

Philippine Clinical Practice Guidelines on the Diagnosis and Management of Chronic Heart failure with reduced Ejection Fraction for Primary Care Physicians

HEART FAILURE CLINICAL PRACTICE GUIDELINE TASK FORCE 2023

Disclaimer and Contact Information

This clinical practice guideline (CPG) is mainly intended for use by physicians, whether general practitioners or specialists, who serve as primary care providers for patients with heart failure. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict clinicians from using their clinical judgment and considering a patient's values, needs, and preferences while handling individual cases. Clinicians and other relevant stakeholders must always exercise sound clinical decision-making as the individual patient's medical history, physical status, and response to treatment may vary.

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The developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of Chronic Heart Failure with Reduced Ejection Fraction management. It provides recommendations on interventions where variability in clinical practice and controversies in decision-making exist.

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Acknowledgments

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The HF CPG task force undertook extensive technical work in (1) searching for and synthesizing the evidence while ensuring objectivity in each stage of the process; (2) presenting the evidence in the panel discussion; and (3) documenting and writing the final report. The task force was also indispensable in carrying out the legwork, in coordinating among various individuals, groups, and committees, and facilitating the en banc meetings. The CPG Central Steering Committee and the Task Force Steering Committee were responsible for the overall organization and management and are accountable for the quality of the CPG. Lastly, this guideline is invaluable because of the contribution and participation of panelists from the different sectors of the healthcare community as well as the laity who committed their time and effort to share not just their knowledge, experience, and expertise in analyzing the scientific evidence but also their values and preferences in formulating the recommendations that consider both the patients and the current healthcare system in the country.

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Participating Societies, Organizations, Agencies, and/or Institutions

This clinical practice guideline will not be possible without the participation of the following institutions and organizations:

- Philippine Heart Center (PHC)
- Philippine Heart Association (PHA)
- Philippine Academy of Family Physicians (PAFP)
- Philippine College of Physicians (PCP)
- Philippine Medical Association (PMA)

List of Acronyms

Acronym	Full Name of the Acronym
ACC	American College of Cardiology
ACEi	Angiotensin Converting Enzyme inhibitor
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
ARNi	Angiotensin Receptor Neprilysin inhibitor
BB	Beta-adrenergic Receptor Blocker
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CHF	Chronic Heart Failure
CHFS	Canadian Heart Failure Society
CKD	Chronic Kidney Disease
COI	Conflict of Interest
CPG	Clinical Practice Guideline
CV	Cardiovascular
DOH	Department of Health
DM	Diabetes Mellitus
DMT	Disease Management Team
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
HF	Heart Failure
HF CPG	Heart Failure Clinical Practice Guideline
HF MDT	Heart Failure Multidisciplinary Team

HFrEF	Heart Failure with reduced Ejection Fraction
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HHF	Hospitalization for Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
JCS	Japanese Circulation Society
JHFS	Japanese Heart Failure Society
JVP	Jugular Venous Pressure
KCCQ	Kansas City Cardiomyopathy Questionnaire
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	Mineralocorticoid Receptor Antagonist
NICE	National Institute of Health and Care Excellence
NIH-ICE	National Institutes of Health - Institute of Clinical Epidemiology
NPV	Negative Predictive Value
NT-pro BNP	N-terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
PICO	Population Intervention/exposure Comparison Outcome
PND	Paroxysmal Nocturnal Dyspnea
POCT	Point-of-Care Testing
POCUS	Point-of-care Ultrasonography
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
QoL	Quality of Life
SGLT2i	Sodium-Glucose Co-transporter-2 inhibitor
12 L ECG	12-Lead Electrocardiogram

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Executive Summary

This Philippine Clinical Practice Guidelines on the Diagnosis and Management of Chronic Heart Failure with reduced ejection fraction for Primary Care Physicians is an output of the joint undertaking of the Philippine Clinical Practice Guideline Task Force on Heart Failure, the Department of Health, and the National Institutes of Health-Institute of Clinical Epidemiology.

The task force acknowledges that heart failure is not merely a single clinical entity but rather a clinical spectrum featuring cardinal signs and symptoms (eg. breathlessness, ankle edema, easy fatigability, elevated jugular venous pressure, pulmonary rales, and peripheral edema) accompanied by objective evidence of cardiac dysfunction (structural and/or functional abnormalities of the heart). A variety of definitions and classifications has been proposed in recent international consensus guidelines.^{1,2} For purposes of this CPG, the definition of chronic heart failure offered in the 2021 ESC Heart Failure guidelines which identifies patients with an established diagnosis of heart failure or those who have a more gradual onset of symptoms will be adopted.¹ Clinical scenarios that are characterized by signs and symptoms severe enough to warrant urgent medical attention such as hospital admission, intravenous diuretic therapy or an emergency department visit will not be covered by this CPG, as these may pertain more to acute, decompensated or worsening heart failure.¹ Heart failure has also been subcategorized into specific “phenotypes” based on the left ventricular ejection fraction (EF), traditionally measured using echocardiography – 1) HF with reduced EF (EF \leq 40%) or HFrEF, 2) HF with mildly reduced EF (EF = 41 – 49%), or HFmrEF, and 3) HF with preserved EF (EF \geq 50%) or HFpEF.

These clinical practice guidelines cover the diagnosis (symptoms, signs, and diagnostic tests) and management (both pharmacologic and nonpharmacologic) of Filipino adults suspected of or diagnosed with chronic heart failure with reduced ejection fraction (HFrEF). The CPG is intended to be used by primary care physicians, general practitioners, family medicine specialists, internists, and cardiologists. The guideline development process followed the widely accepted GRADE approach—Grading of Recommendations, Assessment, Development, and Evaluation—including GRADE Adolopment³, a systematic process of adapting evidence summaries, and the GRADE Evidence to Decision (EtD) framework. It included identification of critical questions and critical outcomes; retrieval of current evidence; assessment and synthesis of the evidence base for these critical questions; formulation of draft recommendations; convening of a multi-sectoral stakeholder panel to discuss values and preferences and assess the strength of the recommendations; and planning for dissemination, implementation, impact evaluation, and updating.

The CPG provides 20 recommendations on prioritized questions in the diagnosis and management of adults with chronic heart failure with reduced ejection fraction. These were based on the appraisal of the best available evidence on each of the 14 identified clinical questions. (Table 1), with each recommendation being supported with comments on certainty of evidence and strength of recommendation by the panel. A recommendation with a high certainty of evidence logically may merit a strong recommendation, but there are instances wherein the panel recommendation is strong despite lack of certainty of evidence, if the said recommendation is deemed to be crucial and practice-changing. The certainty of evidence indicates the volume, robustness and quality of existing literature, with meta-analyses and randomized controlled trials adding significantly more weight to recommendations. The strength of recommendation captures the overall sentiments of the consensus panel, incorporating not just the certainty on evidence but real-world feasibility and applicability. In essence, a strong recommendation is considered prescriptive and is hoped to translate to its application, while a weak recommendation is merely suggestive, as the evidence in support of such a recommendation was deemed to be unconvincing or impractical.

The impact of the local HF guidelines will definitely be far-reaching, especially in the setting of universal healthcare. Heart failure is already widely-considered as a disease that cuts across a large spectrum of specialties and fields of practice, and is not limited to the domain of the specialist. As such, the roll-out of key recommendations from these guidelines is expected to further harmonize processes, not to necessarily limit the scope of clinical practice of healthcare professionals, but rather to elevate and maintain a certain standard of care.

The recommendations in this CPG shall hold for at least three (3) years. If new and compelling evidence arises that will have an impact on relevance and application, the task force may opt to reconvene and update the said guidelines.

¹ McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Rev Esp Cardiol (Engl Ed) 2022;75(6):523. doi: 10.1016/j.rec.2022.05.005. PMID: 35636830.

² Heidenreich PA, Bozkurt B, Aguilar D, et al. 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(18):e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. PMID: 35363499.

³ Schunemann H, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa R, Manja V. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-10.

Table 1. Summary of Recommendations

Recommendation	Certainty of Evidence	Strength of Panel Recommendation
Question 1. Among adult Filipinos presenting with dyspnea at the outpatient clinic, how accurate are other symptoms (easy fatigability, orthopnea, paroxysmal nocturnal dyspnea) and signs (elevated jugular venous pressure, rales, and peripheral edema) in the diagnosis of chronic heart failure?		
1A. Among adult Filipinos presenting with dyspnea at the outpatient clinic, we recommend a careful history to include paroxysmal nocturnal dyspnea for the diagnosis of chronic heart failure.	Low	Strong
1B. Among adult Filipinos presenting with dyspnea at the outpatient clinic, we recommend a careful physical examination to include the measurement of the jugular venous pressure for the diagnosis of chronic heart failure.	Low	Strong
Question 2. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the chest X-ray for the diagnosis of heart failure?		
2A. Among adult Filipinos presenting with dyspnea, PND, and elevated JVP at the outpatient clinic, we recommend using the presence of cardiomegaly and/or pulmonary congestion on chest X-ray as a basis for the diagnosis of chronic heart failure.	Low	Strong
2B. Among adult Filipinos presenting with dyspnea, PND, and elevated JVP at the outpatient clinic, we suggest using the presence of pulmonary congestion on chest X-ray as a basis for the diagnosis of chronic heart failure.	Low	Weak
Question 3. Among adult Filipinos presenting with signs and symptoms of heart failure at the outpatient clinic, how accurate is the 12-lead electrocardiogram for the diagnosis of heart failure?		
3A. Among adult Filipinos presenting with dyspnea, PND, and elevated JVP at the outpatient clinic, we do not recommend relying solely on a 12-lead ECG for the diagnosis of chronic heart failure.	Very Low	Strong
Good Practice Statement: Among adult Filipinos with suspected chronic heart failure at the outpatient clinic, we suggest the use of 12-lead electrocardiogram to determine abnormalities in cardiac structure, function and rhythm to guide management.		

Question 4. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the 2D-echocardiogram for the diagnosis of heart failure?

4. Among adult Filipinos presenting with dyspnea, PND, and elevated JVP at the outpatient clinic, we recommend the use of 2D-echocardiogram with Doppler studies for the diagnosis of heart failure.

Low

Strong

Question 5. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate are cardiac biomarkers (BNP,NT-proBNP) for the diagnosis of heart failure?

5. Among adult Filipinos presenting with unexplained dyspnea at the outpatient clinic, we suggest using point-of-care BNP or NT-proBNP testing, if available, to diagnose or rule out chronic heart failure.

Low

Weak

Question 6. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, what is the effect of baseline determination of serum electrolytes and creatinine on the incidence of cardiovascular mortality, heart failure-related hospitalization, and on quality of life?

6. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, we recommend determining the baseline value of serum sodium, potassium, and creatinine to guide management.

Very Low

Strong

Question 7. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, what is the effect of nonpharmacologic interventions (dietary sodium and fluid restriction, exercise prescription) on the incidence of cardiovascular mortality, heart failure-related hospitalization, and on quality of life?

7A. Among adult Filipinos diagnosed with stable, compensated chronic heart failure at the outpatient clinic, we suggest against routine strict dietary sodium restriction.

Low

Weak

7B. Among adult Filipinos diagnosed with stable, compensated chronic heart failure at the outpatient clinic, we suggest to restrict fluid intake.

Low

Weak

7C. Among adult Filipinos diagnosed with stable compensated chronic heart failure at the outpatient clinic, we suggest supervised exercise training program, and if available, referral to a cardiac rehabilitation facility.

Low

Weak

Question 8. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of diuretics on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

8. Among adult Filipino patients with chronic heart failure with pulmonary congestion at the outpatient clinic, we recommend the judicious use of loop diuretics to relieve congestion.	Low	Strong
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Question 9. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of beta-blockers on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

9. Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we recommend the use of beta-blockers (metoprolol succinate, carvedilol, bisoprolol or nebivolol).	High	Strong
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Question 10. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of renin-angiotensin-aldosterone-blockers (ACEi/ARB or ARNis) on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

10A. Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we recommend the use of RAAS Blockers (ACE-Is or ARBs or ARNis).	Moderate	Strong
10B. Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we suggest the use of ARNis over ACE-Is or ARBs.	Low	Weak

Question 11. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of mineralocorticoid receptor antagonists on the incidence of cardiovascular mortality, heart failure-related hospitalization, and on quality of life?

11. Among patients with chronic HFrEF, with estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m ² , and serum potassium < 5 mEq/L at the outpatient clinic, we recommend the use of a MRA (spironolactone or eplerenone) on top of standard of care.	Low	Strong
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Question 12. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of Sodium-Glucose co-transporter 2 (SGLT2) inhibitors on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

12. Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we recommend treatment with SGLT2 inhibitors.	High	Strong
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Question 13. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of a timely referral to a cardiovascular specialist on the incidence of cardiovascular mortality, heart failure-related hospitalization, and on quality of life?

13. Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we suggest referral of patients with high risk features* and recurrent hospitalizations** to higher levels of care***.	Low	Weak
*High Risk Features: older age, lower BMI, lower SBP, NYHA Class III or IV, presence of pulmonary or peripheral congestion, third heart sound, aortic stenosis, atrial fibrillation, peripheral vascular disease, renal dysfunction, absence of ICD implantation		
**Recurrent Hospitalizations: The suggested definition is ≥ 2 hospitalizations in the past year.		

***"Higher levels of care" refers to secondary and tertiary care.

Question 14. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of palliative care on quality of life and on the incidence of worsening heart failure, heart failure-related hospitalization, and cardiovascular mortality?

14. Among adult Filipinos diagnosed with chronic HFrEF, NYHA class III or IV, at the outpatient clinic, we suggest early integration of palliative care for holistic management.	Low	Weak
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Heart Failure Cascade Algorithm

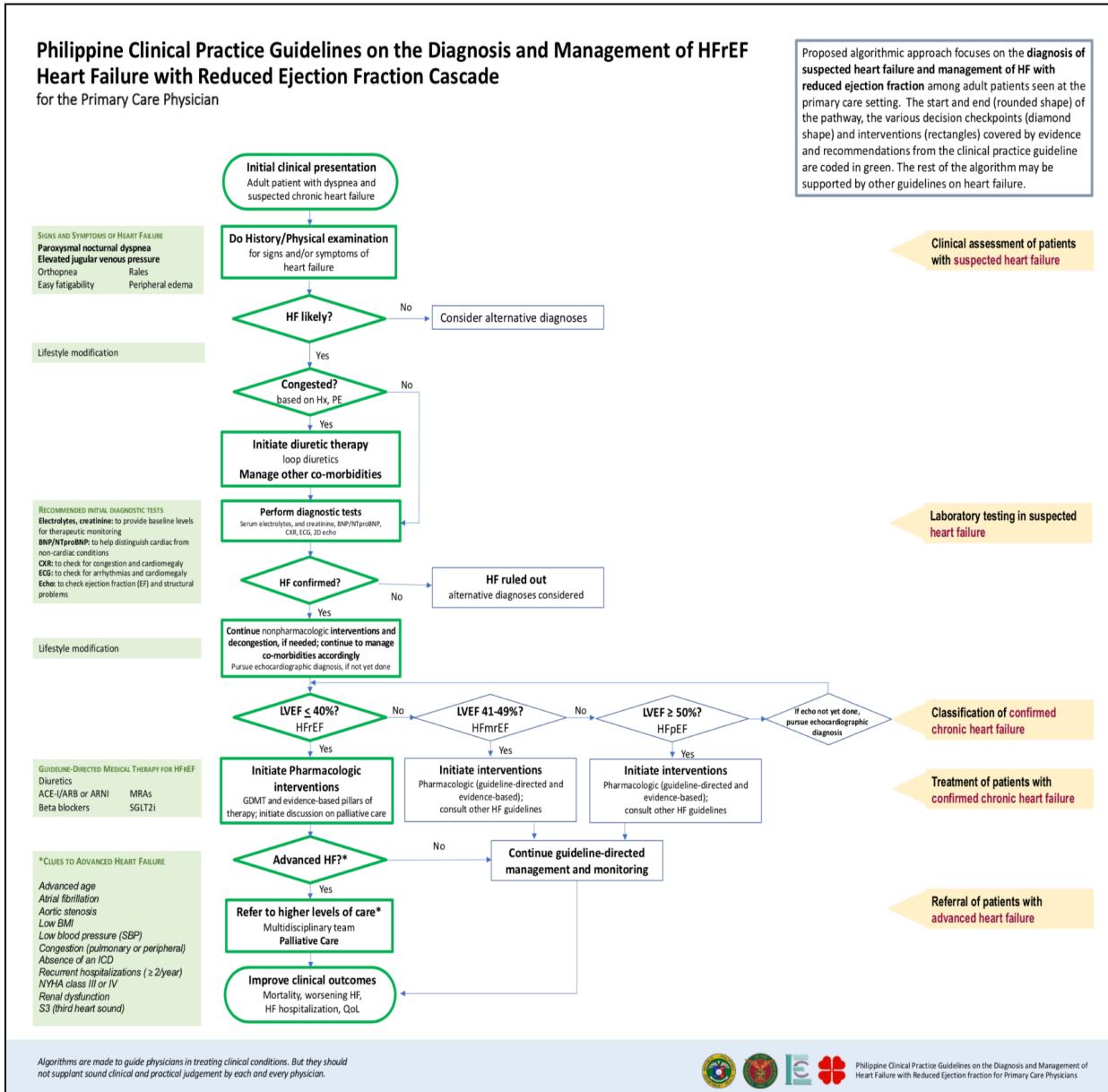


Figure 1. Heart Failure Cascade Algorithm

Heart failure is a complex condition that requires careful management. This algorithm aims to help primary care physicians in managing patients with suspected or confirmed heart failure. It includes steps for the initial clinical assessment, diagnosis, pharmacologic and nonpharmacologic treatment options as well as practice patterns.

The first step or decision checkpoint in the algorithm is to initially assess the clinical likelihood of heart failure in patients presenting with dyspnea based on signs and symptoms suggestive of the condition (Clinical Question 1). If there is paucity of clinical parameters suggestive of heart failure, alternative diagnoses may be pursued. If, however, the history and physical examination suggest heart failure, the next key decision checkpoint is determination of the presence of pulmonary and/or systemic congestion (suggested particularly by paroxysmal nocturnal dyspnea and elevated jugular venous pressure). In such a situation, the clinician is advised to consider diuretic therapy (loop diuretics) and manage any identified co-morbidities, as such interventions need not be unnecessarily delayed in the absence of confirmatory laboratory tests. After the issue of congestion is settled, selected laboratory tests (Clinical Questions 2 to 6) can be requested to support or confirm the diagnosis (natriuretic peptides, chest X-ray, electrocardiogram, echocardiogram) and provide baseline data for therapeutic guidance (serum electrolytes, creatinine). Confirmation of the diagnosis through laboratory testing represents the third decision checkpoint. The selection and prioritization of tests will rest not only on accuracy but also accessibility, affordability, and added information. Certain laboratory tests may provide incremental information beyond diagnosis, such as the capacity to classify, stage, or prognosticate the disease. Notice as well that the algorithm emphasizes the value of echocardiography (whether at the outset or later in the cascade) not just to help confirm the diagnosis of heart failure, but to determine its possible etiologies and classify its severity based on left ventricular ejection fraction. Since this clinical practice guideline puts the spotlight on heart failure with reduced ejection fraction (HFrEF), EF determination (another key decision checkpoint) will greatly aid the clinician in choosing the most appropriate and evidence-based pharmacologic therapies.

Treatment of patients with heart failure includes nonpharmacologic strategies (Clinical Question 7) such as lifestyle modifications (fluid and sodium restrictions) as well as pharmacologic interventions (Clinical questions 8-12) or medications (ARNi/ACE inhibitor/ARB, beta blocker, MRA, SGLT2i). Notice that the recommendation for lifestyle modification is made early on in the algorithm, even ahead of any laboratory tests. This is to emphasize the value of nonpharmacologic interventions not just for heart failure but for many other medical conditions that may accompany it, such as hypertension, diabetes, obesity and dyslipidemia. For patients confirmed to have HFrEF, guideline-directed medical therapies, particularly the evidence-based pillars of treatment, are recommended, as well as early discussion of palliative care. Meanwhile, those with either HFmrEF or HFpEF may still benefit from such therapies, as certain

other heart failure guidelines have pointed out, but the available evidence may not be as robust as that for HFrEF. The final part of the cascade deals with clinical practice patterns (Clinical questions 13-14). The last decision checkpoint is determination of advanced heart failure (e.g. those with recurrent hospitalizations, those refractory to certain treatments, and those requiring devices) and the need for referral to higher levels of care (e.g. Level 2 or Level 3 hospitals equipped to deliver cardiovascular care) as well as palliative care.

This proposed algorithmic approach to the detection, timely diagnosis, and management of heart failure is intended to serve as a blueprint for clinicians caring for patients with suspected or confirmed heart failure. By emphasizing the value of critical thinking backed by science and real-world experience, this algorithm assists the clinician in evidence-based decision-making to afford the best possible clinical care to patients with heart failure. Moreover, such an algorithm helps assure the delivery of high-quality care in a structured manner while allowing the clinician enough elbow room to tailor-fit the strategy according to the clinical scenario. Finally, this process strikes a good balance between prudence and persistence -- the prudence to know when testing is unnecessary or even harmful, and the persistence to forge ahead with investigation to ensure timely diagnosis and treatment. Such is the spirit captured in this heart failure cascade.

Introduction

Background

Based on the latest data from the Philippine Statistics Authority, diseases of the heart currently account for 17.3% of the total deaths in the country, and the numbers are increasing. Among cardiovascular diseases, heart failure has a profound impact on both individual and community health. Despite a seemingly low estimated prevalence of 1.26 to 6.7%, not only is it a common cause of hospitalization, it also has a high in-hospital mortality rate of 3 to 6.7%, a 1-year mortality rate of 3.6 to 17.1% and a 1-year heart failure-related readmission rate of 9.8 to 25.7%, according to both Asian and Western studies.¹ Patients with heart failure may also experience poor quality of life as the signs and symptoms of the disease may restrict their day-to-day activities. Moreover, the estimated total economic burden of heart failure hospitalization in the Philippines was reported to be around PhP 0.85 to 1.84 billion.²

In 2021, key medical societies arrived at a consensus regarding the universal definition of heart failure. Heart failure was defined as "a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion." In the same document, stages of heart failure were discussed: At risk for HF (Stage A), Pre-HF (Stage B), Symptomatic HF (Stage C) and Advanced HF (Stage D). A revised classification for heart failure according to left ventricular ejection fraction was also proposed: HF with reduced ejection fraction (HF_rEF) for symptomatic HF with LVEF ≤40%; HF with mildly reduced ejection fraction (HF_mrEF) for symptomatic HF with LVEF 41-49%; HF with preserved ejection fraction (HF_pEF) for symptomatic HF with LVEF ≥50%; and HF with improved ejection fraction (HF_imEF) for symptomatic HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF after treatment, and a second measurement of LVEF > 40%. Regardless of improvement in ejection fraction, it is recommended by existing guidelines to continue guideline-directed medical therapies for patients with improved ejection fraction.^{3,4,5}

Heart failure remains a major cause of morbidity and mortality worldwide despite optimal medical management and significant advances in preventive and therapeutic strategies. People living with this condition experience bothersome symptoms that result in the restriction of daily activities, loss of productivity, an escalating cost of treatment, and poor quality of life. The real-world impact goes beyond the individual as access to quality healthcare may be compromised especially in resource-limited settings. Moreover, the clinical profile of patients with heart failure as well as the prevailing circumstances that influence clinical practice vary across regions and populations. A locally developed clinical practice guideline therefore becomes increasingly relevant to aid the Filipino clinician in the effective and timely diagnosis and management of patients with heart failure.

