699.
29. Bayes-Genis A, Lopez L, Zapico E, et al. NT-ProBNP reduction percentage during admission for acutely decompensated heart failure predicts long-term cardiovascular mortality. *J Card Fail*. 2005;11:S3–S8.
30. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;62:1365–1372.
31. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA*. 2013;310:66–74.
32. Clerico A, Fontana M, Zyw L, et al. Comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and the N-terminal part of the propeptide of BNP immunoassays in chronic and acute heart failure: a systematic review. *Clin Chem*. 2007;53:813–822.
33. Jensen J, Ma LP, Bjurman C, et al. Prognostic values of NTpro BNP/BNP ratio in comparison with NTpro BNP or BNP alone in elderly patients with chronic heart failure in a 2-year follow up. *Int J Cardiol*. 2012;155:1–5.
34. Kristensen SL, Jhund PS, Mogensen UM, et al. Prognostic value of N-terminal pro-B-type natriuretic peptide levels in heart failure patients with and without atrial fibrillation. *Circ Heart Fail*. 2017;10:e004409.
35. Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *J Am Coll Cardiol*. 2006;47:85–90.
36. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol*. 2004;43:1590–1595.
37. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;318:713–720.
38. Januzzi JL Jr, Ahmad T, Mulder H, et al. Natriuretic peptide response and outcomes in chronic heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;74:1205–1217.
39. Mark DB, Cowper PA, Anstrom KJ, et al. Economic and quality-of-life outcomes of natriuretic peptide-guided therapy for heart failure. *J Am Coll Cardiol*. 2018;72:2551–2562.
40. Aimo A, Januzzi JL Jr, Vergaro G, et al. Prognostic value of high-sensitivity troponin T in chronic heart failure: an individual patient data meta-analysis. *Circulation*. 2018;137:286–297.
41. Evans JDW, Dobbin SJH, Pettit SJ, et al. High-sensitivity cardiac troponin and new-onset heart failure: a systematic review and meta-analysis of 67 063 patients with 4 165 incident heart failure events. *J Am Coll Cardiol HF*. 2018;6:187–197.
42. Pang PS, Fermann GJ, Hunter BR, et al. TACIT (High Sensitivity Troponin T Rules Out Acute Cardiac Insufficiency Trial). *Circ Heart Fail*. 2019;12:e005931.
43. Ahmad T, Fiuzat M, Neely B, et al. Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure. *J Am Coll Cardiol HF*. 2014;2:260–268.
44. Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol*. 2012;60:1249–1256.
45. Kosmala W, Przewlocka-Kosmala M, Rojek A, et al. Comparison of the diastolic stress test with a combined resting echocardiography and biomarker approach to patients with exertional dyspnea: diagnostic and prognostic implications. *J Am Coll Cardiol Img*. 2019;12:771–780.
46. Nymo SH, Aukrust P, Kjekshus J, et al. Limited added value of circulating inflammatory biomarkers in chronic heart failure. *J Am Coll Cardiol HF*. 2017;5:256–264.
47. Emdin M, Aimo A, Vergaro G, et al. sST2 predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. *J Am Coll Cardiol*. 2018;72:2309–2320.
48. Gaggin HK, Szymonifka J, Bhardwaj A, et al. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *J Am Coll Cardiol HF*. 2014;2:65–72.
49. Richards AM. ST2 and prognosis in chronic heart failure. *J Am Coll Cardiol*. 2018;72:2321–2323.
50. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J Am Coll Cardiol*. 2006;47:91–97.
51. Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40:976–982.
52. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol*. 2002;90:254–258.

53. Chang AY, Abdullah SM, Jain T, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. *J Am Coll Cardiol.* 2007;49:109–116.

#### 4.3. Genetic Evaluation and Testing

- Marume K, Noguchi T, Tateishi E, et al. Prognosis and clinical characteristics of dilated cardiomyopathy with family history via pedigree analysis. *Circ J.* 2020;84:1284–1293.
- Waddell-Smith KE, Donoghue T, Oates S, et al. Inpatient detection of cardiac-inherited disease: the impact of improving family history taking. *Open Heart.* 2016;3:e000329.
- Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med.* 2014;16:601–608.
- Haas J, Frese KS, Peil B, et al. Atlas of the clinical genetics of human dilated cardiomyopathy. *Eur Heart J.* 2015;36:1123–1135a.
- Roberts AM, Ware JS, Herman DS, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. *Sci Transl Med.* 2015;7:270ra6.
- Gigli M, Merlo M, Graw SL, et al. Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol.* 2019;74:1480–1490.
- James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol.* 2013;62:1290–1297.

#### 4.4. Evaluation With Cardiac Imaging

- Badgett RG, Mulrow CD, Otto P, et al. How well can the chest radiograph diagnose left ventricular dysfunction? *J Gen Intern Med.* 1996;11:625–634.
- Knudsen CW, Omland T, Clopton P, et al. Diagnostic value of B-type natriuretic peptide and chest radiographic findings in patients with acute dyspnea. *Am J Med.* 2004;116:363–368.
- Tribouilloy C, Rusinaru D, Mahjoub H, et al. Impact of echocardiography in patients hospitalized for heart failure: a prospective observational study. *Arch Cardiovasc Dis.* 2008;101:465–473.
- Doughty RNWG, Gamble G, et al. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *J Am Coll Cardiol.* 1997;29:1060–1066.
- Duncker D, König T, Hohmann S, et al. Avoiding untimely implantable cardioverter/defibrillator implantation by intensified heart failure therapy optimization supported by the wearable cardioverter/defibrillator-the PROLONG study. *J Am Heart Assoc.* 2017;6:e004512.
- Januzzi JL Jr, Prescott MF, Butler J, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA.* 2019;322:1–11.
- Solomon SD, Glynn RJ, Greaves S, et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study. *Ann Intern Med.* 2001;134:451–458.
- Bellenger NG, Burgess MI, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radioisotope ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J.* 2000;21:1387–1396.
- Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol.* 2002;90:29–34.
- Longmore DB, Klipstein RH, Underwood SR, et al. Dimensional accuracy of magnetic resonance in studies of the heart. *Lancet.* 1985;1:1360–1362.
- Doherty JU, Kort S, Mehran R, et al. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCMR/STS 2019 appropriate use criteria for multimodality imaging in the assessment of cardiac structure and function in nonvalvular heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2019;73:488–516.
- van Royen N, Jaffe CC, Krumholz HM, et al. Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *Am J Cardiol.* 1996;77:843–850.
- Fu H, Wang X, Diao K, et al. CT compared to MRI for functional evaluation of the right ventricle: a systematic review and meta-analysis. *Eur Radiol.* 2019;29:6816–6828.
- Kaniewska M, Schuetz GM, Willun S, et al. Noninvasive evaluation of global and regional left ventricular function using computed tomography and magnetic resonance imaging: a meta-analysis. *Eur Radiol.* 2017;27:1640–1659.
- Takx RA, Moscariello A, Schoepf UJ, et al. Quantification of left and right ventricular function and myocardial mass: comparison of low-radiation dose 2nd generation dual-source CT and cardiac MRI. *Eur J Radiol.* 2012;81:e598–e604.
- Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2\*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J.* 2001;22:2171–2179.
- Bruder O, Schneider S, Nothnagel D, et al. EuroCMR (European Cardiovascular Magnetic Resonance) registry: results of the German pilot phase. *J Am Coll Cardiol.* 2009;54:1457–1466.
- Bruder O, Wagner A, Lombardi M, et al. European Cardiovascular Magnetic Resonance (EuroCMR) registry—multi national results from 57 centers in 15 countries. *J Cardiovasc Magn Reson.* 2013;15:9.
- Karamitsos TD, Piechnik SK, Banypersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *J Am Coll Cardiol Img.* 2013;6:488–497.
- Martinez-Naharro A, Treibel TA, Abdel-Gadir A, et al. Magnetic resonance in transthyretin cardiac amyloidosis. *J Am Coll Cardiol.* 2017;70:466–477.
- Puntmann VO, Voigt T, Chen Z, et al. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. *J Am Coll Cardiol Img.* 2013;6:475–484.
- Sado DM, Maestrini V, Piechnik SK, et al. Noncontrast myocardial T1 mapping using cardiovascular magnetic resonance for iron overload. *J Magn Reson Imaging.* 2015;41:1505–1511.
- Sado DM, White SK, Piechnik SK, et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. *Circ Cardiovasc Imaging.* 2013;6:392–398.
- Elhendy A, Sozzi F, van Domburg RT, et al. Effect of myocardial ischemia duringdobutamine stress echocardiography on cardiac mortality in patients with heart failure secondary to ischemic cardiomyopathy. *Am J Cardiol.* 2005;96:469–473.
- Miller WL, Hodge DO, Tointon SK, et al. Relationship of myocardial perfusion imaging findings to outcome of patients with heart failure and suspected ischemic heart disease. *Am Heart J.* 2004;147:714–720.
- Chow BJW, Coyle D, Hossain A, et al. Computed tomography coronary angiography for patients with heart failure (CTA-HF): a randomized controlled trial (IMAGE-HF 1C). *Eur Heart J Cardiovasc Imaging.* 2021;22:1083–1090.
- Ferreira JP, Rossignol P, Demissei B, et al. Coronary angiography in worsening heart failure: determinants, findings and prognostic implications. *Heart.* 2018;104:606–613.
- Allman KC, Shaw LJ, Hachamovitch R, et al. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol.* 2002;39:1151–1158.
- D'Egidio G, Nichol G, Williams KA, et al. PARR-2 Investigators. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *J Am Coll Cardiol Img.* 2009;2:1060–1068.
- Ling LF, Marwick TH, Flores DR, et al. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging.* 2013;6:363–372.
- Orlandini A, Castellana N, Pascual A, et al. Myocardial viability for decision-making concerning revascularization in patients with left ventricular dysfunction and coronary artery disease: a meta-analysis of non-randomized and randomized studies. *Int J Cardiol.* 2015;182:494–499.
- Desideri A, Cortigiani L, Christen AI, et al. The extent of perfusion-F18-fluorodeoxyglucose positron emission tomography mismatch determines mortality in medically treated patients with chronic ischemic left ventricular dysfunction. *J Am Coll Cardiol.* 2005;46:1264–1269.
- Collins SP, Lindsell CJ, Storrow AB, et al. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. *Ann Emerg Med.* 2006;47:13–18.
- Echouffo-Tcheugui JB, Erqou S, Butler J, et al. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart

- failure: a systematic overview and meta-analysis. *J Am Coll Cardiol HF*. 2016;4:237–248.
35. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.
  36. Nauta JF, Hummel YM, van der Meer P, et al. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2018;20:1303–1311.
  37. Solomon SD, Anavekar N, Skali H, et al. Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112:3738–3744.
  38. Al Saikhan L, Park C, Hardy R, et al. Prognostic implications of left ventricular strain by speckle-tracking echocardiography in the general population: a meta-analysis. *Vasc Health Risk Manag*. 2019;15:229–251.
  39. Redfield MM, Jacobsen SJ, Burnett JC Jr, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.
  40. Bosch L, Lam CSP, Gong L, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. *Eur J Heart Fail*. 2017;19:1664–1671.
  41. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
  42. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.
  43. Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: the Copenhagen City Heart Study. *Circ Cardiovasc Imaging*. 2017;10:e005521.
  44. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart*. 2014;100:1673–1680.
  45. Morris DA, Ma XX, Belyavskiy E, et al. Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. *Open Heart*. 4;2017:e000630.
  46. Shah AM, Claggett B, Schweitzer NK, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation*. 2015;132:402–414.
  47. Lipczynska M, Szymanski P, Klisiewicz A, et al. Hand-carried echocardiography in heart failure and heart failure risk population: a community based prospective study. *J Am Soc Echocardiogr*. 2011;24:125–131.
  48. Martin LD, Howell EE, Ziegelstein RC, et al. Hand-carried ultrasound performed by hospitalists: does it improve the cardiac physical examination? *Am J Med*. 2009;122:35–41.
  49. Maw AM, Hassanin A, Ho PM, et al. Diagnostic accuracy of point-of-care lung ultrasonography and chest radiography in adults with symptoms suggestive of acute decompensated heart failure: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e190703.
  50. Platz E, Campbell RT, Claggett B, et al. Lung ultrasound in acute heart failure: prevalence of pulmonary congestion and short- and long-term outcomes. *J Am Coll Cardiol HF*. 2019;7:849–858.
  51. Pivetta E, Goffi A, Nazerian P, et al. Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial. *Eur J Heart Fail*. 2019;21:754–766.
  52. Palazzuoli A, Ruocco G, Beltrami M, et al. Combined use of lung ultrasound, B-type natriuretic peptide, and echocardiography for outcome prediction in patients with acute HFrEF and HFpEF. *Clin Res Cardiol*. 2018;107:586–596.
  53. Ottervanger JP, van't Hof AW, Reijers S, et al. Long-term recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *Eur Heart J*. 2001;22:785–790.
  54. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation*. 1996;94:2793–2799.
  55. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003;107:1985–1990.
  56. Wilcox JE, Fonarow GC, Yancy CW, et al. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J*. 2012;163:49–56.e2.
  57. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation*. 1992;86:431–438.
  58. Lee MMY, Brookbank KJM, Wetherall K, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation*. 2021;143:516–525.
  59. Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *J Am Coll Cardiol HF*. 2017;5:652–659.
  60. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart failure with recovered left ventricular ejection fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2020;76:719–734.
  61. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e698–e800.
  62. Yoshida A, Ishibashi-Ueda H, Yamada N, et al. Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. *Eur J Heart Fail*. 2013;15:166–175.
  63. Kim RJ, Albert TS, Wible JH, et al. Performance of delayed-enhancement magnetic resonance imaging with gadovosetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation*. 2008;117:629–637.
  64. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet*. 2003;361:374–379.
  65. McCrohon JA, Moon JC, Prasad SK, et al. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation*. 2003;108:54–59.
  66. Valle-Muñoz A, Estornell-Erill J, Soriano-Navarro CJ, et al. Late gadolinium enhancement-cardiovascular magnetic resonance identifies coronary artery disease as the aetiology of left ventricular dysfunction in acute new-onset congestive heart failure. *Eur J Echocardiogr*. 2009;10:968–974.
  67. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72:3158–3176.
  68. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. *Circulation*. 2012;126:1206–1216.
  69. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. *Circulation*. 2010;122:138–144.
  70. Miller CA, Naish JH, Bishop P, et al. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. *Circ Cardiovasc Imaging*. 2013;6:373–383.
  71. Vita T, Grani C, Abbasi SA, et al. Comparing CMR mapping methods and myocardial patterns toward heart failure outcomes in nonischemic dilated cardiomyopathy. *J Am Coll Cardiol Img*. 2019;12:1659–1669.
  72. Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. *J Am Coll Cardiol Img*. 2013;6:501–511.
  73. Kuruvilla S, Adenaw N, Katwal AB, et al. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis. *Circ Cardiovasc Imaging*. 2014;7:250–258.
  74. Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation*. 2006;113:2733–2743.
  75. El Aidi H, Adams A, Moons KG, et al. Cardiac magnetic resonance imaging findings and the risk of cardiovascular events in patients with recent myocardial infarction or suspected or known coronary artery disease: a systematic review of prognostic studies. *J Am Coll Cardiol*. 2014;63:1031–1045.

76. Lehrke S, Lossnitzer D, Schob M, et al. Use of cardiovascular magnetic resonance for risk stratification in chronic heart failure: prognostic value of late gadolinium enhancement in patients with non-ischaemic dilated cardiomyopathy. *Heart.* 2011;97:727–732.
77. Fontana M, Pica S, Reant P, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation.* 2015;132:1570–1579.
78. Paterson DI, Wells G, Erthal F, et al. OUTSMART HF: a randomized controlled trial of routine versus selective cardiac magnetic resonance for patients with nonischemic heart failure (IMAGE-HF 1B). *Circulation.* 2020;141:818–827.
79. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med.* 2001;161:996–1002.
80. Bearlands RS, Nichol G, Huszti E, et al. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol.* 2007;50:2002–2012.
81. Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med.* 2011;364:1617–1625.
82. Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med.* 2019;381:739–748.
83. Patel MR, White RD, Abbara S, et al. 2013 ACCF/ACR/AES/ASNC/SCCT/SCMR appropriate utilization of cardiovascular imaging in heart failure: a joint report of the American College of Radiology Appropriateness Criteria Committee and the American College of Cardiology Foundation Appropriate Use Criteria Task Force. *J Am Coll Cardiol.* 2013;61:2207–2231.

#### 4.5. Invasive Evaluation

1. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation.* 2007;116:2216–2233.
2. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018;379:1007–1016.
3. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA.* 2005;294:1625–1633.
4. Shah MRHV, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA.* 2005;294:1664–1670.
5. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol.* 1992;19:43–47.
6. Veress G, Bruce CJ, Kutzke K, et al. Acute thrombus formation as a complication of right ventricular biopsy. *J Am Soc Echocardiogr.* 2010;23:1039–1044.
7. Patel MR, Calhoun JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease. *J Am Coll Cardiol.* 2017;69:2212–2241.
8. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med.* 2011;364:1607–1616.
9. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374:1511–1520.

#### 4.6. Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)

1. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet.* 2011;377:658–666.
2. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail.* 2014;7:935–944.
3. Givertz MM, Stevenson LW, Costanzo MR, et al. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol.* 2017;70:1875–1886.

4. Lindenfeld J, Zile MR, Desai AS, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet.* 2021;398:991–1001.
5. Martinson M, Bharmi R, Dalal N, et al. Pulmonary artery pressure-guided heart failure management: US cost-effectiveness analyses using the results of the CHAMPION clinical trial. *Eur J Heart Fail.* 2017;19:652–660.
6. Sandhu AT, Goldhaber-Fiebert JD, Owens DK, et al. Cost-effectiveness of implantable pulmonary artery pressure monitoring in chronic heart failure. *J Am Coll Cardiol HF.* 2016;4:368–375.
7. Schmier JK, Ong KL, Fonarow GC. Cost-effectiveness of remote cardiac monitoring with the CardioMEMS heart failure system. *Clin Cardiol.* 2017;40:430–436.
8. Heywood JT, Jermyn R, Shavelle D, et al. Impact of practice-based management of pulmonary artery pressures in 2000 patients implanted with the CardioMEMS sensor. *Circulation.* 2017;135:1509–1517.
9. Desai AS, Bhimaraj A, Bharmi R, et al. Ambulatory hemodynamic monitoring reduces heart failure hospitalizations in "real-world" clinical practice. *J Am Coll Cardiol.* 2017;69:2357–2365.
10. Abraham J, Bharmi R, Jonsson O, et al. Association of ambulatory hemodynamic monitoring of heart failure with clinical outcomes in a concurrent matched cohort analysis. *JAMA Cardiol.* 2019;4:556–563.
11. Ong MK, Romano PS, Edgington S, et al. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: the Better Effectiveness After Transition–Heart Failure (BEAT-HF) randomized clinical trial. *JAMA Intern Med.* 2016;176:310–318.
12. Galinier M, Roubille F, Berdague P, et al. Telemonitoring versus standard care in heart failure: a randomised multicentre trial. *Eur J Heart Fail.* 2020;22:985–994.
13. Böhm M, Drexler H, Oswald H, et al. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J.* 2016;37:3154–3363.
14. Boriani G, Da Costa A, Quesada A, et al. Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial. *Eur J Heart Fail.* 2017;19:416–425.
15. Hindricks G, Taborsky M, Glikson M, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet.* 2014;384:583–590.
16. Klersy C, Boriani G, De Silvestri A, et al. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized controlled trials in patients with heart failure. *Eur J Heart Fail.* 2016;18:195–204.
17. Morgan JM, Kitt S, Gill J, et al. Remote management of heart failure using implantable electronic devices. *Eur Heart J.* 2017;38:2352–2360.
18. Parthiban N, Esterman A, Mahajan R, et al. Remote monitoring of implantable cardioverter-defibrillators: a systematic review and meta-analysis of clinical outcomes. *J Am Coll Cardiol.* 2015;65:2591–2600.
19. Loh JP, Barbash IM, Waksman R. Overview of the 2011 Food and Drug Administration circulatory system devices panel of the medical devices advisory committee meeting on the CardioMEMS Champion Heart Failure Monitoring System. *J Am Coll Cardiol.* 2013;61:1571–1576.
20. Ollendorf DA, Sandhu AT, Pearson SD. CardioMEMS HF for the management of heart failure—effectiveness and value. *JAMA Intern Med.* 2016;176:1551–1552.
21. Krumholz HM, Dhruba SS. Real-world data on heart failure readmission reduction: real or real uncertain? *J Am Coll Cardiol.* 2017;69:2366–2368.
22. Inglis SC, Clark RA, Dierckx R, et al. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev.* 2015;CD007228.
23. Koehler F, Koehler K, Deckwart O, et al. Efficacy of telemedical intervention management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet.* 2018;392:1047–1057.

#### 4.7. Exercise and Functional Capacity Testing

1. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* 9th ed. Little, Brown & Co; 1994.
2. Ahmed A, Aronow WS, Fleg JL. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *Am Heart J.* 2006;151:444–450.
3. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients with heart failure. *Eur Heart J.* 2002;23:1861–1866.

4. Brawner CA, Shafiq A, Aldred HA, et al. Comprehensive analysis of cardiopulmonary exercise testing and mortality in patients with systolic heart failure: the Henry Ford Hospital cardiopulmonary exercise testing (FIT-CPX) project. *J Card Fail.* 2015;21:710–718.
5. Corra U, Giordano A, Mezzani A, et al. Cardiopulmonary exercise testing and prognosis in heart failure due to systolic left ventricular dysfunction: a validation study of the European Society of Cardiology Guidelines and Recommendations (2008) and further developments. *Eur J Prev Cardiol.* 2012;19:32–40.
6. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant.* 2013;32:157–187.
7. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778–786.
8. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant.* 2016;35:1–23.
9. Alahdab MT, Mansour IN, Napan S, Stamos TD. Six minute walk test predicts long-term all-cause mortality and heart failure rehospitalization in African-American patients hospitalized with acute decompensated heart failure. *J Card Fail.* 2009;15:130–135.
10. Bitner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. *SOLVD Investigators. JAMA.* 1993;270:1702–1707.
11. Boxer R, Kleppinger A, Ahmad A, et al. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail.* 2010;16:208–213.
12. Forman DE, Fleg JL, Kitzman DW, et al. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *J Am Coll Cardiol.* 2012;60:2653–2661.
13. Grundtvig M, Eriksen-Volnes T, Orn S, et al. 6 min walk test is a strong independent predictor of death in outpatients with heart failure. *ESC Heart Fail.* 2020;7:2904–2911.
14. Keteyian SJ, Patel M, Kraus WE, et al. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. *J Am Coll Cardiol.* 2016;67:780–789.
15. McCabe N, Butler J, Dunbar SB, et al. Six-minute walk distance predicts 30-day readmission after acute heart failure hospitalization. *Heart Lung.* 2017;46:287–292.
16. Ramalho SHR, Cipriano Junior G, Vieira PJC, et al. Inspiratory muscle strength and six-minute walking distance in heart failure: prognostic utility in a 10 years follow up cohort study. *PLoS One.* 2019;14:e0220638.
17. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med.* 2012;185:435–452.
18. Reddy YNV, Olson TP, Obokata M, et al. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF.* 2018;6:665–675.
19. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J.* 1985;132:919–923.
20. Lans C, Cider A, Nylander E, Brudin L. Test-retest reliability of six-minute walk tests over a one-year period in patients with chronic heart failure. *Clin Physiol Funct Imaging.* 2020;40:284–289.
21. Pollentier B, Irons SL, Benedetto CM, et al. Examination of the six minute walk test to determine functional capacity in people with chronic heart failure: a systematic review. *Cardiopulm Phys Ther J.* 2010;21:13–21.
22. Guazzi M, Bandera F, Ozemek C, et al. Cardiopulmonary exercise testing: what is its value? *J Am Coll Cardiol.* 2017;70:1618–1636.
23. Raphael C, Briscoe C, Davies J, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart.* 2007;93:476–482.
24. Parikh MN, Lund LH, Goda A, et al. Usefulness of peak exercise oxygen consumption and the heart failure survival score to predict survival in patients >65 years of age with heart failure. *Am J Cardiol.* 2009;103:998–1002.
25. Pohwani AL, Murali S, Mathier MM, et al. Impact of beta-blocker therapy on functional capacity criteria for heart transplant listing. *J Heart Lung Transplant.* 2003;22:78–86.
26. Peterson LR, Schechtman KB, Ewald GA, et al. Timing of cardiac transplantation in patients with heart failure receiving beta-adrenergic blockers. *J Heart Lung Transplant.* 2003;22:1141–1148.
27. Rostagno C, Olivo G, Comeglio M, et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail.* 2003;5:247–252.
28. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122:191–225.

## 4.8. Initial and Serial Evaluation: Clinical Assessment: HF Risk Scoring

- Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation.* 1997;95:2660–2667.
- Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation.* 2006;113:1424–1433.
- Pocock SJ, Arifi CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J.* 2013;34:1404–1413.
- Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J.* 2006;27:65–75.
- Wedel H, McMurray JJ, Lindberg M, et al. Predictors of fatal and non-fatal outcomes in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and N-terminal pro B-type natriuretic peptide. *Eur J Heart Fail.* 2009;11:281–291.
- Simpson J, Jhund PS, Lund LH, et al. Prognostic models derived in PARADIGM-HF and validated in ATMOSPHERE and the Swedish Heart Failure Registry to predict mortality and morbidity in chronic heart failure. *JAMA Cardiol.* 2020;5:432–441.
- O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail.* 2012;5:63–71.
- O'Connor C, Fiuzat M, Mulder H, et al. Clinical factors related to morbidity and mortality in high-risk heart failure patients: the GUIDE-IT predictive model and risk score. *Eur J Heart Fail.* 2019;21:770–778.
- Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail.* 2011;4:27–35.
- Angraal S, Mortazavi BJ, Gupta A, et al. Machine learning prediction of mortality and hospitalization in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF.* 2020;8:12–21.
- Fonarow GC, Adams KF Jr, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA.* 2005;293:572–580.
- Peterson PN, Rumsfeld JS, Liang L, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association Get With The Guidelines program. *Circ Cardiovasc Qual Outcomes.* 2010;3:25–32.
- Lee DS, Austin PC, Rouleau JL, et al. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA.* 2003;290:2581–2587.
- O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol.* 2010;55:872–878.
- University of Washington. Seattle Heart Failure Model. 2017. Accessed September 16, 2020. <https://deptswashingtonedu/shfm/?width=1440&height=900>
- Meta-AnalysisGlobalGroupinChronicHeartFailure(MAGGIC).HeartFailureRisk Calculator. Accessed September 16, 2020. <http://wwwheartfailurerisk.org/>
- Fonarow GC. GWTG-heart failure risk score. 2021 Accessed September 29, 2021. <https://wwwmdcalcom/gwtg-heart-failure-risk-score>
- Canadian Cardiovascular Outcomes Research Team. EFFECT heart failure mortality prediction. 2016. Accessed September 16, 2020. <http://wwwccor.ca/Research/CHFRiskModelhtml>

## 5.1. Patients at Risk Factor for HF (Stage A-Primary Prevention)

- Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* 2008;358:1887–1898.

2. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967.
3. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *SHEP Cooperative Research Group*. *JAMA*. 1997;278:212–216.
4. Staessen JA, Fagard R, Thijss L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997;350:757–764.
5. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure—meta-analyses of randomized trials. *J Hypertens*. 2016;34:373–384.
6. Upadhyia B, Rocco M, Lewis CE, et al. Effect of intensive blood pressure treatment on heart failure events in the Systolic Blood Pressure Reduction Intervention Trial. *Circ Heart Fail*. 2017;10:e003613.
7. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
8. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557–1562.
9. Butler J, Kalogeropoulos AP, Georgiopoulou VV, et al. Systolic blood pressure and incident heart failure in the elderly. The Cardiovascular Health Study and the Health, Ageing and Body Composition Study. *Heart*. 2011;97:1304–1311.
10. Neal B, Perkovic V, Mahaffey KW, et al. Canaglifllozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
11. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
13. Del Gobbo LC, Kalantarian S, Imamura F, et al. Contribution of major lifestyle risk factors for incident heart failure in older adults: the Cardiovascular Health Study. *J Am Coll Cardiol HF*. 2015;3:520–528.
14. Wang Y, Tuomilehto J, Jousilahti P, et al. Lifestyle factors in relation to heart failure among Finnish men and women. *Circ Heart Fail*. 2011;4:607–612.
15. Young DR, Reynolds K, Sidell M, et al. Effects of physical activity and sedentary time on the risk of heart failure. *Circ Heart Fail*. 2014;7:21–27.
16. Hu G, Jousilahti P, Antikainen R, et al. Joint effects of physical activity, body mass index, waist circumference, and waist-to-hip ratio on the risk of heart failure. *Circulation*. 2010;121:237–244.
17. Folsom AR, Shah AM, Lutsey PL, et al. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med*. 2015;128:970–976.e2.
18. Tektonidis TG, Åkesson A, Gigante B, et al. Adherence to a Mediterranean diet is associated with reduced risk of heart failure in men. *Eur J Heart Fail*. 2016;18:253–259.
19. Levitan EB, Wolk A, Mittleman MA. Consistency with the DASH diet and incidence of heart failure. *Arch Intern Med*. 2009;169:851–857.
20. Levitan EB, Wolk A, Mittleman MA. Relation of consistency with the dietary approaches to stop hypertension diet and incidence of heart failure in men aged 45 to 79 years. *Am J Cardiol*. 2009;104:1416–1420.
21. Lara KM, Levitan EB, Gutierrez OM, et al. Dietary patterns and incident heart failure in US adults without known coronary disease. *J Am Coll Cardiol*. 2019;73:2036–2045.
22. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA*. 2013;310:66–74.
23. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prediction of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;62:1365–1372.
24. Kannel WB, D'Agostino RB, Silbershatz H, et al. Profile for estimating risk of heart failure. *Arch Intern Med*. 1999;159:1197–1204.
25. Butler J, Kalogeropoulos A, Georgiopoulou V, et al. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail*. 2008;1:125–133.
26. Agarwal SK, Chambliss LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. *Circ Heart Fail*. 2012;5:422–429.
27. Aggarwal M, Bozkurt B, Panjwani G, et al. Lifestyle modifications for preventing and treating heart failure. *J Am Coll Cardiol*. 2018;72:2391–2405.
28. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646.
29. Khan SS, Ning H, Shah SJ, et al. 10-year risk equations for incident heart failure in the general population. *J Am Coll Cardiol*. 2019;73:2388–2397.
30. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
31. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39.
32. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *J Am Coll Cardiol HF*. 2017;5:543–551.
33. Packer M, Anker SD, Butler J, et al. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. *JAMA Cardiol*. 2017;2:1025–1029.
34. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61:2108–2117.
35. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *J Am Coll Cardiol HF*. 2019;7:169–172.
36. Allen LA, Matlock DD, Shetterly SM, et al. Use of risk models to predict death in the next year among individual ambulatory patients with heart failure. *JAMA Cardiol*. 2017;2:435–441.
37. Liu Y, Chen PC, Krause J, et al. How to read articles that use machine learning: users' guides to the medical literature. *JAMA*. 2019;322:1806–1816.

## 6.1. Management of Stage B: Preventing the Syndrome of Clinical HF in Patients With Pre-HF

1. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685–691.
2. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *The SAVE Investigators*. *N Engl J Med*. 1992;327:669–677.
3. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet*. 2003;361:1843–1848.
4. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med*. 1995;333:1670–1676.
5. Afifalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. *Heart*. 2007;93:914–921.
6. Heart Protection Study Collaborative GroupEmerson JR, Ng LL, et al. N-terminal Pro-B-type natriuretic peptide, vascular disease risk, and cholesterol reduction among 20 536 patients in the MRC/BHF heart protection study. *J Am Coll Cardiol*. 2007;49:311–319.
7. Preiss D, Campbell RT, Murray HM, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J*. 2015;36:1536–1546.
8. Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol*. 2006;47:2326–2331.
9. Strandberg TE, Holme I, Faergeman O, et al. Comparative effect of atorvastatin (80 mg) versus simvastatin (20 to 40 mg) in preventing hospitalizations for heart failure in patients with previous myocardial infarction. *Am J Cardiol*. 2009;103:1381–1385.
10. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893–1906.
11. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385–1390.
12. Exner DV, Dries DL, Waclawiw MA, et al. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ven-

- tricular systolic dysfunction: a post hoc analysis of the studies of left ventricular dysfunction. *J Am Coll Cardiol.* 1999;33:916–923.
13. Vantrimpont P, Rouleau JL, Wun CC, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. *SAVE Investigators. J Am Coll Cardiol.* 1997;29:229–236.
  14. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877–883.
  15. Dargie HJ, Hildebrandt PR, Rieger GA, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association Functional class I or II heart failure. *J Am Coll Cardiol.* 2007;49:1696–1704.
  16. Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med.* 1988;319:385–392.
  17. Goldstein RE, Bocuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation.* 1991;83:52–60.
  18. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation.* 2007;115:1563–1570.
  19. Shah AM, Claggett B, Loehr LR, et al. Heart failure stages among older adults in the community: the Atherosclerosis Risk in Communities study. *Circulation.* 2017;135:224–240.
  20. Wang Y, Yang H, Huynh Q, et al. Diagnosis of nonischemic stage B heart failure in type 2 diabetes mellitus: optimal parameters for prediction of heart failure. *J Am Coll Cardiol Img.* 2018;11:1390–1400.
  21. Xanthakis V, Enserro DM, Larson MG, et al. Prevalence, neurohormonal correlates, and prognosis of heart failure stages in the community. *J Am Coll Cardiol HF.* 2016;4:808–815.
  22. Al Saikhan L, Park C, Hardy R, et al. Prognostic implications of left ventricular strain by speckle-tracking echocardiography in the general population: a meta-analysis. *Vasc Health Risk Manag.* 2019;15:229–251.
  23. Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: the Copenhagen City Heart Study. *Circ Cardiovasc Imaging.* 2017;10:e005521.
  24. Echouffo-Tcheugui JB, Erqou S, Butler J, et al. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis. *J Am Coll Cardiol HF.* 2016;4:237–248.
  25. Wang TJ, Evans JC, Benjamin EJ, et al. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation.* 2003;108:977–982.
  26. Yang H, Negishi K, Wang Y, et al. Echocardiographic screening for non-ischaemic stage B heart failure in the community. *Eur J Heart Fail.* 2016;18:1331–1339.
  27. Echouffo-Tcheugui JB, Erqou S, Butler J, et al. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis. *J Am Coll Cardiol HF.* 2016;4:237–248.
  28. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol.* 2010;55:300–305.
  29. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA.* 2011;306:856–863.
  30. Kosmala W, Sanders P, Marwick TH. Subclinical myocardial impairment in metabolic diseases. *J Am Coll Cardiol Img.* 2017;10:692–703.
  31. Holland DJ, Marwick TH, Haluska BA, et al. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart.* 2015;101:1061–1066.
  32. Beygui F, Cayla G, Roule V, et al. Early aldosterone blockade in acute myocardial infarction: the ALBATROSS randomized clinical trial. *J Am Coll Cardiol.* 2016;67:1917–1927.
  33. Montalescot G, Pitt B, Lopez de Sa E, et al. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. *Eur Heart J.* 2014;35:2295–2302.
  34. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309–1321.
  35. Jering KS, Claggett B, Pfeffer MA, et al. Prospective ARNI vs. ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. *Eur J Heart Fail.* 2021;23:1040–1048.
  36. Pfeffer MA, Lamas GA, Vaughan DE, et al. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med.* 1988;319:80–86.
  37. Sharpe N, Murphy J, Smith H, et al. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet.* 1988;1:255–259.
  38. Velazquez EJ, Pfeffer MA, McMurray JV, et al. VALsartan In Acute myocardial iNfarCTion (VALIANT) trial: baseline characteristics in context. *Eur J Heart Fail.* 2003;5:537–544.
  39. Dickstein K, Kjekshus JOPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet.* 2002;360:752–760.
  40. Mann DL, Deswal A. Angiotensin-receptor blockade in acute myocardial infarction—a matter of dose. *N Engl J Med.* 2003;349:1963–1965.
  41. Doughty RN, Whalley GA, Walsh HA, et al. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. *Circulation.* 2004;109:201–206.
  42. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;139:e1082–e1143.
  43. Colucci WS, Kolias TJ, Adams KF, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REVerse of VEntricular Remodeling with Toprol-XL (REVERT) trial. *Circulation.* 2007;116:49–56.
  44. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J.* 2018;39:26–35.
  45. Figulla HR, Gietzen F, Zeymer U, et al. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. Results of the diltiazem in dilated cardiomyopathy trial. *Circulation.* 1996;94:346–352.
  46. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II—DAVIT II). *Am J Cardiol.* 1990;66:779–785.
  47. Erdmann E, Charbonnel B, Wilcox RG, et al. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care.* 2007;30:2773–2778.
  48. Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J.* 2010;31:824–831.
  49. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet.* 2007;370:1129–1136.
  50. Giles TD, Miller AB, Elkayam U, et al. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail.* 2008;14:445–452.
  51. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e422.
  52. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130:e344–e426.
  53. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation.* 2016;133:1135–1147.
  54. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American Col-

- lege of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e18–e114.
55. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767.
  56. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *Circulation*. 2011;124:e652–e735.
  57. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159–e1195.
  58. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e72–e227.
  59. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e698–e800.

### 7.1.1. Self-Care Support in HF

1. Holland R, Battersby J, Harvey I, et al. Systematic review of multidisciplinary interventions in heart failure. *Heart*. 2005;91:899–906.
2. McAlister FA, Stewart S, Ferrua S, et al. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol*. 2004;44:810–819.
3. Parajuli DR, Kourbelis C, Franzon J, et al. Effectiveness of the pharmacist-involved multidisciplinary management of heart failure to improve hospitalizations and mortality rates in 4630 patients: a systematic review and meta-analysis of randomized controlled trials. *J Card Fail*. 2019;25:744–756.
4. Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. *Cochrane Database Syst Rev*. 2019;1:CD002752.
5. Jonkman NH, Westland H, Groenvold RH, et al. Do self-management interventions work in patients with heart failure? An individual patient data meta-analysis. *Circulation*. 2016;133:1189–1198.
6. Inglis SC, Clark RA, Dierckx R, et al. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev*. 2015;CD007228.
7. Inglis SC, Clark RA, McAlister FA, et al. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. *Cochrane Database Syst Rev*. 2010;CD007228.
8. Jovicic A, Holroyd-Leduc JM, Straus SE. Effects of self-management intervention on health outcomes of patients with heart failure: a systematic review of randomized controlled trials. *BMC Cardiovasc Disord*. 2006;6:43.
9. Ruppert TM, Cooper PS, Mehr DR, et al. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5:e002606.
10. Butt AA, Omer SB, Yan P, et al. SARS-CoV-2 vaccine effectiveness in a high-risk national population in a real-world setting. *Ann Intern Med*. 2021;174:1404–1408.
11. Gotsman I, Shupy M, Tahiroglu I, et al. Influenza vaccination and outcome in heart failure. *Am J Cardiol*. 2020;128:134–139.
12. Modin D, Jorgensen ME, Gislason G, et al. Influenza vaccine in heart failure. *Circulation*. 2019;139:575–586.
13. Mohseni H, Kiran A, Khorshidi R, et al. Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study. *Eur Heart J*. 2017;38:326–333.
14. Vardeny O, Claggett B, Udel JA, et al. Influenza vaccination in patients with chronic heart failure: the PARADIGM-HF trial. *J Am Coll Cardiol HF*. 2016;4:152–158.
15. Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2021;10:e019636.
16. Ahmed MB, Patel K, Fonarow GC, et al. Higher risk for incident heart failure and cardiovascular mortality among community-dwelling octogenarians without pneumococcal vaccination. *ESC Heart Fail*. 2016;3:11–17.
17. Freedland KE, Carney RM, Rich MW, et al. Depression and multiple rehospitalizations in patients with heart failure. *Clin Cardiol*. 2016;39:257–262.
18. Freedland KE, Hesseler MJ, Carney RM, et al. Major depression and long-term survival of patients with heart failure. *Psychosom Med*. 2016;78:896–903.
19. Murberg TA. Long-term effect of social relationships on mortality in patients with congestive heart failure. *Int J Psychiatry Med*. 2004;34:207–217.
20. Murberg TA, Bru E. Social relationships and mortality in patients with congestive heart failure. *J Psychosom Res*. 2001;51:521–527.
21. Heidari Gorji MA, Fatahian A, Farsavian A. The impact of perceived and objective social isolation on hospital readmission in patients with heart failure: a systematic review and meta-analysis of observational studies. *Gen Hosp Psychiatry*. 2019;60:27–36.
22. Gallagher R, Luttki ML, Jaarsma T. Social support and self-care in heart failure. *J Cardiovasc Nurs*. 2011;26:439–445.
23. Uchmanowicz I, Lee CS, Vitale C, et al. Frailty and the risk of all-cause mortality and hospitalization in chronic heart failure: a meta-analysis. *ESC Heart Fail*. 2020;7:3427–3437.
24. Uchmanowicz I, Wleklik M, Gobbiens RJ. Frailty syndrome and self-care ability in elderly patients with heart failure. *Clin Interv Aging*. 2015;10:871–877.
25. Fabbri M, Murad MH, Wennberg AM, et al. Health literacy and outcomes among patients with heart failure: a systematic review and meta-analysis. *J Am Coll Cardiol HF*. 2020;8:451–460.
26. Macabasco-O'Connell A, DeWalt DA, Broucksou KA, et al. Relationship between literacy, knowledge, self-care behaviors, and heart failure-related quality of life among patients with heart failure. *J Gen Intern Med*. 2011;26:979–986.
27. Bellam N, Kelkar AA, Whellan DJ. Team-based care for managing cardiac comorbidities in heart failure. *Heart Fail Clin*. 2015;11:407–417.
28. Creaser JW, DePasquale EC, Vandenbergbogaart E, et al. Team-based care for outpatients with heart failure. *Heart Fail Clin*. 2015;11:379–405.
29. Vader JM, Rich MW. Team-based care for managing noncardiac conditions in patients with heart failure. *Heart Fail Clin*. 2015;11:419–429.
30. Wever-Pinzon O, Drakos SG, Fang JC. Team-based care for advanced heart failure. *Heart Fail Clin*. 2015;11:467–477.
31. Davidson PM, Newton PJ, Tankumpuan T, et al. Multidisciplinary management of chronic heart failure: principles and future trends. *Clin Ther*. 2015;37:2225–2233.
32. Grady KL, Dracup K, Kennedy G, et al. Team management of patients with heart failure: a statement for healthcare professionals from the Cardiovascular Nursing Council of the American Heart Association. *Circulation*. 2000;102:2443–2456.
33. Cooper LB, Hernandez AF. Assessing the quality and comparative effectiveness of team-based care for heart failure: who, what, where, when, and how. *Heart Fail Clin*. 2015;11:499–506.
34. Riegel B, Moser DK, Anker SD, et al. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation*. 2009;120:1141–1163.
35. Riegel B, Moser DK, Buck HG, et al. Self-care for the prevention and management of cardiovascular disease and stroke: a scientific statement for healthcare professionals from the American Heart Association. *J Am Heart Assoc*. 2017;6:e006997.
36. Moser DK, Dickson V, Jaarsma T, et al. Role of self-care in the patient with heart failure. *Curr Cardiol Rep*. 2012;14:265–275.
37. Riegel B, Lee CS, Dickson VV, et al. Self care in patients with chronic heart failure. *Nat Rev Cardiol*. 2011;8:644–654.
38. Hwang B, Moser DK, Dracup K. Knowledge is insufficient for self-care among heart failure patients with psychological distress. *Health Psychol*. 2014;33:588–596.
39. Allida S, Du H, Xu X, et al. mHealth education interventions in heart failure. *Cochrane Database Syst Rev*. 2020;7:CD011845.
40. Hwang B, Peltier MM, Moser DK, Dracup K. Effects of an educational intervention on heart failure knowledge, self-care behaviors, and health-related quality of life of patients with heart failure: exploring the role of depression. *Patient Educ Couns*. 2020;103:1201–1208.
41. Dracup K, Moser DK, Peltier MM, et al. Randomized, controlled trial to improve self-care in patients with heart failure living in rural areas. *Circulation*. 2014;130:256–264.
42. Van Spall HGC, Lee SF, Xie F, et al. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: the PACT-HF randomized clinical trial. *JAMA*. 2019;321:753–761.

43. Mohseni Z, Spaanderman MEA, Oben J, et al. Cardiac remodeling and pre-eclampsia: an overview of microRNA expression patterns. *Ultrasound Obstet Gynecol.* 2018;52:310–317.
44. Bhatt AS, Adler ED, Albert NM, et al. Coronavirus disease-2019 and heart failure: a scientific statement from the Heart Failure Society of America. *J Card Fail.* 2021;S1071-9164(21)00354-00357.
45. Bhatt AS, Jering KS, Vaduganathan M, et al. Clinical outcomes in patients with heart failure hospitalized with COVID-19. *J Am Coll Cardiol HF.* 2021;9:65–73.
46. Cannata A, Bromage DI, Rind IA, et al. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail.* 2020;22:2219–2224.
47. Tomasoni D, Inciardi RM, Lombardi CM, et al. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. *Eur J Heart Fail.* 2020;22:2238–2247.
48. Patel A, Parikh R, Howell EH, et al. Mini-cog performance: novel marker of post discharge risk among patients hospitalized for heart failure. *Circ Heart Fail.* 2015;8:8–16.
49. Lovell J, Pham T, Noaman SQ, et al. Self-management of heart failure in dementia and cognitive impairment: a systematic review. *BMC Cardiovasc Disord.* 2019;19:99.
50. Cannon JA, Moffitt P, Perez-Moreno AC, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. *J Card Fail.* 2017;23:464–475.
51. Sbolli M, Fiuzat M, Cani D, et al. Depression and heart failure: the lonely comorbidity. *Eur J Heart Fail.* 2020;22:2007–2017.
52. Zambrano J, Celano CM, Januzzi JL, et al. Psychiatric and psychological interventions for depression in patients with heart disease: a scoping review. *J Am Heart Assoc.* 2020;9:e018686.
53. Nishimura M, Bhatia H, Ma J, et al. The impact of substance abuse on heart failure hospitalizations. *Am J Med.* 2020;133:207–213.e1.
54. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56:M146–M156.
55. Smith GH, Shore S, Allen LA, et al. Discussing out-of-pocket costs with patients: shared decision making for sacubitril-valsartan in heart failure. *J Am Heart Assoc.* 2019;8:e010635.
56. Sun Y, Liu B, Rong S, et al. Food insecurity is associated with cardiovascular and all-cause mortality among adults in the United States. *J Am Heart Assoc.* 2020;9:e014629.
57. Makelarski JA, Abramsohn E, Benjamin JH, et al. Diagnostic accuracy of two food insecurity screeners recommended for use in health care settings. *Am J Public Health.* 2017;107:1812–1817.
58. Sims M, Kershaw KN, Breathett K, et al. Importance of housing and cardiovascular health and well-being: a scientific statement from the American Heart Association. *Circ Cardiovasc Qual Outcomes.* 2020;13:e000089.
59. Jayawardana S, Mossialos E. Lives cut short: socioeconomic inequities, homelessness, and cardiovascular disease. *Eur Heart J.* 2020;41:4021–4023.
60. Baggett TP, Liauw SS, Hwang SW. Cardiovascular disease and homelessness. *J Am Coll Cardiol.* 2018;71:2585–2597.
61. US Preventive Services Task Force. Screening for intimate partner violence, elder abuse, and abuse of vulnerable adults: US Preventive Services Task Force Final Recommendation Statement. *JAMA.* 2018;320:1678–1687.
62. Chandan JS, Thomas T, Bradbury-Jones C, et al. Risk of cardiometabolic disease and all-cause mortality in female survivors of domestic abuse. *J Am Heart Assoc.* 2020;9:e014580.
63. Rawal S, Srighanith J, Vasantharoopan A, et al. Association between limited English proficiency and revisits and readmissions after hospitalization for patients with acute and chronic conditions in Toronto, Ontario, Canada. *JAMA.* 2019;322:1605–1607.
64. Magnani JW, Mujahid MS, Aronow HD, et al. Health literacy and cardiovascular disease: fundamental relevance to primary and secondary prevention: a scientific statement from the American Heart Association. *Circulation.* 2018;138:e48–e74.
65. Manemann SM, Chamberlain AM, Roger VL, et al. Perceived social isolation and outcomes in patients with heart failure. *J Am Heart Assoc.* 2018;7:e008069.
3. Kalogeropoulos A, Papadimitriou L, Georgiopoulou VV, et al. Low- versus moderate-sodium diet in patients with recent hospitalization for heart failure: the PROHIBIT (Prevent Adverse Outcomes in Heart Failure by Limiting Sodium) pilot study. *Circ Heart Fail.* 2020;13:e006389.
4. Colin-Ramirez E, McAlister FA, Zheng Y, et al. The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. The SODIUM-HF (Study of Dietary Intervention Under 100 mmol in Heart Failure): a pilot study. *Am Heart J.* 2015;169:274–281.e1.
5. Colin-Ramirez E, McAlister FA, Zheng Y, et al. Changes in dietary intake and nutritional status associated with a significant reduction in sodium intake in patients with heart failure. A sub-analysis of the SODIUM-HF pilot study. *Clin Nutr ESPEN.* 2016;11:e26–e32.
6. Hummel SL, Karmally W, Gillespie BW, et al. Home-delivered meals postdischarge from heart failure hospitalization. *Circ Heart Fail.* 11;2018:e004886.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;128:e240–e327.
8. Yancy CW. The uncertainty of sodium restriction in heart failure: we can do better than this. *J Am Coll Cardiol HF.* 2016;4:39–41.
9. Yancy CW. Sodium restriction in heart failure: too much uncertainty—do the trials. *JAMA Intern Med.* 2018;178:1700–1701.
10. Francis GS. Notice of concern. *J Card Fail.* 2013;19:523.
11. Alexopoulos D, Moulis A, Koutsogiannis N, et al. Differential effect of ticagrelor versus prasugrel on coronary blood flow velocity in patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention: an exploratory study. *Circ Cardiovasc Interv.* 2013;6:277–283.
12. Van Horn L, Carson JA, Appel LJ, et al. Recommended dietary pattern to achieve adherence to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines: a scientific statement from the American Heart Association. *Circulation.* 2016;134:e505–e529.
13. Mahtani KR, Heneghan C, Onakpoya I, et al. Reduced salt intake for heart failure: a systematic review. *JAMA Intern Med.* 2018;178:1693–1700.
14. Jefferson K, Ahmed M, Choleva M, et al. Effect of a sodium-restricted diet on intake of other nutrients in heart failure: implications for research and clinical practice. *J Card Fail.* 2015;21:959–962.
15. Lennie TA, Andreae C, Rayens MK, et al. Micronutrient deficiency independently predicts time to event in patients with heart failure. *J Am Heart Assoc.* 2018;7:e007251.
16. Bonilla-Palomas JL, Gámez-López AL, Castillo-Domínguez JC, et al. Nutritional intervention in malnourished hospitalized patients with heart failure. *Arch Med Res.* 2016;47:535–540.
17. Bilgen F, Chen P, Poggi A, et al. Insufficient calorie intake worsens post-discharge quality of life and increases readmission burden in heart failure. *J Am Coll Cardiol HF.* 2020;8:756–764.
18. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. *JAMA.* 2017;317:1958–1966.
19. Keith M, Quach S, Ahmed M, et al. Thiamin supplementation does not improve left ventricular ejection fraction in ambulatory heart failure patients: a randomized controlled trial. *Am J Clin Nutr.* 2019;110:1287–1295.
20. Rosenblum H, Wessler JD, Gupta A, et al. Zinc deficiency and heart failure: a systematic review of the current literature. *J Card Fail.* 2020;26:180–189.
21. Wang T, Liu Z, Fu J, Min Z. Meta-analysis of vitamin D supplementation in the treatment of chronic heart failure. *Scand Cardiovasc J.* 2019;53:110–116.
22. McKeag NA, McKinley MC, Harbinson MT, et al. The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: a randomized, placebo-controlled trial. *J Am Coll Cardiol HF.* 2014;2:308–317.
23. Ó Miró, Estruch R, Martín-Sánchez FJ, et al. Adherence to Mediterranean diet and all-cause mortality after an episode of acute heart failure: results of the MEDIT-AHF study. *J Am Coll Cardiol HF.* 2018;6:52–62.
24. Aliti GB, Rabelo ER, Clausell N, et al. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. *JAMA Intern Med.* 2013;173:1058–1064.
25. Machado d'Almeida KS, Rabelo-Silva ER, Souza GC, et al. Aggressive fluid and sodium restriction in decompensated heart failure with preserved ejection fraction: results from a randomized clinical trial. *Nutrition.* 2018;54:111–117.
26. Welsh D, Lennie TA, Marcinek R, et al. Low-sodium diet self-management intervention in heart failure: pilot study results. *Eur J Cardiovasc Nurs.* 2013;12:87–95.

### 7.1.2. Dietary Sodium Restriction

- Philipson H, Ekman I, Forslund HB, et al. Salt and fluid restriction is effective in patients with chronic heart failure. *Eur J Heart Fail.* 2013;15:1304–1310.
- Doukky R, Avery E, Mangla A, et al. Impact of dietary sodium restriction on heart failure outcomes. *J Am Coll Cardiol HF.* 2016;4:24–35.

### 7.1.3. Management of Stage C HF: Activity, Exercise Prescription, and Cardiac Rehabilitation

- O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–1450.
- Davies EJ, Moxham T, Rees K, et al. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. *Eur J Heart Fail*. 2010;12:706–715.
- Haykowsky MJ, Timmons MP, Kruger C, et al. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *Am J Cardiol*. 2013;111:1466–1469.
- Santos FV, Chiappa GR, Ramalho SHR, et al. Resistance exercise enhances oxygen uptake without worsening cardiac function in patients with systolic heart failure: a systematic review and meta-analysis. *Heart Fail Rev*. 2018;23:73–89.
- Taylor RS, Walker S, Smart NA, et al. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. *J Am Coll Cardiol*. 2019;73:1430–1443.
- Sagar VA, Davies EJ, Briscoe S, et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. *Open Heart*. 2015;2:e000163.
- Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ*. 2004;328:189.
- Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2014;CD003331.
- Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med*. 2021;385:203–216.
- Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation*. 2003;107:1210–1225.
- Forman DE, Sanderson BK, Josephson RA, et al. Heart failure as a newly approved diagnosis for cardiac rehabilitation: challenges and opportunities. *J Am Coll Cardiol*. 2015;65:2652–2659.
- McKelvie RS. Exercise training in patients with heart failure: clinical outcomes, safety, and indications. *Heart Fail Rev*. 2008;13:3–11.
- Achttien RJ, Staal JB, van der Voort S, et al. Exercise-based cardiac rehabilitation in patients with chronic heart failure: a Dutch practice guideline. *Neth Heart J*. 2015;23:6–17.
- Davies EJ, Moxham T, Rees K, et al. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2010;CD003331.
- Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019;1:CD003331.
- Fukuta H, Goto T, Wakami K, et al. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2019;24:535–547.
- Dieberg G, Ismail H, Giallauria F, et al. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *J Appl Physiol* (1985). 2015;119:726–733.
- Kitzman DW, Brubaker PH, Morgan TM, et al. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail*. 2010;3:659–667.
- Edelmann F, Gelbrich G, Dungen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;58:1780–1791.
- Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *Am Heart J*. 2012;164:869–877.
- Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol*. 2013;62:584–592.
- Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2016;315:36–46.