Objectives

The objective of this clinical practice guideline is to provide evidence-based recommendations for the diagnosis and management of adult Filipino patients with chronic heart failure at the outpatient clinic, with focus on HFrEF, using appropriate scientific information while considering the economic implications of diagnostic tests and non-pharmacologic and pharmacologic treatment.

Specifically, the guideline task force addressed clinical questions that pertain to the following aspects of the diagnosis and management of adult Filipino patients with chronic heart failure:

- a. Identifying signs and symptoms that are highly suggestive of chronic heart failure in adult Filipinos seen at the outpatient clinic;
- b. Recommending the appropriate laboratory tests that will help establish the diagnosis of chronic HF and guide the management of chronic heart failure with reduced ejection fraction (HFrEF);
- c. Justifying the nonpharmacologic and pharmacologic interventions as well as practice patterns that will ensure the delivery of high-quality care to patients with chronic heart failure

Scope and Purpose

The task force on the "Philippine Clinical Practice Guidelines on the Diagnosis and Management of Chronic Heart failure with reduced Ejection Fraction for Primary Care Physicians" considers this landmark effort as the very first attempt to capture key practice recommendations on heart failure at the outpatient clinic in a single guide document. The guideline also takes into consideration existing international recommendations on diagnosis and treatment but more importantly appraises and applies such information using the lens of a Filipino healthcare provider.

Target Population

The guideline focuses on adult patients (≥ 18 years or age) and with chronic heart failure seen at the primary health care setting. Although the first few clinical questions in this practice guideline approach heart failure from a general perspective, succeeding questions on treatment zero in on patients with established heart failure, particularly those with reduced ejection fraction, as the task force is cognizant of the more robust scientific evidence for therapies directed towards this classification of heart failure.

Intended Users

The expected main end-users of this Clinical Practice Guidelines are Filipino healthcare professionals who diagnose and manage Filipino adults with chronic heart failure. This guideline will make an impact on the implementation of Universal Health Care. The main intended users of this guideline are the primary care physicians, general practitioners, family medicine physicians and the internists who will serve as frontliners in the care of the Filipino patients.

Specialists (e.g cardiologists, nephrologists, endocrinologists) and healthcare workers in the allied professions (e.g. nurses, physical therapists) who are involved in the care of patients with chronic heart failure may also benefit from the recommendations stated in this practice guideline. Finally, administrators, policy-makers and other non-medical stakeholders (PhilHealth, HMOs, etc.) may use this document as reference for the development of their respective administrative agenda or reimbursement policies, as the document captures local information and insight regarding burden of disease and socioeconomic impact of various testing modalities and treatment options.

Key Clinical Issues and Questions

The clinical issues tackled by this CPG include:

Question 1. Among adult Filipinos presenting with dyspnea at the outpatient clinic, how accurate are other symptoms (easy fatigability, orthopnea, paroxysmal nocturnal dyspnea) and signs (elevated jugular venous pressure, rales, and peripheral edema) in the diagnosis of chronic heart failure?

Table 2. PICO table for Clinical Question 1

Population	Adult Filipinos with dyspnea at the outpatient clinic
Exposure	Easy fatigability, orthopnea, paroxysmal nocturnal dyspnea, elevated jugular venous pressure, rales, and peripheral edema
Comparison	None
Outcomes	Sensitivity, specificity, diagnostic accuracy, PPV, NPV, Likelihood ratio

Question 2. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the chest X-ray for the diagnosis of heart failure?

Table 3. PICO table for Clinical Question 2

Population	Adult Filipinos with signs and symptoms of chronic heart failure at the outpatient clinic
Intervention/ Exposure	Chest X-ray
Comparison	None
Outcomes	Sensitivity, specificity, diagnostic accuracy, PPV, NPV, Likelihood ratio

Question 3. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the 12-lead electrocardiogram for the diagnosis of chronic heart failure?

Table 4. PICO table for Clinical Question 3

Population	Adult Filipinos with signs and symptoms of chronic heart failure at the outpatient clinic
Intervention/ Exposure	12-lead electrocardiogram
Comparison	None
Outcomes	Sensitivity, specificity, diagnostic accuracy, PPV, NPV, Likelihood ratio

Question 4. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the 2D-echocardiogram for the diagnosis of chronic heart failure?

Table 5. PICO table for Clinical Question 4

Population	Adult Filipinos with signs and symptoms of chronic heart failure at the outpatient clinic
Intervention/ Exposure	Echocardiogram
Comparison	None
Outcomes	Sensitivity, specificity, diagnostic accuracy, PPV, NPV, Likelihood ratio

Question 5. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate are cardiac biomarkers (BNP, NT-proBNP) for the diagnosis of heart failure?

Table 6. PICO table for Clinical Question 5

Population	Adult Filipinos with signs and symptoms of chronic heart failure at the outpatient clinic
Intervention/ Exposure	NT-pro BNP, BNP
Comparison	None
Outcomes	Sensitivity, specificity, diagnostic accuracy, positive predictive value, negative predictive value

Question 6. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, what is the effect of baseline determination of serum electrolytes and creatinine on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 7. PICO table for Clinical Question 6

Population	Adult Filipinos with chronic heart failure at the outpatient clinic
Intervention/ Exposure	Serum electrolytes (sodium, potassium) and creatinine/estimated glomerular filtration rate
Comparison	None
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalization, Quality of life

Question 7. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, what is the effect of non-pharmacologic interventions (dietary sodium and fluid restriction, exercise prescription) on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 8. PICO table for Clinical Question 7

Population	Adult Filipinos with chronic heart failure at the outpatient clinic
Intervention/Treatment	Non-pharmacologic interventions (dietary sodium and fluid restriction, exercise prescription)

Comparison	None
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalization, Quality of life

Question 8. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of diuretics on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 9. PICO table for Clinical Question 8

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/Treatment	Diuretics
Comparison	Placebo, Standard of Care
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalization, Quality of life

Question 9. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of beta-blockers on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 10. PICO table for Clinical Question 9

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/Treatment	Beta-blockers
Comparison	Placebo, Standard of Care
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalization, Quality of life

Question 10. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of renin-angiotensin-aldosterone blockers (ACEi/ARB or ARNis) on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 11. PICO table for Clinical Question 10

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/Treatment	RAAS Blockers (ACE-Is, ARBs, ARNIs)
Comparison	Placebo, Standard of Care
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalizations, Quality of life

Question 11. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of mineralocorticoid receptor antagonists on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 12. PICO table for Clinical Question 11

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/Treatment	MRAs
Comparison	Placebo, Standard of Care
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalization, Quality of life

Question 12. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of Sodium-glucose co-transporter 2 (SGLT2) inhibitors on the incidence of cardiovascular mortality and heart failure-related hospitalization, and on quality of life?

Table 13. PICO table for Clinical Question 12

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/Treatment	SGLT2-inhibitors
Comparison	Placebo, Standard of Care
Outcomes	Cardiovascular mortality, Heart Failure-related hospitalization, Quality of life

Question 13. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of a timely referral to a cardiovascular specialist on the incidence of cardiovascular mortality, worsening heart failure, and heart failure-related hospitalization, and on quality of life?

Table 14. PICO table for Clinical Question 13

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/ Treatment	Timely referral to a cardiovascular specialist
Comparison	No timely referral to a cardiovascular specialist
Outcomes	Cardiovascular mortality, worsening heart failure, heart failure-related hospitalization, and quality of life

Question 14. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of palliative care on quality of life and on the incidence of worsening heart failure, heart failure-related hospitalization, and cardiovascular mortality?

Table 15. PICO table for Clinical Question 14

Population	Adult Filipinos with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic
Intervention/ Treatment	Palliative care
Comparison	No palliative care
Outcomes	Quality of life, worsening heart failure, heart failure-related hospitalization, and cardiovascular mortality

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CPG Development Methodology

Guideline Preparation

This CPG was developed following the prescribed processes of the DOH for CPG development.¹ Following international standards, the DOH outlined the guideline development process into four phases: preparation and prioritization; CPG generation; CPG appraisal; and implementation in the Manual for CPG Development.¹

In the preparation and prioritization phase, the Steering Committee set the CPG objectives, scope, target audience, and clinical questions. The committee consulted different stakeholders in prioritizing and developing the guideline questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included.

The Steering Committee (SC) invited relevant professional organizations to nominate individuals who can become part of the consensus panel. Selected experts, by virtue of their training background and experience in critical appraisal and guideline development were also invited by the SC to serve as evidence review experts (EREs).

The Technical Working Group includes task force members tasked with the preparation and review of evidence, and drafting of the CPG manuscript — technical coordinators, EREs, technical writer. The evidence review experts were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the consensus panel members to finalize the recommendations.

The consensus panel was composed of representatives from multiple sectors tasked to review the evidence summaries and develop recommendations during the en banc meeting moderated by the technical facilitator. In the meeting, they prioritized critical and important outcomes; they also discussed the necessary considerations revolving around the recommendations and voted on each recommendation and its strength.

Composition of the CPG Task Force

The CPG Task force is composed of the 1) steering committee (SC), 2) technical working group (TWG), which includes the evidence review experts, technical coordinators, and technical facilitator, 3) consensus panel (CP), and 4) conflict of interest review committee (COI).

The steering committee (SC) is the main group that spearheaded the development of this CPG. The SC held several regular meetings to discuss organizational, budget, methodological and scientific content issues. It identified the individuals who were to be part of the other committees. They coordinated evidence summaries with the EREs, facilitated ERE and CP meetings, oversaw the writing, editing and finalization of the CPG, forwarded the final CPG manuscript for external review, and finally, submitted the CPG to the DOH for approval.

The Technical Working Group (TWG) is mainly concerned with the review, appraisal, consolidation and presentation of evidence. The Evidence Review Experts (EREs) were tasked with reviewing existing CPGs, creating evidence summaries, and drafting evidence-based recommendations. They developed the PICO questions in coordination with the Lead CPG developers. The Technical Coordinators (TCs) identified, reviewed, and summarized existing CPGs, and evaluated them for possible adaptation. They also coordinated the activities of the EREs, provided guidance to the EREs regarding evidence synthesis and recommendation formulation, and assisted in the writing and subsequent review of the manuscript. The TCs also coordinated with the technical facilitator in clarifying the clinical issues addressed by the research questions and prioritized for consensus panel discussion and decision-making. The Technical Facilitator (TF) was mainly tasked with presiding over the consensus panel meetings.

The Conflict of Interest (COI) review committee reviewed the possible conflicts of interest of everyone involved in the development of this guideline.

Prior to the creation of the guidelines, a formal meeting and consultation was conducted to determine the priority topics and questions to be included in the CPG. The technical coordinators and the SC leads presented the initial clinical questions, and the views of the consensus panel were sought before coming up with the initial clinical statements. A patient who has heart failure and a cardiac rehabilitation nurse were included in the meeting. The SC, TCs, EREs and the multisectoral consensus panel (CP) agreed on PICO questions to be submitted for approval by the National Practice Guideline committee. The panel also prioritized the critical and important outcome measures prior to finalizing the PICO questions, such that stakeholders' values and preferences were incorporated. Furthermore, the panel reviewed evidence summaries and draft recommendations, and voted as well on the recommendations of the CPG. Discussion

and consensus-building during the en banc consensus panel meetings were moderated and guided by a technical facilitator.

After identifying the members of all the committees, the steering committee convened the consensus panel (CP) and considered the possible conflicts of interest of each panel member. To ensure fairness and transparency, the selection process for the composition of the CP was guided by the DOH manual.¹ Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policy makers, patient advocates, allied medical practitioners, and physicians from different settings (e.g., public primary care, private practice, occupational health settings). The physicians were members of different medical societies, namely: Philippine College of Physicians, Philippine Heart Association, Philippine Medical Association, and Philippine Academy of Family Physicians. Although majority of the CPs were specialists, three of them represented the PCP (2) and PMA (1), five members for PHA, and two represented the PHC. Three family medicine practitioners represented the PAFP, two of whom were part of the Doctors to the Barrios (DTTB) program. A nurse and a heart failure patient were invited as voting members of the CP. The task force ensured that they were adequately guided prior to CP sessions so that any technical jargon or issues would be well-comprehended, and that relevant sentiments were appropriately voiced out during CP sessions. An open line between the patient and the task force, through its technical coordinators and technical facilitator, was maintained, and this greatly assisted the patient as well in appreciating the discussions that ensued. No clear distinction was made by the task force regarding patient groups, and the SC felt that the presence of an actual patient living with heart failure would suffice in representing the outpatient heart failure population.

A representative of the DOH was also invited to sit in the en banc meetings as an observer during the proceedings and would be asked to clarify if there are queries from the CP members regarding policies of the department. The DOH representative did not participate in the prioritization of questions and outcomes or in the formulation of and voting on recommendation statements.

Evidence Synthesis

A systematic search of electronic databases such as MEDLINE via PubMed, CENTRAL, and Google Scholar for relevant literature was performed. Guidelines on heart failure management were identified and underwent assessment using the AGREE II tool.² The following guidelines were selected based on the search terms of chronic heart failure guidelines and were approved by the steering committee. The following relevant guidelines were included:

- 2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure³
- 2021 ESC Guidelines on the Management of Acute and Chronic Heart failure⁴
- 2019 Malaysian CPG on Heart Failure⁵

- 2018 JCS/JHFS Guidelines on Heart Failure;⁶ 2021 Focused Update⁷
- 2018 Australian Guidelines on Heart Failure⁸
- 2018 NICE Guidelines on Heart Failure⁹
- 2017 Canadian Guidelines¹⁰

De novo systematic reviews and meta-analysis were done for each question as the guidelines were not able to answer the clinical questions developed by the SC. Databases such as MEDLINE via Pubmed, Google Scholar, and HERDIN were utilized to search the relevant literature. Meta-analysis and systematic review sites such as COCHRANE reviews and PROSPERO were used. Local databases were also reviewed for studies relevant to the clinical questions.

Keywords were based on PICO (population, intervention/exposure, comparison, outcomes), MeSH and free text, set for each question. The ERE contacted authors of related articles to verify details and identify other research studies for appraisal. The specific search terms used by the Evidence Reviewers to search for the relevant literature are found in each annex for the respective topics.

The studies included were prospective, cohort, cross-sectional, and systematic reviews for questions on diagnosis. For questions on therapy, meta-analyses, randomized controlled trials (RCTs), and network meta-analyses were included.

A data extraction tool used by Raftery et al (2015) was utilized by the evidence reviewers. The table includes the type of design, description of the clinical trial, type of RCT (superiority, inferiority, equivalence), results of the study, and other relevant information seen in the tool. Two experts filled out the extraction tool while a third reviewer was called to resolve discrepancies. Similarly, the data extraction tool was also used for clinical practice guidelines.

Health economic outcome research (HEOR) and cost-effectiveness studies, both international and local, were included in the search to answer the cost portion of the evidence-to-decision framework. If there were no studies on cost-effectiveness, the evidence reviewer checked for the cost of the diagnostic test in hospitals or diagnostic centers, and the cost of the drug in the national formulary or in drugstores. Studies on health equity and patient preferences and values were also included in the search terms to answer the EtD table.

Study Quality Assessment

Appraisal tools for clinical studies using the Newcastle Ottawa Scale¹¹ or QUADAS¹² were utilized by the EREs in developing de novo assessments. Systematic reviews and meta-analyses using the Cochrane approach were used. Relevant local databases and websites of medical societies were also utilized in the search.

Data Synthesis

Evidence reviewers appraised the directness, methodological validity, results, and applicability of each relevant clinical study or guidelines included. RevMan, STATA, and GRADE Pro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE-generated evidence created summaries for each of the fourteen questions. Each evidence summary included evidence on the burden of the problem as well as on diagnostic performance, benefits, harm, and the social and economic impact of the screening test/intervention. Evidence/information that will facilitate decision-making (i.e., cost of screening test, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The important step in the creation of this clinical practice guideline (CPG) was determining the strengths of the recommendations. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used in assessing the recommendations. (Table 16)

Table 16. Basis for Assessing the Quality of the Evidence using GRADE Approach

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Factors that lower quality of the evidence are:

- Risk of bias
- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

The SC, EREs and CP identified the outcomes that were used in deciding the recommendations for the clinical questions as critical, important, or of low importance; only critical and important outcomes were selected.¹ After identification, the CP validated and voted on the rating of the outcomes. All the panelists, including the patient advocate and the cardiac rehabilitation nurse, prioritized and rated the clinical outcomes that were either critical or important (Table 17).

Table 17. Cardiovascular Outcomes GRADE Score

OUTCOME	SCORE PRIORITY	RANK
Cardiovascular Mortality	9	Critical
All-cause Mortality	9	Critical
Worsening Heart Failure	9	Critical
Heart Failure hospitalization	8	Critical
Symptom reduction	8	Critical
Quality of Life	8	Critical
Hypotension	8	Critical
Arrhythmia	8	Critical
Deteriorating Renal Function	7	Important

Formulating Recommendations

The evidence was assessed by the reviewers using the GRADE approach. This approach allows reviewers to make clinical recommendations, coverage decisions, and public health recommendations. The framework was built to assess the strength of recommendations.¹³ The recommendations were based on the quality of evidence, trade-off between the benefits and harm of the test or drug, cost-effectiveness, applicability, availability, feasibility, equity, resources and uncertainty. Factors that lowered the quality of evidence, such as publication bias, inconsistency of results and reporting bias, were considered. An Evidence to Decision (EtD) framework was used to process the gathered evidence and come up with decisions and recommendations.

The criteria used in the EtD framework that was followed by this guideline include priority of the problem, test accuracy, benefits and harms, certainty of evidence, outcome importance, balance, resource use, equity, acceptability, and feasibility. These were used by the evidence reviewers to determine the strength of recommendation and by the consensus panel in weighing the evidence and the possibility of recommending it.

The strength of each recommendation (i.e. strong or weak) was determined by the panel by considering all the factors mentioned above. Strong recommendation means that the panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects” while weak recommendation means that the “desirable effects of adherence to a recommendation probably outweigh the undesirable effect” but the panel cannot say so with confidence. A weak recommendation means that the physician may either follow the recommendation or use another option of diagnostic test or treatment management.

The recommendation for each question and strength of each recommendation were determined through voting. A consensus decision was reached if 75% of all CP members agreed. In case that consensus was not reached in the first voting, questions and discussion were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based recommendations were based on input arrived at by consensus in the en banc discussions. The recommendations presented by the evidence-based reviewers were moved forward and revised depending on the decision of the consensus panel during voting. If the decision was not reached even after three rounds of voting, a modified Delphi approach was conducted to be spearheaded by the lead of the steering committee.

There were recommendations that have been graded LOW based on the evidence presented by the reviewer; however, during the en banc meeting, the consensus panelists felt that these recommendations needed to be upgraded to a STRONG

recommendation, based on factors such as feasibility, equity, and applicability in the local setting. Thus, the CPG included recommendations that have low level of evidence but with a strong recommendation.

In cases where direct evidence was lacking and the consensus panel deemed it necessary that a statement be articulated regarding the intervention in question, a good practice statement was included. A good practice statement implies that there is general agreement that the intervention will do more good than harm.

Guideline Dissemination

Plan for Dissemination and Implementation

The SC discussed with relevant stakeholders such as the DOH and medical societies the preparation of a dissemination plan to actively promote the adoption of this guideline with strategies for copyrights.

The dissemination and implementation plan of this CPG includes the following:

- 1) writing of an Executive Summary that will be submitted for publication in a reputable local peer-reviewed medical and cardiology journals. The summary will include a quick reference guide of all the recommendations and the algorithm to be used by primary care physicians, cardiologists and heart failure specialists, and allied medical professionals who are taking care of heart failure patients.
- 2) pilot-testing of the recommended guideline-based pathway of care in identified outpatient clinics in select key cities after the publication of the executive summary. Educational webinars on the HF CPG for primary care physicians will be held. A pre-test/post-test evaluation will be conducted after the medical education. The pilot-testing will run for six months, and a survey will be conducted to measure success of the implementation. A focus group discussion will also be conducted among the primary care physicians to assess their improvement in the management of heart failure. Then, with the approval and endorsement of the DOH, the guidelines will be implemented nationwide.
- 3) Stakeholder medical societies (PHA, PCP, PAFP, PMA, NHFN) will be asked to participate in the dissemination of the guidelines during their annual scientific meetings and in their websites. Once the article is published, the CPG will be presented during scientific conventions and be made available on the websites of the DOH, PHC, different medical societies and organizations. Other avenues of dissemination will include press conferences, social media sites, and professional society conventions.
- 4) Electronic clinical decision support tools will be designed and developed to assist primary care physicians in the implementation of the guideline recommendations.

- 5) Rapid assessment method of evaluating adherence to guideline recommendations may be done after one year of dissemination efforts in selected and representative outpatient practice groups by reviewing outpatient records.

The following criteria will be included to assess the success of implementation of the CPG for HFrEF. These were adapted from the guideline checklist developed by National Health Guidelines of Australia¹⁴. This checklist includes the ff: 1) systems are in place to support comprehensive care for heart failure patients, 2) awareness and distribution of the guidelines among the healthcare professionals, 3) clinical education on the guidelines, and 4) clinical care is aligned with the guidelines.

Applicability of the Guidelines

Facilitators and Barriers

Prior to the start of guideline development, the steering committee members discussed possible facilitators and barriers to the diagnosis and management of heart failure in the process of deciding on the coverage of the contemplated clinical practice guideline. EREs and CP members were also engaged in such discussion during the organizational meeting of the HF Task Force.

These guidelines address the needs of primary care physicians who are first to see patients suffering from heart failure in the outpatient setting. Successful implementation of the guidelines include active dissemination of the knowledge on heart failure management and measuring its impact to clinical practice among all stakeholders. Specialty societies, such as the Philippine Heart Association, and cardiology training institutions will be tapped to educate and train primary care physicians. The task force proposes that heart failure medications recommended in these guidelines be approved for inclusion in the national formulary to improve utilization of the guidelines. However, there may be barriers in the management of heart failure. There is limited availability of specialty centers and support centers for heart failure, such as heart failure clinics and cardiac rehabilitation centers. This CPG recommends that care for patients with HFrEF be coordinated with cardiologists in their hospitals. There may also be a need for heart failure clinics in the country handled by heart failure specialists who will manage difficult to treat heart failure patients.

Guideline Monitoring and Evaluation

The National Institute of Health, in cooperation with the steering committee and the task force, will create guidelines on monitoring of the guidelines, from publication, dissemination, and application in clinical practice. The task force hopes that such guideline recommendations will be properly cascaded to intended users through close collaboration between the national government, key professional societies, and local health administrators. Strategies may be developed to determine real-world use of such guidelines, such as quality of care studies and validation of implementations studies, looking into adherence to key recommendations and impact of their application, whether through scorecard metrics or coordinated research, such as rapid assessment or quality of care studies. Such evaluations may be planned based on pre-specified intervals, depending on the current need of the health industry.

External Review

The Steering Committee invited 3 external reviewers to comprise the Task Force Guideline External Review Panel. The external reviewer panel was composed of an endocrinologist/clinical epidemiologist, a clinical cardiologist, and a clinical epidemiologist/health economist, who reviewed the initial manuscript of the guidelines. All three external reviewers used 2 tools – 1) the AGREE-II checklist, to evaluate the methodological aspects of CPG development, including its reporting, and 2) the AGREE-REX checklist, to assess the technical aspects and implementability of the CPG recommendations.¹⁵ The SC held a meeting after receiving the external reviews and recommendations which were reviewed and considered in the revision of the final draft of the manuscript before submission to the central committee. Below is a summary of the reports of each of the three external reviewers:

Reviewer 1

- The consensus panel should include more general practitioners or doctors from the rural health clinics to have a more balanced point-of-view in terms of applicability and feasibility of the guidelines.
- Consultation or surveys done with patient groups, instead of just including one patient in the consensus panel, should have been done prior to the creation of the guidelines.

Reviewer 2

- Claims on the absence of economic evaluation studies - e.g., cost analysis, cost-effectiveness (CEA), cost-utility analysis (CUA), and studies on values and

preferences in the local setting: This is most probably true. However, this would have been better if validation was expressed through explicit statements regarding the literature search which did not yield any of such studies.

- Use of charges from different providers (government and private hospitals) for diagnostic services, etc. to represent their costs (e.g., cost of chest x-ray). Please note that cost is not the same as charges. Charges may underestimate or overestimate the real cost. For example, a government hospital may charge PHP 100-200/day for ward accommodation. This is obviously, an underestimation of the real cost considering that it must provide at least three (3) full meals a day, nursing care, and other provisions such as electricity and water. Conversely, an overestimation of the true cost can be seen in a private hospital which has higher charges for its services in consideration of profit for its operation.
- Perspective of the analysis: The importance of the perspective undertaken in an economic evaluation cannot be overemphasized. These include taking the societal (the broadest), healthcare provider or payer, or the patient's perspective. Since the CPG is undertaken in the background of universal health care, the healthcare provider or payer perspective (government) should be the approach undertaken. Using the chest x-ray example above, if the government is to provide chest x-ray for free for every Filipino, determination of the real cost of a single chest x-ray will take into consideration the cost of the x-ray machine, the materials needed to produce the chest x-ray, fees for the personnel who are going to operate it inclusive of reader's fees, and maintenance cost, vis-à-vis the number of chest x-rays it can produce for the lifespan of the machine. Unfortunately, this type of study may not be available at present. In the realm of the current healthcare delivery system where most of healthcare is obtained through out-of-pocket spending, "charges" could be used as "cost" using the patient's perspective. Hopefully, as universal health care goes into full implementation the ideal analysis, i.e., the "true cost" will be determined and used.
- Issue of "hidden cost": The tasks of an economic evaluation study consist of the following: identification, measurement, and valuation of resources, and comparison of the options being considered in terms of costs and effectiveness. The perspective of the study plays a big role in the first three tasks. For example, if one gets hospitalized for heart failure, productivity or production losses (loss of income when one gets sick) is one of the resources that is included in the hospitalization cost if the study used either the societal or patient's perspective (but valuation may differ). However, if the healthcare provider's perspective (government as the payer) is utilized, the cost of productivity losses is excluded.

This is seen in the study on the hospitalization costs for congestive heart failure in the Philippines. The study used both the societal and healthcare provider's perspectives. There is no "hidden cost for work interruption for both the patient and the caregiver" since the non-healthcare costs which include production losses were included in the analysis using the societal perspective.

- ICERs, cost-effectiveness, and cost-effectiveness threshold, etc.: The results of CEAAs and CUAs are expressed through incremental cost-effectiveness ratios (ICERs). These ICERs are then compared to a threshold ICER specific to a particular setting or country to determine cost-effectiveness. An intervention is deemed cost-effective if it is below the cost-effectiveness threshold. On the other hand, an intervention assessed to be cost-effective in one country cannot be automatically deemed cost-effective in another country. This may be brought about by the differences in threshold ICERs, variations in the measurement and valuation of resources (two of the tasks of an economic evaluation study mentioned above), and prevalence. The importance of study setting is seen in the case of sacubitril-valsartan, an intervention assessed to be cost-effective for heart failure in many countries. However, a study conducted in Thailand and published in 2018 concluded that it was not cost-effective in Thailand.
- Moreover, in trying to apply or express the ICER obtained in studies conducted in other countries, some resort to using the foreign exchange rate, i.e., converting the ICER expressed for example in US\$ to PHP by multiplying the value in US\$ by the exchange rate to arrive at the ICER in PHP. However, this practice is fraught with errors unless the ICER is expressed in purchasing power parity (PPP), e.g., US\$ PPP.
- The local CUA on dapagliflozin for HFrEF showed that it may be cost-effective in the Philippine setting (58-64% cost-effective for all HFrEF patients and 72-76% cost-effective for HFrEF patients with diabetes). However, there were some limitations mentioned in the study that could affect the ICERs. A recalculation of the ICERs is proposed using newer data on the cost of the medicine using the payer's perspective (government) as well as applying the HTAC-recommended discount rate of 7%. Such data were not yet available when the study was written and subsequently published.
- Lastly, the statement "tests and interventions being done for Heart Failure management was one important consideration discussed in the panel meetings/health technology assessment; it should be a key gatekeeping mechanism to ensure that all payments made by the government (through PhilHealth) are cost-effective" is well appreciated. Please refer to the above comments regarding charges as not the same as costs. In addition, ensuring that

government payments are “cost-effective” would mean that such studies or other economic evaluation studies should have been recommended in the section on Research Implications/Gaps.

- Economic evaluation studies can be used as tools in prioritizing tests and interventions. For example, all 10 tests/interventions may be cost-effective but not affordable to the healthcare provider due to budget constraints. Thus, not all of them can be funded at the same time. The right choice would then be choosing those interventions with the least opportunity costs.

Reviewer 3

- Patient outcomes should also be considered in the recommendations, not just clinical outcomes. Tailoring of recommendations important to patients should be included in clinical practice guidelines. More patient representatives should be included when coming up with recommendations. Patient decision-making tools should be considered in the recommendations.
- The views of policy makers, (eg: Philippine Health Insurance) and administrators (e.g Department of Health and hospital administrators) should also be included in the discussions during the drafting of the clinical questions and even during the voting on recommendations. This would ensure that the recommendations are truly multisectoral in nature, and the values and preferences of the target users are considered.
- The impact of the guidelines on policy making and health funding should be considered by the clinical practice guidelines. Several drugs that were included in the recommendations are not included in the Philippine National Drug Formulary, and the guidelines should anticipate changes on the drug formulary.
- Updating the guidelines should be clear and explicitly state who will initiate the process, e.g. the Philippine Heart Association or the Heart Failure Council.

The comments from the external reviewers were already incorporated in the final draft of the final manuscript.

Guideline Update

A proposed updating process framework for CPGs starts with assembling a group responsible for updating the CPG, consisting of methodologists and experts, similar to the original composition of the heart failure CPG task force.¹⁶ New issues and technologies may require experts from new fields. The actual updating process starts with a systematic search for new relevant evidence. The DOH recommends that updates may be needed if there are identified gaps in the current knowledge on the

diagnosis and management of heart failure, newly released evidence from large scale studies or clinical trials, approval of new interventions or therapies, changes in critical or important outcomes and values placed on outcomes, or changes in resources available for health care.¹ A fixed time frame from two to five years had been reported in previous reviews of methodological handbooks.¹⁷ After identifying new relevant evidence, the effect or impact of this new evidence should next be assessed to determine the need for an update. This assessment should include whether this new evidence alters the validity of the current recommendations. When the need for an update is agreed upon, the new evidence is incorporated and the current recommendations are revised accordingly. A multidisciplinary external review by a panel with members not involved in the development or updating of the CPG, and including clinical and methodological experts, should also be conducted. Finally, when approved by the DOH, a summary of the updated recommendations or de novo recommendations should be published.¹⁶

Thus, updates will be planned three years after publication in anticipation of the potentially practice-changing results of ongoing and future clinical trials on heart failure. The steering committee will organize a CPG update group that will meet annually to assess latest clinical trials and observational studies that may impact the practice of heart failure management in the country. As implementing agency, the Philippine Heart Center will coordinate with the SC in the conduct of this annual review and will contact the National Institutes of Health and Department of Health for possible collaboration in updating the guidelines. Subsequently, a technical working group to look into the latest evidence, and a consensus panel to deliberate on the new recommendations, with members who may have been part of the original CPG task force, will be convened.

Cost Implications of the Guidelines

Evidence review experts were asked to include in their search strategy cost-effectiveness studies on the diagnostic tests and medical treatments for their evidence review of the statement recommendations. The consensus panelists also considered the cost implications of each recommendation prior to voting. During some of these discussions where the ERE was able to present cost-effectiveness studies, the steering committee deemed it to be challenging to present to the Consensus Panel, given the time restrictions. Furthermore, some of the EREs were not able to retrieve such studies and are not capable of performing de novo cost-effectiveness studies. One of the external reviewers is a clinical epidemiologist and a health economist who also checked on the method of reviewing cost-effectiveness studies and offered suggestions. The Steering Committee agreed that this knowledge gap may be addressed in subsequent updates of the CPG.

We are anticipating that dissemination and implementation of the guidelines will require costs. The steering committee will come up with a budget on the implementation,

dissemination, assessment and evaluation of the CPG. This will be discussed with the central committee, the National Institutes of Health and the Department of Health.

Some of the medications that are recommended are not included in the national formulary and maintenance treatment for chronic heart failure at current retail prices may not be affordable to most patients. The guideline developers will hold dialogues with the Health Technology Assessment Committee who are in charge with recommending medications to be part of the national formulary to include the recommended drugs and diagnostic tests so the government can procure these medications and make them accessible to heart failure patients.

Editorial Independence

The funding for the development of this CPG was provided by the Department of Health in preparation for the implementation of Universal Health Care. Clinical practice guideline recommendations were solely and independently formulated by the Task Force.

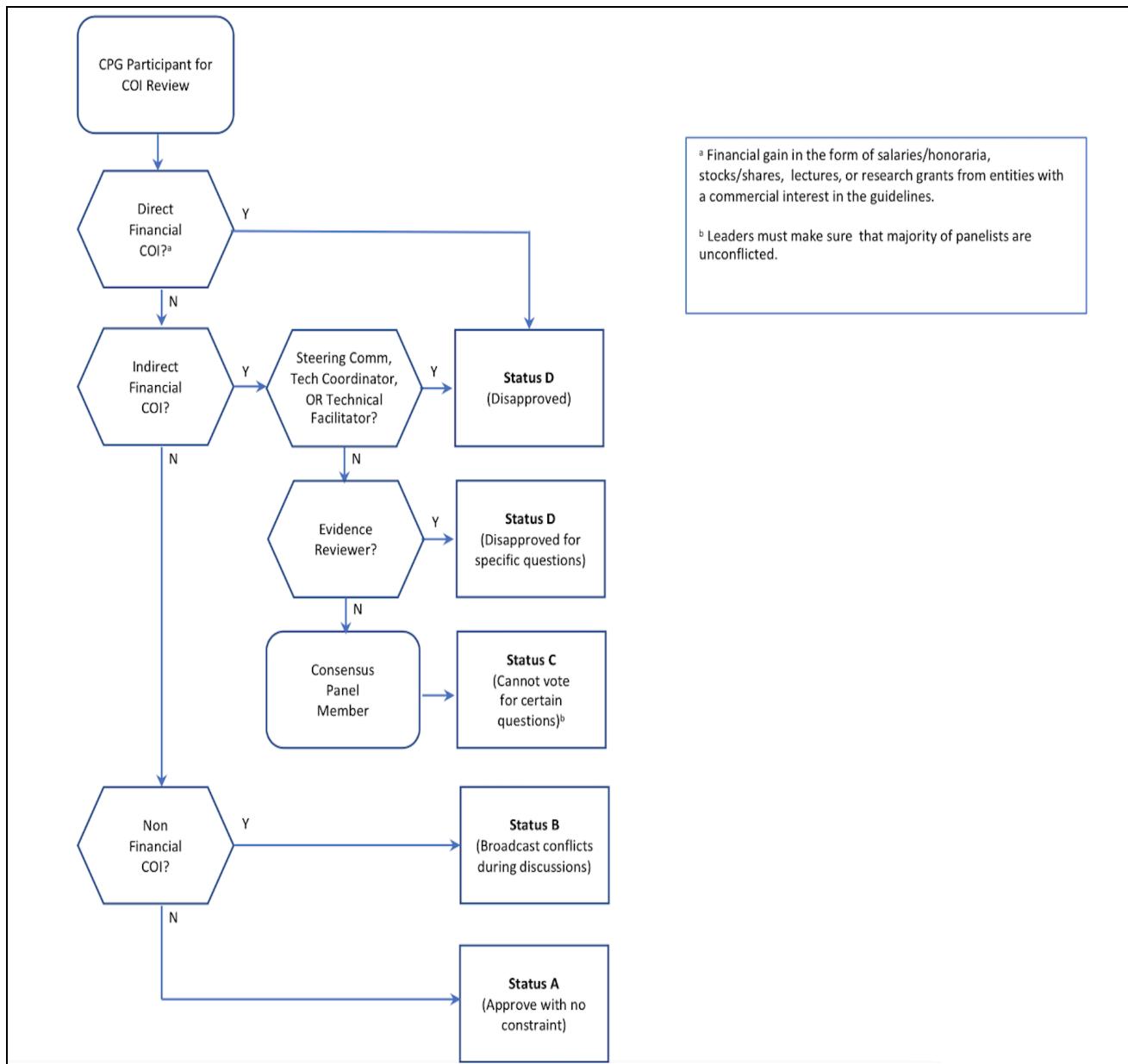
Management of Conflicts of Interest

All members of the CPG Task Force such as the Steering Committee (SC), Evidence Review Experts (ERE), Technical Coordinators (TC), Consensus Panelists (CP), Technical Facilitator, Technical Writer, and Administrative Officer underwent screening for conflicts of interest through their submitted curriculum vitae and accomplished the prescribed declaration of conflict of interest forms. The COI Review Committee of the HF CPG Task Force was composed of three individuals recommended by the Steering Committee and approved by the National Practice Guideline (NPG) COI Review committee. The Steering Committee and the Task Force COI Review Committee (TFCOIRC) underwent training on screening and managing conflicts of interest. The TFCOIRC reviewed the CVs and COI forms of all the members of the task force and made recommendations regarding each CPG Task Force member's extent of participation.

The Steering Committee (SC) invited relevant professional organizations to nominate individuals who can become part of the consensus panel. Selected experts, by virtue of their training background and experience in critical appraisal and guideline development, were also invited by the SC to serve as EREs. Such nominees were initially screened by the SC for any major and obvious conflicts of interest that may introduce bias in their decisions. Those who passed the initial adjudication underwent screening by the HF Task Force COI Review Committee. Certain consensus panelists were prohibited from voting on certain clinical questions if they possessed significant potential COIs relevant to the said questions. The process of COI evaluation was guided by the COI algorithm (Fig. 2) crafted by the UP-NIH National Practice Guideline

Project Team. Each task force member's curriculum vitae and declared conflicts of interest were assessed by the TFCOIRC and a decision on his/her participation was made, as follows: Approved with no constraint (Status A); Broadcast conflict at discussion (Status B); Cannot vote regarding certain guideline question/s (Status C); Disqualified or Disqualified for specific guideline question/s (Status D).

For the first batch of SCs and CPs, major COIs were identified in a significant number of nominees. These recommendations were submitted to the Steering Committee which, in turn, informed the members of the task force regarding the outcome of the COI assessment and the recommendations for the appropriate management of identified potential conflicts of interest. To manage this, the SC recruited additional members without major COI to ensure that the majority of the members of the SC and the CP had no conflicts of interest. Declaration of COI assessment was done at the start of every meeting.



Financial COI - salaries, honorarium of speakers, research grant sponsored by pharmaceutical companies, patents, stocks/shares in a hospital, diagnostic company, pharma company, device company; Non-Financial COI - gains in academic stature, public image, or popularity. Examples include previous statements, declarations, publications or associations that may predispose to pre-judgement on issues yet to be resolved by the CPG.

Figure 2. COI evaluation algorithm

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Recommendation and Evidence Summaries

1. Among adult Filipinos presenting with dyspnea at the outpatient clinic, how accurate are other symptoms (easy fatigability, orthopnea, paroxysmal nocturnal dyspnea) and signs (elevated jugular venous pressure, rales, and peripheral edema) in the diagnosis of chronic heart failure?

RECOMMENDATION 1A

Among adult Filipinos presenting with dyspnea at the outpatient clinic, we recommend a careful history to include paroxysmal nocturnal dyspnea for the diagnosis of chronic heart failure.

(low level of evidence, strong recommendation)

RECOMMENDATION 1B

Among adult Filipinos presenting with dyspnea at the outpatient clinic, we recommend a careful physical examination to include the measurement of the jugular venous pressure for the diagnosis of chronic heart failure.

(low level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- When eliciting the symptom of paroxysmal nocturnal dyspnea (PND) the following questions should be asked: "Have you ever been awakened at night, after 1 to 2 hours of sleep, by shortness of breath, or a sense of drowning? And was this relieved by assuming an upright position?" This question should be translated and explained using the patient's dialect.
- The CP gave a strong recommendation despite low certainty of evidence because, based on the universal definition of HF, the presence of symptoms is the initial requirement in diagnosing heart failure. Of these symptoms, PND is a

red flag with high specificity for HF when present alongside the other signs and symptoms of HF. As such, it should always be asked by the physician at bedside.

- The probability of HF increases with the number of signs and symptoms of HF present in a patient.
- Measuring the JVP is part and parcel of cardiovascular physical examination. When assessing the jugular venous pressure, the normal value of 6 to 8 cm H₂O will be used. Of the physical signs suggestive of HF, elevated JVP has a high specificity for HF.
- Proper measurement of the JVP is essential in making an accurate clinical assessment of right-sided intracardiac pressure and the likelihood of heart failure. Since this bedside maneuver requires a certain degree of skill, the consensus panel raised some concerns regarding its real-world reliability and interoperator variability. Thus, the CP recommended that efforts be made to upskill primary care providers regarding the proper technique of JVP measurement, as elaborated below.
- Guide to measuring the JVP: Ensure the patient is in a relaxed position and raise the bed at 30-45 degrees. Position the neck for optimal viewing of waveforms which are better seen with the head lying directly on the examining table/bed. A well-lit room eliminates the need for direct light. Identify venous waves by looking for bifid, flicking waveform that rises when the head of the bed is lowered and sinks with inspiration. The JVP can be assessed on either side, and a carotid pulsation can be distinguished from the JVP by pressing on the RUQ while watching the neck. The JVP should rise with this maneuver whereas a carotid pulsation should not change. Measure the JVP by identifying the highest point of pulsation, extending a ruler horizontally, and adding 5 cm.¹

KEY FINDINGS

Six studies (2 prospective cohorts, 4 cross-sectional studies) investigated the accuracy of clinical symptoms (easy fatigability, orthopnea, paroxysmal nocturnal dyspnea) and signs (elevated jugular venous pressure, rales and peripheral edema) compared to a reference standard (e.g. the European Society of Cardiology criteria for the diagnosis of heart failure) in the diagnosis of heart failure.

Among the clinical parameters, easy fatigability or dyspnea climbing less than one flight of stairs provided the outlier values, with a moderate sensitivity of 0.72 and a low specificity of 0.44. For the rest of the parameters, the sensitivity was generally very low

ranging from 0.27 to 0.44. On the other hand, the specificity was moderate to high ranging from 0.79 to 0.93.

Two parameters have moderate to high specificity: Paroxysmal Nocturnal Dyspnea, with a specificity of 0.86 (95% CI 0.82 to 0.90), and Elevated Jugular Venous Pressure with a specificity of 0.93 (95% CI 0.81 to 0.98).

The overall certainty of evidence was rated “low” because of incorporation bias, due to the serious risk of bias introduced since the symptoms and signs (index test) being analysed are included in the diagnosis of heart failure (reference standard).

DIAGNOSIS OF HEART FAILURE

The Universal Definition of Heart Failure was formulated through consensus development by the Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society. The report was published in 2021.

The criteria for diagnosis include clinical symptoms and signs corroborated by objective evidence of structural and/or functional abnormality of the heart from Chest X-ray, NT-ProBNP, BNP, or Echocardiography.² In their report, ECG was not mentioned but they noted that an elevated jugular venous pressure estimated by an experienced clinician could be accepted as objective evidence.

In the Philippines, 40% of healthcare services are accessed through primary care facilities, while 58% of those who visited health care facilities were in rural areas.³. It is reasonable to assume that the majority of heart failure patients are diagnosed and managed in primary care with limited access to even simple diagnostic procedures such as ECG and Chest X-ray. The clinical symptoms and signs may be useful in the early detection of heart failure. The benefits of early detection and timely treatment include an increase in life expectancy by 51% and a reduction in hospitalization by 33% when treated with ACE-inhibitors.⁴ On the other hand, eliciting the symptoms and signs requires clinical skills.⁵ A delay in the diagnosis of heart failure due to inadequate clinical skills will lead to worsening symptoms, hospital admission, or sudden death.⁵

REVIEW METHODS

A systematic search was done for all published studies from inception to December 6, 2022 using Medline with combined MeSH and free text search using the terms “heart failure,” “dyspnea,” “easy fatigability,” “orthopnea,” “paroxysmal nocturnal dyspnea,” “elevated jugular venous pressure,” “rales,” “peripheral edema,” “sensitivity,” “specificity,” “predictive value,” “diagnostic accuracy,” and “likelihood ratio,” with supplementary checks of reference lists of all studies that met the inclusion criteria and

the reference list of the 2021 European Society of Cardiology (ESC) Guidelines on Heart Failure.

Only studies on chronic heart failure in adults seen in general, outpatient, or primary care practice were included. The risk of bias was assessed using the Painless Evidence Based Medicine criteria.⁶

For the interpretation of the measures of diagnostic accuracy, the following cut-offs were applied: sensitivity and specificity were considered “High” if they exceeded 90%, “Moderate” if they were at least at 80%, and “Low” if they were less than 60%.^{4,7}

RESULTS

Six studies⁷⁻¹² with a total of 8,813 patients were included in the reviews (Table 1). Two were prospective cohort studies—one from England¹¹ and the other from the U.S.A.¹⁰ and four were cross-sectional studies—three from the Netherlands^{7,9,12} and one from Portugal.⁸

All the studies included patients from a primary care or general practice setting. The symptoms and signs of heart failure were evaluated by general practitioners.

For the symptom of Paroxysmal Nocturnal Dyspnea, only one study described how this was elicited from the patient’s medical history. Participants were asked “Have you ever been awakened at night by troubled breathing?”.¹⁰

For the physical examination finding of elevated jugular venous pressure, one study defined this as greater than 6cm.⁸ None of the studies described the procedure for the measurement.