### 7.2. Diuretics and Decongestion Strategies in Patients With HF

- Patterson JH, Adams KF Jr, Applefeld MM, et al. Oral torsemide in patients with chronic congestive heart failure: effects on body weight, edema, and electrolyte excretion. *Torsemide Investigators Group. Pharmacotherapy*. 1994;14:514–521.
- Goebel KM. Six-week study of torsemide in patients with congestive heart failure. *Clin Ther*. 1993;15:1051–1059.
- Wilson JR, Reichek N, Dunkman WB, et al. Effect of diuresis on the performance of the failing left ventricle in man. *Am J Med*. 1981;70:234–239.
- Parker JO. The effects of oral ibopamine in patients with mild heart failure—a double blind placebo controlled comparison to furosemide. *The Ibopamine Study Group. Int J Cardiol*. 1993;40:221–227.
- Richardson A, Bayliss J, Scriven AJ, et al. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. *Lancet*. 1987;2:709–711.
- Grodin JL, Stevens SR, de Las Fuentes L, et al. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. *J Card Fail*. 2016;22:26–32.
- Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med*. 2017;377:1964–1975.
- Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. *Arch Intern Med*. 1994;154:1905–1914.
- Faselis C, Arundel C, Patel S, et al. Loop diuretic prescription and 30-day outcomes in older patients with heart failure. *J Am Coll Cardiol*. 2020;76:669–679.
- Vargo DL, Kramer WG, Black PK, et al. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther*. 1995;57:601–609.
- Murray MD, Deer MM, Ferguson JA, et al. Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. *Am J Med*. 2001;111:513–520.
- Cosin J, Diez J, TORIC Investigators. Torasemide in chronic heart failure: results of the TORIC study. *Eur J Heart Fail*. 2002;4:507–513.
- Sica DA, Gehl TW. Diuretic combinations in refractory oedema states: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet*. 1996;30:229–249.
- Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. *Ann Intern Med*. 1991;114:886–894.
- Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol*. 2010;56:1527–1534.
- Cox ZL, Hung R, Lenihan DJ, et al. Diuretic strategies for loop diuretic resistance in acute heart failure: the 3T trial. *J Am Coll Cardiol HF*. 2020;8:157–168.
- Brisco-Bacik MA, Ter Maaten JM, Houser SR, et al. Outcomes associated with a strategy of adjuvant metolazone or high-dose loop diuretics in acute decompensated heart failure: a propensity analysis. *J Am Heart Assoc*. 2018;7:e009149.
- Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805.

### 7.3.1. Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

- McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
- Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail*. 2019;21:998–1007.
- Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548.
- Desai AS, Solomon SD, Shah AM, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2019;322:1077–1084.
- Wang Y, Zhou R, Lu C, et al. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: meta-analysis. *J Am Heart Assoc*. 2019;8:e012272.
- Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429–1435.

7. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293–302.
8. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100:2312–2318.
9. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669–677.
10. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet.* 1993;342:821–828.
11. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med.* 1995;333:1670–1676.
12. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA.* 1995;273:1450–1456.
13. Woodard-Grice AV, Lucisano AC, Byrd JB, et al. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet Genomics.* 2010;20:532–536.
14. Cohn JN, Tognoni GV. Sartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345:1667–1675.
15. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both [published correction appears in N Engl J Med. 2004;350:203]. *N Engl J Med.* 2003;349:1893–1906.
16. Konstam MA, Neaton JD, Dickstein K, et al; HEAAI Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAI study): a randomised, double-blind trial. *Lancet.* 2009;374:1840–1848.
17. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008;358:1547–1559.
18. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet.* 2008;372:1174–1183.
19. Banka G, Heidenreich PA, Fonarow GC. Incremental cost-effectiveness of guideline-directed medical therapies for heart failure. *J Am Coll Cardiol.* 2013;61:1440–1446.
20. Dasbach EJ, Rich MW, Segal R, et al. The cost-effectiveness of losartan versus captopril in patients with symptomatic heart failure. *Cardiology.* 1999;91:189–194.
21. Glick H, Cook J, Kinoshian B, et al. Costs and effects of enalapril therapy in patients with symptomatic heart failure: an economic analysis of the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial. *J Card Fail.* 1995;1:371–380.
22. Paul SD, Kuntz KM, Eagle KA, et al. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. *Arch Intern Med.* 1994;154:1143–1149.
23. Reed SD, Friedman JY, Velazquez EJ, et al. Multinational economic evaluation of valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). *Am Heart J.* 2004;148:122–128.
24. Shekelle P, Morton S, Atkinson S, et al. Pharmacologic management of heart failure and left ventricular systolic dysfunction: effect in female, black, and diabetic patients, and cost-effectiveness. *Evid Rep Technol Assess (Summ).* 2003;1–6.
25. Tsevat J, Duke D, Goldman L, et al. Cost-effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol.* 1995;26:914–919.
26. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. *JAMA Cardiol.* 2016;1:666–672.
27. Gaziano TA, Fonarow GC, Velazquez EJ, et al. Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction. *JAMA Cardiol.* 2020;5:1236–1244.
28. King JB, Shah RU, Bress AP, et al. Cost-effectiveness of sacubitril-valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. *J Am Coll Cardiol HF.* 2016;4:392–402.
29. Sandhu AT, Ollendorf DA, Chapman RH, et al. Cost-effectiveness of sacubitril-valsartan in patients with heart failure with reduced ejection fraction. *Ann Intern Med.* 2016;165:681–689.
30. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation.* 2002;106:920–926.
31. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens.* 2004;17:103–111.
32. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *J Am Coll Cardiol HF.* 2014;2:663–670.
33. Messerli FH, Nussberger J. Vasopeptidase inhibition and angio-oedema. *Lancet.* 2000;356:608–609.
34. Braunwald E. The path to an angiotensin receptor antagonist-neprilysin inhibitor in the treatment of heart failure. *J Am Coll Cardiol.* 2015;65:1029–1041.
35. Ruilope LM, Dukat A, Böhm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet.* 2010;375:1255–1266.
36. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am.* 2006;26:725–737.
37. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med.* 2012;172:1582–1589.
38. Makani H, Messerli FH, Romero J, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. *Am J Cardiol.* 2012;110:383–391.
39. Rasmussen ER, Pottegard A, Bygum A, et al. Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors - a nationwide registry-based cohort study. *J Intern Med.* 2019;285:553–561.
40. Jering KS, Claggett B, Pfeffer MA, et al. Prospective ARNI vs. ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. *Eur J Heart Fail.* 2021;23:1040–1048.
41. Zueger PM, Kumar VM, Harrington RL, et al. Cost-effectiveness analysis of sacubitril/valsartan for the treatment of heart failure with reduced ejection fraction in the United States. *Pharmacotherapy.* 2018;38:520–530.

### 7.3.2. Beta Blockers

1. Cardiac Insufficiency Authors. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9–13.
2. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001–2007.
3. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation.* 2002;106:2194–2199.
4. Banka G, Heidenreich PA, Fonarow GC. Incremental cost-effectiveness of guideline-directed medical therapies for heart failure. *J Am Coll Cardiol.* 2013;61:1440–1446.
5. Caro JJ, Migliaccio-Walle K, O'Brien JA, et al. Economic implications of extended-release metoprolol succinate for heart failure in the MERIT-HF trial: a US perspective of the MERIT-HF trial. *J Card Fail.* 2005;11:647–656.
6. Delea TE, Vera-Llonch M, Richner RE, et al. Cost effectiveness of carvedilol for heart failure. *Am J Cardiol.* 1999;83:890–896.
7. Gregory D, Udelson JE, Konstam MA. Economic impact of beta blockade in heart failure. *Am J Med.* 2001;110(suppl 7A):74S–80S.
8. Vera-Llonch M, Menzin J, Richner RE, et al. Cost-effectiveness results from the US Carvedilol Heart Failure Trials Program. *Ann Pharmacother.* 2001;35:846–851.
9. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation.* 1996;94:2807–2816.
10. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J.* 2018;39:26–35.
11. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with

- heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). *JAMA* 2000;283:1295–1302.
- 12. Koteka D, Holmes J, Krum H, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384:2235–2243.
  - 13. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26:215–225.
  - 14. Beta-Blocker Evaluation of Survival Trial Investigators, Eichhorn EJ, Domanski MJ, et al. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–1667.
  - 15. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362:7–13.
  - 16. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation*. 2005;112:2426–2435.
  - 17. Gattis WA, O'Connor CM. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure. *Am J Cardiol*. 2004;93:74B–76B.
  - 18. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393:61–73.
  - 19. Waagstein F, Caidahl K, Wallentin I, et al. Long-term beta-blockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. *Circulation*. 1989;80:551–563.

### 7.3.3. Mineralocorticoid Receptor Antagonists (MRAs)

- 1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.
- 2. Pitt B, Remme W, Zannad F. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
- 3. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
- 4. Banka G, Heidenreich PA, Fonarow GC. Incremental cost-effectiveness of guideline-directed medical therapies for heart failure. *J Am Coll Cardiol*. 2013;61:1440–1446.
- 5. Glick HA, Orzol SM, Tooley JF, et al. Economic evaluation of the randomized aldactone evaluation study (RALES): treatment of patients with severe heart failure. *Cardiovasc Drugs Ther*. 2002;16:53–59.
- 6. Weintraub WS, Zhang Z, Mahoney EM, et al. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. *Circulation*. 2005;111:1106–1113.
- 7. Zhang Z, Mahoney EM, Kolm P, et al. Cost effectiveness of eplerenone in patients with heart failure after acute myocardial infarction who were taking both ACE inhibitors and beta-blockers: subanalysis of the EPHESUS. *Am J Cardiovasc Drugs*. 2010;10:55–63.
- 8. Hernandez AF, Mi X, Hammill BG, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA*. 2012;308:2097–2107.
- 9. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543–551.
- 10. FDA Aldactone label 2008. Accessed June 28, 2021. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/012151s062lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/012151s062lbl.pdf)
- 11. FDA INSPRA label 2008. Accessed June 28, 2021. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/021437s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021437s006lbl.pdf)
- 12. Butler J, Anstrom KJ, Feilker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF Randomized Clinical Trial. *JAMA Cardiol*. 2017;2:950–958.
- 13. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
- 14. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548.

- 15. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J*. 2011;32:820–828.
- 16. Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail*. 2015;17:1050–1056.

### 7.3.4. Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

- 1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.
- 2. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.
- 3. Parizo JT, Goldhaber-Fiebert JD, Salomon JA, et al. Cost-effectiveness of dapagliflozin for treatment of patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;6:926–935.
- 4. Isaza N, Calvachi P, Raber I, et al. Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. *JAMA Netw Open*. 2021;4:e2114501.
- 5. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
- 6. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
- 7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
- 8. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:422–434.
- 9. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPER-OR-Reduced and DAPA-HF trials. *Lancet*. 2020;396:819–829.
- 10. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128.
- 11. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *J Am Coll Cardiol HF*. 2019;7:169–172.

### 7.3.5. Hydralazine and Isosorbide Dinitrate (H-ISDN)

- 1. Carson P, Ziesche S, Johnson G, et al. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail*. 1999;5:178–187.
- 2. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351:2049–2057.
- 3. Angus DC, Linde-Zwirble WT, Tam SW, et al. Cost-effectiveness of fixed-dose combination of isosorbide dinitrate and hydralazine therapy for blacks with heart failure. *Circulation*. 2005;112:3745–3753.
- 4. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314:1547–1552.
- 5. Khazanie P, Liang L, Curtis LH, et al. Clinical effectiveness of hydralazine-isosorbide dinitrate therapy in patients with heart failure and reduced ejection fraction: findings from the Get With The Guidelines-Heart Failure Registry. *Circ Heart Fail*. 2016;9:e002444.
- 6. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303–310.
- 7. Fonarow GC, Chelomsky-Fallick C, Stevenson LW, et al. Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial. *J Am Coll Cardiol*. 1992;19:842–850.

### 7.3.6. Other Drug Treatment

- 1. Macchia A, Levantesi G, Franzosi MG, et al. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. *Eur J Heart Fail*. 2005;7:904–909.
- 2. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1223–1230.

3. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380:11–22.
4. Peterson BE, Bhatt DL, Steg PG, et al. Reduction in revascularization with icosapent ethyl: insights from REDUCE-IT revascularization analyses. *Circulation.* 2021;143:33–44.
5. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF trial). *Eur Heart J.* 2011;32:820–828.
6. Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail.* 2015;17:1050–1056.
7. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation.* 2009;119:1616–1624.
8. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med.* 2012;366:1859–1869.
9. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med.* 2018;379:1332–1342.
10. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation.* 2002;105:1897–1903.
11. Ferreira JP, Butler J, Rossignol P, et al. Abnormalities of potassium in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:2836–2850.
12. Savarese G, Carrero JJ, Pitt B, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2018;20:1326–1334.
13. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA.* 2014;312:2223–2233.
14. Lavie CJ, Milani RV, Mehra MR, et al. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol.* 2009;54:585–594.
15. Malik A, Masson R, Singh S, et al. Digoxin discontinuation and outcomes in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2019;74:617–627.
16. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA.* 2020;324:2268–2280.
17. Dunkman WB, Johnson GR, Carson PE, et al. Incidence of thromboembolic events in congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation.* 87(6 suppl)1993;VI94–VI101.
18. Dunkman WB. Thromboembolism and antithrombotic therapy in congestive heart failure. *J Cardiovasc Risk.* 1995;2:107–117.
19. Cioffi G, Pozzoli M, Forni G, et al. Systemic thromboembolism in chronic heart failure. A prospective study in 406 patients. *Eur Heart J.* 1996;17:1381–1389.
20. Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med.* 1997;336:251–257.
21. Al-Khadra AS, Salem DN, Rand WM, et al. Warfarin anticoagulation and survival: a cohort analysis from the studies of left ventricular dysfunction. *J Am Coll Cardiol.* 1998;31:749–753.
22. Dries DL, Domanski MJ, Waclawiw MA, et al. Effect of antithrombotic therapy on risk of sudden coronary death in patients with congestive heart failure. *Am J Cardiol.* 1997;79:909–913.
3. Djoussé L, Cook NR, Kim E, et al. Supplementation with vitamin D and omega-3 fatty acids and incidence of heart failure hospitalization: VITAL-Heart Failure. *Circulation.* 2020;141:784–786.
4. Wang T, Liu Z, Fu J, Min Z. Meta-analysis of vitamin D supplementation in the treatment of chronic heart failure. *Scand Cardiovasc J.* 2019;53:110–116.
5. Zittermann A, Ernst JB, Prokop S, et al. Vitamin D supplementation of 4000 IU daily and cardiac function in patients with advanced heart failure: the EVITA trial. *Int J Cardiol.* 2019;280:117–123.
6. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA.* 2005;293:1338–1347.
7. Marchioli R, Levantesi G, Macchia A, et al. Vitamin E increases the risk of developing heart failure after myocardial infarction: results from the GISSI-Prevenzione trial. *J Cardiovasc Med (Hagerstown).* 2006;7:347–350.
8. Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *J Am Coll Cardiol HF.* 2014;2:641–649.
9. Madmani ME, Yusuf Solaiman A, Tamr Agha K, et al. Coenzyme Q10 for heart failure. *Cochrane Database Syst Rev.* 2014;CD008684.
10. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II—DAVIT II). *Am J Cardiol.* 1990;66:779–785.
11. Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med.* 1988;319:385–392.
12. Goldstein RE, Bocuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation.* 1991;83:52–60.
13. Figulla HR, Gietzen F, Zeymer U, et al. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. Results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation.* 1996;94:346–352.
14. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med.* 1991;324:781–788.
15. Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. *Survival With Oral d-Sotalol.* *Lancet.* 1996;348:7–12.
16. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med.* 2008;358:2678–2687.
17. Lipscombe LL, Gomes T, Levesque LE, et al. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA.* 2007;298:2634–2643.
18. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet.* 2007;370:1129–1136.
19. Dargie HJ, Hildebrandt PR, Riegger GA, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association functional class I or II heart failure. *J Am Coll Cardiol.* 2007;49:1696–1704.
20. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009;373:2125–2135.
21. Giles TD, Miller AB, Elkayam U, et al. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail.* 2008;14:445–452.
22. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation.* 2014;130:1579–1588.
23. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet.* 2015;385:2067–2076.
24. Verma S, Goldenberg RM, Bhatt DL, et al. Dipeptidyl peptidase-4 inhibitors and the risk of heart failure: a systematic review and meta-analysis. *CMAJ Open.* 2017;5:E152–E177.
25. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart

### 7.3.7. Drugs of Unproven Value or That May Worsen HF

1. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med.* 1996;335:1107–1114.
2. Packer M, Carson P, Elkayam U, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). *J Am Coll Cardiol HF.* 2013;1:308–314.

- failure outcomes in elderly patients: a population-based cohort study. *Lancet*. 2004;363:1751–1756.
26. Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ*. 2005;330:1370.
  27. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med*. 2009;169:141–149.
  28. Feenstra J, Heerdink ER, Grobbee DE, et al. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Arch Intern Med*. 2002;162:265–270.
  29. Packer M, Carson P, Elkayam U, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). *J Am Coll Cardiol HF*. 2013;1:308–314.
  30. Salzano A, Marra AM, D'Assante R, et al. Growth hormone therapy in heart failure. *Heart Fail Clin*. 2018;14:501–515.
  31. Sharma A, Fonarow GC, Butler J, et al. Coenzyme Q10 and heart failure: a state-of-the-art review. *Circ Heart Fail*. 2016;9:e002639.
  32. Vest AR, Chan M, Deswal A, et al. Nutrition, obesity, and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America Scientific Statements Committee. *J Card Fail*. 2019;25:380–400.
  33. Hopper I, Connell C, Briffa T, et al. Nutraceuticals in patients with heart failure: a systematic review. *J Card Fail*. 2020;26:166–179.
  34. Keith M, Quach S, Ahmed M, et al. Thiamin supplementation does not improve left ventricular ejection fraction in ambulatory heart failure patients: a randomized controlled trial. *Am J Clin Nutr*. 2019;110:1287–1295.
  35. Jain A, Mehta R, Al-Ani M, et al. Determining the role of thiamine deficiency in systolic heart failure: a meta-analysis and systematic review. *J Card Fail*. 2015;21:1000–1007.
  36. DiNicolantonio JJ, Niaz AK, Lavie CJ, et al. Thiamine supplementation for the treatment of heart failure: a review of the literature. *Congest Heart Fail*. 2013;19:214–222.
  37. Song X, Qu H, Yang Z, et al. Efficacy and safety of L-carnitine treatment for chronic heart failure: a meta-analysis of randomized controlled trials. *BioMed Res Int*. 2017;2017:6274854.
  38. Azuma J, Sawamura A, Awata N. Usefulness of taurine in chronic congestive heart failure and its prospective application. *Jpn Circ J*. 1992;56:95–99.
  39. Ahmadian M, Dabidi Roshan V, Ashourpore E. Taurine supplementation improves functional capacity, myocardial oxygen consumption, and electrical activity in heart failure. *J Diet Suppl*. 2017;14:422–432.
  40. Tao J, Liu X, Bai W. Testosterone supplementation in patients with chronic heart failure: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2020;11:110.
  41. D'Assante R, Piccoli L, Valente P, et al. Testosterone treatment in chronic heart failure. Review of literature and future perspectives. *Monaldi Arch Chest Dis*. 2018;88:976.
  42. Salzano A, D'Assante R, Lander M, et al. Hormonal replacement therapy in heart failure: focus on growth hormone and testosterone. *Heart Fail Clin*. 2019;15:377–391.
  43. Zhang X, Wang WY, Zhang K, et al. Efficacy and safety of levothyroxine (L-T<sub>4</sub>) replacement on the exercise capability in chronic systolic heart failure patients with subclinical hypothyroidism: study protocol for a multicenter, open label, randomized, parallel group trial (ThyroHeart-CHF). *Trials*. 2019;20:143.
  44. Holmager P, Schmidt U, Mark P, et al. Long-term L-Triiodothyronine (T<sub>3</sub>) treatment in stable systolic heart failure patients: a randomised, double-blind, cross-over, placebo-controlled intervention study. *Clin Endocrinol*. 2015;83:931–937.
  45. Einfeldt MN, Olsen AS, Kristensen SL, et al. Long-term outcome in patients with heart failure treated with levothyroxine: an observational nationwide cohort study. *J Clin Endocrinol Metab*. 2019;104:1725–1734.
  46. Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). *Lancet*. 1994;344:493–498.
  47. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med*. 1995;333:77–82.
  48. Kober L, Bloch Thomsen PE, Moller M, et al. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. *Lancet*. 2000;356:2052–2058.
  49. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med*. 1999;341:857–865.
  50. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327–1335.
  51. McGuire DK, Van de Werf F, Armstrong PW, et al. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2016;1:126–135.
  52. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232–242.
  53. McGuire DK, Alexander JH, Johansen OE, et al. Linagliptin effects on heart failure and related outcomes in individuals with type 2 diabetes mellitus at high cardiovascular and renal risk in CARMELINA. *Circulation*. 2019;139:351–361.
  54. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321:69–79.
  55. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA*. 2019;322:1155–1166.
  56. Communication: FDS. FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. 2018 Accessed June 5, 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-adds-warnings-about-heart-failure-risk-labels-type-2-diabetes>
  57. Page RL 2nd, O'Bryant CL, Cheng D, et al. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e32–e69.

### 7.3.8. Guideline-Directed Medical Therapy (GDMT) Dosing, Sequencing, and Up titration

1. Cardiac Insufficiency Authors. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9–13.
2. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106:2194–2199.
3. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293–302.
4. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450–1456.
5. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
6. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.
7. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
8. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.
9. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.
10. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351:2049–2057.
11. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001–2007.
12. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-inhibitor myocardial infarction collaborative group. *Lancet*. 2000;355:1575–1581.
13. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.

14. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J.* 2009;30:469–477.
15. Bassi NS, Ziaeian B, Yancy CW, et al. Association of optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. *JAMA Cardiol.* 2020;5:948–951.
16. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation.* 1996;94:2807–2816.
17. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100:2312–2318.
18. Konstam MA, Neaton JD, Dickstein K, et al. HEAAI Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAI study): a randomised, double-blind trial. *Lancet.* 2009;374:1840–1848.
19. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669–677.
20. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet.* 2003;362:759–766.
21. Cohn JN, Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345:1667–1675.
22. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004.
23. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344:1651–1658.
24. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med.* 1986;314:1547–1552.
25. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372:807–816.
26. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med.* 2014;371:1091–1099.
27. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–885.
28. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2020;382:1883–1893.
29. Rathore SS, Foody JM, Wang Y, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. *JAMA.* 2003;289:2517–2524.
30. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med.* 1997;336:525–533.
31. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350:2140–2150.
32. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352:1539–1549.
33. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877–883.
34. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005;352:225–237.
35. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307–2318.
36. Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. *Am Heart J.* 2011;161:1024–1030.
37. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol.* 1997;30:27–34.
38. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med.* 2001;134:550–560.
39. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA.* 2007;297:2502–2514.
40. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, et al. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. *Eur Heart J.* 2006;27:2682–2688.
41. Desai AS, Fang JC, Maisel WH, et al. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA.* 2004;292:2874–2879.
42. Ezekowitz JA, Rowe BH, Dryden DM, et al. Systematic review: implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Ann Intern Med.* 2007;147:251–262.

### 7.3.9.1. Management of Stage C HF: Ivabradine

- Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–885.
- Borer JS, Böhm M, Ford I, et al. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study. *Eur Heart J.* 2012;33:2813–2820.
- Fox K, Komajda M, Ford I, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. *Eur Heart J.* 2013;34:2263–2270.
- Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372:807–816.
- Böhm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol.* 2013;102:11–22.
- Bohm M, Robertson M, Ford I, et al. Influence of cardiovascular and noncardiovascular co-morbidities on outcomes and treatment effect of heart rate reduction with ivabradine in stable heart failure (from the SHIFT Trial). *Am J Cardiol.* 2015;116:1890–1897.

### 7.3.9.2. Pharmacological Treatment for Stage C Heart Failure With Reduced Ejection Fraction (HF<sub>RF</sub>) (Digoxin)

- Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med.* 1997;336:525–533.
- Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J.* 2006;27:178–186.
- Lader E, Egan D, Hunsberger S, et al. The effect of digoxin on the quality of life in patients with heart failure. *J Card Fail.* 2003;9:4–12.
- Ahmed A, Pitt B, Rahimtoola SH, et al. Effects of digoxin at low serum concentrations on mortality and hospitalization in heart failure: a propensity-matched study of the DIG trial. *Int J Cardiol.* 2008;123:138–146.
- Aguirre Dávila L, Weber K, Bavendiek U, et al. Digoxin–mortality: randomized vs. observational comparison in the DIG trial. *Eur Heart J.* 2019;40:3336–3341.
- Ambrosy AP, Butler J, Ahmed A, et al. The use of digoxin in patients with worsening chronic heart failure: reconsidering an old drug to reduce hospital admissions. *J Am Coll Cardiol.* 2014;63:1823–1832.
- Gheorghiade M, Patel K, Filippatos G, et al. Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. *Eur J Heart Fail.* 2013;15:551–559.
- Adams KF Jr, Butler J, Patterson JH, et al. Dose response characterization of the association of serum digoxin concentration with mortality outcomes in the Digitalis Investigation Group trial. *Eur J Heart Fail.* 2016;18:1072–1081.
- Lopes RD, Rordorf R, De Ferrari GM, et al. Digoxin and mortality in patients with atrial fibrillation. *J Am Coll Cardiol.* 2018;71:1063–1074.
- Malik A, Masson R, Singh S, et al. Digoxin discontinuation and outcomes in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2019;74:617–627.
- Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. *J Am Coll Cardiol.* 1993;22:955–962.

### 7.3.9.3. Pharmacological Treatment for Stage C HF<sub>RF</sub>: Soluble Guanylyl Cyclase Stimulators

- Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2020;382:1883–1893.

2. Arnold WP, Mittal CK, Katsuki S, et al. Nitric oxide activates guanylate cyclase and increases guanosine 3';5'-cyclic monophosphate levels in various tissue preparations. *Proc Natl Acad Sci U S A.* 1977;74:3203–3207.
3. Hardman JG, Davis JW, Sutherland EW. Effects of some hormonal and other factors on the excretion of guanosine 3';5'-monophosphate and adenosine 3';5'-monophosphate in rat urine. *J Biol Chem.* 1969;244:6354–6362.
4. Hardman JG, Sutherland EW. Guanyl cyclase, an enzyme catalyzing the formation of guanosine 3';5'-monophosphate from guanosine triphosphate. *J Biol Chem.* 1969;244:6363–6370.
5. McNamara DB, Kadowitz PJ, Hyman AL, et al. Adenosine 3';5'-monophosphate formation by preparations of rat liver soluble guanylate cyclase activated with nitric oxide, nitroso ferrohemoglobin, S-nitrosothiols, and other nitroso compounds. *Can J Physiol Pharmacol.* 1980;58:1446–1456.
6. Moncada S, Higgs EA. Nitric oxide and the vascular endothelium. *Handb Exp Pharmacol.* 2006;213:23–254.
7. Moncada S, Palmer RM, Higgs EA. The discovery of nitric oxide as the endogenous nitrovasodilator. *Hypertension.* 1988;12:365–372.
18. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352:1539–1549.
19. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol.* 2008;52:1834–1843.
20. Goldenberg I, Kutya FA, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med.* 2014;370:1694–1701.
21. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* 2010;363:2385–2395.
22. Feldman AM, de Lisssov G, Bristow MR, et al. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. *J Am Coll Cardiol.* 2005;46:2311–2321.
23. Gold MR, Padhari A, Mealing S, et al. Economic value and cost-effectiveness of cardiac resynchronization therapy among patients with mild heart failure: projections from the REVERSE long-term follow-up. *J Am Coll Cardiol HF.* 2017;5:204–212.
24. Heerey A, Lauer M, Alsolaiman F, et al. Cost effectiveness of biventricular pacemakers in heart failure patients. *Am J Cardiovasc Drugs.* 2006;6:129–137.
25. Nichol G, Kaul P, Huszti E, et al. Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure. *Ann Intern Med.* 2004;141:343–351.
26. Noyes K, Veazie P, Hall WJ, et al. Cost-effectiveness of cardiac resynchronization therapy in the MADIT-CRT trial. *J Cardiovasc Electrophysiol.* 2013;24:66–74.
27. Woo CY, Strandberg EJ, Schmiegelow MD, et al. Cost-effectiveness of adding cardiac resynchronization therapy to an implantable cardioverter-defibrillator among patients with mild heart failure. *Ann Intern Med.* 2015;163:417–426.
28. Sipahi I, Chou JC, Hyden M, et al. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Am Heart J.* 2012;163:260–267.e3.
29. Gervais R, Leclercq C, Shankar A, et al. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail.* 2009;11:699–705.
30. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation.* 2011;123:1061–1072.
31. Gold MR, Thebault C, Linde C, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *Circulation.* 2012;126:822–829.
32. Birnie DH, Ha A, Higginson I, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail.* 2013;6:1190–1198.
33. Nery PB, Ha AC, Keren A, et al. Cardiac resynchronization therapy in patients with left ventricular systolic dysfunction and right bundle branch block: a systematic review. *Heart Rhythm.* 2011;8:1083–1087.
34. Curtis AB. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med.* 2013;369:579.
35. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol.* 2005;16:1160–1165.
36. Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med.* 2014;16:601–608.
37. Gigli M, Merlo M, Graw SL, et al. Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol.* 2019;74:1480–1490.
38. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmic cardiomyopathy. *Heart Rhythm.* 2019;16:e301–e372.
39. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* 2009;361:1329–1338.
40. Beshai JF, Grimm RA, Naque SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med.* 2007;357:2461–2471.
41. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med.* 2013;369:1395–1405.