The population of patients were mostly from a random selection of patients presenting with non-acute symptoms of heart failure, except for one study on COPD patients.⁹ One study reported dyspnea at less than one flight of stairs and this was interpreted as easy fatigability.⁷ Four studies used the European Society of Cardiology’s criteria for heart failure (signs and symptoms alongside evidence of cardiac dysfunction by chest X-ray or echocardiography) as reference standard.^{7,8,11,12} Two studies used clinical consensus based on signs and symptoms of heart failure alongside chest X-ray or the use of heart failure medicines¹⁰; and signs and symptoms of heart failure alongside ECG, chest X-ray, NT-ProBNP, or echocardiography.⁹

Table 18. Characteristics of included studies on signs and symptoms of heart failure

study ID	type of study, n	setting	Mean age, years (\pm SD)	population	index test	reference standard
Hobbs et al 2002	Prospective cohort n=273	Primary care/general practice	66 \pm 11	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	rales, peripheral edema	ESC criteria
Fonseca et al. 2004	cross-sectional study n=1058	Primary care/general practice	68 \pm 15	Randomly selected patients (stratified by age)	orthopnea, PND, JVP, rales, edema	ESC criteria
Rutten et al. 2005	cross-sectional study n=405	Primary care/general practice	73 \pm 5	COPD patients with no previous diagnosis of heart failure	orthopnea, PND, JVP, rales, edema	clinical consensus
Ekundayo et al. 2009	Prospective cohort n=5771	Primary care/general practice	73 \pm 6.0	community dwelling patients with orthopnea and PND	orthopnea, PND	clinical consensus
Kelder et al. 2011	cross-sectional study n=721	Primary care/general practice	75. 5 \pm 9.7	Patients presenting with symptoms and signs of heart failure with no previous diagnosis of heart failure	EF, orthopnea, PND, JVP, rales, peripheral edema	ESC criteria
van Riet et al. 2016	cross-sectional study n=585	Primary care/general practice	74.1 \pm 6.3	patients with non acute shortness of breath	rales, peripheral edema	ESC criteria

Table 19. The GRADE Summary of Findings Table for individual clinical parameters

Clinical Symptoms and Signs of heart failure	Sensitivity 95% CI	Specificity 95% CI	prevalence 1.6%, Effect per 1,000 patients tested				Certainty of Evidence	
			Sensitivity		Specificity			
			True positive (correctly diagnosed with)	False negative (missed diagnosis)	True negative (correctly diagnosed without)	False positive (incorrectly diagnosed with)		
dyspnea < 1 flight of stairs	0.72 (95% CI 0.66 to 0.79)	0.44 (95% CI 0.40 to 0.48)	12 (11-14)	4 (3-5)	433 (390-475)	551 (509-594)	very low	
Orthopnea	0.32 (95% CI 0.25 to 0.39)	0.86 (95% CI 0.77 to 0.92)	5 (4-6)	11 (10-12)	846 (755-905)	138 (79-229)	low	
Paroxysmal Nocturnal Dyspnea	0.31 (95% CI 0.26 to 0.36)	0.86 (95% CI 0.82 to 0.90)	5 (4-6)	11 (10-12)	849 (810-881)	135 (103-174)	low	
Elevated JVP	0.27 (95% CI 0.19 to 0.36)	0.93 (95% CI 0.81 to 0.98)	4 (3-6)	12 (10-13)	919 (797-963)	65 (21-187)	low	
Rales	0.31 (95% CI 0.25 to 0.37)	0.84 (95% CI 0.73 to 0.91)	5 (4-6)	11 (10-12)	825 (718-893)	159 (91-266)	low	
Peripheral edema	0.44 (95% CI 0.34 to 0.55)	0.79 (95% CI 0.68 to 0.87)	7 (5-9)	9 (7-11)	777 (669-856)	207 (128-315)	low	

DIAGNOSTIC ACCURACY FINDINGS

Each study contributed to one or more parameters for the clinical signs and symptoms (Table 19): easy fatigability, one study,⁷ n=721; orthopnea, four studies,⁷⁻¹⁰ n=7,955; paroxysmal nocturnal dyspnea, three studies,^{7,8,10} n=7,550; elevated jugular venous pressure, three studies,⁷⁻⁹ n=2,184; rales or lung crepitations, five studies,^{7,8,9,11,12} n=3,042; and peripheral edema, five studies,^{7,8,9,10,12} n=3,042.

Among the clinical parameters, easy fatigability or dyspnea at less than one flight of stairs provided the outlier values, with a moderate sensitivity of 0.72 and a low specificity of 0.44. For the rest of the parameters, the sensitivity was generally very low ranging from 0.27 to 0.44. The specificity was moderate to high ranging from 0.79 to 0.93.

Two parameters have moderate to high specificity: Paroxysmal Nocturnal Dyspnea with a specificity of 0.86 (95% CI 0.82 to 0.90) and Elevated Jugular Venous Pressure with a specificity of 0.93 (95% CI 0.81 to 0.98).

CERTAINTY OF EVIDENCE

All studies had incorporation bias since the index test results (the symptoms and signs of heart failure) are part of the reference standard (the symptoms and signs of heart failure alongside objective evidence of cardiac dysfunction from ECG, chest x-ray, or echocardiography). The certainty of evidence was downgraded two steps to “Low.”

All the studies had a significant degree of inconsistency or heterogeneity but this could be explained by differences in the definition of symptoms and in the manner by which these were elicited, which is highly dependent on experience and skill. As a result of these differences, inter-observer variability in the assessment of clinical parameters was an expected outcome and could not be eliminated; thus, the certainty of evidence was not rated down for this parameter.

(<https://gdt.gradepro.org/app/handbook/handbook.html#h.g2dqzi9je57e>)

The studies were not rated down for directness except for the parameter for easy fatigability. Easy fatigability was defined as dyspnea on climbing one flight of stairs. There is no generally accepted definition of easy fatigability but this is usually a perception of tiredness rather than dyspnea. The certainty of evidence for this parameter was downgraded to very low.

The studies had narrow confidence intervals for sensitivity and specificity and had no serious imprecision.

RECOMMENDATIONS FROM OTHER GROUPS

The Universal Definition of Heart Failure was formulated through consensus development by the Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society. It has been endorsed by the Canadian Heart Failure Society among others.¹³⁻¹⁶ They recommend a careful and thorough history taking and physical examination to guide the choice of subsequent tests and management.

Guidelines	Date	Recommendation	Level of evidence	Strength of recommendation
AHA/ACC/HFSA Guideline for the Management of Heart Failure	2022	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	Moderate quality	Strong
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure	2021	Symptoms and signs lack sufficient accuracy to be used alone to make the diagnosis of HF. Diagnostic tests are recommended for the assessment of patients with suspected chronic HF	moderate to low (B or C)	strong (class I)
JCS/JHFS Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart	2021	In the diagnosis of heart failure, patients should be examined first for symptoms, medical history, their family history, physical findings, electrocardiogram, and chest radiographic findings.	Not stated	Not stated
Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure	2017	We recommend the choice of investigations should first be guided by careful history and physical examination and when clinical evidence suggests a possible cause and the planned test(s) result(s) would be reasonably expected to lead to a change in clinical care.	Low	Strong

Table 20. Recommendations from recent guidelines on the use of symptoms and signs of heart failure

ONGOING STUDIES

There is one local study on the accuracy of history taking and physical examination in the diagnosis of heart failure. This was excluded because it was conducted in a cardiology specialty clinic at the Philippine General Hospital.¹⁷ This study was done in 1999 and the reference standard used was echocardiographic findings. The sensitivity of orthopnea, paroxysmal nocturnal dyspnea, and pedal edema were moderate to low (81, 60, and 45 respectively), while elevated JVP and pedal edema had high specificity (95 to 100%).

COST

There are many challenges on the conduct of economic evaluations especially on cost-effectiveness studies for diagnostic tests. Modelling will not only include accuracy of the

tests but also time to diagnosis and other considerations. Despite these problems, there are economic evaluation studies on the use of some diagnostic tests in the diagnosis of chronic HF in the community setting. However, because of applicability problems, their results cannot be used in the local setting. The reviewers did not come across any local economic evaluation studies comparing the cost-effectiveness of diagnosing heart failure based on clinical parameters alone and diagnosing heart failure based on a combination of clinical parameters and laboratory procedures (ECG, chest x-ray, NT ProBNP or echocardiography).

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

The diagnosis of heart failure requires the presence of symptoms and signs elicited by a physician or a trained health worker corroborated by objective evidence of cardiac dysfunction from 12L ECG, Chest X-ray, NT ProBNP, or Echocardiography. The feasibility of carrying out the diagnostic process depends on the availability of health resources.

Primary Care in the Philippines¹⁸

Health Care Facilities

Only half of the population has access to Rural Health Units (RHUs) within 30 minutes. BARMM (Bangsamoro Autonomous Region in Muslim Mindanao), Bicol and MIMAROPA (Mindoro, Marinduque, Romblon, Palawan) have the highest share of populations without access to an RHU. Only half of the total barangays have at least 1 Barangay Health Station (BHS). Meanwhile, the country has 1,112 X-ray machines or one X-ray machine for every 10,000 people.

Human Resources

In primary care facilities such as Rural Health Units and Barangay Health Stations, human resources for health are scarce. Although 90% of RHUs have at least 1 medical doctor, less than 10% of BHSs have medical doctors and nurses. These are manned by midwives and barangay health workers.

Health Care Financing

In 2018, 54% of health care spending was from household out-of-pocket expenses. The Philippines spends USD 12 (Php 675) per person on primary care. On average, local government units (LGUs) spend PHP 390 per person on health.

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2. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the chest X-ray for the diagnosis of heart failure?

Recommendation 2A

Among adult Filipinos presenting with dyspnea, paroxysmal nocturnal dyspnea, and elevated jugular venous pressure at the outpatient clinic, we recommend using the presence of cardiomegaly and/or pulmonary congestion on chest X-ray as a basis for the diagnosis of chronic heart failure.

(low level of evidence, strong recommendation)

Recommendation 2B

Among adult Filipinos presenting with dyspnea, paroxysmal nocturnal dyspnea and elevated jugular venous pressure at the outpatient clinic, we suggest using the presence of pulmonary congestion on chest X-ray as a basis for the diagnosis of chronic heart failure.

(low level of evidence, weak recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- The availability of chest X-ray and its affordability in different localities, especially in far-flung areas, are variable.
- Pulmonary congestion is characterized by an increase in pulmonary vascular markings bilaterally according to the interpretation of a skillful physician.
- The severe form of pulmonary congestion is pulmonary edema seen as fluffy infiltrates or alveolar flooding.
- Pulmonary congestion may occur even in the absence of cardiomegaly.
- A strong recommendation for the test was made despite low certainty of evidence since the presence of pulmonary congestion and/or cardiomegaly seen on the

chest X-ray coupled with signs and symptoms of heart failure would make the diagnosis of heart failure more accurately satisfy the Universal Definition of HF".

KEY FINDINGS

- A pooled de-novo meta-analyses had seven studies that investigated the accuracy of the chest X-ray in diagnosing heart failure (HF) among adult patients presenting with signs and symptoms of chronic heart failure in a non-emergency setting was performed. All had an observational cross-sectional study design with prospective data collection.
- Key results on radiographic cardiomegaly:
 1. The sensitivity and specificity of cardiomegaly on chest X-ray to diagnose HF among adult patients with signs and symptoms of chronic HF ranges from 59-71% and 59-81%, respectively.
 2. The overall certainty of evidence is high.
- Key results on radiographic pulmonary congestion:
 1. The sensitivity and specificity of pulmonary congestion on chest x-ray to diagnose HF among adult patients with signs and symptoms of chronic HF ranges from 25-86% and 73-96%, respectively.
 2. The overall certainty of evidence is low due to inconsistency and imprecision.

INTRODUCTION

The chest X-ray is a projection radiograph of the chest that is used to visualize certain organs (heart, lungs, aorta, major airways, trachea) and the bones of the thorax. Its important, direct benefits in the evaluation of patients presenting with the signs and symptoms of chronic HF are the following: it enables the diagnosis of the clinical characteristics of HF (cardiomegaly, cardiac chamber enlargement, pulmonary venous congestion, and interstitial or alveolar edema); and assesses alternative cardiopulmonary causes of the patient's signs and symptoms.^{1,2} Its main, direct harm is radiation exposure. The radiation dose of a single posteroanterior chest film ranges from 0.02 mSv^{3,4} to 0.1 mSv⁵ which is comparable to 10 days' exposure to natural background radiation⁵ and corresponds to a negligible estimated cancer risk.⁶ For

context, a round-trip flight from New York to London has an approximate mean individual radiation dose of 0.1 mSV.⁷

The chest x-ray has also been shown to have prognostic value for heart failure onset, morbidity, and mortality. Epidemiologic population-based data from the Framingham Study reported that cardiomegaly (defined as a cardiothoracic ratio exceeding 0.5 on chest film) had an OR of 2.22 (95% CI 1.63-3.01, p <0.01) in men and an OR of 1.61 (95% CI 1.21-2.16, p 0.001) in women for developing new heart failure across 38 years of follow-up.⁸ In a population of 7,599 patients with symptomatic heart failure of at least four weeks' duration (with mixed HFpEF and HFrEF etiologies), cardiomegaly (defined by current or prior chest X-ray having cardiothoracic ratio of ≥ 0.5) had a hazard ratio of 1.35 (95% CI 1.23, 1.47) while pulmonary edema had a hazard ratio of 1.26 (95% CI 1.03, 1.54) for predicting cardiovascular death or heart failure-related hospitalization during a median follow-up of 38 months (range 2–4 years).⁹ In ambulatory patients with chronic heart failure from the Digitalis Investigation Group Trial, patients with high cardiothoracic ratio (>0.50) had a higher all-cause mortality rate (34.3% or 1,185 per 10,000 patient-years of follow-up) compared to patients with a normal cardiothoracic ratio (28.5% or 919 per 10,000 patient-years of follow-up), and a computed hazard ratio of 1.35 (95% CI 1.21-1.51, p<0.0001). All-cause hospitalization occurred in 66.2% (a rate of 3,932 per 10,000 patient-years) of patients with high cardiothoracic ratio compared to 64.8% (rate of 3,513 per 10,000 patient-years) of patients with a normal cardiothoracic ratio, with a computed hazard ratio of 1.10 (95% CI 1.01-1.20, p=0.032).¹⁰

REVIEW METHODS

The following are the inclusion and exclusion criteria for this review:

Table 21. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Population: adult patients with signs and symptoms of chronic HF	Pediatric patients
Index test: Chest X-ray (cardiomegaly or pulmonary congestion)	Acute HF
Reference standard: Diagnosis of HF (laboratory test or physician assessment)	Decompensated HF
Disease: chronic HF, HFrEF	HFpEF
Types of studies: Meta-analyses, observational studies	

A systematic literature search was done on electronic databases (Medline, Google Scholar, HERDIN Plus, and Cochrane Database for Systematic Reviews) on January 2, 2023. Both MeSH and free text search was done using the key words: “congestive heart failure”, “chest x-ray/chest radiography”, “sensitivity”, “specificity”, “ambulatory care”, and “primary care”. The references of the included studies and published meta-analyses were also searched. The inclusive dates of the search were from database inception until January 2, 2023. There were no limits on publication language. The search strategy is available in Annex 4, Appendix II.

The included studies for the meta-analysis were appraised using the QUADAS-2 Tool as recommended by Cochrane for Cochrane Reviews of diagnostic test accuracy. The data was summarized using RevMan 5.4. The PRISMA flow diagram for the pooled meta-analysis is available in Annex 4, Appendix III.

- In this review, cardiomegaly on chest X-ray is defined as a cardiothoracic ratio measurement of greater than 0.50 on a postero-anterior view chest X-ray. Pulmonary congestion on chest X-ray is defined as the presence of cephalization, Kerley lines, and/or bilateral alveolar edema on a postero-anterior view chest X-ray.

RESULTS

Characteristics of Included Studies

Seven observational cross-sectional studies were found eligible from the systematic literature search and were subsequently included in the pooled meta-analysis. Six were foreign studies and one was a local study.¹¹ Of these seven studies, four studies had a study population of primary/ambulatory care patients with signs and symptoms of chronic HF^{12,14,15,16}; one study had a population of diagnosed chronic HF patients¹⁷; one study had a population of angiographically significant coronary artery disease¹³; and one study had a population of patients referred for echocardiography.¹¹

Five studies utilized the postero-anterior view of the chest x-ray; two of these studies had an additional lateral view; while two other studies did not specify the chest x-ray view.^{14,17}

The reference standard differed among the included studies—three studies used clinical HF diagnosis by a physician;^{12,14,16} two studies used echocardiographic left ventricular dysfunction only;^{11,15} and two studies used left ventricular dysfunction on invasive hemodynamic studies only.^{13,17}

Patient numbers for three studies^{13,15,17} were not reported and were derived from the reported sensitivity and specificity percentages to be able to construct the forest plots. The full text of one study conducted by Spinar in 1992 was not available.

The characteristics of the included studies in the meta-analysis are summarized in Annex 4, Appendix IV.

Accuracy Measures and Certainty of Evidence

Cardiomegaly on CXR

Meta-analysis of five studies¹¹⁻¹⁵ on cardiomegaly on chest X-ray resulted in a sensitivity point estimate range of 0.59-0.71 and a specificity point estimate range of 0.59-0.81. Cardiomegaly was defined as a cardiothoracic ratio greater than 0.5 in all studies. Patient numbers for two studies (Harlan 1977 and Shah 2004) were not reported and were derived from the reported sensitivity and specificity percentages. The forest plot of this meta-analysis is available in Annex 4, Appendix I. There was no visually significant heterogeneity for both the sensitivity and the specificity forest plots.

Overall risk of bias for all studies was low, with two studies with a risk-of-bias issue (Harlan 1977 had unclear risk of bias in the index test criterion, and Shah 2004 had unclear risk of bias in the flow and timing criterion). The risk of bias summary is shown in Annex 4, Appendix V. The details of the QUADAS-2 Tool risk of bias assessments are available in Annex 4, Appendix VI.

The overall test accuracy certainty of evidence (CoE) for cardiomegaly on chest x-ray is high. The GRADEPRO Summary of Findings table for this meta-analysis is available in Annex 4, Appendix VII.

Accuracy Measures and Certainty of Evidence

Cardiomegaly on CXR

The meta-analysis of five studies¹¹⁻¹⁵ on cardiomegaly on chest x-ray resulted in a sensitivity point estimate range of 0.59-0.71 and a specificity point estimate range of 0.59-0.81. Cardiomegaly was defined as a cardiothoracic ratio >0.5 in all studies. Patient numbers for two studies^{13,15} were not reported and were instead derived from the reported sensitivity and specificity percentages. The forest plot of this meta-analysis is available in Appendix I.

The overall risk of bias for all studies was low, while two studies had a risk-of-bias issue (Harlan 1977 had an unclear risk of bias in the index test criterion and Shah 2004 had an unclear risk of bias in the flow and timing criterion). The risk of bias summary is

shown in Annex 4, Appendix V. The details of the QUADAS-2 Tool risk of bias assessments are available in Annex 4, Appendix VI.

The overall test accuracy certainty of evidence (CoE) for cardiomegaly on chest x-ray is high. The GRADEPRO Summary of Findings table for this meta-analysis is available in Annex 4, Appendix VII.

Table 22. Summary of the Diagnostic Accuracy and Certainty of Evidence of Cardiomegaly on CXR

Basis	Sensitivity Range	Specificity Range	Estimate of Effect per 1000 Patients Tested (pre-test probability of 1.6%*)		Certainty of the evidence (GRADE)
			Estimated # diagnosed	Estimated # missed	
5 studies	59 – 71 %	59 – 81 %	True Positives: 9 to 11 True Negatives: 581 to 797	False Positives: 187 to 403 False Negatives: 5 to 7	⊕⊕⊕ HIGH

* Patient numbers are estimated only since the patient numbers for two studies (Harlan 1977 and Shah 2004) were not reported and were derived from the reported sensitivity and specificity percentages.

** The pre-test probability of 1.6% is taken from the reported prevalence of hospitalization due to CHF among adult patients aged 19 years and above in the Philippines last 2014. (34)

Table 23. Summary of the Diagnostic Accuracy and Certainty of Evidence of Cardiomegaly on CXR when the Pretest Probability is High

Basis	Sensitivity Range	Specificity Range	Estimate of Effect per 1000 Patients Tested (pre-test probability of 29%**)		Certainty of the evidence (GRADE)
			Estimated # diagnosed	Estimated # missed	
5 studies	59 – 71 %	59 – 81 %	True Positives: 171 to 206 True Negatives: 419 to 575	False Positives: 135 to 291 False Negatives: 84 to 119	⊕⊕⊕ HIGH

* Patient numbers are estimated only since patient numbers for two studies (Harlan 1977 and Shah 2004) were not reported and were derived from the reported sensitivity and specificity percentages.

** The pre-test probability of 29% is taken from the post-test probability of heart failure in the presence of dyspnea, paroxysmal nocturnal dyspnea, and high jugular venous pressure (from HF CPG Question #1).

Pulmonary Congestion on CXR

The meta-analysis of five studies^{11,12,14,16,17} regarding pulmonary congestion on chest X-ray resulted in a sensitivity point estimate range of 0.25-0.86 and a specificity point estimate range of 0.73-0.96. Pulmonary congestion was defined in four studies as pulmonary vascular redistribution or interstitial edema or alveolar edema, except for Spinar 1992 (definition was not available). Patient numbers for one study¹⁷ were not reported and were instead derived from the reported sensitivity and specificity percentages. The forest plot of this meta-analysis is available in Annex 4, Appendix I.

Qualitative analysis showed that the overall risk of bias for all studies was low, although two studies had risk-of-bias issues (Fox 2000 had an unclear risk of bias in the index test criterion, while Spinar 1992 had an unclear risk of bias in the patient selection and index test criteria because the full text of this study was not available). The risk of bias summary is shown in Annex 4, Appendix V. The details of the QUADAS-2 Tool risk of bias assessments are available in Annex 4, Appendix VI.

The overall test accuracy certainty of evidence (CoE) for pulmonary congestion on chest X-ray is low due to heterogeneity among the study methods and visual heterogeneity in the forest plot. The GRADEPRO Summary of Findings table for this meta-analysis is available in Annex 4, Appendix VII.

Table 24. Summary of the Diagnostic Accuracy and Certainty of Evidence of Pulmonary Congestion on CXR

Basis	Sensitivity Range	Specificity Range	Estimate of Effect per 1000 Patients Tested (pre-test probability of 1.6%*)		Certainty of the evidence (GRADE)
			Estimated # diagnosed	Estimated # missed	
5 studies	25–86 %	73–96 %	True Positives: 4 to 14 True Negatives: 718 to 945	False Positives: 39 to 266 False Negatives: 2 to 12	⊕⊕○○ LOW

* Patient numbers are only estimated since patient numbers for one study (Spinar 1992) were not reported and were instead derived from the reported sensitivity and specificity percentages.

** The pre-test probability of 1.6% is taken from the reported prevalence of hospitalization due to CHF among adult patients aged 19 years and above in the Philippines last 2014. (34)

Cardiomegaly and pulmonary congestion on CXR

A local study reported that among Filipino adult patients referred for echocardiography, the chest radiograph with both cardiomegaly and pulmonary congestion has a sensitivity of 18.7% and a specificity of 52.6% to detect echocardiographic left ventricular systolic dysfunction.¹¹

Cardiomegaly or pulmonary congestion on CXR

Landray et al. reported that among primary care patients suspected of heart failure, the chest X-ray with cardiomegaly or pulmonary edema has a sensitivity of 65% and a specificity of 45% to detect echocardiographic left ventricular systolic dysfunction.¹⁸ The overall risk of bias of this study is low. The details of the QUADAS-2 Tool risk of bias assessment for this study is available in Annex 4, Appendix VI.

RECOMMENDATIONS FROM OTHER GROUPS

The predetermined seven medical society guidelines mention the chest X-ray as a diagnostic test for patients suspected of heart failure. Three guidelines found limited/low quality of evidence but have a strong strength of recommendation (AHA/ACC, ESC, Australia and New Zealand). Three guidelines with a strength of recommendation system did not specify their strength of recommendation (Malaysian, Canadian, Japanese). UK's NICE has no strength of recommendation system.

Table 24. Summary of recommendations from medical society clinical practice guidelines on the use of the chest X-ray in heart failure.

Guidelines	Date	Statement	Level of Evidence	Strength of recommendation
AHA/ACC/HFSA Guideline for the Management of Heart Failure ²	2022	In patients with suspected or new-onset HF, or in 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. Considering the limited sensitivity and specificity, the chest x-ray should not be used as the only determinant of the specific cause or of the presence of HF.	LOE C-LD (Limited Data)	COR 1 (Strong)
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure ²⁰	2021	A chest X-ray is recommended to investigate other potential causes of breathlessness (e.g. pulmonary disease). It may also provide supportive evidence of HF (e.g. pulmonary congestion or cardiomegaly).	C (consensus of experts and/or opinion of the or is indicated) C (small studies, retrospective studies, registries)	I (is recommended or is indicated)

Malaysian Clinical Practice Guideline (CPG) on the Management of Heart Failure ²⁵	2019	To confirm the diagnosis and determine the type of HF and its etiology, the following should be performed: Basic investigations such as ECG, Chest Radiography, blood and urine tests.	None given	None given
NICE Guideline on Chronic heart failure in adults: diagnosis and management ²¹	2018	Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses: chest X-ray.	N/A	N/A
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia ²²	2018	A chest X-ray is recommended in patients with either a suspected diagnosis or a new diagnosis of heart failure to detect signs of pulmonary congestion, and to identify alternative cardiac or noncardiac causes for the patient's symptoms.. A chest X-ray may rule in the diagnosis of heart failure or identify an alternative cause for the patient's symptoms; however, a normal chest X-ray does not rule out heart failure.	Very low quality of evidence	Strong recommendation FOR
Canadian Cardiovascular Society Guidelines for the Management of Heart Failure ²³	2017	Chest X-ray is included in the list of initial investigations in a patient suspected of heart failure (Figure 1)	None given	None given
JCS/JHFS Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure ²⁴	2017	Chest X-ray to examine patients with a new-onset or an acute worsening of heart failure.	None given	None given

ONGOING STUDIES

There were no relevant ongoing studies identified from the systematic literature search.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

The reviewer did not come across any local economic evaluation studies on the chest X-ray for the diagnosis of heart failure.

Meanwhile, indicated below are the prices for an outpatient adult postero-anterior chest X-ray prices from clinics/hospitals in Metro Manila (as of January 9, 2023), to provide the reader some idea regarding financial considerations of doing the said test:

- Philippine Heart Center: PhP 590 (private), PhP 120 (service category C3), PhP 75 (service category D)
- Lung Center of the Philippines: PhP 850 (private), PhP 700 (service)
- National Kidney and Transplant Institute: PhP 700 (private), PhP 450 (service)
- Philippine General Hospital: PhP 370 (private); PhP 165 (charity)
- Premiere Cardiovascular Laboratory: PhP 250

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Feasibility

There is reported variability in the ability of physicians to diagnose HF from a CXR. Specialty training is a factor in the accuracy of chest X-ray interpretation for heart failure. The accuracy measurements of the ability of emergency physicians to recognize congestion from heart failure on chest X-ray had a sensitivity of 59%, and a specificity of 96%; while those of a radiologist had a sensitivity of 88% and a specificity of 100%.²⁶ Another study reported that the proportion of agreement between emergency physician interpretations and radiologist reports for congestive heart failure cases was 41.4%.²⁷

Clinical experience is also a factor in the accuracy of chest X-ray interpretation for heart failure. The agreement in chest X-ray heart failure interpretation between radiology residents and a radiology expert panel was 35%, while the agreement between radiology attendings and the radiology expert panel was 65%.²⁸

Acceptability

There is available evidence from the following international data on physicians' use and perceptions of the chest X-ray for the diagnosis of heart failure:

1. According to physician specialty/subspecialty

The Study group on HF Awareness and Perception in Europe (SHAPE) surveyed 2,041 randomly selected cardiologists, 1,881 internists and geriatricians, and 2,965 primary care physicians (PCP) regarding the diagnosis and treatment of HF (left ventricular ejection fraction <40%). The chest X-ray was reported to be used routinely in patients under clinical suspicion of heart failure of unknown etiology by 85% of the internists/geriatricians compared to 79% of the

cardiologists. The chest X-ray was considered necessary to detect heart failure by 61% of the PCPs. The PCPs' direct access to a chest X-ray within one month was reported by 65% of the PCPs.²⁹

A study on a random sample of primary care physicians across six European countries regarding their perceptions on diagnostic and prescription issues in heart failure reported that the chest X-ray was the most routinely used test for the diagnosis of heart failure (86% or 252/294 of the study participants), followed by the electrocardiograph (72% or 212/294), and then by echocardiography (38% or 111/294).³⁰

A Polish study on the knowledge of primary care physicians, cardiologists, and internal medicine physicians about CHF diagnosis and treatment reported that 58-86% of the questioned physicians ordered a chest X-ray to establish the diagnosis of chronic heart failure.³¹

A Polish study on the knowledge of primary care physicians regarding the diagnosis and treatment of chronic heart failure reported that almost 80% of surveyed physicians routinely performed ECG and chest radiogram in order to diagnose CHF.³²

2. According to age

A Polish study on 591 general practitioners' (GP) knowledge about heart failure reported that the chest X-ray was used in heart failure diagnosis by 34.3% of GPs aged 24-39 years, by 50.5% of GPs aged 40-55 years, and by 62.6% of GPs aged 56 years and older.³³

Aside from medical societies' guideline recommendations and the aforementioned studies on physicians' use of the chest X-ray for the diagnosis of HF, there are no other currently available studies regarding the acceptability of using a chest X-ray for the diagnosis of heart failure among different stakeholders (eg, patients, health insurance, health policymakers, etc.).

Patient's Values and Preferences

The reviewer likewise did not encounter any local studies on patients' values and preferences regarding the chest X-ray as a diagnostic test for heart failure.

Equity

The reviewer did not come across studies on the impact of using the chest X-ray for the diagnosis of heart failure on health equity.

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3. Among adult Filipinos presenting with signs and symptoms of heart failure at the outpatient clinic, how accurate is the 12-lead electrocardiogram for the diagnosis of heart failure?

Recommendation 3A

Among adult Filipinos presenting with dyspnea, paroxysmal nocturnal dyspnea, and elevated jugular venous pressure at the outpatient clinic, we do not recommend relying solely on a 12-lead electrocardiogram for the diagnosis of chronic heart failure.

(very low level of evidence, strong recommendation)

Good Practice Statement:

Among adult Filipinos with suspected chronic heart failure at the outpatient clinic, we suggest the use of 12-lead electrocardiogram to determine abnormalities in cardiac structure, function and rhythm to guide management.

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- The CP gave a strong recommendation to not use the 12L ECG solely for the diagnosis of chronic heart failure despite low certainty of evidence because the 12 L ECG can be utilized to guide management as it may provide information on underlying structural, functional, or rhythm abnormalities, as well as effects of medications.
- Despite lack of studies regarding the utility of the 12L ECG in the diagnosis of HF, the panel suggested that it is good practice to include 12L ECG in the initial evaluation of HF.
- The panelists discussed concerns regarding the accuracy of ECG interpretation among physicians. There is a lack of local data comparing ECG reading accuracy between general physicians, primary care physicians, and specialists.

KEY FINDINGS

Seven studies (all cross-sectional studies) investigated the accuracy of a 12L-ECG compared to a reference standard (ESC criteria for the diagnosis of heart failure or signs and symptoms of heart failure and left ventricular systolic dysfunction) in the diagnosis of chronic heart failure in a general practice setting.

In all of these studies, the ECG criteria for defining abnormality were broad and not limited to findings of chamber enlargement or atrial fibrillation.

A de novo meta-analysis based on these seven studies showed that an abnormal ECG has a sensitivity of 0.755 (95%, CI 0.657 to 0.832) and a specificity of 0.672 (95%, CI 0.564 to 0.765).

The certainty of evidence is very low due to risk of bias, indirectness, inconsistency, and imprecision.

Despite low certainty of evidence, the consensus panel still gave a strong recommendation to use the 12L ECG for the diagnosis of chronic heart failure but not as the sole diagnostic test.

INTRODUCTION

The electrocardiogram (ECG) is a graphical display of electrical signals recorded on the body surface. These signals are generated by the atrial and ventricular heart muscles in each cardiac cycle. The ECG can reflect underlying cardiac pathology such as:

- a. Chamber enlargement, represented by ECG changes that suggest left ventricular hypertrophy or left atrial enlargement;
- b. Ischemia, represented by Q waves and ST-T wave changes that suggest myocardial infarction; and
- c. Arrhythmia such as atrial fibrillation, the most common type of arrhythmia in patients with heart failure

In determining the accuracy of ECG in the diagnosis of chronic heart failure, it is important to consider who is doing the interpretation and the criteria used for defining an abnormal ECG.

In a study conducted in the UK that compared the ECG interpretation of a general practitioner and that of a hospital physician for 137 suspected heart failure patients from the community, the sensitivity of an ECG interpreted by the general practitioner (53%)

was significantly lower than an ECG interpreted by a hospital physician (95%).¹ On the other hand, the mean sensitivity of 123 Scottish GPs reviewing 180 ECGs was higher at 94%.² In South Africa, a cross-sectional study among 93 GPs showed a competency of less than 35% for correctly identifying atrial fibrillation and myocardial infarction.³

Studies on the diagnostic accuracy of the ECG also used different criteria to define abnormality. Using a broad criteria for ECG abnormality increases the sensitivity but decreases the specificity.

A study estimating the accuracy of 19 ECG variables for the diagnosis of heart failure in 1,058 patients in a community setting showed the following (Table 26)⁴:

Table 26. Estimated sensitivity and specificity of ECG variables for the diagnosis of heart failure in the primary care setting⁴

Characteristic	Sensitivity %	Specificity %
Abnormal ECG	81.14	51.01
Atrial fibrillation	13.45	95.66
Left atrial enlargement	17.88	91.97
Left ventricular hypertrophy	29.77	89.24
Abnormal Q wave	3.4	98.11
Poor R wave progression	9.49	96.01
Ischemic ST-T changes	15.21	93.11
Nonspecific ST-T abnormalities	41.83	74.52
Left bundle branch block	6.52	98.1
Right bundle branch block	6.69	92.82

Each individual ECG parameter has a very low sensitivity of 3-40% but taken together as any abnormal ECG, the sensitivity increases to 81%. Conversely, each individual ECG parameter has a very high specificity, mostly greater than 90%, but taken together as any abnormal ECG, the specificity decreases to 51%.

REVIEW METHODS

A systematic search using MeSH and free text search using the following keywords: “heart failure”, “electrocardiogram”, “sensitivity”, “specificity”, and “primary care” was performed on Medline in , on HERDIN online on April 18, 2023, and on the Cochrane Database for Systematic Review on April 19, 2023. Citations from the retrieved studies and guidelines were also reviewed and appraised. The inclusive dates of the search were from database inception to the date of the search.

The criteria for inclusion for this clinical question are the following:

Table 27. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Population: adult population with signs and symptoms of heart failure Index test: 12L ECG Reference Standard: ESC criteria for the diagnosis of heart failure or signs and symptoms of heart failure and left ventricular systolic dysfunction. Types of studies: meta-analyses, validity studies in the community or out-patient setting	Acute heart failure Admitted patients Pediatric patients

The risk of bias of the studies included in the meta-analysis were appraised using the Painless Evidence-Based Medicine criteria.⁵ The data was summarized using Meta-DiSC 2.0, a freeware software for the meta-analysis of studies on Diagnostic Test Accuracy.⁶

RESULTS

Characteristics of included studies

A systematic search of the published literature yielded 7 cross-sectional studies.

For the population:

These were adult patients from a general practice setting. Four studies were on patients with signs and symptoms of heart failure,^{7-9,12} two studies were on randomly selected patients, with or without symptoms of heart failure,^{4,11} and one study was on COPD patients.¹⁰

For the Index test:

Only one study was on ECG as the primary index test.⁴ The other studies included ECG in the baseline characteristics.⁷⁻¹²

Regarding the criteria for defining abnormal ECG, two studies included any abnormality;^{8,9} four studies included atrial fibrillation^{4,7,10,12}; three studies included left ventricular hypertrophy;^{4,10,11} and three studies included ischemia.^{4,7,10}

Regarding the ECG reader, four studies had their ECGs read by cardiologists;^{4,7,9,10} the reader was not reported in three studies^{8,11,12} but in a meta-analysis, it was mentioned that they were either read by a cardiologist or by automatic reading.¹³

Regarding the reference standard, four studies used the ESC criteria for heart failure;^{4,9,11,12} two studies used signs and symptoms of heart failure accompanied by a LVEF <40% or atrial fibrillation;^{7,8} one study used a consensus diagnosis.¹⁰

Regarding the measurement of accuracy, the sensitivity and specificity of the ECG was reported in two studies.^{4,10} Meanwhile, it was computed from a 2 x 2 table in five studies^{7,8,9,11,12} and only one reported the sensitivity and specificity of the individual ECG parameters.⁴

Regarding the risk of bias, four studies had high risk of bias from incorporation bias.^{7,9,10,12} The characteristics of the included studies are summarized in Appendix III.

Accuracy Measures and Certainty of Evidence

A de novo meta-analysis based on these seven studies showed that an abnormal ECG has a sensitivity of 0.755 (95%, CI 0.657 to 0.832) and a specificity of 0.672 (95%, CI 0.564 to 0.765).

The certainty of evidence was rated “very low” because of incorporation bias (ECG was part of the reference standard for the diagnosis of heart failure), indirectness (the ECG reading was not done by general practitioners), and inconsistency and imprecision from the broad ECG criteria used for defining abnormality.

The forest plot for the meta-analysis is shown in Annex 5, Appendix IV, while the GRADEpro Summary of Findings table is shown in Annex 5, Appendix V.

Based on the sensitivity and specificity, the estimate of effect per 1000 patients tested in terms of the number of patients correctly diagnosed is shown in Table 27.

Table 28. Summary of the Diagnostic Accuracy and the Certainty of Evidence of ECG

Basis	Sensitivity	Specificity	Estimate of Effect per 1000 Patients Tested (pre-test probability of 1.6%*)		Certainty of the evidence (GRADE)
			Estimated # diagnosed	Estimated # missed	
7 Cross-sectional studies	0.755 (95%, CI 0.657 to 0.832)	0.672 (95%, CI 0.564 to 0.765)	True Positives: 11 to 13 True Negatives: 555 to 753	False Positives: 231 to 429 False Negatives: 3 to 5	⊕○○○ Very low
			Estimate of Effect per 1000 Patients Tested (pre-test probability of 29%**)		Certainty of the evidence (GRADE)
			Estimated # diagnosed	Estimated # missed	
			True Positives: 191 to 241 True Negatives: 400 to 543	False Positives: 167 to 310 False Negatives: 49 to 99	⊕○○○ Very low

* The pre-test probability of 1.6% is taken from the reported prevalence of hospitalization due to CHF among adult patients aged 19 years and above in the Philippines last 2014.¹⁴ [14]

** The pre-test probability of 29% is taken from the prevalence of heart failure in patients presenting with dyspnea in a primary care setting.¹⁵

RECOMMENDATION FROM OTHER GROUPS

Table 29. Recommendations of different CPGs regarding the use of 12L ECG for the diagnosis of heart failure.

Guideline	Recommendation	COR/LOE
2022 AHA/ACC/HFSA Heart Failure Guideline ¹⁶	For all patients presenting with HF, a 12-lead ECG should be performed at the initial encounter to optimize management	1 / C-EO
2021 ESC Guidelines on the Management of Acute and Chronic Heart failure ¹⁷	The 12-lead ECG is a recommended diagnostic test in all patients with suspected CHF.	1-C

2019 Malaysian CPG on Heart Failure ¹⁸	<p>Key Recommendation # 2:</p> <p>To confirm the diagnosis and determine the type of HF and the aetiology, the following should be performed:</p> <p>Basic investigations such as ECG, Chest Radiography, blood and urine tests.</p>	None
2018 JCS/JHFS Guidelines on Heart Failure; 2021 Focused Update ¹⁹	In the diagnosis of heart failure, patients should be examined first for symptoms, medical history, their family history, physical findings, ECG, and chest X-ray findings.	None
2018 Australian Guidelines on Heart Failure ²⁰	A 12-lead ECG is recommended in patients with either a suspected diagnosis or new diagnosis of heart failure to assess cardiac rhythm, QRS duration, and the presence of underlying conditions such as myocardial ischaemia or LV hypertrophy.	Strong recommendation FOR; Low quality of evidence
2018 NICE Guidelines on Heart Failure ²¹	Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses: CXR, Blood tests, urinalysis, spirometry	None
2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure ²²	We recommend that a 12-lead electrocardiogram (ECG) be performed to determine heart rhythm, heart rate, QRS duration, and morphology, and to detect possible etiologies	Strong recommendation; Low-Quality Evidence

COR-Class of Recommendation, 1=Strong,

LOE - Level of Evidence, C-EO - Consensus of expert opinion

Class 1 - Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective

Level C - Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Seven clinical practice guidelines from other medical groups were reviewed. The AHA, ESC, Australian Guidelines, and the Canadian Cardiovascular Society recommended taking an ECG to optimize management, identify etiologies or underlying conditions, or guide therapy. They gave a strong recommendation based on low quality evidence. Two guidelines recommended taking an ECG (Malaysian guidelines, Japanese guidelines) for the diagnosis of heart failure. These did not specify the strength of recommendation or quality of evidence.

The NICE also mentioned taking an ECG to identify underlying conditions such as atrial fibrillation but did not specify the strength of recommendation or quality of evidence.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The 12 L ECG is relatively affordable and is available in almost all centers in the country. The cost of the test ranges from Php 250 to Php 1,500.

A health economic study in India showed that ECG screening at primary health centers among patients with high risk cardiovascular disease saves 2.90 life years at an incremental cost of 89.97 USD (6657.47 INR), yielding a cost-effectiveness ratio of 31.07 USD (2,299.06 INR) per life-year saved, which is below the willingness to pay threshold.²³

The reviewer did not encounter local health economic studies or cost-effectiveness studies done on the performance of the test on our specific subset of patients.

PATIENT'S VALUES AND PREFERENCES, EQUITY, ACCEPTABILITY, AND FEASIBILITY

There are no studies on patients' values and preferences regarding 12L ECG as a diagnostic test for heart failure in our population.

ONGOING STUDIES

SOBOTA-HF is a **cross-sectional heart failure prevalence study** which will target 2861 patients in urban communities in Slovenia. Diagnostic studies will include the 12L ECG. Adjudication of a diagnosis of heart failure will be done by an international expert panel.²⁴

GOOD PRACTICE STATEMENTS

The GRADE working group has provided guidance for the writing of good practice statements despite their concern over the inappropriate use of good practice statements by guideline panels.²⁵ "A good practice statement is developed when there appears to be high certainty that the desirable effects of an intervention clearly outweigh its undesirable effects, but the body of supportive evidence is indirect and other criteria for their development are fulfilled."²⁶ The GRADE working group guidance proposes the following five criteria for considering the development of good practice statements: "1) the statement should be clear and actionable; (2) the message should be necessary for actual healthcare practice (ie, without the guidance, clinicians would fail to make the appropriate decision); (3) after considering all relevant outcomes and potential downstream consequences, implementing the GPS would result in large net positive consequences; (4) collection and summary of the evidence would be a poor use of a

guideline panel's time and resources; and (5) a well-documented, clear and explicit rationale connecting the indirect evidence should be constructed".²⁵

Notwithstanding the lack of direct evidence supporting the accuracy of the 12L ECG in the diagnosis of chronic heart failure, the Consensus Panel averred that it is still good practice to perform the 12L ECG in the initial evaluation of patients with chronic heart failure in the outpatient setting to determine abnormalities in cardiac structure, function and rhythm to guide management.

These abnormalities identified through an ECG include myocardial ischemia and infarction and arrhythmia. These conditions are addressed in specific guidelines such as guidelines on ST-elevation MI and NonST-elevation MI, or guidelines on Atrial fibrillation, the comprehensive care of which is beyond the scope of the heart failure guidelines.

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4. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate is the 2D echocardiogram for the diagnosis of heart failure?

Recommendation 4

Among adult Filipinos presenting with dyspnea, PND, and elevated JVP at the outpatient clinic, we recommend the use of 2D-echocardiogram with doppler studies for the diagnosis of heart failure.

(low level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- There are regions in which echocardiograms are unavailable but efforts are being undertaken to improve their availability in the country.
- The CP gave a strong recommendation despite low certainty of evidence because 2D echocardiogram with doppler studies can determine systolic and diastolic function and currently the diagnosis of HF is now echocardiogram-centric.
- Aside from the ejection fraction, 2D echocardiogram can also identify the underlying etiology of HF (i.e. valvular disease, other structural abnormalities) which will help direct management, thus it is considered as a very useful test for heart failure.

KEY FINDINGS

This evidence summary is based on two meta-analyses and three cohort studies which determined the accuracy of using echocardiographic measures of elevated left ventricular filling pressures (LVFP) in the diagnosis of heart failure.

Pooled analysis based on the three cohort studies showed that echocardiographic measures of increased left ventricular filling pressures (LVFP) have a sensitivity of 0.63 (CI 0.378-0.828) and a specificity of 0.89 (CI 0.819-0.93) in diagnosing elevated LVFP, a surrogate indicator of heart failure. Subgroup analysis of patients with heart failure with reduced ejection fraction (HFrEF) showed that echocardiography has a sensitivity of 0.76 (CI 0.61-0.859) and a specificity of 0.70 (CI 0.485-0.847).

One meta-analysis showed that the sensitivity and specificity of Tissue Doppler Imaging has a wide confidence interval, significant heterogeneity, and poor correlation ($r=<0.5$) for the diagnosis of heart failure with preserved ejection fraction (HFpEF). Another meta-analysis showed a statistically significant association (pooled correlation coefficient overall was $r = 0.69$ [95% confidence interval (CI) 0.63–0.75, $P < 0.01$]) between invasive hemodynamic assessment and echocardiographic methods of LVFP assessment. Results are more significant in patients with heart failure with reduced ejection fraction (HFrEF) as compared to heart failure with preserved ejection fraction (HFpEF).