42. Smith T, Jordaens L, Theuns DA, et al. The cost-effectiveness of primary prophylactic implantable defibrillator therapy in patients with ischaemic or non-ischaemic heart disease: a European analysis. *Eur Heart J.* 2013;34:211–219.
43. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med.* 1997;337:1569–1575.
44. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549–556.
45. Healey JS, Hohnloser SH, Exner DV, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail.* 2012;5:566–570.
46. Tolosana JM, Hernandez Madrid A, Brugada J, et al. Comparison of benefits and mortality in cardiac resynchronization therapy in patients with atrial fibrillation versus patients in sinus rhythm (results of the Spanish Atrial Fibrillation And Resynchronization [SPARE] study). *Am J Cardiol.* 2008;102:444–449.
47. Kalscheuer MM, Saxon LA, Lee BK, et al. Outcomes of cardiac resynchronization therapy in patients with intermittent atrial fibrillation or atrial flutter in the COMPANION trial. *Heart Rhythm.* 2017;14:858–865.
48. Adelstein E, Schwartzman D, Gorcsan J 3rd, et al. Predicting hyperresponse among pacemaker-dependent nonischemic cardiomyopathy patients upgraded to cardiac resynchronization. *J Cardiovasc Electrophysiol.* 2011;22:905–911.
49. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2018;138:e272–e391.
50. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med.* 2013;369:1395–1405.
51. Thibault B, Harel F, Ducharme A, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation Of Resynchronization Therapy For Heart Failure (LESSER-EARTH) trial. *Circulation.* 2013;127:873–881.
52. Muto C, Solimene F, Gallo P, et al. A randomized study of cardiac resynchronization therapy defibrillator versus dual-chamber implantable cardioverter-defibrillator in ischemic cardiomyopathy with narrow QRS: the NARROW-CRT study. *Circ Arrhythm Electrophysiol.* 2013;6:538–545.

#### 7.4.2. Other Implantable Electrical Interventions

- Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol.* 2017;14:30–38.
- Wagner BR, Frishman WH. Devices for autonomic regulation therapy in heart failure with reduced ejection fraction. *Cardiol Rev.* 2018;26:43–49.
- Zile MR, Lindenfeld J, Weaver FA, et al. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2020;76:1–13.
- Gold MR, Van Veldhuisen DJ, Hauptman PJ, et al. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. *J Am Coll Cardiol.* 2016;68:149–158.
- Leclercq C, Gadler F, Kranig W, et al. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. *J Am Coll Cardiol.* 2008;51:1455–1462.
- Niazi I, Baker J 2nd, Corbisiero R, et al. Safety and efficacy of multipoint pacing in cardiac resynchronization therapy: the multipoint pacing trial. *J Am Coll Cardiol EP.* 2017;3:1510–1518.
- LeClercq C. Personal communication about phase 2 trial data. 2020.
- Abdelrahman M, Subzposh FA, Beer D, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol.* 2018;71:2319–2330.
- Upadhyay GA, Vijayaraman P, Nayak HM, et al. On-treatment comparison between corrective his bundle pacing and biventricular pacing for cardiac resynchronization: a secondary analysis of the His-SYNC pilot trial. *Heart Rhythm.* 2019;16:1797–1807.
- Upadhyay GA, Vijayaraman P, Nayak HM, et al. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. *J Am Coll Cardiol.* 2019;74:157–159.
- Neelagaru SB, Sanchez JE, Lau SK, et al. Nonexcitatory, cardiac contractility modulation electrical impulses: feasibility study for advanced heart failure in patients with normal QRS duration. *Heart Rhythm.* 2006;3:1140–1147.
- Borggrefe MM, Lawo T, Butter C, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. *Eur Heart J.* 2008;29:1019–1028.
- Kadish A, Nademanee K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Am Heart J.* 2011;161:329–337.e1–2.
- Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. *J Am Coll Cardiol HF.* 2018;6:874–883.

#### 7.4.3. Revascularization for Coronary Artery Disease

- Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation.* 1995;91:2335–2344.
- Howlett JG, Stebbins A, Petrie MC, et al. CABG improves outcomes in patients with ischemic cardiomyopathy: 10-year follow-up of the STICH Trial. *J Am Coll Cardiol HF.* 2019;7:878–887.
- Mark DB, Knight JD, Velazquez EJ, et al. Quality-of-life outcomes with coronary artery bypass graft surgery in ischemic left ventricular dysfunction: a randomized trial. *Ann Intern Med.* 2014;161:392–399.
- Park S, Ahn JM, Kim TO, et al. Revascularization in patients with left main coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol.* 2020;76:1395–1406.
- Petrie MC, Jhund PS, She L, et al. Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: an analysis of the extended follow-up of the STICH Trial (Surgical Treatment for Ischemic Heart Failure). *Circulation.* 2016;134:1314–1324.
- Tam DY, Dharma C, Rocha R, et al. Long-term survival after surgical or percutaneous revascularization in patients with diabetes and multivessel coronary disease. *J Am Coll Cardiol.* 2020;76:1153–1164.
- Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med.* 2011;364:1607–1616.
- Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374:1511–1520.
- Perera D, Clayton T, Petrie MC, et al. Percutaneous revascularization for ischemic ventricular dysfunction: rationale and design of the REVIVED-BCIS2 Trial: percutaneous coronary intervention for ischemic cardiomyopathy. *J Am Coll Cardiol HF.* 2018;6:517–526.
- Nagendran J, Bozso SJ, Norris CM, et al. Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction. *J Am Coll Cardiol.* 2018;71:819–827.
- Chaitman BR, Fisher LD, Bourassa MG, et al. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol.* 1981;48:765–777.
- Jolicoeur EM, Dunning A, Castelvecchio S, et al. Importance of angina in patients with coronary disease, heart failure, and left ventricular systolic dysfunction: insights from STICH. *J Am Coll Cardiol.* 2015;66:2092–2100.
- Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. *N Engl J Med.* 1984;311:1333–1339.
- VA Coronary Artery Bypass Surgery Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for stable angina. *Circulation.* 1992;86:121–130.
- Jones RH, Velazquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med.* 2009;360:1705–1717.
- Dor V, Civaia F, Alexandrescu C, et al. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. *J Thorac Cardiovasc Surg.* 2011;141:905–916, 916e1–4.

#### 7.5. Valvular Heart Disease

- Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *J Am Coll Cardiol HF.* 2017;5:652–659.
- Lowes BD, Gill EA, Abraham WT, et al. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. *Am J Cardiol.* 1999;83:1201–1205.

3. Capomolla S, Febo O, Gnemmi M, et al.  $\beta$ -Blockade therapy in chronic heart failure: diastolic function and mitral regurgitation improvement by carvedilol. *Am Heart J.* 2000;139:596–608.
4. Kang DH, Park SJ, Shin SH, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation.* 2019;139:1354–1365.
5. van Bommel RJ, Marsan NA, Delgado V, et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. *Circulation.* 2011;124:912–919.
6. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med.* 2018;379:2297–2306.
7. Inohara T, Manandhar P, Kosinski AS, et al. Association of renin-angiotensin inhibitor treatment with mortality and heart failure readmission in patients with transcatheter aortic valve replacement. *JAMA.* 2018;320:2231–2241.
8. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet.* 2015;385:2485–2491.
9. Evangelista A, Tornos P, Sambola A, et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med.* 2005;353:1342–1349.
10. Bhudia SK, McCarthy PM, Kumpati GS, et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. *J Am Coll Cardiol.* 2007;49:1465–1471.
11. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet.* 2015;385:2477–2484.
12. Agricola E, Ielasi A, Oppizzi M, et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. *Eur J Heart Fail.* 2009;11:581–587.
13. Karaca O, Omayenc MO, Cakal B, et al. Effect of QRS narrowing after cardiac resynchronization therapy on functional mitral regurgitation in patients with systolic heart failure. *Am J Cardiol.* 2016;117:412–419.
14. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation.* 2003;107:1985–1990.
15. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143:e72–e227.
16. De la Espriella R, Santas E, Miñana G, et al. Functional mitral regurgitation predicts short-term adverse events in patients with acute heart failure and reduced left ventricular ejection fraction. *Am J Cardiol.* 2017;120:1344–1348.
17. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol.* 2003;41:765–770.
18. Kheiri B, Zayed Y, Barbarawi M, et al. Interventions for secondary mitral regurgitation in patients with heart failure: a network meta-analysis of randomized controlled comparisons of surgery, medical therapy and transcatheter intervention. *Cardiovasc Revasc Med.* 2020;21:155–163.
19. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT Trials. *J Am Coll Cardiol Img.* 2019;12:353–362.
20. Packer M. Disproportionate functional mitral regurgitation: a new therapeutic target in patients with heart failure and a reduced ejection fraction. *Eur J Heart Fail.* 2020;22:23–25.
21. Packer M, Grayburn PA. Contrasting effects of pharmacological, procedural, and surgical interventions on proportionate and disproportionate functional mitral regurgitation in chronic heart failure. *Circulation.* 2019;140:779–789.
22. Yu C-M, Chan J-S, Zhang Q, et al. Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. *J Am Coll Cardiol Img.* 2009;2:1341–1349.
23. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J.* 2016;7:2645–2657.
24. Vamvakidou A, Jin W, Danylenko O, et al. Low transvalvular flow rate predicts mortality in patients with low-gradient aortic stenosis following aortic valve intervention. *J Am Coll Cardiol Img.* 2019;12:1715–1724.
25. Spitzer E, Van Mieghem NM, Pibarot P, et al. Rationale and design of the Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADVanced heart failure (TAVR UNLOAD) trial. *Am Heart J.* 2016;182:80–88.
26. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:e521–e643.
27. Packer M, Grayburn PA. Neurohormonal and transcatheter repair strategies for proportionate and disproportionate functional mitral regurgitation in heart failure. *J Am Coll Cardiol HF.* 2019;7:518–521.
28. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307–2318.
29. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597–1607.
30. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med.* 2012;366:1696–1704.
31. Tribouilloy C, Levy F, Rusinaru D, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol.* 2009;53:1865–1873.
32. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation.* 2013;127:2316–2326.
33. Anjan VY, Herrmann HC, Pibarot P, et al. Evaluation of flow after transcatheter aortic valve replacement in patients with low-flow aortic stenosis: a secondary analysis of the PARTNER randomized clinical trial. *JAMA Cardiol.* 2016;1:584–592.
34. Klodas E, Enriquez-Sarano M, Tajik AJ, et al. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. *J Am Coll Cardiol.* 1997;30:746–752.
35. Chaliki HP, Mohty D, Avierinos JF, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. *Circulation.* 2002;106:2687–2693.

### 7.6.1. Heart Failure With Mildly Reduced Ejection Fraction (HFmrEF)

1. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461.
2. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J.* 2018;39:26–35.
3. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381:1609–1620.
4. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2019;393:61–73.
5. Nilsson BB, Lunde P, Grogård HK, et al. Long-term results of high-intensity exercise-based cardiac rehabilitation in revascularized patients for symptomatic coronary artery disease. *Am J Cardiol.* 2018;121:21–26.
6. Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction: the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. *Circ Heart Fail.* 2016;9:e002744.
7. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction—a report from the CHART-2 Study. *Eur J Heart Fail.* 2017;19:1258–1269.
8. Solomon SD, Vaduganathan M, Claggett BL, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation.* 2020;141:352–361.
9. Zheng SL, Chan FT, Nabeboccus AA, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart.* 2018;104:407–415.
10. Packer M, Butler J, Zannad F, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and a preserved ejection fraction: the EMPEROR-Preserved trial. *Circulation.* 2021;144:1284–1294.

### 7.6.2. HF With Improved Ejection Fraction

1. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy

- (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2019;393:61–73.
2. Wilcox JE, Fang JC, Margulies KB, et al. Heart failure with recovered left ventricular ejection fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol.* 2020;76:719–734.
  3. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail.* 2021;27:387–413.

### 7.7.1. HF With Preserved EF (HFpEF)

1. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. *J Hypertens.* 2016;34:1921–1932.
2. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years: a randomized clinical trial. *JAMA.* 2016;315:2673–2682.
3. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;373:2103–2116.
4. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461.
5. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370:1383–1392.
6. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation.* 2015;131:34–42.
7. Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction: the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. *Circ Heart Fail.* 2016;9:e002744.
8. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet.* 2003;362:777–781.
9. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail.* 2018;20:1230–1239.
10. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381:1609–1620.
11. Solomon SD, Vaduganathan M, B LC, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation.* 2020;141:352–361.
12. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med.* 2015;373:2314–2324.
13. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA.* 2013;309:1268–1277.
14. Cincin A, Abul Y, Ozben B, et al. Pleural fluid amino-terminal brain natriuretic peptide in patients with pleural effusions. *Respir Care.* 2013;58:313–319.
15. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol.* 2012;59:998–1005.
16. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol.* 2014;64:2281–2293.
17. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* 2013;62:263–271.
18. Ho JE, Zerr EK, Wooster L, et al. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation.* 2019;140:353–365.
19. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med.* 2008;359:2456–2467.
20. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J.* 2006;27:2338–2345.
21. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* 2008;358:1887–1898.
22. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA.* 1997;278:212–216.
23. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with heart failure in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *Circulation.* 2011;124:1811–1818.
24. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet.* 2016;387:435–443.
25. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009;338:b1665.
26. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13–e115.
27. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction  $> = 40\%$  treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol.* 1997;80:207–209.
28. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol.* 2009;53:2150–2158.
29. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol.* 2010;56:845–854.
30. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461.
31. Packer M, Butler J, Zannad F, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and a preserved ejection fraction: the EMPEROR-Preserved trial. *Circulation.* 2021;144:1284–1294.
32. Kotecha D, Bunting KV, Gill SK, et al. Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial. *JAMA.* 2020;324:2497–2508.
33. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2014;130:e199–e267.
34. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2019;140:e125–e151.
35. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA.* 2013;309:781–791.
36. Martos R, Baugh J, Ledwidge M, et al. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation.* 2007;115:888–895.
37. Yamamoto K, Masuyama T, Sakata Y, et al. Roles of renin-angiotensin and endothelin systems in development of diastolic heart failure in hypertensive hearts. *Cardiovasc Res.* 2000;47:274–283.
38. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet.* 2003;362:777–781.
39. Nilsson BB, Lunde P, Groggaard HK, et al. Long-term results of high-intensity exercise-based cardiac rehabilitation in revascularized patients for symptomatic coronary artery disease. *Am J Cardiol.* 2018;121:21–26.
40. Lumbers RT, Martin N, Manoharan K, et al. Do beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve outcomes in

- patients with heart failure and left ventricular ejection fraction >40. *Heart*. 2019;105:1533–1535.
41. Martin N, Manoharan K, Thomas J, et al. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev*. 2018;6:CD012721.
  42. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387–1395.
  43. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation*. 2020;141:338–351.
  44. Solomon SD, Vaduganathan M, Claggett BL, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141:352–361.
  45. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med*. 2015;373:2314–2324.

### 7.8.1. Diagnosis of Cardiac Amyloidosis

1. Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38:2879–2887.
2. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J*. 2015;36:2585–2594.
3. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol*. 2018;72:2040–2050.
4. Westermark P, Westermark GT, Suhr OB, et al. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. *Ups J Med Sci*. 2014;119:223–228.
5. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161–172.
6. Muchtar E, Gertz MA, Kyle RA, et al. A modern primer on light chain amyloidosis in 592 patients with mass spectrometry-verified typing. *Mayo Clin Proc*. 2019;94:472–483.
7. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133:2404–2412.
8. Brown EE, Lee YZJ, Halushka MK, et al. Genetic testing improves identification of transthyretin amyloid (ATTR) subtype in cardiac amyloidosis. *Amyloid*. 2017;24:92–95.
9. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e7–e22.
10. Quarta CC, Solomon SD, Uraizee I, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation*. 2014;129:1840–1849.
11. Katzmann JA, Abraham RS, Dispizio A, et al. Diagnostic performance of quantitative kappa and lambda free light chain assays in clinical practice. *Clin Chem*. 2005;51:878–881.
12. Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. *JAMA Cardiol*. 2016;1:880–889.
13. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:11–21.
14. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22–31.

### 7.8.2. Treatment of Cardiac Amyloidosis

1. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007–1016.
2. Kazi DS, Bellows BK, Baron SJ, et al. Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation*. 2020;141:1214–1224.
3. El-Am EA, Dispizio A, Melduni RM, et al. Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. *J Am Coll Cardiol*. 2019;73:589–597.
4. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;119:2490–2497.

5. Kim EJ, Holmes BB, Huang S, et al. Outcomes in patients with cardiac amyloidosis and implantable cardioverter-defibrillator. *Europace*. 2020;22:1216–1223.
6. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22–31.
7. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:11–21.
8. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310:2658–2667.
9. Wixner J, Pilebo B, Lundgren HE, Olsson M, Anan I. Effect of doxycycline and ursodeoxycholic acid on transthyretin amyloidosis. *Amyloid*. 2017;24:78–79.
10. Obici L, Cortese A, Lozza A, et al. Doxycycline plus taurooursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid*. 2012;19(suppl 1):34–36.
11. aus dem Siepen F, Bauer R, Aurich M, et al. Green tea extract as a treatment for patients with wild-type transthyretin amyloidosis: an observational study. *Drug Des Devel Ther*. 2015;9:6319–6325.
12. Feng D, Edwards WD, Oh JK, et al. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation*. 2007;116:2420–2426.
13. Donnellan E, Elshazly MB, Vakamudi S, et al. No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *J Am Coll Cardiol EP*. 2019;5:1473–1474.

### 8.1. Specialty Referral for Advanced HF

1. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20:1505–1535.
2. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. *J Card Fail*. 2015;21:519–534.
3. Greenberg B, Fang J, Mehra M, et al. Advanced heart failure: trans-atlantic perspectives on the heart failure association of the European Society of Cardiology position statement. *Eur J Heart Fail*. 2018;20:1536–1539.
4. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;119:e391–e479.
5. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
6. Thomas R, Huntley A, Mann M, et al. Specialist clinics for reducing emergency admissions in patients with heart failure: a systematic review and meta-analysis of randomised controlled trials. *Heart*. 2013;99:233–239.
7. Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant*. 2009;28:535–541.
8. Ambardekar AV, Fonarow GC, Hernandez AF, et al. Characteristics and in-hospital outcomes for nonadherent patients with heart failure: findings from Get With The Guidelines-Heart Failure (GWTG-HF). *Am Heart J*. 2009;158:644–652.
9. Andrews AM, Russell CL, Cheng AL. Medication adherence interventions for older adults with heart failure: a systematic review. *J Gerontol Nurs*. 2017;43:37–45.
10. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail*. 2011;17:664–669.
11. Ruppert TM, Cooper PS, Mehr DR, et al. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5:e002606.
12. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327.
13. Russell SD, Miller LW, Pagani FD. Advanced heart failure: a call to action. *Congest Heart Fail*. 2008;14:316–321.
14. Yancy CW, Januzzi JL Jr, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 piv-

- otal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Task Force on expert consensus decision pathways. *J Am Coll Cardiol.* 2018;71:201–230.
15. Guglin M, Zucker MJ, Borlaug BA, et al. Evaluation for heart transplantation and LVAD implantation: JACC council perspectives. *J Am Coll Cardiol.* 2020;75:1471–1487.
  16. Thorvaldsen T, Benson L, Stahlberg M, et al. Triage of patients with moderate to severe heart failure: who should be referred to a heart failure center? *J Am Coll Cardiol.* 2014;63:661–671.
  17. Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation.* 2007;116:497–505.
  18. Baumwol J. “I Need Help”—A mnemonic to aid timely referral in advanced heart failure. *J Heart Lung Transplant.* 2017;36:593–594.
  19. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant.* 2013;32:157–187.
  20. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant.* 2016;35:1–23.
  21. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J.* 2013;34:1404–1413.
  22. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation.* 2006;113:1424–1433.
  23. Ambrosy AP, Pang P, Khan S, et al; Everest Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J.* 2013;34:835–843.
  24. Cadentey G, Khairy P, Roy D, et al. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: insights from the AF-CHF trial (atrial fibrillation and chronic heart failure). *J Am Coll Cardiol HF.* 2014;2:15–23.
  25. Drazner MH, Rame JE, Stevenson L, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med.* 2001;345:574–581.
  26. Fudim M, Parikh KS, Dunning A, et al. Relation of volume overload to clinical outcomes in acute heart failure (from ASCEND-HF). *Am J Cardiol.* 2018;122:1506–1512.
  27. Selvaraj S, Claggett B, Shah SJ, et al. Utility of the cardiovascular physical examination and impact of spironolactone in heart failure with preserved ejection fraction. *Circ Heart Fail.* 2019;12:e006125.
  28. Selvaraj S, Claggett B, Pozzi A, et al. Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. *Circulation.* 2019;140:1369–1379.
  29. Simonavicius J, Sanders van-Wijk S, Rickenbacher P, et al. Prognostic significance of longitudinal clinical congestion pattern in chronic heart failure: insights from TIME-CHF Trial. *Am J Med.* 2019;132:e679–e692.
  30. Gorodeski EZ, Chu E, Reese JR, et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail.* 2009;2:320–324.
  31. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol.* 2006;97:1759–1764.
  32. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med.* 2008;359:1009–1017.
  33. Zamora E, Diez-Lopez C, Lupon J, et al. Weight loss in obese patients with heart failure. *J Am Heart Assoc.* 2016;5:e002468.
  34. Anker SD, Negassa A, Coats AJ, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet.* 2003;361:1077–1083.
  35. Kittleson M, Hurwitz S, Shah MR, et al. Development of circulatory-renal limitations to angiotensin-converting enzyme inhibitors identifies patients with severe heart failure and early mortality. *J Am Coll Cardiol.* 2003;41:2029–2035.
  36. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J.* 2007;154:260–266.
  37. Cook JL, Colvin M, Francis GS, et al. Recommendations for the use of mechanical circulatory support: ambulatory and community patient care: a scientific statement from the American Heart Association. *Circulation.* 2017;135:e1145–e1158.

## 8.2. Nonpharmacological Management: Advanced HF

1. Dunlap ME, Hauptman PJ, Amin AN, et al. Management of hyponatremia in acute heart failure: a report from the hyponatremia registry for patients with euolemic and hypervolemic hyponatremia (HN Registry). *J Am Heart Assoc.* 2017;6:e005261.
2. Philipson H, Ekman I, Forslund HB, et al. Salt and fluid restriction is effective in patients with chronic heart failure. *Eur J Heart Fail.* 2013;15:1304–1310.
3. Albert NM, Nutter B, Forney J, et al. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). *J Card Fail.* 2013;19:1–9.
4. De Vecchis R, Baldi C, Cioppa C, et al. Effects of limiting fluid intake on clinical and laboratory outcomes in patients with heart failure. Results of a meta-analysis of randomized controlled trials. *Herz.* 2016;41:63–75.
5. Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J.* 2007;28:980–988.
6. Lu DY, Cheng HM, Cheng YL, et al. Hyponatremia and worsening sodium levels are associated with long-term outcome in patients hospitalized for acute heart failure. *J Am Heart Assoc.* 2016;5:e002668.
7. Allen LA, Gheorghiade M, Reid KJ, et al. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. *Circ Cardiovasc Qual Outcomes.* 2011;4:389–398.
8. Wang J, Zhou W, Yin X. Improvement of hyponatremia is associated with lower mortality risk in patients with acute decompensated heart failure: a meta-analysis of cohort studies. *Heart Fail Rev.* 2019;24:209–217.
9. Omar HR, Charnigo R, Guglin M. Prognostic significance of discharge hyponatremia in heart failure patients with normal admission sodium (from the ESCAPE Trial). *Am J Cardiol.* 2017;120:607–615.
10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;128:e240–e327.
11. Vest AR, Chan M, Deswal A, et al. Nutrition, obesity, and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America Scientific Statements Committee. *J Card Fail.* 2019;25:380–400.
12. Expression of concern: normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? *Clin Sci (Lond).* 2020;134:1841.

## 8.3. Inotropic Support

1. Al-Kindi SG, Farhoud M, Zacharias M, et al. Left ventricular assist devices or inotropes for decreasing pulmonary vascular resistance in patients with pulmonary hypertension listed for heart transplantation. *J Card Fail.* 2017;23:209–215.
2. Hübner T, Nickel T, Steinbeck G, et al. A single German center experience with intermittent inotropes for patients on the high-urgent heart transplant waiting list. *Clin Res Cardiol.* 2015;104:929–934.
3. Aranda JM Jr, Schofield RS, Pauly DF, et al. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J.* 2003;145:324–329.
4. Brozena SC, Twomey C, Goldberg LR, et al. A prospective study of continuous intravenous milrinone therapy for status IB patients awaiting heart transplant at home. *J Heart Lung Transplant.* 2004;23:1082–1086.
5. Gorodeski EZ, Chu E, Reese JR, et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail.* 2009;2:320–324.
6. O’Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J.* 1999;138:78–86.
7. Hershberger RE, Nauman D, Walker TL, et al. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. *J Card Fail.* 2003;9:180–187.
8. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol.* 2005;46:57–64.
9. Nizamic T, Murad MH, Allen LA, et al. Ambulatory inotrope infusions in advanced heart failure: a systematic review and meta-analysis. *J Am Coll Cardiol HF.* 2018;6:757–767.

10. Oliva F, Latini R, Politi A, et al. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial. *Am Heart J.* 1999;138:247–253.
11. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA.* 2002;287:1541–1547.
12. Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J.* 2007;153:98–104.
13. Mebazaa A, Nieminen MS, Filippatos GS, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. *Eur J Heart Fail.* 2009;11:304–311.
14. Acharya D, Sanam K, Revilla-Martinez M, et al. Infections, arrhythmias, and hospitalizations on home intravenous inotropic therapy. *Am J Cardiol.* 2016;117:952–956.
15. Hashim T, Sanam K, Revilla-Martinez M, et al. Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure. *Circ Heart Fail.* 2015;8:880–886.
16. Greenberg B, Butler J, Felker GM, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *Lancet.* 2016;387:1178–1186.
17. Nassif ME, Spertus JA, Jones PG, et al. Changes in disease-specific versus generic health status measures after left ventricular assist device implantation: insights from INTERMACS. *J Heart Lung Transplant.* 2017;36:1243–1249.
18. Rogers JG, Butler J, Lansman SL, et al. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTREPID Trial. *J Am Coll Cardiol.* 2007;50:741–747.
19. Starling RC, Estep JD, Horstmann DA, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. *J Am Coll Cardiol HF.* 2017;5:518–527.
20. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, et al. Cost-effectiveness of left ventricular assist devices in ambulatory patients with advanced heart failure. *J Am Coll Cardiol HF.* 2017;5:110–119.
21. Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. *Circ Heart Fail.* 2014;7:470–478.
22. Mahr C, McGee E Jr, Cheung A, et al. Cost-effectiveness of thoracotomy approach for the implantation of a centrifugal left ventricular assist device. *ASAIO J.* 2020;66:855–861.
23. Rogers JG, Bostic RR, Tong KB, et al. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. *Circ Heart Fail.* 2012;5:10–16.
24. Silvestry SC, Mahr C, Slaughter MS, et al. Cost-effectiveness of a small intra-pericardial centrifugal left ventricular assist device. *ASAIO J.* 2020;66:862–870.
25. Garbade J, Gustafsson F, Shaw S, et al. Postmarket experience with HeartMate 3 left ventricular assist device: 30-day outcomes from the ELEVATE registry. *Ann Thorac Surg.* 2019;107:33–39.
26. Trivedi JR, Cheng A, Singh R, Williams ML, Slaughter MS. Survival on the heart transplant waiting list: impact of continuous flow left ventricular assist device as bridge to transplant. *Ann Thorac Surg.* 2014;98:830–834.
27. Thiele H, Jobs A, Ouweneel DM, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J.* 2017;38:3523–3531.
28. den Uil CA, Van Mieghem NM, M BB, et al. Primary intra-aortic balloon support versus inotropes for decompensated heart failure and low output: a randomised trial. *EuroIntervention.* 2019;15:586–593.
29. Ouyang D, Gulati G, Ha R, et al. Incidence of temporary mechanical circulatory support before heart transplantation and impact on post-transplant outcomes. *J Heart Lung Transplant.* 2018;37:1060–1066.
30. Arnold SV, Jones PG, Allen LA, et al. Frequency of poor outcome (death or poor quality of life) after left ventricular assist device for destination therapy: results from the INTERMACS registry. *Circ Heart Fail.* 2016;9:e002800.
31. Rogers JG, Pagani FD, Tatooles AJ, et al. Intraoperative left ventricular assist device for advanced heart failure. *N Engl J Med.* 2017;376:451–460.
32. Allen JG, Weiss ES, Schaffer JM, et al. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. *J Heart Lung Transplant.* 2010;29:278–285.
33. Slaughter MS, Pagani FD, McGee EC, et al. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. *J Heart Lung Transplant.* 2013;32:675–683.
34. Bellavia D, Iacovoni A, Scardulla C, et al. Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies. *Eur J Heart Fail.* 2017;19:926–946.
35. Joseph SM, Manghelli JL, Vader JM, et al. Prospective assessment of frailty using the Fried criteria in patients undergoing left ventricular assist device therapy. *Am J Cardiol.* 2017;120:1349–1354.
36. Adamo L, Tang Y, Nassif ME, et al. The HeartMate risk score identifies patients with similar mortality risk across all INTERMACS profiles in a large multicenter analysis. *J Am Coll Cardiol HF.* 2016;4:950–958.
37. Baumann Kreuziger LM, Kim B, Wieselthaler GM. Antithrombotic therapy for left ventricular assist devices in adults: a systematic review. *J Thromb Haemost.* 2015;13:946–955.
38. Goldstein DJ, John R, Salerno C, et al. Algorithm for the diagnosis and management of suspected pump thrombus. *J Heart Lung Transplant.* 2013;32:667–670.
39. Coffin ST, Haglund NA, Davis ME, et al. Adverse neurologic events in patients bridged with long-term mechanical circulatory support: a device-specific comparative analysis. *J Heart Lung Transplant.* 2015;34:1578–1585.