INTRODUCTION

Congestive heart failure is one of the most important public health problems worldwide.^{1,2} It is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. This condition can be classified as HF with reduced EF (HFrEF) in patients with $EF \leq 40\%$, HF with preserved EF (HFpEF) in patient with $EF \geq 50\%$, or HF with mildly reduced EF (HFmrEF). Ejection Fraction is important in the classification of HF because of differing prognoses. According to the ASIAN-HF registry, the one-year crude all-cause mortality rate was 9.6% for the entire population with heart failure, but mortality was greater among patients with HFrEF (10.6%) as compared to those with HFpEF (5.4%).³

The main pathophysiological process in heart failure (HF) is elevation of intracardiac pressures. This is associated with increased left ventricular filling pressure (LVFP) or left ventricular end-diastolic pressure (LVEDP) caused by either systolic or diastolic impairment of left ventricle (LV) function, which has been proven to be a strong predictor of mortality. Measurement of the pulmonary capillary wedge pressure with the Swan-Ganz catheter has become the gold standard for determining LV filling pressure.⁴

An echocardiogram is an ultrasound scan that evaluates the structure and function of the heart and the adjacent major vessels; a two-dimensional echocardiogram provides longitudinal and cross-sectional views of the chambers of the beating heart and great vessels that enter and exit from the heart. Echocardiograms are performed by placing an ultrasound transducer over the chest of the patient and directing it towards the heart. Echocardiography is one of the most readily available non-invasive diagnostic modalities that can assess LV systolic function. Aside from determining the LVEF, echocardiography also provides information on other parameters such as cardiac chamber size, regional wall motion abnormalities, right ventricular function, pulmonary hypertension (pulmonary artery pressure), valvular function, and markers of diastolic function.⁵

REVIEW METHODS

A systematic search was done until December 31, 2022 using Pubmed, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms “congestive heart failure”, “chronic heart failure”, “diagnosis”, “diagnostic accuracy”, “accuracy”, “echocardiogram”, “transthoracic echocardiogram”, and “2d echocardiogram”.

Only studies (systematic reviews, meta-analyses, cohorts) that used echocardiography and compared it to invasive measurements of elevated LV filling pressure in the diagnosis of heart failure among adult patients were included in this review. Outcomes of interest included diagnostic accuracy parameters (sensitivity, specificity, positive predictive value, negative predictive value).

RESULTS

Characteristics of included studies

Two systematic reviews and meta-analyses investigated the accuracy of echocardiographic measures of increased Left Ventricular Filling Pressures (LVFP) in the diagnosis of heart failure. Both were found to be valid using AMSTAR 2.

A systematic review and meta-analysis by Sharifov et al. evaluated the diagnostic accuracy of Tissue Doppler Index (TDI) in estimating left ventricular filling pressure (LVFP) and diastolic dysfunction in patients with heart failure with preserved ejection fraction (HFpEF).⁶ This study included 24 original clinical studies which compared echocardiographic measures of elevated LVFP using TDI (E/e' septal, E/e' lateral, E/e' mean) with the gold standard— invasive LVFP measurements such as LV end diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP). Only studies with HFrEF patients included in the analysis were included in this review. Studies on HFpEF were not appraised since this did not answer our clinical question.

Another systematic review and meta-analysis by Jones et al. evaluated the accuracy of different echocardiographic measures of LVFP compared with invasive hemodynamic studies in the diagnosis of heart failure.⁷ The study included 27 studies with 2,058 patients which used invasive hemodynamic studies as the gold standard. Among the 27 studies included in the meta-analysis, eight focused on patients with HfrEF, eleven included patients with HFpEF, and another eleven used a heterogeneous population.

A study by Lancelloti et al. compared the diagnostic accuracy of the 2009 and 2016 echocardiographic grading algorithms for predicting invasively measured left ventricular filling pressure.⁸ The study included 159 patients undergoing clinically indicated

coronary angiography. The study participants included patients with HF with reduced EF (25%) and patients with NYHA \geq II (64%).

Another study by Andersen et al. also evaluated the diagnostic accuracy of comprehensive echocardiography in identifying patients with elevated LV filling pressure.⁹ The study included 450 patients referred for right or left heart catheterization. LVEF was <50% in 209 of 450 patients (46.4%) with a mean LVEF of 47%.

A study by Balaney et al. studied the accuracy of the 2016 American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines for echocardiographic evaluation of LV diastolic function against invasively measured LV filling pressures using right heart catheterization and compared it with the accuracy of the 2009 guidelines.¹⁰ The study included 90 patients who were referred for clinically indicated left heart catheterization and underwent transthoracic echocardiography prior to the procedure. The reference standard was increased invasive LV preatrial contraction (pre-A) pressure measurements defined as >12 mm Hg.

Efficacy outcomes

In the systematic review and meta-analysis by Sharifov et al., the summary data for the diagnostic accuracy of TDI E/e (lateral, mean and septal) to identify elevated LVFP showed low sensitivity ranging from 0.25-0.37 and high specificity ranging from 0.91-0.98 with wide confidence intervals and significant heterogeneity⁶ (Annex 6, Appendix V, Figure 1). Only the E/e septal had a sufficiently high positive likelihood ratio (LR+12) in identifying elevated LVFP. The LR+ for E/e lateral and E/e mean were both low (3.8 and 4.1, respectively). Results of the meta-analysis showed that in random-effects models, TDI E/e had poor to mediocre linear correlation with LVFP ($r=<0.5$) (Annex 6, Appendix V, Figure 2).

In the meta-analysis of Jones et al., results showed a statistically significant association between invasive hemodynamic assessment and echocardiographic methods of LVFP assessment.⁷ The pooled correlation coefficient overall was $r = 0.69$ [95% confidence interval (CI) 0.63–0.75, $P < 0.01$] (Annex 6, Appendix V, Figure 3). Analysis of cohort showed that different disease states have varying correlation coefficients with HFrEF showing a higher correlation coefficient ($r = 0.67$, 95% CI 0.61–0.72) compared with that of HFpEF ($r = 0.59$, 95% CI 0.53–0.64) (Annex 6, Appendix V, Figure 4 and Figure 5.). However, there was also significant heterogeneity in both the quality of the studies and their findings due to inclusion of a heterogeneous population.

Pooled analysis of the three cohort studies (Lancelloti, Andersen and Balaney) showed that echocardiography using the 2016 ASE/EACVI guidelines had a sensitivity of 0.63 (CI 0.378-0.828), a specificity of 0.89 (CI 0.819-0.93), a LR+ of 5.5, and a LR- of 0.41 in

diagnosing elevated LVFP (Annex 6, Appendix V, Figure 6-A). Subgroup analysis of patients with HFrEF showed that echocardiography had a sensitivity of 0.76 (CI 0.61-0.859), a specificity of 0.70 (CI 0.485-0.847), a LR+ of 2.5 and a LR- of 0.35 (Annex 6, Appendix V, Figure 6-B).

Safety outcomes

There are no studies which directly showed evidence that performing echocardiography reduces the risk of poor outcomes from heart failure. There is also no direct evidence that shows that performing echocardiography resulted in harm.

Certainty of evidence

The two meta-analyses included in this review were assessed to be of moderate quality using the AMSTAR2 critical appraisal tool; neither of the meta-analyses performed graphical or statistical tests for publication bias. Both meta-analyses were also downgraded to low certainty because of significant heterogeneity in both the quality of the studies and their findings due to a heterogeneous population. Meanwhile, the systematic review and meta-analysis by Sharifov et al.⁶ was downgraded to very low certainty due to its indirectness since it only included patients with heart failure with preserved ejection fraction.

The certainty of evidence of the three cohort studies included in the review was considered low due to their indirectness (all three studies included patients with or without heart failure who were admitted for clinically indicated left or right heart catheterization) and imprecision (all three had small sample sizes).

RECOMMENDATIONS FROM OTHER GROUPS

Table 30. Recommendations from different guidelines regarding the use of echocardiography for the diagnosis of heart failure

Group	Recommendation	Strength of recommendation and certainty of evidence
ACC/AHA 2022	In patients with suspected or newly diagnosed HF, transthoracic echocardiography (TTE) should be performed during initial evaluation to assess cardiac structure and function.	IC-LD

ESC 2021	Echocardiography is recommended as the key investigation for the assessment of cardiac function and of the LVEF. Echocardiography also provides information on other parameters such as chamber size, eccentric or concentric LVH, regional wall motion abnormalities (that may suggest underlying CAD, Takotsubo syndrome, or myocarditis), RV function, pulmonary hypertension, valvular function, and markers of diastolic function.	IC
NICE 2018	<p>Studies which used echocardiography as the reference standard which was included in the 2010 update have been excluded within the current update as the committee agreed that echocardiography was not an appropriate reference standard for the diagnosis of heart failure.</p> <ol style="list-style-type: none"> Because very high levels of NT-proBNP suggest poor prognosis, refer people with suspected heart failure and an NT-proBNP level above 2,000 ng/litre (236 pmol/litre) urgently to obtain specialist assessment and transthoracic echocardiography within two weeks. Refer people with suspected heart failure and an NT-pro BNP level between 400 and 2,000 ng/litre (47 to 236 pmol/litre) to obtain specialist assessment and transthoracic echocardiography within six weeks Perform transthoracic echocardiography to exclude important valve disease, assess the systolic (and diastolic) function of the (left) ventricle, and detect intracardiac shunts. 	
Australian 2018	A transthoracic echocardiogram is recommended in patients with suspected heart failure to improve diagnostic accuracy as well as in patients with a new diagnosis of heart failure to assess cardiac structure and function (including the measurement of LV ejection fraction [LVEF]), assist in classification, and, therefore, guide management.	Strong recommendation FOR-Low quality of evidence
Malaysian 2019	To confirm the diagnosis and to determine the type of HF and its aetiology, the following should be performed: an echocardiogram to help determine the type of HF (HFrEF, HFmrEF or HFpEF) and identify structural cardiac defects.	I-C
JCS 2017	Perform echocardiography to assess cardiac function, left ventricular wall motion, valvular disease, right ventricular function, and pulmonary hypertension in patients suspected of having heart failure.	I-C

Canadian 2017	We recommend that echocardiography be performed in all patients with suspected HF to assess cardiac structure and function, to quantify systolic function for planning and monitoring of treatment, and to perform prognostic stratification.	Strong Recommendation, Moderate Quality of Evidence
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ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

The reviewer did not encounter studies on the cost-effectiveness of using echocardiography to diagnose HF in the Philippines. The cost of performing 2D Echocardiography with Doppler Studies in the different government and private hospitals in Manila and Laguna is between Php 3,000 and Php 5,000.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Echocardiography is non-invasive and available in most secondary and tertiary hospitals, as well as in most diagnostic centers in the country. According to the PHIL-SCREEN study by Magno et al., as of 2021, the Philippines has at least 651 physician echocardiographers, 2,487 cardiac sonographers, and 539 cardiac laboratories.¹¹ Based on the surveys, the majority of cardiac laboratories where echocardiograms are performed are located in the National Capital Region (28.7%), followed by Region 4A Calabarzon (17.8%), and Region 3 Central Luzon (15.9%). In comparison, according to the Philippine Society of Cardiac Catheterization and Intervention (PSCCI), as of 2022, there are only 55 cardiac catheterization laboratories in the country that can perform the invasive procedures that are considered as the gold standard in diagnosing elevated LVFP.

OTHER STUDIES

Other forms of cardiac imaging such as the Point of Care Ultrasonography or POCUS echo that is done at the bedside have been studied on patients presenting with signs and symptoms of Acute Heart Failure in the emergency room. Studies on its benefits and accuracy in diagnosing patients with chronic heart failure will be beneficial especially for Filipinos living in the far-flung areas of the country where there are no available 2D echocardiograms with doppler studies.

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5. Among adult Filipinos presenting with signs and symptoms of chronic heart failure at the outpatient clinic, how accurate are cardiac biomarkers (BNP, NT-pro BNP) for the diagnosis of heart failure?

Recommendation 5

Among adult Filipinos presenting with unexplained dyspnea at the outpatient clinic, we suggest point-of-care BNP or NT proBNP testing, if available, to diagnose or rule out chronic heart failure.

(low level of evidence, weak recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- Availability of point of care testing in the locality
- The use of BNP or NTproBNP not only to diagnose but to rule out HF in patients with unexplained dyspnea

KEY FINDINGS

In the systematic review by Taylor et al.,³ 42 publications of 39 individual studies met the inclusion criteria and 37 studies were included in the analysis. Of these, 30 studies evaluated BNP POCT and seven studies evaluated NT proBNP. Fifteen (15) studies were done in an ambulatory care setting with low prevalence of chronic HF. Five studies were done in primary care settings.

- At thresholds of more than 100 pg/mL, the pooled sensitivity of BNP, measured with the point-of-care index device Triage, was generally high at 0.95 (95% confidence interval 0.90 to 0.98) at 100 pg/mL and had a pooled specificity of 0.56 (0.39-0.60).
- At thresholds of less than 100 pg/mL, the sensitivity ranged from 0.46 to 0.97 while the specificity ranged from 0.31 to 0.98. BNP was measured with the point-of-care index device Triage.

- Primary care studies that used NT proBNP testing reported a sensitivity of 0.99 (0.57 to 1.00) and a specificity of 0.60 (0.44 to 0.74) at 135 pg/mL.
- No statistically significant difference in diagnostic accuracy was found between point-of-care BNP and NT proBNP testing.

Subgroup analysis of patients presenting with dyspnea alone

In Worster et al.,⁴ 4,338 studies were screened and 9 studies were included in the analysis. BNP and NT pro-BNP at thresholds of more than 100 and 400 pg/mL, respectively, were determined at an ambulatory care setting using POCT. The use of BNP had a sensitivity of 0.94 (0.87-0.98) and a specificity of 0.94 (0.89-0.97). Meanwhile, the use of NT pro-BNP had a sensitivity of 0.96 (0.89-0.99) and a specificity of 0.73 (0.45 – 0.92).

In McCullough et al.,⁵ 1,586 patients presenting with dyspnea were included in the study. BNP levels at a threshold of more than 100 pg/ml were determined in primary and ambulatory care settings by POCT and had a sensitivity of 0.90 (0.86–0.93) and a specificity of 0.73 (0.64 – 0.81).

INTRODUCTION:

Brain natriuretic peptide (BNP) is a member of a family of four human natriuretic peptides that share a common 17-peptide ring structure. The first was identified in 1983 and was named atrial natriuretic peptide (ANP). ANP is a 28-amino acid polypeptide resulting from the C-terminal end of the prohormone pro-ANP. ANP is largely produced in the cardiac atria, and is quickly secreted in response to atrial stretching. Normal hearts secrete extremely small amounts of ANP but elevated levels are found in patients with left ventricular (LV) hypertrophy and mitral valve disease. After proBNP is secreted in response to volume overload and the resulting myocardial stretch, it is cleaved into the 76-peptide, biologically inert N -terminal fragment NT-proBNP and the 32-peptide, biologically active hormone BNP. The two fragments are secreted into the plasma in equimolar amounts and have both been clinically evaluated for use in the management of congestive heart failure (CHF). High ventricular filling pressures stimulate the release of ANP and BNP. Both peptides have diuretic, natriuretic, and antihypertensive effects which they exert by inhibiting the renin-angiotensin-aldosterone system. They also have systemic and renal sympathetic activity. In addition, BNP may also provide a protective effect against the detrimental fibrosis and remodeling that occurs in progressive heart failure.¹

Natriuretic peptide receptors and plasma endopeptidases actively clear BNP from circulation. As such, the plasma half-life of BNP is short at approximately 20 minutes. Meanwhile, no receptor-mediated clearance of NT-proBNP is known to occur. As such, NT-proBNP has a correspondingly prolonged half-life of 60-120 minutes. As a result, plasma levels of NT-proBNP tend to be three to five times higher than BNP levels. Clearance of NT-proBNP is thought to be primarily renal. Therefore, the renal clearance of NT-proBNP confounds its diagnostic utility in patients with renal insufficiency.¹

As a laboratory specimen, NT-proBNP is more stable during storage than BNP. NT-proBNP samples are stable at room temperature for 72 hours, in contrast to BNP samples which are stable at room temperature for less than 4 hours.²

Reference Range:

The reference values of brain-type natriuretic peptide (BNP) and N-terminal (NT) proBNP are different to exclude or confirm a diagnosis of heart failure. These values also depend on age and gender and are higher in elderly persons and women.

Normal findings are as follows²

- BNP: < 100 pg/mL
- NT-proBNP: < 300 pg/mL

Critical values¹¹

- **BNP**
BNP >400 pg/mL (heart failure likely)
BNP >100 pg/ml (NICE and ESC consensus)
- **NT-proBNP**
NT-proBNP > 400 pg/ml (NICE and ESC consensus)

REVIEW METHODS

- A systematic search was done from the date of the last search, January 15, until February 3, 2023 using Medline and Google Scholar with a combined MeSH and free text search using the terms “chronic congestive heart failure”, “accuracy of BNP and NT proBNP”, “POCT”, “diagnosis”, “ambulatory care”, “primary care”, and “outpatient department”.

- Only cross-sectional and cohort studies that used BNP and NT-proBNP as index tests and a combination of clinical, radiologic (including 2D echocardiography), and various laboratory tests as reference standard were included in the review. Measures of accuracy such as sensitivity, specificity, positive and negative predictive values, and likelihood ratios were considered as outcome measures. No limits were placed on age, sex, race, or severity of illness. However, limits regarding the setting in which the tests were performed were observed—the tests must have been done only in an ambulatory care/outpatient setting using a point-of-care platform—and the studies must have only been conducted in the last 10 years.
- The risk of bias of the individual studies was evaluated using the QUADAS risk of bias assessment.

RESULTS:

CHARACTERISTICS OF THE INCLUDED STUDIES

The Medline search yielded one result while the free search using Google Scholar yielded 5,940 results. Out of these hits, two systematic reviews and one cross-sectional study were retrieved and appraised. Two systematic reviews by Taylor et al.,³ Worster et al.,⁴ and an observational study by McCullough⁵ were used in this review.

In the systematic review by Taylor et al.,³ 42 publications of 39 individual studies met the inclusion criteria and 37 studies were included in the analysis. Thirty studies evaluated BNP POCT and seven studies evaluated NT-proBNP. Fifteen studies were conducted in an ambulatory care setting with low prevalence of chronic HF. Meanwhile, five studies were conducted in primary care settings. Reference tests included clinical assessment with retrospective review by one or more doctors (which was usually a cardiologist) and echocardiography.

The population included all adults with the following presentations: Dyspnea (15 studies); Several CHF symptoms (6 studies); Echocardiography referrals (5 studies); CV risk factors (2 studies); Cardiac rehab referral with stable CHF (2 studies); Acute coronary embolism (1 study); and Non-cardiac on mechanical ventilator (1 study).

The prevalence of the condition ranged from 19% to 44% in a primary care setting and was below 50% in an acute care setting. In the primary care setting, two studies assessed BNP and the results ranged from 5.1 to 412 pg/ml. Meanwhile, three studies assessed NT pro-BNP with results ranging from 117 to 1000 pg/mL.

The reference standard used across all studies included clinical assessment and retrospective review of diagnosis by one or more doctors (usually a cardiologist), and a 2D echocardiogram.

Subgroup analysis of patients presenting with dyspnea alone:

In Worster et al.,⁴ 4,338 studies were screened and nine studies were included in the analysis. BNP and NT-proBNP at thresholds of more than 100 pg/mL and 400 pg/mL, respectively, were determined at an ambulatory care setting using POCT .

In McCullough et al.,⁵ 1,586 patients presenting with dyspnea were included in the study and BNP levels at a threshold of more than 100 pg/ml were determined in a primary and ambulatory care setting using POCT.

EFFICACY OUTCOMES:

In a systematic review by Taylor et al.,³ the results are as follows:

1. At thresholds of <100 pg/mL, sensitivity ranged from 0.46 (95% confidence interval 0.32 to 0.61) to 0.98 (0.93 to 1.00) while specificity ranged from 0.31 (0.22 to 0.41) to 0.98 (0.95 to 1.00). The two studies in primary care settings reported sensitivities ranging from 0.46 (0.32 to 0.61) to 0.92 (0.81 to 0.98) and specificities ranging from 0.38 (0.31 to 0.46) to 0.82 (0.79 to 0.85) at a range of thresholds <100 pg/mL (10-50 ng/mL).
2. Pooled data at thresholds recommended by the ESC^{7,8} and the NICE guidelines¹⁰ for studies in ambulatory care settings with a low prevalence of CHF showed that the sensitivity of BNP was highest at 100 pg/mL, as recommended by NICE¹⁰ in all settings. Meanwhile, the use of BNP as recommended by ESC for acute settings had a pooled sensitivity of 0.95 (95% confidence interval 0.90 to 0.98) and a pooled specificity 0.64 (0.46 to 0.78). This was based on seven studies in emergency settings with a prevalence of CHF between 20% and 48%.
3. In studies done in ambulatory care settings with a cross-sectional/cohort design and a threshold of 125 pg/mL, as recommended by the ESC^{7,8} for non-acute settings, the paired sensitivity and specificity plots for the Cardiac Reader test showed high sensitivity pooled sensitivity (0.99) (95% confidence interval 0.57 to 1.00), moderate specificity (pooled specificity 0.60 (0.44 to 0.74)), and increased specificity at higher thresholds, based on three primary care studies. At 400 pg/mL, the threshold recommended by NICE,¹⁰ sensitivity ranged from 0.59 (0.49 to 0.68) to 0.88 (0.77 to 0.96) while specificity ranged from 0.79 (0.73 to 0.84) to 0.90 (0.84 to 0.94) in the two studies conducted in a primary care setting.

Subgroup analysis of patients presenting with dyspnea alone:

In Worster et al.,⁴ 4,338 studies were screened and nine studies were included in the analysis. BNP and NT-proBNP at thresholds of more than 100 pg/mL and 400 pg/mL, respectively, were determined at an ambulatory care setting using POCT. The results showed that the use of BNP had a sensitivity 0.94 (0.87-0.98) and a specificity 0.94 (0.89-0.97), while the use of NT-proBNP had a sensitivity of 0.96 (0.89-0.99) and a specificity of 0.73 (0.45 – 0.92)

In McCullough et al.,⁵ 1,586 patients presenting with dyspnea were included in the study. BNP levels at a threshold of more than 100 pg/mL were determined in primary and ambulatory care settings through POCT. The results revealed a sensitivity of 0.90 (0.86–0.93) and a specificity of 0.73 (0.64–0.81).

Despite the high sensitivity and moderate specificity at different cut-off thresholds, serious risks of biases were seen in the study, such as:

1. Setting the cut-off at pre-specified values – it is also unclear if the studies followed the prescribed thresholds.
2. Issues regarding blinding – it is unsure if the interpreter of the index test was truly unaware of the results of the reference standards.
3. The issue of different reported accuracies with different POCT brands, the low prevalence of the condition in the ambulatory care setting, as well as the scarcity of studies with only a few studies having analyzed NT-proBNP.