40. Kato TS, Schulze PC, Yang J, et al. Pre-operative and post-operative risk factors associated with neurologic complications in patients with advanced heart failure supported by a left ventricular assist device. *J Heart Lung Transplant.* 2012;31:1–8.
41. Zhigalov K, Mashhour A, Szczechowicz M, et al. Clinical outcome and comparison of three different left ventricular assist devices in a high-risk cohort. *Artif Organs.* 2018;42:1035–1042.
42. Hawkins RB, Go K, Raymond SL, et al. Laparoscopic sleeve gastrectomy in patients with heart failure and left ventricular assist devices as a bridge to transplant. *Surg Obes Relat Dis.* 2018;14:1269–1273.
43. Kerrigan DJ, Williams CT, Ehrman JK, et al. Muscular strength and cardiorespiratory fitness are associated with health status in patients with recently implanted continuous-flow LVADs. *J Cardiopulm Rehabil Prev.* 2013;33:396–400.
44. Kumarsinghe G, Jain P, Jabbour A, et al. Comparison of continuous-flow ventricular assist device therapy with intensive medical therapy in fixed pulmonary hypertension secondary to advanced left heart failure. *ESC Heart Fail.* 2018;5:695–702.
45. Pham BN, Chaparro SV. Left ventricular assist device recovery: does duration of mechanical support matter? *Heart Fail Rev.* 2019;24:237–244.
46. Lampropulos JF, Kim N, Wang Y, et al. Trends in left ventricular assist device use and outcomes among Medicare beneficiaries, 2004–2011. *Open Heart.* 2014;1:e000109.
47. Mehra MR, Salerno C, Cleveland JC, et al. Healthcare resource use and cost implications in the MOMENTUM 3 long-term outcome study. *Circulation.* 2018;138:1923–1934.
48. Teuteberg JJ, Cleveland JC Jr, Cowger J, et al. The Society of Thoracic Surgeons Intermacs 2019 annual report: the changing landscape of devices and indications. *Ann Thorac Surg.* 2020;109:649–660.

## 8.5. Cardiac Transplantation

- Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant.* 2019;38:1056–1066.
- Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2018 annual data report: heart. *Am J Transplant.* 2020;20(Suppl 1):340–426.
- Teuteberg JJ, Cleveland JC Jr, Cowger J, et al. The Society of Thoracic Surgeons Intermacs 2019 annual report: the changing landscape of devices and indications. *Ann Thorac Surg.* 2020;109:649–660.
- Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. *Circ Heart Fail.* 2014;7:470–478.
- US Department of Health and Human Services. Adult heart allocation. 2018. Accessed September 15, 2020. <https://optn.transplant.hrsa.gov/learn/professional-education/adult-heart-allocation/>
- Cogswell R, John R, Estep JD, et al. An early investigation of outcomes with the new 2018 donor heart allocation system in the United States. *J Heart Lung Transplant.* 2020;39:1–4.
- Goff RR, Uccellini K, Lindblad K, et al. A change of heart: preliminary results of the US 2018 adult heart allocation revision. *Am J Transplant.* 2020;20:2781–2790.
- Jawitz OK, Fudim M, Raman V, et al. Reassessing recipient mortality under the new heart allocation system: an updated UNOS registry analysis. *J Am Coll Cardiol HF.* 2020;8:548–556.
- Kilic A, Hickey G, Mathier MA, et al. Outcomes of the first 1300 adult heart transplants in the United States after the allocation policy change. *Circulation.* 2020;141:1662–1664.
- Trivedi JR, Slaughter MS. “Unintended” consequences of changes in heart transplant allocation policy: impact on practice patterns. *ASAIO J.* 2020;66:125–127.
- Varshney AS, Hirji SA, Givertz MM. Outcomes in the 2018 UNOS donor heart allocation system: a perspective on disparate analyses. *J Heart Lung Transplant.* 2020;39:1191–1194.
- Habedank D, Ewert R, Hummel M, et al. Changes in exercise capacity, ventilation, and body weight following heart transplantation. *Eur J Heart Fail.* 2007;9:310–316.
- Kobashigawa JA, Leaf DA, Lee N, et al. A controlled trial of exercise rehabilitation after heart transplantation. *N Engl J Med.* 1999;340:272–277.
- Salyer J, Flattery MP, Joyner PL, et al. Lifestyle and quality of life in long-term cardiac transplant recipients. *J Heart Lung Transplant.* 2003;22:309–321.
- Grady KL, Naftel DC, Kobashigawa J, et al. Patterns and predictors of quality of life at 5 to 10 years after heart transplantation. *J Heart Lung Transplant.* 2007;26:535–543.
- Kanwar M, Raina A, Aponte MP, et al. Pulmonary hypertension in potential heart transplant recipients: current treatment strategies. *Curr Opin Organ Transplant.* 2015;20:570–576.
- Givertz MM, DeFilippis EM, Landzberg MJ, et al. Advanced heart failure therapies for adults with congenital heart disease: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;74:2295–2312.
- Maron MS, Kalsmith BM, Udelson JE, et al. Survival after cardiac transplantation in patients with hypertrophic cardiomyopathy. *Circ Heart Fail.* 2010;3:574–579.
- Wu RS, Gupta S, Brown RN, et al. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. *J Heart Lung Transplant.* 2010;29:432–438.
- Crawford TC, Okada DR, Magruder JT, et al. A contemporary analysis of heart transplantation and bridge-to-transplant mechanical circulatory support outcomes in cardiac sarcoidosis. *J Card Fail.* 2018;24:384–391.
- Barrett CD, Alexander KM, Zhao H, et al. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation. *J Am Coll Cardiol HF.* 2020;8:461–468.
- Arena R, Myers J, Aslam SS, et al. Peak VO<sub>2</sub> and VE/VCO<sub>2</sub> slope in patients with heart failure: a prognostic comparison. *Am Heart J.* 2004;147:354–360.
- Kato TS, Collado E, Khawaja T, et al. Value of peak exercise oxygen consumption combined with B-type natriuretic peptide levels for optimal timing of cardiac transplantation. *Circ Heart Fail.* 2013;6:6–14.
- Ferreira AM, Tabet JY, Frankenstein L, et al. Ventilatory efficiency and the selection of patients for heart transplantation. *Circ Heart Fail.* 2010;3:378–386.
- Corra U, Agostoni PG, Anker SD, et al. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2018;20:3–15.
- Peterson LR, Schechtman KB, Ewald GA, et al. The effect of beta-adrenergic blockers on the prognostic value of peak exercise oxygen uptake in patients with heart failure. *J Heart Lung Transplant.* 2003;22:70–77.
- Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778–786.
- O’Neill JO, Bott-Silverman CE, McRae AT 3rd, et al. B-type natriuretic peptide levels are not a surrogate marker for invasive hemodynamics during management of patients with severe heart failure. *Am Heart J.* 2005;149:363–369.
- Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant.* 2016;35:1–23.
- Kazi DS, Bellows BK, Baron SJ, et al. Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation.* 2020;141:1214–1224.

## 9.1. Assessment of Patients Hospitalized With Decompensated HF

- Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. *Circ Heart Fail.* 2008;1:170–177.
- Chioncel O, Mebazaa A, Maggioni AP, et al. Acute heart failure congestion and perfusion status-impact of the clinical classification on in-hospital and long-term outcomes: insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2019;21:1338–1352.
- Cleland JG, Chiswell K, Teerlink JR, et al. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function (PROTECT) study. *Circ Heart Fail.* 2014;7:76–87.
- Ambrosy AP, Pang P, Khan S, et al Everest Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J.* 2013;34:835–843.

5. Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2019;74:1966–2011.
6. Kapoor JR, Kapoor R, Ju C, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. *J Am Coll Cardiol HF.* 2016;4:464–472.
7. Kocioł RD, Cooper LT, Fang JC, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation.* 2020;141:e69–e92.
8. Peretto G, Sala S, Rizzo S, et al. Ventricular arrhythmias in myocarditis: characterization and relationships with myocardial inflammation. *J Am Coll Cardiol.* 2020;75:1046–1057.
9. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *J Am Coll Cardiol HF.* 2018;6:543–551.
10. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol.* 2003;41:1797–1804.
11. Campbell P, Drazner MH, Kato M, et al. Mismatch of right and left-sided filling pressures in chronic heart failure. *J Card Fail.* 2011;17:561–568.
12. Zymlinski R, Biegus J, Sokolski M, et al. Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion. *Eur J Heart Fail.* 2018;20:1011–1018.
13. Bhagat AA, Greene SJ, Vaduganathan M, et al. Initiation, continuation, switching and withdrawal of heart failure medical therapies during hospitalization. *J Am Coll Cardiol.* 2019;7:1–12.
14. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. *J Am Coll Cardiol.* 2008;52:190–199.
15. Fonarow GC, Abraham WT, Albert NM, et al. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J.* 2007;153:82e1–e11.
16. Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol.* 2009;53:184–192.
17. Bhatia V, Bajaj NS, Sanam K, et al. Beta-blocker use and 30-day all-cause readmission in Medicare beneficiaries with systolic heart failure. *Am J Med.* 2015;128:715–721.
18. Sanam K, Bhatia V, Bajaj NS, et al. Renin-angiotensin system inhibition and lower 30-day all-cause readmission in Medicare beneficiaries with heart failure. *Am J Med.* 2016;129:1067–1073.
19. Hernandez AF, Mi X, Hammill BG, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA.* 2012;308:2097–2107.
20. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med.* 2021;384:117–128.
21. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;380:539–548.
22. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol.* 2018;72:351–366.
23. Deschaseaux C, McSharry M, Hudson E, et al. Treatment initiation patterns, modifications, and medication adherence among newly diagnosed heart failure patients: a retrospective claims database analysis. *J Manag Care Spec Pharm.* 2016;22:561–571.
24. Wirtz HS, Sheer R, Honarpour N, et al. Real-world analysis of guideline-based therapy after hospitalization for heart failure. *J Am Heart Assoc.* 2020;9:e015042.
25. Wirtz HS, Sheer R, Honarpour N, et al. Real-world analysis of guideline-based therapy after hospitalization for heart failure. *J Am Heart Assoc.* 2020;9:e015042.
26. Greene SJ, Fonarow GC, DeVore AD, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2019;73:2365–2383.
27. Yancy CW, Januzzi JL Jr, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2018;71:201–230.
28. Bhagat AA, Greene SJ, Vaduganathan M, et al. Initiation, continuation, switching and withdrawal of heart failure medical therapies during hospitalization. *J Am Coll Cardiol.* 2019;7:1–12.
29. Curtis LH, Mi X, Qualls LG, et al. Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. *Am Heart J.* 2013;165:979–986.e1.

## 9.2. Maintenance or Optimization of GDMT During Hospitalization

1. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. *J Am Coll Cardiol.* 2008;52:190–199.
2. Gilstrap LG, Fonarow GC, Desai AS, et al. Initiation, continuation, or withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. *J Am Heart Assoc.* 2017;6:e004675.
3. Maisel A, Xue Y, van Veldhuizen DJ, et al. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH Study). *Am J Cardiol.* 2014;114:737–742.
4. Prins KW, Neill JM, Tyler JO, et al. Effects of beta-blocker withdrawal in acute decompensated heart failure: a systematic review and meta-analysis. *J Am Coll Cardiol HF.* 2015;3:647–653.
5. Tran RH, Aldemerdash A, Chang P, et al. Guideline-directed medical therapy and survival following hospitalization in patients with heart failure. *Pharmacotherapy.* 2018;38:406–416.
6. Peri-Oknony PA, Mi X, Khariton Y, et al. Target doses of heart failure medical therapy and blood pressure: insights from the CHAMP-HF Registry. *J Am Coll Cardiol HF.* 2019;7:350–358.
7. Bohm M, Young R, Jhund PS, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. *Eur Heart J.* 2017;38:1132–1143.
8. Montero-Perez-Barquero M, Flather M, Roughton M, et al. Influence of systolic blood pressure on clinical outcomes in elderly heart failure patients treated with nebivolol: data from the SENIORS trial. *Eur J Heart Fail.* 2014;16:1009–1015.
9. Anand IS, Rector TS, Kuskowski M, et al. Effect of baseline and changes in systolic blood pressure over time on the effectiveness of valsartan in the Valsartan Heart Failure Trial. *Circ Heart Fail.* 2008;1:34–42.
10. Ahmad T, Jackson K, Rao VS, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation.* 2018;137:2016–2028.
11. Brunner-La Rocca HP, Knackstedt C, Eurlings L, et al. Impact of worsening renal function related to medication in heart failure. *Eur J Heart Fail.* 2015;17:159–168.

8. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;380:539–548.
9. Wan S-H, Stevens SR, Borlaug BA, et al. Differential response to low-dose dopamine or low-dose nesiritide in acute heart failure with reduced or preserved ejection fraction. *Circ Heart Fail.* 2016;9:1–12.
10. Cox ZL, Stevenson LW. The weight of evidence for diuretics and parachutes. *J Am Coll Cardiol.* 2020;76:680–683.
11. Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2019;74:1966–2011.
12. Gilstrap LG, Stevenson LW, Small R, et al. Reasons for guideline nonadherence at heart failure discharge. *J Am Heart Assoc.* 2018;7:e008789.
13. Metra M, Cotter G, Senger S, et al. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post hoc analysis of the PROTECT Data. *Circ Heart Fail.* 2018;11:e004644.
14. Testani JM, Chen J, McCauley BD, et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation.* 2010;122:265–272.
15. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007;49:675–683.
16. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *J Am Coll Cardiol HF.* 2016;4:95–105.

#### 9.4a. Parenteral Vasodilation Therapy in Patients Hospitalized With HF

1. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA.* 2002;287:1531–1540.
2. Cioffi G, Stefanelli C, Tarantini L, et al. Hemodynamic response to intensive unloading therapy (furosemide and nitroprusside) in patients >70 years of age with left ventricular systolic dysfunction and decompensated chronic heart failure. *Am J Cardiol.* 2003;92:1050–1056.
3. Elkayam U, Kulick D, McIntosh N, et al. Incidence of early tolerance to hemodynamic effects of continuous infusion of nitroglycerin in patients with coronary artery disease and heart failure. *Circulation.* 1987;76:577–584.
4. Fung HL, Bauer JA. Mechanisms of nitrate tolerance. *Cardiovasc Drugs Ther.* 1994;8:489–499.
5. Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med.* 2003;348:1756–1763.
6. Kozuharow N, Goudev A, Flores D, et al. Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure rehospitalization among patients with acute heart failure: the GALACTIC randomized clinical trial. *JAMA.* 2019;322:2292–2302.
7. Peacock WF, Chandra A, Char D, et al. Clevidipine in acute heart failure: results of the A Study of Blood Pressure Control in Acute Heart Failure—A Pilot Study (PRONTO). *Am Heart J.* 2014;167:529–536.

#### 9.4b. Venous Thromboembolism (VTE) Prophylaxis in Hospitalized Patients

1. Kleber FX, Witt C, Vogel G, et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J.* 2003;145:614–621.
2. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med.* 2013;368:513–523.
3. Mebazaa A, Spiro TE, Buller HR, et al. Predicting the risk of venous thromboembolism in patients hospitalized with heart failure. *Circulation.* 2014;130:410–418.
4. Aispuru GR, Clavier MM, Cardone AJ, et al. Thrombotic biomarkers and left ventricle characteristics as short-term predictors of thrombotic events in patients hospitalized for acute decompensated heart failure. *Eur J Intern Med.* 2012;23:545–551.

5. Fanola CL, Norby FL, Shah AM, et al. Incident heart failure and long-term risk for venous thromboembolism. *J Am Coll Cardiol.* 2020;75:148–158.
6. Smilowitz NR, Zhao Q, Wang L, et al. Risk of venous thromboembolism after new onset heart failure. *Sci Rep.* 2019;9:17415.
7. Al Yami MS, Silva MA, Donovan JL, et al. Venous thromboembolism prophylaxis in medically ill patients: a mixed treatment comparison meta-analysis. *J Thromb Thrombolysis.* 2018;45:36–47.
8. Tang L, Wu YY, Lip GY, et al. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. *Lancet Haematol.* 2016;3:e30–e44.
9. Barba R, Zapatero A, Losa JE, et al. Venous thromboembolism in acutely ill hospitalized medical patients. *Thromb Res.* 2010;126:276–279.
10. Riess H, Haas S, Tebbe U, et al. A randomized, double-blind study of certoparin vs. unfractionated heparin to prevent venous thromboembolic events in acutely ill, non-surgical patients: CERTIFY Study. *J Thromb Haemost.* 2010;8:1209–1215.
11. Spyropoulos AC, Ageno W, Albers GW, et al. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med.* 2018;379:1118–1127.
12. Miranda S, Le Cam-Duchez V, Benichou J, et al. Adjusted value of thromboprophylaxis in hospitalized obese patients: a comparative study of two regimens of enoxaparin: the ITOHENOX study. *Thromb Res.* 2017;155:1–5.
13. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med.* 1999;341:793–800.
14. Belch JJ, Lowe GD, Ward AG, et al. Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J.* 1981;26:115–117.
15. Tebbe U, Schellong SM, Haas S, et al. Certoparin versus unfractionated heparin to prevent venous thromboembolic events in patients hospitalized because of heart failure: a subgroup analysis of the randomized, controlled CERTIFY study. *Am Heart J.* 2011;161:322–328.
16. King CS, Holley AB, Jackson JL, et al. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a metaanalysis. *Chest.* 2007;131:507–516.
17. Phung OJ, Kahn SR, Cook DJ, et al. Dosing frequency of unfractionated heparin thromboprophylaxis: a meta-analysis. *Chest.* 2011;140:374–381.

#### 9.5. Evaluation and Management of Cardiogenic Shock

1. Mathew R, Di Santo P, Jung RG, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. *N Engl J Med.* 2021;385:516–525.
2. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362:779–789.
3. Lewis TC, Aberle C, Altshuler D, et al. Comparative effectiveness and safety between milrinone or dobutamine as initial inotrope therapy in cardiogenic shock. *J Cardiovasc Pharmacol Ther.* 2019;24:130–138.
4. Levy B, Cleré-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* 2018;72:173–182.
5. Levy B, Perez P, Perny J, et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med.* 2011;39:450–455.
6. Pirracchio R, Parenica J, Resche Rigan M, et al. The effectiveness of inotropes in reducing short term mortality among patient with severe cardiogenic shock: a propensity-based analysis. *PLoS One.* 2013;8:e71659.
7. Schumann J. Cochrane corner: inotropic agents and vasodilator strategies for cardiogenic shock or low cardiac output syndrome. *Heart.* 2019;105:178–179.
8. Belletti A, Castro ML, Silvetti S, et al. The effect of inotropes and vasopressors on mortality: A meta-analysis of randomized clinical trials. *Br J Anaesth.* 2015;115:656–675.
9. Stretch R, Sauer CM, Yuh DD, et al. National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis. *J Am Coll Cardiol.* 2014;64:1407–1415.
10. Lauten A, Engstrom AE, Jung C, et al. Percutaneous left-ventricular support with the Impella-2.5-assist device in acute cardiogenic shock: results of the Impella-EUROSHOCK-registry. *Circ Heart Fail.* 2013;6:23–30.
11. Flaherty MP, Khan AR, O'Neill WW. Early initiation of Impella in acute myocardial infarction complicated by cardiogenic shock improves survival: a meta-analysis. *J Am Coll Cardiol Intv.* 2017;10:1805–1806.

12. Basir MB, Schreiber TL, Grines CL, et al. Effect of early initiation of mechanical circulatory support on survival in cardiogenic shock. *Am J Cardiol.* 2017;119:845–851.
13. Takayama H, Truby L, Koekort M, et al. Clinical outcome of mechanical circulatory support for refractory cardiogenic shock in the current era. *J Heart Lung Transplant.* 2013;32:106–111.
14. Schrage B, Ibrahim K, Loehn T, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation.* 2019;139:1249–1258.
15. Xie A, Phan K, Tsai YC, et al. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. *J Cardiothorac Vasc Anesth.* 2015;29:637–645.
16. Dangers L, Brechot N, Schmidt M, et al. Extracorporeal membrane oxygenation for acute decompensated heart failure. *Crit Care Med.* 2017;45:1359–1366.
17. Basir MB, Schreiber T, Dixon S, et al. Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: the Detroit cardiogenic shock initiative. *Catheter Cardiovasc Interv.* 2018;91:454–461.
18. Basir MB, Kapur NK, Patel K, et al. Improved outcomes associated with the use of shock protocols: updates from the national cardiogenic shock initiative. *Catheter Cardiovasc Interv.* 2019;93:1173–1183.
19. Taleb I, Koliopoulos AG, Tandar A, et al. Shock team approach in refractory cardiogenic shock requiring short-term mechanical circulatory support: a proof of concept. *Circulation.* 2019;140:98–100.
20. Tehrani BN, Truesdell AG, Sherwood MW, et al. Standardized team-based care for cardiogenic shock. *J Am Coll Cardiol.* 2019;73:1659–1669.
21. Lee F, Hutson JH, Boodhwani M, et al. Multidisciplinary code shock team in cardiogenic shock: a Canadian centre experience. *CJC Open.* 2020;2:249–257.
22. Shaefi S, O'Gara B, Kociol RD, et al. Effect of cardiogenic shock hospital volume on mortality in patients with cardiogenic shock. *J Am Heart Assoc.* 2015;4:e001462.
23. Garan AR, Kanwar M, Thayer KL, et al. Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *J Am Coll Cardiol HF.* 2020;8:903–913.
24. Vallabhajosyula S, Shankar A, Patlolla SH, et al. Pulmonary artery catheter use in acute myocardial infarction–cardiogenic shock. *ESC Heart Fail.* 2020;7:1234–1245.
25. Hernandez GA, Lemor A, Blumer V, et al. Trends in utilization and outcomes of pulmonary artery catheterization in heart failure with and without cardiogenic shock. *J Card Fail.* 2019;25:364–371.
26. Nalluri N, Patel NJ, Atti V, et al. Temporal trends in utilization of right-sided heart catheterization among percutaneous ventricular assist device recipients in acute myocardial infarction complicated by cardiogenic shock. *Am J Cardiol.* 2018;122:2014–2017.
27. Rossello X, Vila M, Rivas-Lasarte M, et al. Impact of pulmonary artery catheter use on short- and long-term mortality in patients with cardiogenic shock. *Cardiology.* 2017;136:61–69.
28. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation.* 2017;136:e232–e268.
29. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheter Cardiovasc Interv.* 2019;94:29–37.
30. Kivikko M, Pollesello P, Tarvasmaki T, et al. Effect of baseline characteristics on mortality in the SURVIVE trial on the effect of levosimendan vs dobutamine in acute heart failure: sub-analysis of the Finnish patients. *Int J Cardiol.* 2016;215:26–31.
31. O'Neill WW, Grines C, Schreiber T, et al. Analysis of outcomes for 15 259 US patients with acute myocardial infarction cardiogenic shock (AMICS) supported with the Impella device. *Am Heart J.* 2018;202:33–38.
32. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J.* 2015;36:2246–2256.
33. Thiele H, Jobs A, Ouweneel DM, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J.* 2017;38:3523–3531.
34. Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK trial for attenuation of multiorgan dysfunction syndrome. *Crit Care Med.* 2010;38:152–160.
35. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* 2012;367:1287–1296.
36. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol.* 2008;52:1584–1588.
37. Ouweneel DM, Eriksen E, Sjaauw KD, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* 2017;69:278–287.
38. Thiele H, Sick P, Boudriot E, et al. Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J.* 2005;26:1276–1283.
39. Burkhoff D, Cohen H, Brunckhorst C, et al. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J.* 2006;152:469.e1–469.e8.
40. Thayer KL, Zweck E, Ayouty M, et al. Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail.* 13;2020:e007099.
41. Saxena A, Garan AR, Kapur NK, et al. Value of hemodynamic monitoring in patients with cardiogenic shock undergoing mechanical circulatory support. *Circulation.* 2020;141:1184–1197.
42. Hernandez-Montfort J, Sinha SS, Thayer KL, et al. Clinical outcomes associated with acute mechanical circulatory support utilization in heart failure related cardiogenic shock. *Circ Heart Fail.* 14;2021:e007924.
43. Rab T, Ratanapo S, Kern KB, et al. Cardiac shock care centers: JACC review topic of the week. *J Am Coll Cardiol.* 2018;72:1972–1980.

## 9.6. Integration of Care: Transitions and Team-Based Approaches

1. Feltner C, Jones CD, Cene CW, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med.* 2014;160:774–784.
2. Kalogirou F, Forsyth F, Kyriakou M, et al. Heart failure disease management: a systematic review of effectiveness in heart failure with preserved ejection fraction. *ESC Heart Fail.* 2020;7:194–212.
3. Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. *Cochrane Database Syst Rev.* 2019;1:CD002752.
4. Van Spall HGC, Rahman T, Mytton O, et al. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail.* 2017;19:1427–1443.
5. Koelling TM, Johnson ML, Cody RJ, et al. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation.* 2005;111:179–185.
6. The Joint Commission. Heart failure (HF): specifications manual for Joint Commission National Quality core measures (2010A1). 2010. Accessed September 27, 2020. <https://manual.jointcommission.org/releases/archive/TJC2010B/HeartFailure.html>
7. Driscoll A, Meagher S, Kennedy R, et al. What is the impact of systems of care for heart failure on patients diagnosed with heart failure: a systematic review. *BMC Cardiovasc Disord.* 2016;16:195.
8. Fonarow GC, Abraham WT, Albert NM, et al. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). *Arch Intern Med.* 2007;167:1493–1502.
9. Lappe JM, Muhlestein JB, Lappe DL, et al. Improvements in 1-year cardiovascular clinical outcomes associated with a hospital-based discharge medication program. *Ann Intern Med.* 2004;141:446–453.
10. Heidenreich P. Improving heart failure care with a reminder attached to the echocardiography report. *Am J Med.* 2008;121:853–854.
11. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA.* 2010;303:1716–1722.
12. Lee KK, Yang J, Hernandez AF, et al. Post-discharge follow-up characteristics associated with 30-day readmission after heart failure hospitalization. *Med Care.* 2016;54:365–372.