It was due to these serious methodological issues that the certainty of evidence was downgraded to low certainty. It is therefore not recommended for routine testing in the outpatient setting as a stand alone test

CERTAINTY OF EVIDENCE:

The certainty of evidence of the systematic review by Taylor et al.³ included in this review was evaluated using GRADEPRO and was assessed to be low because of the following reasons:

1. Setting the cut-off at pre-specified values. It is also unclear if the studies actually followed the prescribed thresholds.
2. Blinding issues; it is uncertain if the interpreter of the index test was truly unaware of the results of the reference standards.

3. Different accuracies were reported among the different POCT brands. The prevalence of the condition was also low in an ambulatory care setting. Only a handful of studies have analyzed the use of NT-proBNP.

RECOMMENDATIONS FROM OTHER GROUPS

Table 31. Recommendations from different guidelines regarding the use of cardiac biomarkers for the diagnosis of heart failure

Group or Agency	Recommendation	Strength of recommendation/ certainty/ quality of evidence
American College of Cardiology Foundation (ACCF), American Heart Association (AHA), 2013, 2017	<p>Recommendation for the use of BNP or NT-proBNP values in the diagnosis of heart failure in ambulatory patients with dyspnea, especially when the diagnosis is uncertain, as well as their use in establishing the prognosis or disease severity in ambulatory patients with chronic heart failure.</p> <p>Recommendation to use BNP or NT-proBNP in determining optimal dosing for select ambulatory patients who are clinically euvolemic and are undergoing medical therapy in a well-structured heart failure management program.</p>	<p>Class I</p> <p>Class IIa</p>
European Society of Cardiology 2012	Recommends obtaining BNP or NT-proBNP levels in the workup of heart failure particularly when the diagnosis is unclear.	No grading for strength of recommendation and certainty of evidence
Canadian Cardiovascular Society (2017)	<p>Recommends that BNP/NT-proBNP levels be measured to help confirm or rule out a diagnosis of HF in the acute or ambulatory care setting in patients whose cause of dyspnea is in doubt</p> <p>Recommends that the measurement of BNP/NT- proBNP levels be considered in patients with an established diagnosis of HFrEF for prognostic stratification, in view of optimizing medical therapy</p>	<p>Strong Recommendation; High-Quality Evidence).</p> <p>Strong Recommendation; High-Quality Evidence).</p>
NICE 2018	Recommends the testing for NT-proBNP in patients with suspected heart failure.	No grading for strength of recommendation and certainty of evidence

	Patients with NT-proBNP between 400 to 2000 pg/mL should be referred to a specialist and must undergo echocardiography within 6 weeks	
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ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The cost of testing for NT-pro BNP ranges from 3,000 to 4500 pesos. Point of care testing costs around 2,000 pesos.

The reviewer did not encounter local studies on the financial impact of testing. However, some studies conducted in Sweden have shown that sequential testing can reduce costs for a negative NT-proBNP result (rule-out), and that it could be compared with the cost of echocardiography. These studies have also shown that a strict sequential testing strategy that minimizes the demand for echocardiography could potentially save two to three euros per capita per year. By strictly implementing this simple screening strategy, the health care system could potentially save as much as 19 to 28 million euros per year.¹¹ As to whether such a strategy would be applicable to the Philippine setting has yet to be validated through real-world data and research.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Equity

The cost of testing is the primary concern. Furthermore, the test is only available in big healthcare facilities in urbanized areas making it less accessible to those who live in remote rural areas.

A point of care platform for the test is available and remains a good option for fully automated analyzers.

Feasibility

The test is readily available in most big healthcare institutions that use expensive, fully-automated analyzers. As such, access is a challenge for healthcare facilities with low resources.

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6. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, what is the effect of baseline determination of serum electrolytes and creatinine on cardiovascular mortality, heart failure-related hospitalization, and quality of life?

Recommendation 6

Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, we recommend determining the baseline value of serum sodium, potassium, and creatinine to guide management.

(very low level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- The CP gave a strong recommendation despite low certainty of evidence for performing laboratory examinations for kidney function, serum sodium and potassium levels because these tests are needed prior to starting treatment to determine the presence of contraindications to the use of pharmacologic therapy.
- Physicians need to determine baseline serum creatinine and electrolytes since the treatment and management of chronic heart failure is continuous. These laboratory examinations can also be used to monitor the adverse effects of treatment and treatment response.

KEY FINDINGS

Cohort Studies

Four cohort studies^{2,3,4,5} included in the de novo meta-analysis showed a pooled RR of 1.46 (95% CI 1.32 – 1.62, p <0.00001) for mortality among patients diagnosed with chronic heart failure at the outpatient clinic with a **baseline serum sodium of <135 mEq/L (Hyponatremia)**.

One cohort study⁶ showed a RR of 1.09 (95% CI 1.05 – 1.14, p <0.0001) for mortality among patients diagnosed with chronic heart failure at the outpatient clinic with a **baseline serum sodium of >145 mEq/L (Hypernatremia)**.

Two cohort studies^{7,8} included in the de novo meta-analysis showed a pooled RR of 1.16 (95% CI 1.07 – 1.25, p<0.0003) for mortality among patients diagnosed with chronic heart failure at the outpatient clinic with a **baseline serum potassium of <4 mEq/L (Hypokalemia)**.

One cohort study⁹ showed a RR of 1.67 (95% CI 1.48 – 1.89, p <0.00001) for mortality among patients diagnosed with chronic heart failure at the outpatient clinic with a **baseline serum potassium of >5 mEq/L (Hyperkalemia)**.

Two cohort studies^{10,11} included in the de novo meta-analysis showed a pooled RR of 1.89 (95% CI 1.67–2.14 p<0.00001) for mortality among patients diagnosed with chronic heart failure at the outpatient clinic with a **baseline serum creatinine of >1.2 mg/dL**.

INTRODUCTION

The physiologic actions of the heart and kidneys are so tightly intertwined that any disturbance in one can have an impact on the action of the other. The preload of the heart depends on the sodium and water homeostasis of the kidneys, while the kidney depends on the adequate contraction and relaxation of the heart to maintain renal blood flow. This normal physiology becomes impacted by congestive heart failure, which initially leads to electrolyte imbalance and, eventually, to kidney dysfunction. Several pathophysiologic mechanisms are involved in this derangement such as the reduction of renal blood flow and glomerular filtration rate, the activation of the renin-angiotensin II-aldosterone axis, the elevation of arginine vasopressin levels, the enhancement of sympathetic nervous system tone, catecholamine release, and other factors. Kidney dysfunction and electrolyte imbalances may also have an arrhythmogenic effect on diseased myocardium.¹⁴

Chronic kidney disease, defined as the presence of a glomerular filtration rate less than 60 mL/min/1.73 m² or of albuminuria, is present in 4.5% of the general population and afflicts about 50% of patients with heart failure. The normal range of serum creatinine is 0.7 – 1.2 mg/dL for men, and 0.6 – 1.1 mg/dL for women. Renal impairment is defined as a serum creatinine level greater than 1.0 mg/dL, creatinine clearance or estimated GFR less than 60 mL/min/1.73m². Renal dysfunction is extremely common in patients with chronic heart failure.⁷ The presence of CKD is associated with doubling the risk of all-cause mortality and is a stronger predictor of adverse outcomes. In addition to the

prognostic role of CKD, dynamic changes in kidney function have also been recognized to cause poorer prognosis.

Low serum sodium (hyponatremia), low serum potassium (hypokalemia), and low serum magnesium (hypomagnesemia) are the most common electrolyte derangements in chronic heart failure. Although these conditions are usually seen in patients with more advanced and refractory stages, they can also be seen in mild or compensated heart failure in the presence of therapy-related complications, particularly in the excessive use of diuretics. Hyponatremia is defined as a serum sodium concentration of less than 135 mEq/L but may vary to some extent depending on the set values of various laboratories.¹³ Hypernatremia is defined as a serum sodium concentration of greater than 145 mEq/L. Serum potassium is maintained between 3.5 and 5.3 mmol/L by renal excretion and by shifts between cellular compartments. Hypokalemia is a strong independent predictor of mortality in heart failure because of its arrhythmogenic property. These electrolyte imbalances are of vast clinical importance because they not only represent an immediate risk to the patient with chronic heart failure, but also can lead to an unfavorable clinical course and an adverse therapeutic response. The optimal care of the chronic heart failure patient includes the recognition and management of these serum electrolyte disturbances.¹⁴

REVIEW METHODS

The initial approach for this clinical question was to use the serum electrolyte abnormalities as a screening tool for congestive heart failure. Upon searching the literature for answers, however, the evidence reviewers found that their search yielded negative results for the use of electrolyte abnormalities as a screening tool for heart failure. The studies encountered during the initial search yielded studies regarding electrolyte abnormalities and their association to outcomes among patients with congestive heart failure. Thus, it was recommended by the steering committee that the clinical question be of prognostic value, with each serum electrolyte abnormality associated with a disease outcome—cardiovascular mortality, hospitalization, and quality of life.

A systematic search was done on electronic databases (Medline, Google Scholar, HERDIN Plus, and Cochrane Database for Systematic Reviews) between November and March 2023. Combined MeSH and free text search using the terms “serum sodium”, “hyponatremia”, “hypernatremia”, “serum potassium”, “hypokalemia”, “hyperkalemia”, “serum creatinine”, “heart failure”, “chronic heart failure”, “outpatient clinic”, “ambulatory care”, “primary care”, “mortality and hospitalizations”, “RCT”, “cohort”, and “case-control studies”. The references of included studies and published

meta-analyses were also searched. Inclusive dates of the search were from database inception until March 30, 2023. There were no limits on publication language.

The included studies for the meta-analysis were appraised using Newcastle Ottawa Scale (NOS).

RESULTS

Characteristics of the included studies

We were able to identify four cohort studies for hyponatremia, two cohort studies for hypokalemia, and two cohort studies for elevated serum creatinine in answering the dilemma of determining prognosis among chronic heart failure patients. We could only find one study each for hypernatremia and hyperkalemia. All of the studies were cohort studies, mostly retrospective with a few prospective studies. Patients were monitored based on their measured serum electrolyte levels and were compared to patients with the same condition albeit with normal serum electrolyte levels (See Tables 32-35).

Table 32. Summary of included studies on the use of serum electrolytes and serum creatinine

	Guideline	Evidence Review
M		10 cohort studies
P	Adult patients with chronic heart failure at outpatient clinics	8 cohort studies (baseline serum electrolytes and creatinine were taken during the first visit at the outpatient clinics), 2 cohort studies (baseline serum electrolytes and creatinine were taken during last hospital visit and first visit at the outpatient clinics)
I	Abnormal levels of serum Na, K and creatinine	4 cohort studies (serum Na level <135 mEq/L) 1 cohort study (serum Na >144 mEq/L) 2 cohort studies (serum K<3.5 mEq/L) 1 cohort study (serum K >5 mEq/L) 2 cohort studies (serum creatinine >1.2 mg/dl)
C	Normal levels of serum Na, K, and creatinine	All compared to normal levels of serum Na, K, and creatinine
O	All-cause mortality	All-cause mortality (10)
RoB		High risk of bias (10)

Table 33. Included studies for chronic heart failure with baseline serum sodium of <135 mEq/L (hyponatremia)

Authors, Country Study design	Population	Exposure	Outcome	Comments
Alem 2020 Saudi Arabia Retrospective cohort	241 patients with chronic heart failure Mean age: 60.6 ± 12.6 65.1% male	Serum Na <135 mEq/L N= 207 Serum Na 135-144 mEq/L N= 34	All-cause mortality Serum Na <135 mEq/L 87/207 = 42% Serum Na 135-145 mEq/L 17/ 34 = 50% RR: 1.19 (95%CI: 0.82, 1.73)	Mixed inpatients and outpatients diagnosed with chronic heart failure 24-month follow-up (from the time serum Na measurements were taken)
Balling 2014 Denmark 18 Danish HF clinics Retrospective cohort	3465 patients with heart failure Mean age: 68 73% male	Serum Na <136 mEq/L N= 2863 Serum Na 136-144 mEq/L N= 602	All-cause mortality Serum Na <136 mEq/L 429/2863 = 15% Serum Na 136-145 mEq/L 147/602 = 24.4% RR: 1.63 (95% CI:1.38, 1.92)	A baseline measurement of serum Na obtained at the initial clinic visit All endpoints were obtained from The Danish National Patient Registry Median follow-up time was 495 (1–1660) days
Bavishi 2018 USA ambulatory clinics of US Dept of Veterans Affairs (VA) medical center Retrospective cohort	6158 patients with heart failure Mean age: 70 95% male	Serum Na ≤135 mEq/L N= 847 Serum Na 136-144 mEq/L N= 5311	Serum Na ≤135 mEq/L 292/847 = 34.5% Serum Na 136-145 mEq/L 1307/5311 = 24.6% RR: 1.40 (95% CI: 1.26, 1.55)	Variables with >20% missing values were excluded 2-year follow-up

DeWolfe 2008 Louisiana, USA Heart Failure Disease Management Program (HFMDP) Prospective Cohort	364 patients with heart failure Mean age: 55 Majority were male	Serum Na <135 mEq/L N= 48 Serum Na 135-144 mEq/L N= 316	Serum Na <135 mEq/L 8/48 = 17% Serum Na 135-144 mEq/L 31/316 = 9.8% RR: 1.70 (95% CI: 0.83, 3.27)	Mortality information was obtained through the Social Security Death Index 40-month follow-up
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Table 34. Included studies with chronic heart failure at the outpatient clinic with serum potassium of <3.5 mEq/L (hypokalemia)

Authors, Country, Study design	Population	Exposure	Outcome	Comments
Ahmed 2008 USA 302 centres (186 in the United States and 116 in Canada) Cohort	6845 HF patients in the Digitalis Investigation Group trial Mean age: 63 ± 11 69% were male	Serum K <4 mEq/L N = 1187 Serum K 4-4.9 mEq/L N = 1187	Serum K <4 mEq/L 441/1187 = 37.2% Serum K ≥4 mEq/L 379 / 1187 = 31.9% RR: 1.16 (95% CI: 1.07, 1.25)	A median follow-up of 36.7 months
Alper 2009 USA Cohort	2231 HF patients in the Digitalis Investigation Group trial Mean age: 72 ± 6 71% were male	Serum K <4 mEq/L N = 561 Serum K 4-4.9 mEq/L N = 1670	Serum K <4 mEq/L 242 / 561 = 43.1% Serum K 4-4.9 mEq/L N = 625 /1670 = 37.4% RR: 1.15 (95%CI: 1.03, 1.29)	32-month follow-up

Table 35. Included studies with chronic heart failure at the outpatient clinic with baseline serum creatinine of >1.1 mg/dL

Authors, Country, Study Design	Population	Exposure	Outcome	Comments
Hillege 2006 Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Overall program Cohort	1087 enrolled from CHARM-Preserved, 931 from CHARM-Added, and 662 from CHARM-Alternative	Serum Creatinine >1.2 mg/dL N=996 Serum Creatinine ≤1.2 mg/dL N=1714	Serum Creatinine >1.2 mg/dl 330/996= 33.1% Serum Creatinine ≤1.2 mg/dl 295/1714= 17.2% RR: 1.93 (95%CI: 1.68, 2.21)	Median follow-up of 34.4 months (range, 1 day to 45.2 months)
Mahon 2002 Ohio, USA Digitalis investigation group (DIG) trial Cohort	585 participants of the 6-min walk substudy of the Digitalis Investigation Group (DIG) trial. Mean age: 65±12 Majority are male	Serum Creatinine >1.2 mg/dl N=291 Serum Creatinine ≤1.2 mg/dl N=294	Serum Creatinine >1.2 mg/dl 97/291 = 33.3% Serum Creatinine ≤1.2 mg/dl 56/294 = 19% RR: 1.75 (95% CI: 1.31, 2.33)	Follow-up for up to five years (median 3.2 years)

Efficacy Outcomes

Impact of Serum sodium levels on Mortality

Based on the four cohort studies, serum sodium (Na) levels of < 135 mmol/L are associated with a significant risk for overall mortality (RR = 1.46, 95% CI 1.34-1.59) compared to chronic heart failure patients with normal serum sodium levels. The results verified that the lower the serum sodium level, the higher the risk for mortality in several observational studies. We could only find one cohort study for hypernatremia (> 145 mmol/L) and it showed a significant risk for overall mortality (RR= 1.09, 95% CI 1.05-1.14).

Impact of Serum potassium levels in Mortality

Two cohort studies were used in the outcomes, and low serum potassium (K) levels of < 3.5 mEq/L were associated with an increased overall mortality (RR 1.09, 95% CI 1.05-1.14) compared to chronic heart failure patients with normal levels of potassium. Chronic heart failure patients seen at the OPD with a baseline serum potassium of > 5 mEq/L are 1.7 times more likely to die as compared to chronic heart failure patients with normal baseline serum potassium.

Impact of Elevated Serum creatinine in Mortality

Two cohort studies were used to gauge overall mortality in chronic heart failure patients. The studies showed that patients with elevated serum creatinine levels of > 1.2 mg/dL have a higher risk of overall mortality (RR 1.89, 95% CI 1.67-2.14) compared to chronic heart failure patients with normal serum creatinine levels. Chronic heart failure patients seen at the OPD with a baseline serum creatinine of > 1.2 mg/dl are 1.89 times more likely to die as compared to chronic heart failure patients with normal baseline serum creatinine.

Certainty of Evidence

Among the studies found for each electrolyte abnormality, the risk of bias was downgraded to serious because all of them had a risk of bias (retrospective cohorts) and thus, the certainty of evidence was very low.

Table 36. Certainty of evidence table for serum electrolyte and serum creatinine abnormalities

	Critical OUTCOMES	BASIS (No. and Type Of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Baseline serum Na of <135 mEq/L	All-cause Mortality	4 cohort studies N = 10228	1.46	1.34, 1.59	Harm	Very low
Baseline serum Na of >144 mEq/L	All-cause Mortality	1 cohort study N = 21800	1.09	1.05, 1.14	Harm	Very low

Baseline serum K of <3.5 mEq/L	All-cause Mortality N = 4605	2 cohort studies N = 4605	1.16	1.07, 1.25	Harm	Very low
Baseline serum K of >5 mEq/L	All-cause Mortality N = 43,137	1 cohort study N = 43,137	1.71	1.50, 1.96	Harm	Very low
Baseline serum Creatinine of >1.2 mg/dl	All-cause Mortality N = 3295	2 cohort studies N = 3295	1.89	1.67, 2.14	Harm	Very low

RECOMMENDATIONS FROM OTHER GROUPS

The European Society of Cardiology has recommended a better understanding of serum electrolytes and cardio-renal interactions in heart failure because misinterpretation of the tests could lead to insufficient dosing of the guideline-directed medical therapy, failure to attain decongestion, and worsening of heart failure.

Table 37. Recommendation by the European Society of Cardiology (2021) regarding the use of serum electrolytes for the diagnosis of heart failure

Group or Agency	Recommendation	Class of recommendation	Level of Evidence
European Society of Cardiology (2021)	Routine blood tests for comorbidities, including electrolytes	I	C

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

Listed below are the costs of serum sodium, serum potassium, and serum creatinine at the outpatient setting.

Table 38. Comparative costs of serum sodium and serum potassium and serum creatinine

Institution	Serum sodium Serum potassium	Serum creatinine
Philippine Heart Center	PhP 750	PhP 350
St. Luke's Medical Center	PhP 1040	PhP 759

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

The reviewer did not encounter local studies on patients' values and preferences regarding the effect of baseline serum electrolytes (sodium and potassium) and serum creatinine on mortality among patients with chronic heart failure.

Likewise, there are no studies regarding the impact on health equity of determining the baseline serum electrolytes (sodium and potassium) and serum creatinine on mortality among patients with chronic heart failure.

Serum electrolytes and creatinine are readily available in outpatient diagnostic clinics and in the laboratory sections or pathology departments of government and private hospitals in the country.

Thiazide/loop diuretics and RAAS blockers are associated with dyskalemia and spironolactone is associated with hyperkalemia.

Thiazide/loop diuretics, ACE-I and spironolactone are associated with hyponatremia.

ACE-Is are associated with elevated creatinine (worsening renal function).

Clinicians should regularly monitor serum sodium, potassium, and creatinine, and treat dyskalemia, especially in chronic heart failure patients with CKD and DM.

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7. Among adult Filipinos diagnosed with chronic heart failure at the outpatient clinic, what is the effect of nonpharmacologic interventions (dietary sodium and fluid restriction, exercise prescription) on the incidence of cardiovascular mortality, heart failure-related hospitalization, and quality of life?

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

1. The studies reviewed did not give a specific threshold for sodium restriction but several groups have recommendations regarding sodium intake.
2. In areas where cardiac rehabilitation centers are not available, supervised exercise training is suggested while in areas with cardiac rehabilitation centers, patients should be referred to the rehabilitation facility.
3. Stable heart failure patients are patients whose signs and symptoms are controlled and have remained unchanged for at least one month, and who are able to tolerate guideline-directed medical therapy without red flag signs such as chest pain, fainting, severe weakness, tachycardia, sudden, severe shortness of breath, and coughing with frothy secretions.
4. The patients for whom these recommendations will apply are those in a compensated state with no evidence of congestion and who do not need additional diuretic dose.

KEY FINDINGS

Five randomized controlled trials (RCTs) investigated the effect of dietary sodium and/or fluid restriction on the incidence of all-cause mortality and heart failure hospitalization, as well as on the quality of life in adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction at the outpatient clinic. A meta-analysis provided data on the effect of exercise for the same population.

There is low-quality evidence that **sodium and fluid restriction** increases the incidence of all-cause death and hospitalization for heart failure in patients with chronic heart failure with reduced ejection fraction seen at the outpatient clinic. This is from two RCTs, both underpowered for the outcome of mortality.

Sodium restriction alone does not affect the incidence of all-cause death in patients with chronic heart failure and low ejection fraction. This is from only one study and the quality of evidence is moderate. There is also low-quality evidence that it does not affect the rate of HF hospitalization for the same population. Reasons for the downgrade of certainty include the variability in methodology of the studies which used different sodium levels, the small number of events, and the sample size.

For quality of life, there is low-quality evidence that **sodium restriction with or without fluid restriction may improve quality of life** using the KCCQ score in patients with chronic heart failure and low ejection fraction seen at the outpatient clinic. Reasons for the downgrade of certainty include risk of bias from different study methodologies.

One study on **fluid restriction alone** reported quality of life as an outcome where the median QoL score using MLWHF score was not statistically different between the liberal fluid group and the restricted fluid group.

There was no difference between intervention and control groups for safety end points of changes in systolic blood pressure and creatinine levels.

There is low quality of evidence that **exercise-based cardiac rehabilitation programs** have no effect on the incidence of all-cause mortality (up to 12-month follow-up) based on a meta-analysis of 27 trials. The review suggests that exercise may decrease rates of hospitalization for heart failure, based on low-quality evidence from 14 trials. There is improved quality of life with exercise-based cardiac rehabilitation but quality of evidence is also low based on a review of 17 trials. Downgrade of certainty of evidence for cardiac rehabilitation was due to the presence of risk of bias due to unspecified allocation concealment and imprecision from the low number of events.