13. Dharmarajan K, Hsieh AF, Lin Z, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA*. 2013;309:355–363.
14. Albert NM, Barnason S, Deswal A, et al. Transitions of care in heart failure: a scientific statement from the American Heart Association. *Circ Heart Fail*. 2015;8:384–409.
15. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. *Circulation*. 2007;116:737–744.
16. Naylor MD, Broten DA, Campbell RL, et al. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *J Am Geriatr Soc*. 2004;52:675–684.
17. Chan WV, Pearson TA, Bennett GC, et al. ACC/AHA special report: clinical practice guideline implementation strategies: a summary of systematic reviews by the NHLBI implementation science work group: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2017;135:e122–e137.
18. Ellrodt AG, Fonarow GC, Schwamm LH, et al. Synthesizing lessons learned from get with the guidelines: the value of disease-based registries in improving quality and outcomes. *Circulation*. 2013;128:2447–2460.
19. Coma E, Medina M, Mendez L, et al. Effectiveness of electronic point-of-care reminders versus monthly feedback to improve adherence to 10 clinical recommendations in primary care: a cluster randomized clinical trial. *BMC Med Inform Decis Mak*. 2019;19:245.
20. DeVore AD, Granger BB, Fonarow GC, et al. Care optimization through patient and hospital engagement clinical trial for heart failure: rationale and design of CONNECT-HF. *Am Heart J*. 2020;220:41–50.
21. Hansen LO, Young RS, Hinami K, et al. Interventions to reduce 30-day rehospitalization: a systematic review. *Ann Intern Med*. 2011;155:520–528.
22. Lee KK, Thomas RC, Tan TC, et al. The heart failure readmission intervention by variable early follow-up (THRIVE) study. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006553.
23. O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol*. 2010;55:872–878.
24. Keenan PS, Normand SL, Lin Z, et al. An administrative claims measure suitable for profiling hospital performance on the basis of 30-day all-cause readmission rates among patients with heart failure. *Circ Cardiovasc Qual Outcomes*. 2008;1:29–37.
25. Win S, Hussain I, Hebl VB, et al. Inpatient mortality risk scores and post-discharge events in hospitalized heart failure patients: a community-based study. *Circ Heart Fail*. 2017;10:e003926.
10. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CAN-PAP). *Circulation*. 2007;115:3173–3180.
11. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular outcomes with minute ventilation-targeted adaptive servo-ventilation therapy in heart failure: the CAT-HF trial. *J Am Coll Cardiol*. 2017;69:1577–1587.
12. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med*. 2015;373:1095–1105.
13. Yamamoto S, Yamaga T, Nishie K, et al. Positive airway pressure therapy for the treatment of central sleep apnoea associated with heart failure. *Cochrane Database Syst Rev*. 2019;12:CD012803.
14. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020;396:819–829.
15. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139:2528–2536.
16. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.
17. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.
18. Chamberlain AM, St Sauver JL, Gerber Y, et al. Multimorbidity in heart failure: a community perspective. *Am J Med*. 2015;128:38–45.
19. Wong CY, Chaudry SI, Desai MM, et al. Trends in comorbidity, disability, and polypharmacy in heart failure. *Am J Med*. 2011;124:136–143.
20. Angermann CE, Gelbrich G, Stork S, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA*. 2016;315:2683–2693.
21. Rutledge T, Reis VA, Linke SE, et al. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006;48:1527–1537.
22. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701–709.
23. Tuegel C, Bansal N. Heart failure in patients with kidney disease. *Heart*. 2017;103:1848–1853.
24. Lunney M, Ruospo M, Natale P, et al. Pharmacological interventions for heart failure in people with chronic kidney disease. *Cochrane Database Syst Rev*. 2020;2:CD012466.
25. Groenveld HF, Januzzi JL, Damman K, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol*. 2008;52:818–827.
26. Ebner N, Jankowska EA, Ponikowski P, et al. The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. results from the studies investigating co-morbidities aggravating heart failure. *Int J Cardiol*. 2016;205:6–12.
27. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail*. 2018;20:125–133.
28. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. *JAMA*. 2017;317:1958–1966.
29. Kapoor M, Schleinitz MD, Gemignani A, et al. Outcomes of patients with chronic heart failure and iron deficiency treated with intravenous iron: a meta-analysis. *Cardiovasc Hematol Disord Drug Targets*. 2013;13:35–44.
30. Montero D, Haider T, Flammer AJ. Erythropoietin response to anaemia in heart failure. *Eur J Prev Cardiol*. 2019;26:7–17.
31. Nagai T, Nishimura K, Honma T, et al. Prognostic significance of endogenous erythropoietin in long-term outcome of patients with acute decompensated heart failure. *Eur J Heart Fail*. 2016;18:803–813.
32. Bello NA, Lewis EF, Desai AS, et al. Increased risk of stroke with darbepoetin alfa in anaemic heart failure patients with diabetes and chronic kidney disease. *Eur J Heart Fail*. 2015;17:1201–1207.
33. Zhang Y, Liang M, Sun C, et al. Effect of intensive lowering of systolic blood pressure treatment on heart failure events: a meta-analysis of randomized controlled studies. *J Hum Hypertens*. 2019;33:648–657.
34. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2017;377:2506.

## 10.1. Management of Comorbidities in Patients With HF

1. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361:2436–2448.
2. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015;36:657–668.
3. Beck-da-Silva L, Piardi D, Soder S, et al. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. *Int J Cardiol*. 2013;168:3439–3442.
4. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396:1895–1904.
5. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med*. 2013;368:1210–1219.
6. Kang J, Park J, Lee JM, et al. The effects of erythropoiesis stimulating therapy for anemia in chronic heart failure: A meta-analysis of randomized clinical trials. *Int J Cardiol*. 2016;218:12–22.
7. Banach M, Bhatia V, Feller MA, et al. Relation of baseline systolic blood pressure and long-term outcomes in ambulatory patients with chronic mild to moderate heart failure. *Am J Cardiol*. 2011;107:1208–1214.
8. Lee TT, Chen J, Cohen DJ, et al. The association between blood pressure and mortality in patients with heart failure. *Am Heart J*. 2006;151:76–83.
9. Arzt M, Schroll S, Series F, et al. Auto-servoventilation in heart failure with sleep apnoea: a randomised controlled trial. *Eur Respir J*. 2013;42:1244–1254.

35. Upadhyia B, Rocco M, Lewis CE, et al. Effect of intensive blood pressure treatment on heart failure events in the Systolic Blood Pressure Reduction Intervention Trial. *Circ Heart Fail.* 2017;10:e003613.
36. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/APA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13–e115.
37. Mehra R, Wang L, Andrews N, et al. Dissociation of objective and subjective daytime sleepiness and biomarkers of systemic inflammation in sleep-disordered breathing and systolic heart failure. *J Clin Sleep Med.* 2017;13:1411–1422.
38. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med.* 2005;353:2025–2033.
39. Zhang XB, Yuan YT, Du YP, et al. Efficacy of positive airway pressure on brain natriuretic peptide in patients with heart failure and sleep-disorder breathing: a meta-analysis of randomized controlled trials. *Lung.* 2015;193:255–260.
40. Aggarwal S, Nadeem R, Loomba RS, et al. The effects of continuous positive airways pressure therapy on cardiovascular end points in patients with sleep-disordered breathing and heart failure: a meta-analysis of randomized controlled trials. *Clin Cardiol.* 2014;37:57–65.
41. Voigt J, Emani S, Gupta S, et al. Meta-analysis comparing outcomes of therapies for patients with central sleep apnea and heart failure with reduced ejection fraction. *Am J Cardiol.* 2020;127:73–83.
42. Yamamoto S, Yamaga T, Nishie K, et al. Positive airway pressure therapy for the treatment of central sleep apnoea associated with heart failure. *Cochrane Database Syst Rev.* 2019;12:CD012803.
43. American Diabetes Association. Addendum. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43 (suppl 1):S98–S110.
44. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol.* 2021;6:148–158.
45. Li J, Woodward M, Perkovic V, et al. Mediators of the effects of canagliflozin on heart failure in patients with type 2 diabetes. *J Am Coll Cardiol HF.* 2020;8:57–66.
46. US National Library of Medicine. Clinical Trials.gov. Dapagliflozin Evaluation to Improve the Lives of Patients With PReserved Ejection Fraction Heart Failure. (DELIVER). 2018. Accessed June 28, 2021. <https://clinicaltrials.gov/ct2/show/NCT03619213>
47. Anker SD, Butler J, Filippatos GS, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. *Eur J Heart Fail.* 2019;21:1279–1287.
48. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med.* 2021;384:117–128.
49. Liu D, Chen H, Song F, et al. Adverse drug events observed with the novel sodium/glucose co-transporter 2 inhibitor ipragliflozin for the treatment of patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized studies. *Adv Ther.* 2020;37:4356–4369.
50. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;128:e240–e327.
7. McMurray JJ, Ezekowitz JA, Lewis BS, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail.* 2013;6:451–460.
8. Siller-Matula JM, Pecen L, Patti G, et al. Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: the PREFER in AF - HF substudy. *Int J Cardiol.* 2018;265:141–147.
9. Magnani G, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban compared with warfarin in patients with atrial fibrillation and heart failure: insights from ENGAGE AF-TIMI 48. *Eur J Heart Fail.* 2016;18:1153–1161.
10. Savarese G, Giugliano RP, Rosano GM, et al. Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure: a meta-analysis. *J Am Coll Cardiol HF.* 2016;4:870–880.
11. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation.* 2016;133:1637–1644.
12. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018;378:417–427.
13. Chen S, Purerfellner H, Meyer C, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. *Eur Heart J.* 2020;41:2863–2873.
14. Packer DL, Piccini JP, Monahan KH, et al. Ablation versus drug therapy for atrial fibrillation in heart failure: results from the CABANA trial. *Circulation.* 2021;143:1377–1390.
15. Wood MA, Brown-Mahoney C, Kay GN, et al. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation.* 2000;101:1138–1144.
16. Brignole M, Menozzi C, Gianfranchi L, et al. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. *Circulation.* 1998;98:953–960.
17. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation Post AV nodal ablation Evaluation (the PAVE study). *J Cardiovasc Electrophysiol.* 2005;16:1160–1165.
18. Brignole M, Gammie M, Puggioni E, et al. Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. *Eur Heart J.* 2005;26:712–722.
19. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J.* 2011;32:2420–2429.
20. Brignole M, Pokushalov E, Pentimalli F, et al. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J.* 2018;39:3999–4008.
21. Chatterjee NA, Upadhyay GA, Ellenbogen KA, et al. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J Heart Fail.* 2012;14:661–667.
22. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol.* 2017;70:1949–1961.
23. Freudenberger RS, Hellkamp AS, Halperin JL, et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT). *Circulation.* 2007;115:2637–2641.
24. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31:2369–2429.
25. Melgaard L, Gorst-Rasmussen A, Lane DA, et al. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA.* 2015;314:1030–1038.
26. Mogensen UM, Jhund PS, Abraham WT, et al. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol.* 2017;70:2490–2500.
27. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2014;130:e199–e267.
28. January CT, Wann LS, Calkins CH, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/

## 10.2. Management of Atrial Fibrillation (AF) in HF

- Mason PK, Lake DE, DiMarco JP, et al. Impact of the CHA2DS2-VASc score on anticoagulation recommendations for atrial fibrillation. *Am J Med.* 2012;125:603a1–603e6.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–1151.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891.
- Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–982.
- Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–2104.
- Ferreira J, Ezekowitz MD, Connolly SJ, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. *Eur J Heart Fail.* 2013;15:1053–1061.

- American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019;140:e125–e151.
29. Witt BJ, Brown RD Jr, Jacobsen SJ, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J*. 2006;152:102–109.

## 11.1. Disparities and Vulnerable Populations

1. Colvin M, Sweitzer NK, Albert NM, et al. Heart failure in non-Caucasians, women, and older adults: a white paper on special populations from the Heart Failure Society of America Guideline Committee. *J Card Fail*. 2015;21:674–693.
2. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report From the American Heart Association. *Circulation*. 2020;141:e139–e596.
3. Ziaeian B, Kominski GF, Ong MK, et al. National differences in trends for heart failure hospitalizations by sex and race/ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003552.
4. Nayak A, Hicks AJ, Morris AA. Understanding the complexity of heart failure risk and treatment in black patients. *Circ Heart Fail*. 2020. CIRCHEART-FAILURE120007264.
5. Schultz WM, Kelli HM, Lisko JC, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation*. 2018;137:2166–2178.
6. Bevan GH, Josephson R, Al-Kindi SG. Socioeconomic deprivation and heart failure mortality in the United States. *J Card Fail*. 2020;26:1106–1167.
7. Rodriguez CJ, Allison M, Daviglus ML, et al. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. *Circulation*. 2014;130:593–625.
8. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e393–e423.
9. Sterling MR, Ringel JB, Pinheiro LC, et al. Social determinants of health and 90-day mortality after hospitalization for heart failure in the REGARDS study. *J Am Heart Assoc*. 2020;9:e014836.
10. Khariton Y, Nassif ME, Thomas L, et al. Health status disparities by sex, race/ethnicity, and socioeconomic status in outpatients with heart failure. *J Am Coll Cardiol HF*. 2018;6:465–473.
11. Breathett K, Sims M, Gross M, et al. Cardiovascular health in American Indians and Alaska Natives: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e948–e959.
12. Eberly LA, Richterman A, Beckett AG, et al. Identification of racial inequities in access to specialized inpatient heart failure care at an academic medical center. *Circ Heart Fail*. 2019;12:e006214.
13. Sentell T, Miyamura J, Ahn HJ, et al. Potentially preventable hospitalizations for congestive heart failure among Asian Americans and Pacific Islanders in Hawai'i. *J Immigr Minor Health*. 2015;17:1289–1297.
14. Brown AF, Liang LJ, Vassar SD, et al. Trends in racial/ethnic and nativity disparities in cardiovascular health among adults without prevalent cardiovascular disease in the United States, 1988 to 2014. *Ann Intern Med*. 2018;168:541–549.
15. Lawson CA, Zaccardi F, Squire I, et al. Risk factors for heart failure: 20-year population-based trends by sex, socioeconomic status, and ethnicity. *Circ Heart Fail*. 2020;13:e006472.
16. Brewer LC, Cooper LA. Race, discrimination, and cardiovascular disease. *Virtual Mentor*. 2014;16:455–460.
17. Cresci S, Pereira NL, Ahmad F, et al. Heart failure in the era of precision medicine: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2019;12:458–485.
18. White-Williams C, Rossi LP, Bittner VA, et al. Addressing social determinants of health in the care of patients with heart failure: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e841–e863.
19. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859–3868c.
20. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344–350.
21. Ehrmann Feldman D, Xiao Y, Bernatsky S, et al. Consultation with cardiologists for persons with new-onset chronic heart failure: a population-based study. *Can J Cardiol*. 2009;25:690–694.
22. Feldman DE, Huynh T, Des Lauriers J, et al. Gender and other disparities in referral to specialized heart failure clinics following emergency department visits. *J Womens Health (Larchmt)*. 2013;22:526–531.
23. Al-Khatib SM, Hellkamp AS, Hernandez AF, et al. Trends in use of implantable cardioverter-defibrillator therapy among patients hospitalized for heart failure: have the previously observed sex and racial disparities changed over time? *Circulation*. 2012;125:1094–1101.
24. Hsich EM. Sex differences in advanced heart failure therapies. *Circulation*. 2019;139:1080–1093.
25. Rethy L, Petito LC, Vu THT, et al. Trends in the prevalence of self-reported heart failure by race/ethnicity and age from 2001 to 2016. *JAMA Cardiol*. 2020;5:1–5.
26. Bahrami H, Kronmal R, Bluemke DA, et al. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med*. 2008;168:2138–2145.
27. Glynn P, Lloyd-Jones DM, Feinstein MJ, et al. Disparities in cardiovascular mortality related to heart failure in the United States. *J Am Coll Cardiol*. 2019;73:2354–2355.
28. Churchwell K, Elkind MSV, Benjamin RM, et al. Call to action: structural racism as a fundamental driver of health disparities: a presidential advisory from the American Heart Association. *Circulation*. 2020;142:e454–e468.
29. Butrous H, Hummel SL. Heart failure in older adults. *Can J Cardiol*. 2016;32:1140–1147.
30. Allen LA, Hernandez AF, Peterson ED, et al. Discharge to a skilled nursing facility and subsequent clinical outcomes among older patients hospitalized for heart failure. *Circ Heart Fail*. 2011;4:293–300.
31. Silver JK, Bean AC, Slocum C, et al. Physician workforce disparities and patient care: a narrative review. *Health Equity*. 2019;3:360–377.
32. Mehta LS, Fisher K, Rzeszut AK, et al. Current demographic status of cardiologists in the United States. *JAMA Cardiol*. 2019;4:1029–1033.
33. Hall WJ, Chapman MV, Lee KM, et al. Implicit racial/ethnic bias among health care professionals and its influence on health care outcomes: a systematic review. *Am J Public Health*. 2015;105:e60–e76.
34. Williams JS, Walker RJ, Egede LE. Achieving equity in an evolving health-care system: opportunities and challenges. *Am J Med Sci*. 2016;351:33–43.
35. Serchen J, Doherty R, Atiq O, Hilden D. Racism and health in the United States: a policy statement from the American College of Physicians. *Ann Intern Med*. 2020;173:556–557.
36. Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, et al. Epidemiology of incident heart failure in a contemporary elderly cohort: the health, aging, and body composition study. *Arch Intern Med*. 2009;169:708–715.
37. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/APA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMVA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
38. Leiby DA, Rentas FJ, Nelson KE, et al. Evidence of Trypanosoma cruzi infection (Chagas' disease) among patients undergoing cardiac surgery. *Circulation*. 2000;102:2978–2982.
39. Bank IEM, Gijsberts CM, Teng TK, et al. Prevalence and clinical significance of diabetes in Asian versus white patients with heart failure. *J Am Coll Cardiol HF*. 2017;5:14–24.
40. Bitton A, Zaslavsky AM, Ayanian JZ. Health risks, chronic diseases, and access to care among US Pacific Islanders. *J Gen Intern Med*. 2010;25:435–440.
41. Sharma A, Zhao X, Hammill BG, et al. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: insights from the Get With The Guidelines-Heart Failure Registry. *Circ Heart Fail*. 2018;11:e004646.
42. Manemann SM, Chamberlain AM, Roger VL, et al. Perceived social isolation and outcomes in patients with heart failure. *J Am Heart Assoc*. 2018;7:e008069.
43. Orr NM, Boxer RS, Dolansky MA, et al. Skilled nursing facility care for patients with heart failure: can we make it "heart failure ready"? *J Card Fail*. 2016;22:1004–1014.
44. Gorodeski EZ, Goyal P, Hummel SL, et al. Domain management approach to heart failure in the geriatric patient: present and future. *J Am Coll Cardiol*. 2018;71:1921–1936.
45. Jurgens CY, Goodlin S, Dolansky M, et al. Heart failure management in skilled nursing facilities: a scientific statement from the American Heart Association and the Heart Failure Society of America. *Circ Heart Fail*. 2015;8:655–687.
46. Akwo EA, Kabagambe EK, Harrell FE Jr, et al. Neighborhood deprivation predicts heart failure risk in a low-income population of blacks and whites in the Southeastern United States. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004052.
47. Topel ML, Kim JH, Mujahid MS, et al. Neighborhood socioeconomic status and adverse outcomes in patients with cardiovascular disease. *Am J Cardiol*. 2019;123:284–290.

48. Baggett TP, Liauw SS, Hwang SW. Cardiovascular disease and homelessness. *J Am Coll Cardiol.* 2018;71:2585–2597.
49. Rich MW, Beckham V, Wittenberg C, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med.* 1995;333:1190–1195.
50. Fonarow GC, Abraham WT, Albert NM, et al. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). *Am J Cardiol.* 2009;104:107–115.
51. Steinberg RS, Nayak A, O'Connell C, et al. Sex differences in eligibility for advanced heart failure therapies. *Clin Transplant.* 2020;34:e13839.
52. DeFilippis EM, Truby LK, Garan AR, et al. Sex-related differences in use and outcomes of left ventricular assist devices as bridge to transplantation. *J Am Coll Cardiol HF.* 2019;7:250–257.
53. Breathett K, Yee E, Pool N, et al. Does race influence decision making for advanced heart failure therapies? *J Am Heart Assoc.* 2019;8:e013592.
54. Breathett K, Yee E, Pool N, et al. Association of gender and race with allocation of advanced heart failure therapies. *JAMA Netw Open.* 3;2020:e2011044.
55. Breathett K, Liu WG, Allen LA, et al. African Americans are less likely to receive care by a cardiologist during an intensive care unit admission for heart failure. *J Am Coll Cardiol HF.* 2018;6:413–420.
56. Aviles-Santa ML, Heintzman J, Lindberg NM, et al. Personalized medicine and Hispanic health: improving health outcomes and reducing health disparities - a National Heart, Lung, and Blood Institute workshop report. *BMC Proc.* 2017;11:11.
57. Vivo RP, Krim SR, Cevik C, et al. Heart failure in Hispanics. *J Am Coll Cardiol.* 2009;53:1167–1175.
58. Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med.* 2018;378:1291–1301.
59. Ebinger J, Blyler CA, Brettler J, et al. Barbershop management of hypertension in the African American population: pitfalls and opportunities for extension to other underserved communities. *Curr Cardiol Rep.* 2020;22:64.
60. Weiss B. *Health Literacy: A Manual for Clinicians*. American Medical Association Foundation; 2003.
61. Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation.* 2020;141:540–548.
62. Khan MS, Shahid I, Siddiqi TJ, et al. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration approval of novel cardiometabolic drugs. *J Am Heart Assoc.* 2020;9:e015594.
63. Tahhan AS, Vaduganathan M, Greene SJ, et al. Enrollment of older patients, women, and racial and ethnic minorities in contemporary heart failure clinical trials: a systematic review. *JAMA Cardiol.* 2018;3:1011–1019.
64. Sullivan LT 2nd, Randolph T, Merrill P, et al. Representation of black patients in randomized clinical trials of heart failure with reduced ejection fraction. *Am Heart J.* 2018;197:43–52.
65. Ortega RF, Yancy CW, Mehran R, et al. Overcoming lack of diversity in cardiovascular clinical trials: a new challenge and strategies for success. *Circulation.* 2019;140:1690–1692.
66. Ho JE, Gona P, Pencina MJ, et al. Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community. *Eur Heart J.* 2012;33:1734–1741.
67. Suthahar N, Lau ES, Blaha MJ, et al. Sex-specific associations of cardiovascular risk factors and biomarkers with incident heart failure. *J Am Coll Cardiol.* 2020;76:1455–1465.
68. Medina-Inojosa JR, Vinnakota S, Garcia M, et al. Role of stress and psychosocial determinants on women's cardiovascular risk and disease development. *J Womens Health (Larchmt).* 2019;28:483–489.
69. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation.* 2020;141:e139–e596.
70. Motiejunaite J, Akiyama E, Cohen-Solal A, et al. The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions. *Eur Heart J.* 2020;41:1357–1364.
71. Dewan P, Rorth R, Jhund PS, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol.* 2019;73:29–40.
72. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002;106:3068–3072.
73. Shah AM, Claggett B, Loehr LR, et al. Heart failure stages among older adults in the community: the Atherosclerosis Risk in Communities study. *Circulation.* 2017;135:224–240.
74. Sung SH, Wang TJ, Cheng HM, et al. Clinical characteristics and outcomes in the very elderly patients hospitalized for acute heart failure: importance of pharmacologic guideline adherence. *Sci Rep.* 2018;8:14270.
75. Graham G. Disparities in cardiovascular disease risk in the United States. *Curr Cardiol Rev.* 2015;11:238–245.
76. Lewis EF, Claggett B, Shah AM, et al. Racial differences in characteristics and outcomes of patients with heart failure and preserved ejection fraction in the treatment of preserved cardiac function heart failure trial. *Circ Heart Fail.* 11;2018:e004457.
77. Lui C, Fraser CD 3rd, Zhou X, et al. Racial disparities in patients bridged to heart transplantation with left ventricular assist devices. *Ann Thorac Surg.* 2019;108:1122–1126.
78. Morris AA, Krandsorf EP, Coleman BL, et al. Racial and ethnic disparities in outcomes after heart transplantation: a systematic review of contributing factors and future directions to close the outcomes gap. *J Heart Lung Transplant.* 2016;35:953–961.
79. Wayda B, Clemons A, Givens RC, et al. Socioeconomic disparities in adherence and outcomes after heart transplant: a UNOS (United Network for Organ Sharing) registry analysis. *Circ Heart Fail.* 2018;11:e004173.
80. Balfour PC Jr, Ruiz JM, Talavera GA, Allison MA, Rodriguez CJ. Cardiovascular disease in Hispanics/Latinos in the United States. *J Lat Psychol.* 2016;4:98–113.
81. Alexander M, Grumbach K, Remy L, et al. Congestive heart failure hospitalizations and survival in California: patterns according to race/ethnicity. *Am Heart J.* 1999;137:919–927.
82. Vivo RP, Krim SR, Krim NR, et al. Care and outcomes of Hispanic patients admitted with heart failure with preserved or reduced ejection fraction: findings from Get With The Guidelines-Heart Failure. *Circ Heart Fail.* 2012;5:167–175.
83. Shulman E, Shah T, Mazori AY, et al. Heart failure and the development of atrial fibrillation in Hispanics, African Americans and non-Hispanic Whites. *Int J Cardiol.* 2018;271:186–191.
84. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation.* 2018;138:e1–e34.
85. Palaniappan LP, Araneta MR, Assimes TL, et al. Call to action: cardiovascular disease in Asian Americans: a science advisory from the American Heart Association. *Circulation.* 2010;122:1242–1252.
86. Jose PO, Frank AT, Kapphahn KI, et al. Cardiovascular disease mortality in Asian Americans. *J Am Coll Cardiol.* 2014;64:2486–2494.
87. Muller CJ, Noonan CJ, MacLehose RF, et al. Trends in cardiovascular disease morbidity and mortality in American Indians over 25 years: the Strong Heart study. *J Am Heart Assoc.* 2019;8:e012289.
88. Benjamin EJ, Munther P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation.* 2019;139:e56–e528.

## 11.2. Cardio-Oncology

- Wang SY, Long JB, Hurria A, et al. Cardiovascular events, early discontinuation of trastuzumab, and their impact on survival. *Breast Cancer Res Treat.* 2014;146:411–419.
- Guarnieri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol.* 2006;24:4107–4115.
- Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol.* 2010;55:213–220.
- Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation.* 2015;131:1981–1988.
- Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol.* 2013;31:4222–4228.
- Goldhar HA, Yan AT, Ko DT, et al. The temporal risk of heart failure associated with adjuvant trastuzumab in breast cancer patients: a population study. *J Natl Cancer Inst.* 2016;108:dv301.
- Armenian SH, Sun CL, Shannon T, et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood.* 2011;118:6023–6029.
- Henry ML, Niu J, Zhang N, et al. Cardiotoxicity and cardiac monitoring among chemotherapy-treated breast cancer patients. *J Am Coll Cardiol Img.* 2018;11:1084–1093.
- Wang L, Tan TC, Halpern EF, et al. Major cardiac events and the value of echocardiographic evaluation in patients receiving anthracycline-based chemotherapy. *Am J Cardiol.* 2015;116:442–446.

10. Seferina SC, de Boer M, Derkzen MW, et al. Cardiotoxicity and cardiac monitoring during adjuvant trastuzumab in daily Dutch practice: a study of the Southeast Netherlands Breast Cancer Consortium. *Oncologist*. 2016;21:555–562.
11. Abu-Khalaf MM, Safonov A, Stratton J, et al. Examining the cost-effectiveness of baseline left ventricular function assessment among breast cancer patients undergoing anthracycline-based therapy. *Breast Cancer Res Treat*. 2019;176:261–270.
12. Truong SR, Barry WT, Moslehi JJ, et al. Evaluating the utility of baseline cardiac function screening in early-stage breast cancer treatment. *Oncologist*. 2016;21:666–670.
13. Jeyakumar A, DiPenta J, Snow S, et al. Routine cardiac evaluation in patients with early-stage breast cancer before adjuvant chemotherapy. *Clin Breast Cancer*. 2012;12:4–9.
14. Steuter J, Bociek R, Loberiza F, et al. Utility of prechemotherapy evaluation of left ventricular function for patients with lymphoma. *Clin Lymphoma Myeloma Leuk*. 2015;15:29–34.
15. Conrad AL, Gundrum JD, McHugh VL, et al. Utility of routine left ventricular ejection fraction measurement before anthracycline-based chemotherapy in patients with diffuse large B-cell lymphoma. *J Oncol Pract*. 2012;8:336–340.
16. O'Brien PMK, Jeyakumar A, et al. The clinical utility of baseline cardiac assessments prior to adjuvant anthracycline chemotherapy in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2019;174:357–363.
17. Akpek M, Ozdogru I, Sahin O, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. *Eur J Heart Fail*. 2015;17:81–89.
18. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY trial. *J Am Coll Cardiol*. 2018;71:2281–2290.
19. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol*. 2013;61:2355–2362.
20. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114:2474–2481.
21. Guglin M, Krischer J, Tamura R, et al. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. *J Am Coll Cardiol*. 2019;73:2859–2868.
22. Gulati G, Heck SL, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J*. 2016;37:1671–1680.
23. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2006;48:2258–2262.
24. Pituskin E, Mackey JR, Koshman S, et al. Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. *J Clin Oncol*. 2017;35:870–877.
25. Shah P, Garris R, Abboud R, et al. Meta-analysis comparing usefulness of beta blockers to preserve left ventricular function during anthracycline therapy. *Am J Cardiol*. 2019;124:789–794.
26. Cardinale D, Ciceri F, Latini R, et al. Anthracycline-induced cardiotoxicity: a multicenter randomised trial comparing two strategies for guiding prevention with enalapril: the International CardioOncology Society-one trial. *Eur J Cancer*. 2018;94:126–137.
27. Vaduganathan M, Hirji SA, Qamar A, et al. Efficacy of neurohormonal therapies in preventing cardiotoxicity in patients with cancer undergoing chemotherapy. *J Am Coll Cardiol CardioOnc*. 2019;1:54–65.
28. Wittayakorn S, Qian J, Westrick SC, et al. Prevention of trastuzumab and anthracycline-induced cardiotoxicity using angiotensin-converting enzyme inhibitors or beta-blockers in older adults with breast cancer. *Am J Clin Oncol*. 2018;41:909–918.
29. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004;109:2749–2754.
30. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol*. 2010;28:3910–3916.
31. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36:517–522.
32. Zardavas D, Suter TM, Van Veldhuisen DJ, et al. Role of troponins I and T and N-terminal prohormone of brain natriuretic peptide in monitoring cardiac safety of patients with early-stage human epidermal growth factor receptor 2-positive breast cancer receiving trastuzumab: a herceptin adjuvant study cardiac marker substudy. *J Clin Oncol*. 2017;35:878–884.
33. Howlader N, Noone A, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2014, based on November 2016 SEER data submission, posted to the SEER website, April 2017*. National Cancer Institute; 2014.
34. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018 CA. *Cancer J Clin*. 2018;68:7–30.
35. Bluthmann SM, Mariotto AB, Rowland JH. Anticipating the “silver tsunami”: prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016;25:1029–1036.
36. Barac A, Murtagh G, Carver JR, et al. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. *J Am Coll Cardiol*. 2015;65:2739–2746.
37. Albini A, Pennesi G, Donatelli F, et al. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst*. 2010;102:14–25.
38. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342:1077–1084.
39. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749–1755.
40. Mahmood SS, Fradely MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am College Cardiol*. 2018;71:1755–1764.
41. Tarantini L, Gori S, Faggiano P, et al. Adjuvant trastuzumab cardiotoxicity in patients over 60 years of age with early breast cancer: a multicenter cohort analysis. *Ann Oncol*. 2012;23:3058–3063.
42. Seidman A, Hudis C, Pieri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20:1215–1221.
43. Hershman DL, McBride RB, Eisenberger A, et al. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:3159–3165.
44. Chow EJ, Mueller BA, Baker KS, et al. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. *Ann Intern Med*. 2011;155:21–32.
45. Hequet O, Le QH, Mouillet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol*. 2004;22:1864–1871.
46. Doyle JJ, Neugut AI, Jacobson JS, et al. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol*. 2005;23:8597–8605.
47. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007;25:3808–3815.
48. Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiography. *N Engl J Med*. 1979;300:278–283.
49. Ky B, Putt M, Sawaya H, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol*. 2014;63:809–816.
50. van Boxtel W, Bulten BF, Mavrikurve-Groothuis AM, et al. New biomarkers for early detection of cardiotoxicity after treatment with docetaxel, doxorubicin and cyclophosphamide. *Biomarkers*. 2015;20:143–148.
51. Dodos F, Halbsguth T, Erdmann E, et al. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. *Clin Res Cardiol*. 2008;97:318–326.
52. Ruggiero A, De Rosa G, Rizzo D, et al. Myocardial performance index and biochemical markers for early detection of doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukaemia. *Int J Clin Oncol*. 2013;18:927–933.
53. Armenian SH, Gelehrter SK, Vase T, et al. Screening for cardiac dysfunction in anthracycline-exposed childhood cancer survivors. *Clin Cancer Res*. 2014;20:6314–6323.
54. Hoeger CW, Hayek SS. Role of cardiovascular biomarkers in the risk stratification, monitoring, and management of patients with cancer. *Cardiol Clin*. 2019;37:505–523.

55. Doxorubicin hydrochloride for injection, USP [package insert]. New York, NY: Pharmacia & Upjohn Company; 2010.
56. Murbraech K, Wethal T, Smeland KB, et al. Valvular dysfunction in lymphoma survivors treated with autologous stem cell transplantation: a national cross-sectional study. *J Am Coll Cardiol Img.* 2016;9:230–239.
57. Epirubicin hydrochloride for injection [package insert]. VIC, Australia: Mayne Pharma Limited Mulgrave; 2006.
58. Cyclophosphamide [package insert]. Deerfield, IL: Baxter Healthcare Corporation Deerfield; 2013.
59. Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med.* 1993;118:31–36.
60. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf.* 2000;22:263–302.
61. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352:2302–2313.
62. Docetaxel [package insert]. Princeton, NJ: Sandoz; 2012.
63. Fluorouracil [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc; 2016.
64. Meyer CC, Calis KA, Burke LB, et al. Symptomatic cardiotoxicity associated with 5-fluorouracil. *Pharmacotherapy.* 1997;17:729–736.
65. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol.* 2009;53:2231–2247.
66. Sasson Z, Morgan CD, Wang B, et al. 5-Fluorouracil related toxic myocarditis: case reports and pathological confirmation. *Can J Cardiol.* 1994;10:861–864.
67. Killu A, Madhavan M, Prasad K, et al. 5-fluorouracil induced pericarditis. *BMJ Case Rep.* 2011;2011:bcr0220113883.
68. Van Cutsem E, Hoff PM, Blum JL, et al. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol.* 2002;13:484–485.
69. Capecitabine (Xeloda) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2015.
70. Fludarabine (Fludara) [package insert]. Montville, NJ: Berlex; 2003.
71. Hussein MA, Gundacker H, Head DR, et al. Cyclophosphamide followed by fludarabine for untreated chronic lymphocytic leukemia: a phase II SWOG TRIAL 9706. *Leukemia.* 2005;19:1880–1886.
72. Decitabine (Dacogen) [package insert]. Bloomington, MN: MGI Pharma, Inc; 2006.
73. Pertuzumab (Perjeta) [package insert]. South San Francisco, CA: Genentech, Inc; 2012.
74. Trastuzumab (Herceptin) [package insert]. South San Francisco, CA: Genentech, Inc; 2010.
75. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over-expresses HER2. *N Engl J Med.* 2001;344:783–792.
76. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol.* 2007;25:3859–3865.
77. Rituximab [package insert]. South San Francisco, CA: Genentech, Inc; 2010.
78. Dabrafenib (Tafinlar) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2014.
79. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med.* 2012;367:1694–1703.
80. Bronte E, Bronte G, Novo G, et al. What links BRAF to the heart function? New insights from the cardiotoxicity of BRAF inhibitors in cancer treatment. *Oncotarget.* 2015;6:35589–35601.
81. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol.* 2015;33:4210–4218.
82. Dasatinib (Sprycel) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2010.
83. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc.* 2008;83:679–686.
84. Battistini NML, Tong D, Ring A, et al. Long-term outcome with targeted therapy in advanced/metastatic HER2-positive breast cancer: the Royal Marsden experience. *Breast Cancer Res Treat.* 2019;178:401–408.
85. Lapatinib (Tykerb) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2007.
86. Pazopanib (Votrient) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
87. Motzer RJ, Hutson TE, Celli D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med.* 2013;369:722–731.
88. Ponatinib (Iclusig) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; 2012.
89. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med.* 2013;369:1783–1796.
90. Sudasena D, Balanescu DV, Donisan T, et al. Fulminant vascular and cardiac toxicity associated with tyrosine kinase inhibitor sorafenib. *Cardiovasc Toxicol.* 2019;19:382–387.
91. Abdel-Rahman O, Fouad M. Risk of cardiovascular toxicities in patients with solid tumors treated with sorafenib: an updated systematic review and meta-analysis. *Future Oncol.* 2014;10:1981–1992.
92. Pantaleo MA, Mandrioli A, Saponara M, et al. Development of coronary artery stenosis in a patient with metastatic renal cell carcinoma treated with sorafenib. *BMC Cancer.* 2012;12:231.
93. Sorafenib (Nexavar) [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; 2010.
94. Trametinib (Mekinist) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2014.
95. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med.* 2012;367:107–114.
96. Sunitinib (Sutent) [package insert]. New York, NY: Pfizer Labs; 2011.
97. Li W, Croce K, Steensma DP, et al. Vascular and metabolic implications of novel targeted cancer therapies: focus on kinase inhibitors. *J Am Coll Cardiol.* 2015;66:1160–1178.
98. Imatinib [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2001.
99. Vandetanib (Caprelsa) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.
100. Santoni M, Guerra F, Conti A, et al. Incidence and risk of cardiotoxicity in cancer patients treated with targeted therapies. *Cancer Treat Rev.* 2017;59:123–131.
101. Ganatra S, Neilan TG. Immune checkpoint inhibitor associated myocarditis. *Oncologist.* 2018;23:879–886.
102. Bortezomib [package insert]. Cambridge, MA: Millennium Pharmaceuticals Inc; 2014.
103. Zangari M, Fink L, Zhan F, et al. Low venous thromboembolic risk with bortezomib in multiple myeloma and potential protective effect with thalidomide/lenalidomide-based therapy: review of data from phase 3 trials and studies of novel combination regimens. *Clin Lymphoma Myeloma Leuk.* 2011;11:228–236.
104. Carfilzomib [package insert]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc; 2016.
105. Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica.* 2013;98:1753–1761.
106. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2015;372:142–152.
107. Goserelin (Zoladex) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
108. Leuprorelin (Lupron) [package insert]. North Chicago, IL: AbbVie Inc; 2014.
109. Flutamide [package insert]. Kenilworth, NJ: Schering Corp; 2001.
110. Bicalutamide [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
111. Nilutamide [package insert]. Baudette, MN: ANI Pharmaceuticals, Inc; 2015.
112. Tisagenlecleucel (Kymriah) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017.
113. Axicabtagene ciloleucel (Yescarta) [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2017.
114. Albloushi R, Kanfar S, Lord B, et al. Clinical prevalence and outcome of cardiovascular events in the first 100 days post allogeneic HSCT. *Eur J Haematol.* 2021;106:32–39.
115. Gul Z, Bashir Q, Cremer M, et al. Short-term cardiac toxicity of autologous hematopoietic stem cell transplant for multiple myeloma. *Leuk Lymphoma.* 2015;56:533–535.
116. Mo XD, Xu LP, Liu DH, et al. Heart failure after allogeneic hematopoietic stem cell transplantation. *Int J Cardiol.* 2013;167:2502–2506.
117. Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977–1997. *Bone Marrow Transplant.* 2001;28:283–287.
118. van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood.* 2017;129:2257–2265.
119. Nolan MT, Russell DJ, Negishi K, et al. Meta-analysis of association between mediastinal radiotherapy and long-term heart failure. *Am J Cardiol.* 2016;118:1685–1691.

### 11.3. HF and Pregnancy

- Cauldwell M, Steer PJ, Swan L, et al. Pre-pregnancy counseling for women with heart disease: a prospective study. *Int J Cardiol*. 2017;240:374–378.
- Roos-Hesselink JW, Ruyt TP, Stein JL, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J*. 2013;34:657–665.
- Dawson AJ, Krastev Y, Parsonage WA, et al. Experiences of women with cardiac disease in pregnancy: a systematic review and metasynthesis. *BMJ Open*. 2018;8:e022755.
- Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med*. 2001;344:1567–1571.
- Elkayam U. Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy. *J Am Coll Cardiol*. 2014;64:1629–1636.
- Hilfiker-Kleiner D, Haghikia A, Masuko D, et al. Outcome of subsequent pregnancies in patients with a history of peripartum cardiomyopathy. *Eur J Heart Fail*. 2017;19:1723–1728.
- Yameogo NV, Samadoulougou AK, Kagambega LJ, et al. Maternal and fetal prognosis of subsequent pregnancy in black African women with peripartum cardiomyopathy. *BMC Cardiovasc Disord*. 2018;18:119.
- Codsi E, Rose CH, Blauwet LA. Subsequent pregnancy outcomes in patients with peripartum cardiomyopathy. *Obstet Gynecol*. 2018;131:322–327.
- Sliwa K, Forster O, Libhaber E, et al. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J*. 2006;27:441–446.
- Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J*. 2006;152:509–513.
- Moulij V, Pfeffer TJ, Riecke-Hoch M, et al. Long-term follow-up in peripartum cardiomyopathy patients with contemporary treatment: low mortality, high cardiac recovery, but significant cardiovascular co-morbidities. *Eur J Heart Fail*. 2019;21:1534–1542.
- Laghari AH, Khan AH, Kazmi KA. Peripartum cardiomyopathy: ten year experience at a tertiary care hospital in Pakistan. *BMC Res Notes*. 2013;6:495.
- Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39:3165–3241.
- Bauersachs J, Konig T, van der Meer P, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail*. 2019;21:827–843.
- Halpern DG, Weinberg CR, Pinnelis R, et al. Use of medication for cardiovascular disease during pregnancy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:457–476.
- Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e579–e646.
- Mehta LS, Warnes CA, Bradley E, et al. Cardiovascular considerations in caring for pregnant patients: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e884–e903.
- Schaufelberger M. Cardiomyopathy and pregnancy. *Heart*. 2019;105:1543–1551.
- Davis MB, Arany Z, McNamara D, et al. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:207–221.
- Honigberg MC, Givertz MM. Peripartum cardiomyopathy. *BMJ*. 2019;364:k5287–k14.
- Lindley KJ. Heart failure and pregnancy: thinking beyond peripartum cardiomyopathy. *J Card Fail*. 2021;27:153–156.
- Ruyt TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart*. 2014;100:231–238.
- Sliwa K, Mebazaa A, Hilfiker-Kleiner D, et al. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. *Eur J Heart Fail*. 2017;19:1131–1141.
- Mogos MF, Piano MR, McFarlin BL, et al. Heart failure in pregnant women: a concern across the pregnancy continuum. *Circ Heart Fail*. 2011;2018:e004005.
- Kolte D, Khera S, Aronow WS, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. *J Am Heart Assoc*. 2014;3:e001056.
- Afana M, Brinjikji W, Kao D, et al. Characteristics and in-hospital outcomes of peripartum cardiomyopathy diagnosed during delivery in the United States from the Nationwide Inpatient Sample (NIS) Database. *J Card Fail*. 2016;22:512–519.
- Krishnamoorthy P, Garg J, Palaniswamy C, et al. Epidemiology and outcomes of peripartum cardiomyopathy in the United States: findings from the Nationwide Inpatient Sample. *J Cardiovasc Med (Hagerstown)*. 2016;17:756–761.
- Nizamuddin J, Gupta A, Patel V, et al. Hypertensive diseases of pregnancy increase risk of readmission with heart failure: a national readmissions database study. *Mayo Clin Proc*. 2019;94:811–819.
- Barasa A, Rosengren A, Sandström TZ, et al. Heart failure in late pregnancy and postpartum: incidence and long-term mortality in Sweden from 1997 to 2010. *J Card Fail*. 2017;23:370–378.
- Davis MB, Jarvie J, Gambahaya E, et al. Risk prediction for peripartum cardiomyopathy in delivering mothers: a validated risk model: PPCM risk prediction model. *J Card Fail*. 2021;27:159–167.
- Hilfiker-Kleiner D, Haghikia A, Podewski E, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. *Basic Res Cardiol*. 2013;108:366.
- Horne BD, Rasmussen KD, Alharethi R, et al. Genome-wide significance and replication of the chromosome 12p11.22 locus near the PTHLH gene for peripartum cardiomyopathy. *Circ Cardiovasc Genet*. 2011;4:359–366.
- Morales A, Painter T, Li R, et al. Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. *Circulation*. 2010;121:2176–2182.
- van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, et al. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. *Eur Heart J*. 2014;35:2165–2173.
- Ware JS, Li J, Mazaike E, et al. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med*. 2016;374:233–241.
- Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell*. 2007;128:589–600.
- Sliwa K, Blauwet L, Tibazarwa K, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation*. 2010;121:1465–1473.
- Hilfiker-Kleiner D, Haghikia A, Berliner D, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. *Eur Heart J*. 2017;38:2671–2679.
- Yaméogo NV, Kagambéga LJ, Seghda A, et al. Bromocriptine in management of peripartum cardiomyopathy: a randomized study on 96 women in Burkina Faso. *J Cardiol Clin Res*. 2017;5:1098.
- Tremblay-Gravel M, Marquis-Gravel G, Avram R, et al. The effect of bromocriptine on left ventricular functional recovery in peripartum cardiomyopathy: insights from the BRO-HF retrospective cohort study. *ESC Heart Fail*. 2019;6:27–36.
- Haghikia A, Schwab J, Vogel-Claussen J, et al. Bromocriptine treatment in patients with peripartum cardiomyopathy and right ventricular dysfunction. *Clin Res Cardiol*. 2019;108:290–297.
- Sieweke JT, Pfeffer TJ, Berliner D, et al. Cardiogenic shock complicating peripartum cardiomyopathy: importance of early left ventricular unloading and bromocriptine therapy. *Eur Heart J Acute Cardiovasc Care*. 2020;9:173–182.
- Sliwa K, Petrie MC, Hilfiker-Kleiner D, et al. Long-term prognosis, subsequent pregnancy, contraception and overall management of peripartum cardiomyopathy: practical guidance paper from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. *Eur J Heart Fail*. 2018;20:951–962.
- Irizary OC, Levine LD, Lewey J, et al. Comparison of clinical characteristics and outcomes of peripartum cardiomyopathy between African American and non-African American women. *JAMA Cardiol*. 2017;2:1256–1260.
- Blauwet LA, Delgado-Montero A, Ryo K, et al. Right ventricular function in peripartum cardiomyopathy at presentation is associated with subsequent left ventricular recovery and clinical outcomes. *Circ Heart Fail*. 2016;9:e002756.
- McNamara DM, Elkayam U, Alharethi R, et al. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol*. 2015;66:905–914.
- Lindley KJ, Conner SN, Cahill AG, et al. Impact of preeclampsia on clinical and functional outcomes in women with peripartum cardiomyopathy. *Circ Heart Fail*. 2017;10:e003797.
- Goland S, Bitar F, Modi K, et al. Evaluation of the clinical relevance of baseline left ventricular ejection fraction as a predictor of recovery or persistence of severe dysfunction in women in the United States with peripartum cardiomyopathy. *J Card Fail*. 2011;17:426–430.

49. Dayoub EJ, Datwani H, Lewey J, et al. One-year cardiovascular outcomes in patients with peripartum cardiomyopathy. *J Card Fail.* 2018;24:711–715.
50. Pfaller B, Sathananthan G, Grewal J, et al. Preventing complications in pregnant women with cardiac disease. *J Am Coll Cardiol.* 2020;75:1443–1452.
51. Billebeau G, Etienne M, Cheikh-Khelifa R, et al. Pregnancy in women with a cardiomyopathy: outcomes and predictors from a retrospective cohort. *Arch Cardiovasc Dis.* 2018;111:199–209.
52. Lima F, Nie L, Yang J, et al. Postpartum cardiovascular outcomes among women with heart disease from a nationwide study. *Am J Cardiol.* 2019;123:2006–2014.
53. Krul SP, van der Smagt JJ, van den Berg MP, et al. Systematic review of pregnancy in women with inherited cardiomyopathies. *Eur J Heart Fail.* 2011;13:584–594.
54. Ng AT, Duan L, Win T, et al. Maternal and fetal outcomes in pregnant women with heart failure. *Heart.* 2018;104:1949–1954.
55. Elkayam U, Goland S, Pieper PG, et al. High-risk cardiac disease in pregnancy: part I. *J Am Coll Cardiol.* 2016;68:396–410.
56. van Hagen IM, Boersma E, Johnson MR, et al. Global cardiac risk assessment in the Registry Of Pregnancy And Cardiac disease: results of a registry from the European Society of Cardiology. *Eur J Heart Fail.* 2016;18:523–533.
57. Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II study. *J Am Coll Cardiol.* 2018;71:2419–2430.
58. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J.* 2010;31:2124–2132.
59. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med.* 2006;354:2443–2451.
60. Buawangpong N, Teekachunhatean S, Koonrungsosomboon N. Adverse pregnancy outcomes associated with first-trimester exposure to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: a systematic review and meta-analysis. *Pharmacol Res Perspect.* 8;2020:e00644.
61. Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. *Obstet Gynecol.* 2017;129:174–184.
62. Liszewski W, Boull C. Lack of evidence for feminization of males exposed to spironolactone in utero: a systematic review. *J Am Acad Dermatol.* 2019;80:1147–1148.
63. Tanaka K, Tanaka H, Kamiya C, et al. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. *Circ J.* 2016;80:2221–2226.
64. Bateman BT, Heide-Jorgensen U, Einarsdottir K, et al. Beta-blocker use in pregnancy and the risk for congenital malformations: an international cohort study. *Ann Intern Med.* 2018;169:665–673.
65. Bergman JEH, Lutke LR, Gans ROB, et al. Beta-blocker use in pregnancy and risk of specific congenital anomalies: a European case-malformed control study. *Drug Saf.* 2018;41:415–427.
66. Kearney L, Wright P, Fhadil S, et al. Postpartum cardiomyopathy and considerations for breastfeeding. *Card Fail Rev.* 2018;4:112–118.
67. Koczo A, Marino A, Jeyabalan A, et al. Breastfeeding, cellular immune activation, and myocardial recovery in peripartum cardiomyopathy. *J Am Coll Cardiol Basic Trans Science.* 2019;4:291–300.
68. Arany Z, Feldman AM. To breastfeed or not to breastfeed with peripartum cardiomyopathy. *J Am Coll Cardiol Basic Trans Science.* 2019;4:301–303.
69. Koenig T, Hilfiker-Kleiner D, Bauersachs J. Breastfeeding in patients with heart failure: lack of evidence and consensus. *J Am Coll Cardiol Basic Trans Science.* 2019;4:866–867.
70. Safirstein JG, Ro AS, Grandhi S, et al. Predictors of left ventricular recovery in a cohort of peripartum cardiomyopathy patients recruited via the internet. *Int J Cardiol.* 2012;154:27–31.
71. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics.* 2001;108:776–789.
72. National Library of Medicine. *Drugs and Lactation Database (LactMed)* [Internet]. Bethesda (MD). Accessed October 2, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK501922/>
73. Kampman MA, Balci A, van Veldhuisen DJ, et al. N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. *Eur Heart J.* 2014;35:708–715.
74. Tanous D, Siu SC, Mason J, et al. B-type natriuretic peptide in pregnant women with heart disease. *J Am Coll Cardiol.* 2010;56:1247–1253.
75. Gammill HS, Chettier R, Brewer A, et al. Cardiomyopathy and preeclampsia. *Circulation.* 2018;138:2389–2366.
76. Ersboll AS, Arany Z, Gustafsson F. Bromocriptine for the treatment of peripartum cardiomyopathy: comparison of outcome with a Danish cohort. *Eur Heart J.* 2018;39:3476–3477.

## 12.1. Performance Measurement

1. Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation.* 2010;122:585–596.
2. Nakano A, Vinter N, Egstrup K, et al. Association between process performance measures and 1-year mortality among patients with incident heart failure: a Danish nationwide study. *Eur Heart J Qual Care Clin Outcomes.* 2019;5:28–34.
3. Patel DB, Shah RM, Bhatt DL, et al. Guideline-appropriate care and in-hospital outcomes in patients with heart failure in teaching and nonteaching hospitals: findings from Get With The Guidelines-Heart Failure. *Circ Cardiovasc Qual Outcomes.* 2016;9:757–766.
4. Patel J, Sandhu A, Parizo J, et al. Validity of performance and outcome measures for heart failure. *Circ Heart Fail.* 2018;11:e0005035.
5. Heidenreich PA, Hernandez AF, Yancy CW, et al. Get With The Guidelines program participation, process of care, and outcome for Medicare patients hospitalized with heart failure. *Circ Cardiovasc Qual Outcomes.* 2012;5:37–43.
6. Heidenreich PA, Lewis WR, LaBresh KA, et al. Hospital performance recognition with the Get With The Guidelines Program and mortality for acute myocardial infarction and heart failure. *Am Heart J.* 2009;158:546–553.
7. Ivers NM, Grimshaw JM, Jamtvedt G, et al. Growing literature, stagnant science? Systematic review, meta-regression and cumulative analysis of audit and feedback interventions in health care. *J Gen Intern Med.* 2014;29:1534–1541.
8. Heidenreich PA, Fonarow GC, Breathett K, et al. 2020 ACC/AHA clinical performance and quality measures for adults with heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes.* 2020;13:e000099.
9. Tu JV, Donovan LR, Lee DS, et al. Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. *JAMA.* 2009;302:2330–2337.
10. Thomas RJ, Balady G, Banka G, et al. 2018 ACC/AHA clinical performance and quality measures for cardiac rehabilitation: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes.* 2018;11:e000037.

## 13.1. Palliative and Supportive Care, Shared Decision-Making, and End-of-Life

1. Datla S, Verberkt CA, Hoye A, et al. Multi-disciplinary palliative care is effective in people with symptomatic heart failure: a systematic review and narrative synthesis. *Palliat Med.* 2019;33:1003–1016.
2. Goldstein N, Carlson M, Livote E, et al. Brief communication: management of implantable cardioverter-defibrillators in hospice: a nationwide survey. *Ann Intern Med.* 2010;152:296–299.
3. McIvennan CK, Jones J, Allen LA, et al. Bereaved caregiver perspectives on the end-of-life experience of patients with a left ventricular assist device. *JAMA Intern Med.* 2016;176:534–539.
4. Rogers JG, Patel CB, Mentz RJ, et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. *J Am Coll Cardiol.* 2017;70:331–341.
5. Bekelman DB, Allen LA, McBryde CF, et al. Effect of a collaborative care intervention vs usual care on health status of patients with chronic heart failure: the CASA randomized clinical trial. *JAMA Intern Med.* 2018;178:511–519.
6. O'Donnell AE, Schaefer KG, Stevenson LW, et al. Social Worker-Aided Palliative Care Intervention in High-risk Patients With Heart Failure (SWAP-HF): a pilot randomized clinical trial. *JAMA Cardiol.* 2018;3:516–519.
7. Schichtel M, Wee B, Perera R, et al. The effect of advance care planning on heart failure: a systematic review and meta-analysis. *J Gen Intern Med.* 2020;35:874–884.
8. Candy B, Holman A, Leurent B, et al. Hospice care delivered at home, in nursing homes and in dedicated hospice facilities: a systematic review of quantitative and qualitative evidence. *Int J Nurs Stud.* 2011;48:121–133.
9. Braun LT, Grady KL, Kutner JS, et al. Palliative care and cardiovascular disease and stroke: a policy statement from the American Heart Association/American Stroke Association. *Circulation.* 2016;134:e198–e225.
10. McIvennan CK, Allen LA. Palliative care in patients with heart failure. *BMJ.* 2016;353:i1010.
11. Casarett D, Fishman J, O'Dwyer PJ, et al. How should we design supportive cancer care? The patient's perspective. *J Clin Oncol.* 2008;26:1296–1301.
12. Allen LA, Stevenson LW, Grady KL, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation.* 2012;125:1928–1952.
13. Lanken PN, Terry PB, Delisser HM, et al. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med.* 2008;177:912–927.

14. World Health Organization Expert Committee on Cancer Pain Relief and Active Supportive Care. Cancer pain relief and palliative care. World Health Organization Technical Report Series, No. 804. World Health Organization; 1990. Accessed December 15, 2020. [https://apps.who.int/iris/bitstream/handle/10665/39524/WHO\\_TRS\\_804.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/39524/WHO_TRS_804.pdf?sequence=1&isAllowed=y)
15. Gelfman LP, Kalman J, Goldstein NE. Engaging heart failure clinicians to increase palliative care referrals: overcoming barriers, improving techniques. *J Palliat Med.* 2014;17:753–760.
16. Tulsky JA, Beach MC, Butow PN, et al. A research agenda for communication between health care professionals and patients living with serious illness. *JAMA Intern Med.* 2017;177:1361–1366.
17. Allen LA, Yager JE, Funk MJ, et al. Discordance between patient-predicted and model-predicted life expectancy among ambulatory patients with heart failure. *JAMA.* 2008;299:2533–2542.
18. Matlock DD, Jones J, Nowels CT, et al. Evidence of cognitive bias in decision making around implantable-cardioverter defibrillators: a qualitative framework analysis. *J Card Fail.* 2017;23:794–799.
19. Ferrell BR, Twaddle ML, Melnick A, et al. National consensus project clinical practice guidelines for quality palliative care guidelines, 4th edition. *J Palliat Med.* 2018;21:1684–1689.
20. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363:733–742.
21. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA.* 1995;274:1591–1598.
22. Bakitas MA, Dionne-Odom JN, Ejem DB, et al. Effect of an early palliative care telehealth intervention vs usual care on patients with heart failure: the ENABLE CHF-PC randomized clinical trial. *JAMA Intern Med.* 2020;180:1203–1213.
23. Carson SS, Cox CE, Wallenstein S, et al. Effect of palliative care-led meetings for families of patients with chronic critical illness: a randomized clinical trial. *JAMA.* 2016;316:51–62.
24. Sudore RL, Lum HD, You JJ, et al. Defining advance care planning for adults: a consensus definition from a multidisciplinary Delphi Panel. *J Pain Symptom Manage.* 2017;53:821–832.e1.
25. Yadav KN, Gabler NB, Cooney E, et al. Approximately one in three US adults completes any type of advance directive for end-of-life care. *Health Aff (Millwood).* 2017;36:1244–1251.
26. Keating NL, Huskamp HA, Kouri E, et al. Factors contributing to geographic variation in end-of-life expenditures for cancer patients. *Health Aff (Millwood).* 2018;37:1136–1143.
27. Chuiz S, Molsberry R, Ogunseitan A, et al. Trends in place of death for cardiovascular mortality related to heart failure in the United States from 2003 to 2017. *Circ Heart Fail.* 2020;13:e006587.

## 14.1. Patient-Reported Outcomes

1. Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol.* 2000;35:1245–1255.
2. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J.* 2005;150:707–715.
3. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure Questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. *Am Heart J.* 1992;124:1017–1025.
4. Demers C, McKelvie RS, Negassa A, et al. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. *Am Heart J.* 2001;142:698–703.
5. Rector TS, Anand IS, Cohn JN. Relationships between clinical assessments and patients' perceptions of the effects of heart failure on their quality of life. *J Card Fail.* 2006;12:87–92.
6. Gorkin L, Norvell NK, Rosen RC, et al. Assessment of quality of life as observed from the baseline data of the Studies of Left Ventricular Dysfunction (SOLVD) trial quality-of-life substudy. *Am J Cardiol.* 1993;71:1069–1073.
7. Quittan M, Wiesinger GF, Crevenna R, et al. Cross-cultural adaptation of the Minnesota living with heart failure questionnaire for German-speaking patients. *J Rehabil Med.* 2001;33:182–186.
8. van den Berg-Emons RJ, Bussmann JB, Balk AH, et al. Factors associated with the level of movement-related everyday activity and quality of life in people with chronic heart failure. *Phys Ther.* 2005;85:1340–1348.
9. Rector TS, Carson PE, Anand IS, et al. Assessment of long-term effects of irbesartan on heart failure with preserved ejection fraction as measured by the Minnesota Living with Heart Failure Questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial. *Circ Heart Fail.* 2012;5:217–225.
10. Carson P, Tam SW, Ghali JK, et al. Relationship of quality of life scores with baseline characteristics and outcomes in the African-American heart failure trial. *J Card Fail.* 2009;15:835–842.
11. Alla F, Briancon S, Guillemin F, et al. Self-rating of quality of life provides additional prognostic information in heart failure: insights into the EPICAL study. *Eur J Heart Fail.* 2002;4:337–343.
12. Tate CW 3rd, Robertson AD, Zolty R, et al. Quality of life and prognosis in heart failure: results of the Beta-Blocker Evaluation of Survival Trial (BEST). *J Card Fail.* 2007;13:732–737.
13. Moser DK, Yamokoski L, Sun JL, et al. Improvement in health-related quality of life after hospitalization predicts event-free survival in patients with advanced heart failure. *J Card Fail.* 2009;15:763–769.
14. Hoekstra T, Jaarsma T, van Veldhuisen DJ, et al. Quality of life and survival in patients with heart failure. *Eur J Heart Fail.* 2013;15:94–102.
15. Soto GE, Jones P, Weintraub WS, et al. Prognostic value of health status in patients with heart failure after acute myocardial infarction. *Circulation.* 2004;110:546–551.
16. Pokharel Y, Khariton Y, Tang Y, et al. Association of serial Kansas City Cardiomyopathy Questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials. *JAMA Cardiol.* 2017;2:1315–1321.
17. Dunlay SM, Gheorghiade M, Reid KJ, et al. Critical elements of clinical follow-up after hospital discharge for heart failure: insights from the EVEREST trial. *Eur J Heart Fail.* 2010;12:367–374.
18. Heidenreich PA, Spertus JA, Jones PG, et al. Health status identifies heart failure outpatients at risk for hospitalization or death. *J Am Coll Cardiol.* 2006;47:752–756.
19. Arnold SV, Spertus JA, Vemulapalli S, et al. Association of patient-reported health status with long-term mortality after transcatheter aortic valve replacement: report from the STS/ACC TVT Registry. *Circ Cardiovasc Interv.* 2015;8:e002875.
20. Tran AT, Chan PS, Jones PG, et al. Comparison of patient self-reported health status with clinician-assigned New York Heart Association classification. *JAMA Netw Open.* 2020;3:e2014319.
21. Goode KM, Nabb S, Cleland JG, et al. A comparison of patient and physician-rated New York Heart Association class in a community-based heart failure clinic. *J Card Fail.* 2008;14:379–387.
22. Khariton Y, Hernandez AF, Fonarow GC, et al. Health status variation across practices in outpatients with heart failure: insights from the CHAMP-HF (Change the Management of Patients With Heart Failure) Registry. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004668.
23. Stehlík J, Rodriguez-Correa C, Spertus JA, et al. Implementation of real-time assessment of patient-reported outcomes in a heart failure clinic: a feasibility study. *J Card Fail.* 2017;23:813–816.
24. Turgeon RD, Barry AR, Hawkins NM, et al. Pharmacotherapy for heart failure with reduced ejection fraction and health-related quality of life: a systematic review and meta-analysis. *Eur J Heart Fail.* 2021;23:578–589.
25. Chen S, Yin Y, Kruckoff MW. Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: a meta-analysis. *Europace.* 2012;14:1602–1607.
26. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* 2009;301:1439–1450.
27. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation.* 2016;133:1637–1644.
28. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med.* 2008;359:1778–1785.
29. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet.* 2011;377:658–666.
30. Mark DB, Knight JD, Velazquez EJ, et al. Quality-of-life outcomes with coronary artery bypass graft surgery in ischemic left ventricular dysfunction: a randomized trial. *Ann Intern Med.* 2014;161:392–399.
31. Arnold SV, Chinnakondapalli KM, Spertus JA, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. *J Am Coll Cardiol.* 2019;73:2123–2132.

**Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Paul A. Heidenreich, Chair	Stanford University School of Medicine—Professor and Vice-Chair for Quality, Department of Medicine	None	None	None	None	None	None	None
Biykem Bozkurt, Vice Chair	Baylor College of Medicine and De-Bakey VA Medical Center Cardiology Department—Mary and Gordon Cain Chair; W.A. “Tex” and Deborah Moncrief, Jr., Chair; Professor of Medicine Medical Care Line Executive, DeBakey VA Medical Center; Director, Winters Center for Heart Failure Research; Associate Director, Cardiovascular Research Institute; Vice-Chair of Medicine, Baylor College of Medicine	<ul style="list-style-type: none"> <li>• Abbott*</li> <li>• Amgen</li> <li>• Baxter</li> <li>• Bristol-Myers Squibb*</li> <li>• E.R. Squibb &amp; Sons, L.L.C.*</li> <li>• Relypsa</li> <li>• Sanofi-aventis*</li> <li>• scPharmaceuticals</li> <li>• Vifor</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• Abbott*</li> <li>• Amgen</li> <li>• Relypsa</li> <li>• Respicardia</li> <li>• Sanofi-Aventis†</li> <li>• Past President, HFSA (2019-2020)</li> </ul>	None	None
David Aguilar	University of Kentucky—Professor of Medicine, Department of Medicine, Division of Cardiovascular Medicine	None	None	None	None	None	None	None
Larry A. Allen	University of Colorado School of Medicine, Anschutz Medical Campus—Professor of Medicine, Department of Medicine, Division of Cardiology	<ul style="list-style-type: none"> <li>• Abbott</li> <li>• ACI Clinical*</li> <li>• Amgen*</li> <li>• Boston Scientific*</li> <li>• Cytokinetics</li> <li>• Novartis</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• Abbott‡</li> <li>• Amgen</li> <li>• Boston Scientific*‡</li> <li>• Janssen Pharmaceuticals</li> <li>• Medtronic Vascular Inc.</li> <li>• Novartis‡</li> </ul>	None	None
Joni J. Byun	Penultimate PR—President	None	None	None	None	None	None	None
Monica M. Colvin	University of Michigan—Professor of Medicine, Department of Medicine, Cardiovascular Division; Associate Director, Heart Transplant Program, Advanced Heart Failure, Transplant, and MCS Natera	None	None	None	• CareDX	• Abbott‡	None	None
Anita Deswal	UT MD Anderson Cancer Center—Ting Tsung and Wei Fong Chao Distinguished Chair, Professor of Medicine, and Chair of Cardiology	None	None	None	None	None	None	None
Mark H. Drazner	UT Southwestern Medical Center—Professor and Clinical Chief of Cardiology, Department of Internal Medicine, Cardiology	None	None	None	None	None	None	None
Shannon M. Dunlay	Mayo Clinic—Professor of Health Services Research and Medicine, Department of Cardiovascular Medicine	None	None	None	None	None	None	None
Linda R. Evers	Stevens & Lee—Shareholder and Chair of Stevens & Lee’s Energy, Communications and Public Utility Group	None	None	None	None	None	None	None
James C. Fang	University of Utah—Professor of Medicine, Division of Cardiovascular Medicine	<ul style="list-style-type: none"> <li>• Boston Scientific†</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• ACI Clinical (Adjudication Committee)*</li> <li>• Amgen (Steering Committee)</li> <li>• AstraZeneca (Steering Committee)</li> <li>• Boston Scientific†</li> <li>• Novartis (Executive Committee)</li> </ul>	None	None

(Continued)

**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Savitri E. Fedson	Michael E. DeBakey Medical Center—Professor, Medical Director, Advanced Heart Failure and Transplantation, Section of Cardiology	None	None	None	None	None	None	None
Gregg C. Fonarow	Geffen School of Medicine at UCLA—Professor of Cardiovascular Medicine, Chief, UCLA Division of Cardiology, Department of Medicine	<ul style="list-style-type: none"> <li>• Abbott*</li> <li>• Amgen</li> <li>• AstraZeneca</li> <li>• CHF Solutions</li> <li>• Cytokinetics</li> <li>• Edwards Life-sciences*</li> <li>• Janssen Pharmaceuticals</li> <li>• Medtronic</li> <li>• Merck*</li> <li>• Novartis*</li> <li>• Regeneron</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• Boston Scientific</li> <li>• Novartis*</li> <li>• Medtronic</li> </ul>	None	None
Salim S. Hayek	University of Michigan in Ann Arbor—Assistant Professor, Department of Medicine, Division of Cardiology	None	None	None	None	None	None	None
Adrian F. Hernandez	Duke University School of Medicine—Vice Dean of Clinical Research	<ul style="list-style-type: none"> <li>• Amgen</li> <li>• AstraZeneca</li> <li>• Bayer</li> <li>• BioFourmis</li> <li>• Boehringer Ingelheim*</li> <li>• Boston Scientific*</li> <li>• Cytokinetics</li> <li>• Eli Lilly</li> <li>• Merck*</li> <li>• Myokardia</li> <li>• Novartis*</li> <li>• Pfizer</li> <li>• Relypsa</li> <li>• Sanofi-aventis*</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• American Regent</li> <li>• Amgen</li> <li>• Boston Scientific</li> <li>• AstraZeneca*</li> <li>• Boehringer Ingelheim</li> <li>• Daiichi Sankyo</li> <li>• Genentech</li> <li>• GlaxoSmithKline*</li> <li>• Janssen Pharmaceuticals*</li> <li>• Merck*</li> <li>• Novartis*</li> <li>• Verily*</li> </ul>	None	None	None
Prateeti Kharazanie	University of Colorado—Assistant Professor of Medicine, Department of Medicine, Division of Cardiology	None	None	None	None	None	None	None
Michelle M. Kittleson	Smidt Heart Institute Cedars-Sinai—Professor of Medicine, Cardiology	None	None	None	None	None	None	None
Christopher S. Lee	Boston College, William F. Connell School of Nursing—Professor and Associate Dean for Research	None	None	None	None	None	None	None
Mark S. Link	UT Southwestern Medical Center, Dallas—Professor of Medicine and Director, Cardiac Electrophysiology; Laurence and Susan Hirsch/Centex Distinguished Chair in Heart Disease, Department of Internal Medicine, Division of Cardiology	None	None	None	None	None	None	None
Carmelo A. Milano	Duke University Medical Center—Professor of Surgery, Surgery Department	<ul style="list-style-type: none"> <li>• Abbott*</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Abbott*</li> <li>• Medtronic*</li> <li>• NuPulset</li> </ul>	<ul style="list-style-type: none"> <li>• Abbott*</li> <li>• AbioMed†</li> <li>• Allergan†</li> <li>• CryoLife†</li> <li>• Ethicon†</li> <li>• LivaNova†</li> </ul>	None	None

(Continued)

**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Lorraine C. Nnacheta <sup>§</sup>	American Heart Association/American College of Cardiology—Guideline Advisor	None	None	None	None	• AHA/ACC salaried employee	None	None
Alexander T. Sandhu	Stanford University—Instructor of Medicine, Division of Cardiology, Department of Medicine	None	None	None	None	None	None	None
Lynne Warner Stevenson	Vanderbilt University Medical Center, Vanderbilt Heart and Vascular Institute—Director of Cardiomyopathy and Lisa M. Jacobson Professor of Cardiovascular Medicine	• Novartis	None	None	None	• Abbott <sup>#</sup> • Biotronik • Boston Scientific • Bristol-Myers Squibb <sup>#</sup> • Endotronic <sup>†</sup> • Gore Medical <sup>†</sup> • Johnson & Johnson	None	None
Orly Vardeny	Minneapolis VA Health Care System and University of Minnesota—Associate Professor of Medicine, Department of Medicine	• Amgen • Novartis • Sanofi-Pasteur	None	None	• AstraZeneca <sup>*</sup> • Bayer <sup>*</sup>	• AstraZeneca <sup>#</sup>	None	None
Amanda R. Vest	Tufts Medical Center, Cardiovascular Center—Assistant Professor of Medicine	None	None	None	None	• Boehringer Ingelheim <sup>†*</sup> • CareDx <sup>#</sup> • Corvia <sup>#</sup> • Transmedics <sup>#</sup>	None	None
Clyde W. Yancy	Northwestern University, Feinberg School of Medicine; Northwestern Memorial Hospital—Professor of Medicine (Cardiology); Professor of Medical Social Sciences; Chief of Cardiology; Vice-Dean, Diversity & Inclusion; Associate Director Cardiovascular Institute Internal Medicine/Cardiology & Medical Social Sciences	None	None	None	None	• Abbott <sup>†</sup> • JAMA Cardiology, Deputy Editor	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the ACC/AHA, a person has a *relevant relationship IF:* a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*. Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

\*Significant relationship.

<sup>†</sup>No financial benefit.

<sup>‡</sup>This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no *direct or institutional* relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

<sup>§</sup>Lorraine Nnacheta is an AHA/ACC joint staff member and acts as the guideline advisor for the "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure." No relevant relationships to report. Non-voting author on recommendations and not included/ counted in the RWI balance for this committee.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; HFSA, Heart Failure Society of America; RWI, relationships with industry and other entities; UCLA, University of California, Los Angeles; UT, University of Texas; and VA, Veterans Affairs.

**Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure (June 2021)**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Anastasia Armbruster	Content Reviewer—Joint Committee on Clinical Practice Guidelines	University of Health Sciences & Pharmacy in St. Louis	None	• AstraZeneca Pharmaceuticals	None	None	None	None
Alison Bailey	Content Reviewer—ACC	Centennial Heart at Parkridge	None	None	None	None	• American Society of Preventive Cardiology† • OptumRx	None
Joshua A. Beckman	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Vanderbilt University	• Amgen • JanOne • Janssen Pharmaceuticals*	None	• EMX† • JanaCare†	• Bayer (DSMB) • Novartis	• Vascular Interventional Advances* • NovoNordisk‡	None
Claudio Bravo	Content Reviewer—AHA	University of Washington	None	None	None	None	None	None
Patricia Chang	Content Reviewer—AHA/ACC	University of North Carolina	None	None	None	None	None	None
Richard Cheng	Content Reviewer—AHA	University of Washington	None	None	None	• Eidos‡ • Ionis‡	None	None
Lisa de las Fuentes	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Washington University in St. Louis	• Acceleron • Aerovate • Altavant • Arena • Bayer • Complexa* • Express Scripts • Gossamer • Johnson&Johnson • Phase Bio • Somometrics • V-wave • Vaderis • WebMD*	• Simply Speaking*	None	• Acceleron* • Bayer • Complexa* • Johnson&Johnson* • Liquidia* • Medtronic* • NIH* • Trio Analytics • United Therapeutics* • University of Kentucky (DSMB)† • University of Toronto (DSMB)†	• ACC† • AHA† • Circulation Journals • Foundation for the NIH† • Pulmonary Hypertension Association*	None
Akshay Desai	Content Reviewer—AHA/ACC	Brigham and Women's Hospital	• Abbott Laboratories* • Alnylam* • Amgen* • AstraZeneca Pharmaceuticals* • Biofourmis* • Boehringer Ingelheim • Boston Scientific* • Corvidia Therapeutics* • Cytokinetics • Dalcor Pharma* • Lupin Pharma • Merck • Novartis* • Regeneron* • Relapsa* • Sun Pharma	None	None	• Alnylam* • AstraZeneca Pharmaceuticals* • Bayer† • Myokardia† • Novartis*	• Baim Clinical Research Institute* • TIMI Study Group*	None
Howard Eisen	Official Reviewer—AHA	Penn State Health	None	None	None	None	None	None
Mona Fiuzat	Content Reviewer—AHA/ACC	Duke University	• Fire1	None	None	• Roche*	None	None
Bulent Gorenek	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Eskisehir Osmangazi University	• AstraZeneca Pharmaceuticals • Bayer • Daiichi Sankyo • Roche • Sandoz • Sanofi	None	None	None	None	None

(Continued)

**Appendix 2. Continued**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
José A. Joglar	Content Reviewer—Joint Committee on Clinical Practice Guidelines	UT Southwestern Medical Center	None	None	None	None	None	None
W. Schuyler Jones	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Duke University	• Bayer* • Janssen Pharmaceuticals	None	None	• Boehringer Ingelheim • Bristol Myers Squibb • PCORI	None	None
Daniel Judge	Content Reviewer—AHA/ACC	The Medical University of South Carolina	• ADRx • Cytokinetics • Pfizer • Tenaya Therapeutics	None	None	• Capricor (DSMB) • TRINDS (DSMB)	• Array Biopharma† • Eidos Therapeutics‡ • Myokardia‡	None
Kimberly Ketter	Lay Reviewer	Morris Cardiovascular & Risk Reduction Center	None	None	None	None	• Verilogue	None
Dharam Kumbhani	Content Reviewer—AHA/ACC	UT Southwestern Medical Center	• ACC*	None	None	None	• Circulation, Associate Editor*	None
Daniel Mark	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Duke University	• Novartis	None	None	None	• Elsevier* • Heartflow* • Merck* • NIH*	None
Paul Mather	Content Reviewer—AHA/ACC	University of Pennsylvania	None	None	None	• Novartis*	None	None
Shweta Motiwala	Content Reviewer—AHA/ACC	Harvard University	• Baim Institute for Clinical Research* • Eli Lilly • Relay Therapeutics*	None	• Relay Therapeutics*	• Puma Biotechnology* • Relysat†	• American Regent‡ • Boehringer Ingelheim‡ • Edwards Lifesciences‡ • NuPulse CV‡	None
Debabrata Mukherjee	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Texas Tech University	• ACC*	None	None	None	None	None
Patrick T. O'Gara	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Brigham and Women's Hospital	None	None	None	None	• Edwards Lifesciences† • Medtronic† • JAMA* • NIH*	None
Francis D. Pagani	Official Reviewer—AHA	University of Michigan	None	None	None	None	None	None
Gurusher Panjwani	Content Reviewer—ACC	George Washington University	• CVRx	• Pfizer*	None	None	• Abbott Laboratories‡	None
Mariann Piano	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Vanderbilt University	None	None	None	None	None	None
Sean Pinney	Content Reviewer—AHA/ACC	University of Chicago	• Abbott Laboratories • CareDX, Inc. • Medtronic • NuPulse • Procytron • Transmedics	None	None	None	None	None
Bunny Pozehl	Content Reviewer—AHA/ACC	University of Nebraska	None	None	None	None	None	None
Tanveer Rab	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Emory University	None	None	None	None	• ABIM • ACC† • American Bifurcation Club†	None

(Continued)

**Appendix 2. Continued**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nosheen Reza	Content Reviewer—ACC	University of Pennsylvania	None	None	None	None	None	None
Jo E. Rodgers	Content Reviewer—AHA	University of North Carolina	None	None	None	• Novartis†	• Duke Clinical Research Institute‡ • GlaxoSmithKline	None
Chris Salerno	Content Reviewer—ACC	St. Vincent Hospital	• Abbott	• Medtronic	None	None	• Abbott‡ • Medtronic‡	None
Sanjiv Shah	Official Reviewer—HFSA	Northwestern University	• Abbott • ABIM • Amgen • Aria • AstraZeneca Pharmaceuticals* • Axon • Bayer • Boehringer Ingelheim • Boston Scientific • Bristol Myers Squibb • Cardiora • CVRx • Cycleron • Cytokinetics • Eisai • Ekoi.ai • GlaxoSmithKline • Imara • Ionis • Ironwood • Janssen Pharmaceuticals • Keyto • Eli Lilly • Merck • Myokardia • Novartis* • NovoNordisk • Pfizer • Prothena • Regeneron • Sanofi • Shifamed • Tenax • United Therapeutics	• Pulmonary Hypertension Association	None	• Actelion* • AHA* • Covia* • NIH*	None	None
Erica S. Spatz	Official Reviewer, Joint Committee on Clinical Practice Guidelines	Yale University	None	None	None	None	• Centers for Medicare & Medicaid Services* • US Food and Drug Administration*	None
Nancy Sweitzer	Official Reviewer—HFSA	University of Arizona	• Medscape* • Myokardia	None	None	• NIH* • Merck • Novartis†	• AHA* • Amgen‡ • Array BioPharma‡ • Cellular Logistics‡ • Corvia Medical‡ • CVRx‡ • NIH*‡ • University of Arizona*	None
Jacqueline E. Tamis-Holland	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Mount Sinai	• Gaffney Events Educational Trust	None	None	None	• AHA† • Bronx Lebanon Hospital, Cardiology Fellowship Program Director† • NYST • The NGS Predict Study‡	None

(Continued)

**Appendix 2. Continued**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jennifer Thibodeau	Content Reviewer—AHA	UT Southwestern Medical Center	None	None	None	None	<ul style="list-style-type: none"> <li>• CareDX‡</li> <li>• Cytokinetics‡</li> <li>• Eidos Therapeutics‡</li> <li>• NIH‡</li> </ul>	None
Sanjeev Trehan	Official Reviewer—ACC (Board of Governors)	Saint Francis Health System	None	None	None	None	None	None
Mary Norine Walsh	Content Reviewer—AHA/ACC	Ascension Medical Group	None	None	None	None	<ul style="list-style-type: none"> <li>• Amgen‡</li> <li>• EBR Systems</li> <li>• PCORI‡</li> <li>• Thoratec‡</li> <li>• Uppsala University‡</li> </ul>	None
Barbara Wiggins	Content Reviewer—ACC	Medical University of South Carolina	• Lexicomp	None	None	None	<ul style="list-style-type: none"> <li>• ACC†</li> <li>• <i>American Journal of Cardiovascular Drugs†</i></li> <li>• PERT Consortium Clinical Protocol†</li> </ul>	None
Y. Joseph Woo	Content Reviewer—Joint Committee on Clinical Practice Guidelines	Stanford University School of Medicine	None	None	None	None	<ul style="list-style-type: none"> <li>• Associate Editor, <i>Journal of Thoracic and Cardiovascular Disease</i></li> <li>• NIH*</li> </ul>	None

This table represents all relationships of reviewers with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

\*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

ABIM indicates American Board of Internal Medicine; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; DSMB, Data and Safety Monitoring Board; JAMA, Journal of the American Medical Association; NGS, Next-generation sequencing; NIH, National Institutes of Health; NYS, New York State; PCORI, Patient-Centered Outcomes Research Institute; PERT, Pulmonary Embolism Response Team; TIMI, Thrombolysis in Myocardial Infarction; and UT, University of Texas.

**Appendix 3. Appendix for Tables 3 and 4: Suggested Thresholds for Structural Heart Disease and Evidence of Increased Filling Pressures**

Morphology	<ul style="list-style-type: none"> <li>• LAVI <math>\geq 29 \text{ mL/m}^2</math></li> <li>• LVMI <math>&gt; 116/95 \text{ g/m}^2</math></li> <li>• RWT <math>&gt; 0.42</math></li> <li>• LV wall thickness <math>\geq 12 \text{ mm}</math></li> </ul>
Ventricular systolic function	<ul style="list-style-type: none"> <li>• LVEF <math>&lt; 50\%</math></li> <li>• GLS <math>&lt; 16\%</math></li> </ul>
Ventricular diastolic function	<ul style="list-style-type: none"> <li>• Average E/e' <math>\geq 15</math> for increased filling pressures</li> <li>• Septal e' <math>&lt; 7 \text{ cm/s}</math></li> <li>• Lateral e' <math>&lt; 10 \text{ cm/s}</math></li> <li>• TR velocity <math>&gt; 2.8 \text{ m/s}</math></li> <li>• Estimated PA systolic pressure <math>&gt; 35 \text{ mm Hg}</math></li> </ul>
Biomarker	<ul style="list-style-type: none"> <li>• BNP <math>\geq 35 \text{ pg/mL}^*</math></li> <li>• NT-proBNP <math>\geq 125 \text{ pg/mL}^*</math></li> </ul>

AF indicates atrial fibrillation; BNP, brain natriuretic peptide; CKD, chronic kidney disease; GLS, global longitudinal strain; HF, heart failure; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, natriuretic peptide tests; PA, pulmonary artery; RWT, relative wall thickness; and TR, tricuspid regurgitation.

\*Cutoffs provided for natriuretic peptide levels may have lower specificity, especially in older patients or in patients with AF or CKD. Usually, higher cutoff values are recommended for the diagnosis of HF in these patients. Natriuretic peptide cutoffs selected for population screening for pre-HF (stage B HF) may be  $< 99\%$  reference limits and need to be defined according to the population at risk.