INTRODUCTION

Heart failure affects more than 64 million people worldwide with health costs amounting to 37 billion US dollars in 2012.^{1,2,3} Although pharmacologic treatment of heart failure has been dynamic and effective in improving quality of life, the non-pharmacological aspect of treatment remains important. Dietary salt and water restriction have been historically part of heart failure treatment. The perceived poor quality of life from excess fluid and the knowledge of heart failure pathology, wherein sodium and water retention are known to be compensatory mechanisms for preserving cardiac output, have promoted this practice in spite of a lack of evidence regarding its impact on important clinical outcomes. This strategy became controversial when studies that showed that the intervention did not have the expected effect on clinical outcomes began coming out. While there are studies that show the benefit of salt restriction, there is also evidence that sodium restriction may lead to detrimental renal and neurohormonal effects that worsen clinical outcomes.^{4,5}

Physical deconditioning in patients with heart failure is believed to be the main cause of the fatigue that stems from decreased nutritive blood flow to the muscles and alterations in mitochondrial oxidative metabolism.⁶ Exercise rehabilitation has been promoted to counteract this but studies have still been unable to demonstrate a consistent benefit; safety concerns for patients with reduced ejection fraction have also come up with regards to this intervention.

It is therefore important to review the evidence whether non-pharmacologic intervention will benefit patients with heart failure, particularly regarding mortality, hospitalization, and quality of life.

REVIEW METHODS

A systematic search was done from November to December 2022 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms “chronic heart failure”, “stable heart failure”, “dietary sodium restriction”, “salt restriction”, “fluid restriction”, “mortality”, “hospitalizations”, “admission”, and “quality of life”. Another search was performed using the terms “exercise”, “aerobic exercise”, “rehabilitation”, and “chronic heart failure”. We also looked at the references from the guidelines commonly used in clinical practice. Herdin was also used but no search results were found.

Randomized controlled trials, meta-analyses, and systematic reviews that compared sodium and/or water restriction against usual care were included in this review. Randomized controlled trials, meta-analyses, and systematic reviews that compared exercise to no exercise in stable patients with chronic heart failure with reduced ejection fraction were also included. Outcomes of interest included mortality, hospitalization, and quality of life. No limits were placed on age and year of publication. Articles on decompensated heart failure, preserved ejection fraction, and hospitalized study participants were excluded.

Articles in which sodium and water restriction were used were entered in REVMAN for a de novo meta-analysis using the Cochrane risk of Bias tool. Recommendation regarding the strength of evidence was based on Grading of Recommendations Assessment. The meta-analysis for exercise was found in the Cochrane database and therefore also used GradePro for assessment.

RESULTS

Characteristics of included studies for sodium and water restriction

We found five randomized controlled trials (RCTs) that included a total of 1,205 patients with chronic heart failure, predominantly with reduced ejection fraction. One RCT had

more than 800 study participants,⁷ contributing to about 66% of the total population. In the studies that included patients with both preserved and reduced ejection fraction, the majority of the study participants with reduced ejection fraction—at least 65% of the total population—had low ejection fraction.

All included studies had restricted dietary sodium or salt as intervention or exposure versus usual care. The level of sodium restriction varied among the studies. Usual care was routine dietary advice from the physicians with no specified sodium level. Data on hospitalization were obtained for all included studies and only two reported data for mortality rate.^{4,7} One trial⁸ reported on quality of life. The follow-up period was also variable among the studies: 84 days,^{8,9} 12 months,⁷ and 180 days.⁴

Two studies³ used salt restriction alone as intervention,^{7,8} two studies used salt restriction with constant water intake,^{4,9} and one study used fluid restriction alone.¹¹

Characteristics of included studies for exercise

We found 1 large RCT¹¹ and several meta-analyses that looked at exercise training and its impact on mortality and hospitalization.

We based our recommendation on a meta-analysis conducted in 2019¹² that included 44 trials, mostly on patients with reduced ejection fraction that engaged in physical exercise either at baseline or as part of a rehabilitation program. These studies used one to three sessions per week of aerobic and resistance exercises with a minimum follow-up of six months. The largest RCT which engaged 2,331 participants under this intervention was included in this meta-analysis.

The meta-analysis by Long et al.¹² answered the question of interest regarding the impact of exercise training on mortality, hospitalization, and quality of life. Although it included a few studies that included patients with preserved ejection fraction, the majority of studies included in the meta-analysis was focused on patients with reduced ejection fraction. The review methods were established prior to the conduct of the review. An extensive literature search using at least two databases and trial registries was also conducted. There appears to be some bias for small studies and publication bias but this was declared and addressed by the authors. There was adequate description of the included studies and method of review. Sensitivity analysis was done considering the risk of bias.

Efficacy outcomes

Dietary restriction of both sodium and fluid resulted in higher rates of hospitalization (2.72 , 95% CI 1.39 – 5.31) and death (RR 2.83, 95% CI 1.06 - 7.57).^{4,8} Dietary restriction of sodium alone did not affect rates of hospitalization (RR 1.18, 95% CI 0. 89-

1.57) and death (RR 1.23, 95% CI 0.86 1.77).⁷ For quality of life, there was an improvement of 10.75 in the mean KCCQ scores (9.26 to 12.25) in favor of the treatment group which used sodium and/or fluid restriction.^{8,9} For fluid restriction alone, there was only one study found where quality of life was reported as an outcome. This was a randomized cross-over study and there was no difference in the median MLWHFQ scores for study participants whether they were in the restricted or the liberal fluid intake intervention. Scores were 20 and 17 respectively.¹⁰

Based on the meta-analysis by Long et al.¹², cardiac rehabilitation did not make a difference in the incidence of all-cause mortality over the short term (\leq one year of follow-up); 5.1% vs control 5.8%; risk ratio (RR) 0.89, 95% (CI) 0.66 to 1.21. Cardiac rehabilitation may reduce HF-specific hospitalizations (RR 0.59, 95% CI 0.42 to 0.84). Meanwhile, a clinically important improvement in short-term, disease-specific, health-related quality of life using the Minnesota Living With Heart Failure questionnaire was noted, with a mean difference in scores (MD) of -7.11 points, 95% CI -10.49 to -3.7.

Safety outcomes

Safety endpoints for sodium restriction in the study by Kalogeropoulos included a drop in systolic blood pressure (SBP) of more than 20mmHg and worsening creatinine.⁹ Only one participant in the 1,500 mg group was withdrawn due to a drop in BP and one participant in the 3,000 mg group had worsening creatinine. The study by Hummel had the same safety endpoints of interest but none showed a significant difference from enrollment to the end of the study.⁸

For exercise, HF-ACTION, the largest RCT, reports 37 patients in the intervention group and 22 in the control group suffering from events within three hours of the exercise training. Events included angina, arrhythmia, dizziness, and presyncope.¹¹

Certainty of evidence

For combined sodium and fluid restriction, certainty of evidence for all-cause death is low due to high risk of bias from imprecision as there was only one study that looked into this. For the outcome of hospitalization, certainty of evidence is low. This downgrade was due to very serious imprecision caused by the low number of events and small sample size. Blinding was also an issue due to the intervention that could not be undisclosed to the patient with some crossovers occurring in some studies. The different cut-off levels for sodium content also make it difficult to make conclusions as to the level of restriction that will have an impact on outcomes.

If sodium restriction is isolated, certainty of evidence for death rate improves to moderate; however, only one trial has this outcome and is associated with an inconclusive interpretation due to a very wide confidence interval. As for heart failure hospitalization, quality of evidence is low from two trials due to imprecision and indirectness. Indirectness in the studies is caused by the character of their populations which had a mixture of patients with reduced ejection fraction and patients with preserved ejection fraction in one study. Meanwhile, the other study only included patients older than 65 years old.

As for the quality of life outcome, level of evidence was considered moderate. The downgrade was due to a small sample size.

For exercise-based rehabilitation, the certainty of evidence is low for mortality, HF-related hospitalization, and quality of life. The downgrade is due to the risk of bias and imprecision due to the small number of events (n=300). The risk of bias is due to poor reporting of the authors' generation and concealment of allocation sequence and blinding. Although blinding was not feasible due to the nature of the intervention, the authors still identified some studies to be at high risk. Other sources of bias include the lack of explanation regarding the imbalance in the baseline characteristics between groups in most of the studies. These were also some studies with high dropout rates on which no details were given.

RECOMMENDATIONS FROM OTHER GROUPS¹³

Table 39. Recommendations from various guidelines regarding sodium intake in the setting of heart failure.

Guideline	Year	Sodium Intake Recommendation	Level of Evidence
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand	2018	< 2 g/d	Not stated
Canadian Cardiovascular Society	2017	2-3 g/d	Weak recommendation; low quality evidence
American College of Cardiology	2022	For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms	C

Academy of Nutrition and Diabetes	2018	2-3 g/d	Fair
Heart Failure Society of America	2010	2-3 g/d; 2 g/d in severe HF	C
European Society of Cardiology	2021	Avoiding excessive salt intake	Not stated
National Institutes of Health and Care Excellence	2018	Do not routinely advise people with HF to restrict their sodium consumption. Reduce intake for those with high levels of salt consumption	Not stated

Table 40. Recommendations from various guidelines regarding the prescription of exercise in the setting of heart failure.

Guideline	Year	Exercise Recommendation	Level of Evidence
Canadian Cardiovascular Society	2017	We recommend regular exercise to improve exercise capacity, symptoms, and quality of life in all HF patients. We recommend regular exercise in HF patients with reduced EF to decrease hospital admissions.	Strong Recommendation; Moderate-Quality Evidence Strong Recommendation; Moderate-Quality Evidence
American College of Cardiology	2022	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 In patients with HF, a cardiac rehabilitation program can be useful to improve functional capacity, exercise tolerance, and health-related QOL	Class !A 2A B-NR
European Society of Cardiology	2021	Exercise is recommended for all patients who are able in order to improve exercise capacity and QOL, as well as to reduce HF-related hospitalization A supervised, exercise-based, cardiac rehabilitation program should be considered in patients with more severe disease, frailty, or comorbidities.	1A 2A - C

ONGOING STUDIES

Studies on dietary sodium and fluid restriction remain challenging for patients who are not hospitalized because of the issue of monitoring adherence and the provision of standardized intervention. Large trials are still unavailable though they may help establish whether or not certain non-pharmacologic treatments are necessary for certain subsets of heart failure patients. The optimal amount of sodium and fluid intake are still to be determined.

Several meta-analyses have been written in the past year for sodium restriction in patients with heart failure but due to studies with small sample size, hard data for the subset of patients that are not decompensated and not hospitalized is still inadequate.

FRESH UP is an ongoing randomized controlled open label multicenter trial that is trying to investigate the effect of restricted fluid intake vs liberal fluid intake in stable outpatients with CHF.¹⁴ Recruitment will continue up to 2024 with an estimated enrollment of 506 participants.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

The cost for the intervention of sodium restriction will be from the cost of education and guidance of patients as to how they can adhere to the prescribed sodium amount without sacrificing nutritional content. For exercise, Long et al.¹² cited a cost-effectiveness analysis of long-term moderate exercise training performed by Georgiou and colleagues on patients in stable heart failure seen at the Lancisi Institute in Ancona, Italy. The incremental cost-effectiveness ratio was USD1773/life-year saved; factors considered included cost of hospitalization, cost of exercise training, and wages lost from training. The estimated increment in life expectancy with exercise was 1.82 years/person compared with control. In the local setting, at the Philippine Heart Center, an exercise program for heart failure costs Php 16,500 for 16 sessions, 2 sessions per week at the rehabilitation facility of the hospital. The reviewer did not find any economic evaluation studies in the local setting.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

For sodium and water restriction, acceptability will be a challenge since Asian cuisine is high in salt. Sodium and fluid restriction may not be easily acceptable to most patients and self-restriction may not be effective. Reviewed studies used medical staff, a dietitian or a third party to facilitate adherence to the sodium limitation while keeping to the required nutrients.^{4,8,9} Some studies had meals delivered and prepared by a third party.¹⁰ In spite of this, adherence to the restriction remained a challenge. Coaching for this diet will require a dietitian or other medical staff. Since we are dealing with patients seen in the outpatient clinic, referring patients to a coaching team will surely be a challenge to the attending physician. The study by Kalogeropoulos had only 27 patients because, in spite of having meals delivered to the study participants, only 52% complied with the restriction. A systematic review of dietary sodium restriction trials in 2020 showed that out of the 10 trials and 25 descriptive studies included, dietary sodium was decreased in only seven (7) studies and none of them achieved 1,500 mg/day . The study opined that the failure may be due to non-inclusion of the determinants of successful sodium restriction such as social support, taste preference, food access, and sociocultural norms.¹⁵

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8. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of diuretics on the incidence of cardiovascular mortality, heart failure-related hospitalization, and quality of life?

Recommendation 8

Among adult Filipino patients with chronic heart failure with pulmonary congestion at the outpatient clinic, we recommend the judicious use of loop diuretics to relieve congestion.

(low level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- Since the trials included in the evidence review did not give information on the ejection fraction of the patients included in the trials, those included were patients with signs of congestion as per physician discretion and loop diuretics were used. The final recommendation reflected this.
- The CP gave a strong recommendation despite low certainty of evidence for the use of diuretics in patients with heart failure with pulmonary congestion because of the benefits gained in reducing all-cause mortality and relief of signs and symptoms of fluid overload.
- Physicians must be judicious in starting the use of loop diuretics, titrating the dose, and withholding loop diuretics, taking physical examination findings, hemodynamic status, and electrolyte levels into account.

KEY FINDINGS

- There were 14 RCTs in the published meta-analysis that compared the effect of diuretics against placebo or standard of care among patients with chronic heart failure. Only eight studies determined the outcomes regarding all-cause mortality, hospitalization due to worsening heart failure, and exercise tolerance. Quality of life

was not assessed among the studies. Six observational studies that indirectly assess the adverse effects of diuretics were likewise evaluated.

- Diuretics were shown to be beneficial in terms of reducing all-cause mortality, hospitalization due to heart failure, and exercise tolerance based on this published meta-analysis. All these RCTs had small sample sizes; the maximum number of participants was 202 for the mortality outcome.
- Adverse events, such as hypokalemia, hyponatremia, and arrhythmia were more frequently observed in the group that received diuretics based on the observational studies.
- All RCTs in the published meta-analysis have issues on allocation concealment. All of these RCTs were done between 1977 to 1994. The published meta-analysis did not assess publication bias. As such, the certainty of evidence for the efficacy outcomes is low. On the other hand, only observational studies were included for the appraisal of the adverse event since these were not included in the published meta-analysis.

INTRODUCTION

Given the crucial role of congestion in heart failure, diuretics remain to be a cornerstone in heart failure management. Among the therapies for heart failure, diuretics are the only group of drugs with a Class I recommendation in patients with heart failure with reduced, mid-range, or preserved ejection fraction. They are recommended in acute decompensation as well as in chronic heart failure for managing signs and symptoms of congestion. For patients with a history of congestion, a maintenance dose is recommended to prevent the recurrence of symptoms.¹ Besides ultrafiltration, the only pathway to get rid of sodium and water related to volume overload and congestion is through natriuresis and diuresis. Different types of diuretics work on different sites in the nephrons and with varying potency, as measured by the fractional excretion of sodium (FENa). Acetazolamide works on the proximal nephron, while loop diuretics work on the ascending loop of Henle. Thiazide-like diuretics work on the early distal convoluted tubules, while mineralocorticoid receptor antagonists (MRAs) work on the distal tubule. Among these diuretics, loop diuretics are the most potent with a FENa of 20-25%. MRAs, on the other hand, are not usually used since they also have a different mode of action on the renin-angiotensin-aldosterone system (RAAS).¹

The use of oral furosemide as diuretic therapy has been “the cornerstone of heart failure therapy for >20 years, before construction of the modern bases of evidence for HF therapies.”² In fact, more than 80% of the patients enrolled in the randomized clinical trials that have served as the bases for guideline-directed medical therapy (GDMT) received the background of diuretic therapy to treat and prevent recurrence of

congestion.³ A critique of published heart failure guidelines published in Acta Medica in 2014 elaborated that “baseline HF drug therapy” using diuretics and digoxin is cited in 79-100% of trials on heart failure. In the aforementioned analysis, the authors extrapolated that survival rate on this “baseline HF drug therapy” is 8-51% based on a 38% natural HF survival rate for the time period.⁴ The introduction of furosemide in the 1960s provided evidence for the use of loop diuretics in treating patients with heart failure. Until then, heart failure was considered a terminal condition. When furosemide was introduced orally and parenterally, there was dramatic resolution of congestive symptoms. As a result, diuretics have been given to heart failure patients because they obviously worked. These agents have not been tested in bigger trials that evaluate their effect on survival because they are already routinely used.⁵

REVIEW METHODS

A systematic search was done from the date of the last search, Dec. 7, 2022, until January 20, 2023 using the following databases: Medline, Cochrane Reviews, Google Scholar, and HERDIN Plus. We used a combined MeSH and free text search for the following main search terms: [“Heart Failure”] AND [“Diuretics”] AND [“mortality” OR “hospitalizations due to heart failure” OR “quality of life” OR “exercise capacity”]. The clinicaltrials.gov website and WHO international clinical trials registry platform were also reviewed for ongoing studies. We excluded studies on the pediatric population as well those that included acute heart failure or decompensated heart failure. We excluded studies using mineralocorticoid receptor antagonists since these have additional actions aside from diuresis. These agents will be reviewed in a separate section. The search strategy is presented in Annex 10, Appendix A. Since the randomized controlled trials/meta-analyses did not include assessments of adverse events pertinent to diuretics (e.g. electrolyte abnormalities, arrhythmias), we conducted a separate search using the search terms “hypokalemia”, “hyponatremia”, “potassium”, “sodium”, “arrhythmia”, “diuretics”, and “heart failure”, as per the recommendation of the steering committee in the initial presentation meeting.

For the efficacy outcomes, we only included randomized controlled trials or meta-analyses that used randomized controlled trials which compared diuretics against placebo or standard care. We retrieved and appraised the Cochrane review on Diuretics for Heart Failure by Faris et al.⁵ using AMSTAR II.⁶ Overall, there are some non-critical flaws in this meta-analysis by Faris⁵: they did not provide the doses of the interventions; they did not report the sources of funding for the individual studies included in the review; they did not perform graphical or statistical tests for publication bias; and did not provided an explanation for including only RCTs, which is expected from a Cochrane review.

RESULTS

Characteristics of included studies

We used the Cochrane review by Farris et al. which included RCTs on diuretics for chronic heart failure. The Cochrane review included 14 trials (525 participants), of which seven were placebo-controlled. The other seven compared diuretics against other agents such as digoxin or ACE inhibitors. All-cause mortality data was available in three of the placebo-controlled trials, with a total of 202 participants. Data regarding hospitalization for worsening heart failure were available in two trials involving 169 participants. These trials were withdrawal of diuretic studies. There were six cross-over studies and they have stated explicitly that these trials were treated in the same fashion as parallel group studies since there was a washout period and the authors perceived that there were no carry-over effects. The study periods range from 3 weeks to 52 weeks and trial sizes ranged from 10 to 202 participants. More than 85% of participants completed the planned follow-up period. The diuretic drugs and dose regimens used in the studies varied, although loop diuretics were used in the majority of the studies. The mean age of the participants was 59 ± 11 years and there was a predominance of males among the study participants. Most of the participants are in NYHA Class II (40%) or III (29%). The choice of outcomes varied from study to study: there were four studies on LV performance; five on symptoms; three on hemodynamic effects; four on exercise capacity and two on the side effects of treatment. None of the studies reported the effect of diuretics on quality of life.⁵ Overall, the methodological quality of the studies included in the meta analysis was moderate. Allocation concealment was unclear for all the studies and assessment of outcomes was unclear for only some of them.

Since this meta-analysis did not include safety outcomes such as electrolyte abnormalities, we included six observational studies that were either a retrospective analysis of clinical trials regarding other HF medications⁷ or a review of heart failure patient registries (both acute and chronic).⁸⁻¹⁰

Efficacy outcomes

Table 41. Beneficial effects of diuretics on clinical outcomes of chronic heart failure patients⁵

Outcome	# of RCTs	Relative Risk, 95% CI	Interpretation
All-cause Mortality	3	0.28 [0.09, 0.87]	Favors diuretics
Hospitalizations due to worsening Heart Failure	2	0.08 [0.01, 0.59]	Favors diuretics
Weighted Mean Difference (WMD), 95% CI			

Exercise Capacity	4	0.72 [0.4, 1.04]	Favors diuretics
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Table 41 describes the beneficial effects of diuretics on the clinical outcomes of patients with chronic heart failure. Three placebo-controlled trials reported a total of 15 deaths in 202 subjects. Mortality was also lower for those who received diuretics than for those under placebo [(3/101 -vs-12/101), RR 0.28; 95% CI 0.09 to 0.87; p=0.02].⁵

Two trials on the withdrawal of diuretic use involving 169 subjects reported hospitalization caused by worsening heart failure. The rate of hospitalization was lower for those who received diuretics compared to those under placebo [(0/81-vs-13/88), RR 0.08; 95% CI 0.01 to 0.59; p=0.01].⁵

No study in this meta-analysis explored the effect of diuretics on quality of life. Instead, exercise capacity was used as a surrogate for quality of life in four RCTs and was then measured to compare the outcome of diuretic use against that of active controls in 91 participants. Diuretics were found to improve exercise capacity in participants with chronic heart failure, WMD 0.72, 95% CI 0.4 to 1.04, p <0.0001.⁵

Safety outcomes

There is no data from the meta-analysis regarding the adverse effects of diuretic use in the management of chronic heart failure.⁵ However, based on its pharmacologic properties, diuretics may have an adverse effect on electrolyte balance, particularly on sodium and potassium.¹

A retrospective analysis of the data from the Studies on Left Ventricular Dysfunction (SOLVD) trial, a trial that compared enalapril and placebo, showed that in patients with EF <36% and who received non-potassium-sparing diuretics, there is an increased risk for arrhythmia-related death (RR 1.78, 95% CI 1.47 to 2.13).⁷ Two observational studies demonstrated that diuretics are associated with hyponatremia (RR 1.10, 95% CI 1.05 to 1.14).^{8,9} Meanwhile, three observational studies, two of which used registry data, showed that diuretics are associated with hypokalemia (RR 1.57, 95% CI 1.49 to 1.65).^{10,11,12}

Table 42. GRADE summary of finding table: diuretiucs vs placebo or standard of care

Outcomes	Basis # and Type of Studies, Total Participants	Effect Size	95% CI	Interpreta- tion	Certainty of Evidence
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All-cause Mortality	3 RCTs n = 202	RR = 0.28	0.09, 0.87	Benefit	Low Certainty
Hospitalizations due to worsening Heart Failure	2 RCTs n = 169	RR = 0.08	0.01, 0.59	Benefit	Low Certainty
Quality of Life	No evidence				
Exercise Capacity	4 RCTs n = 91	WMD = 0.72	0.4, 1.04	Benefit	Low Certainty
Arrhythmia-related Death	1 Observational n = 6797	RR = 1.77	1.47, 2.13	Harm	Low Certainty
Hyponatremia	2 observational, n = 48,178	RR = 1.10	1.05, 1.14	Harm	Low Certainty
Hypokalemia	3 Observational n = 151,209	RR = 1.57	1.49, 1.65	Harm	Low Certainty

Certainty of Evidence

Since the majority of the trials included in the meta analysis were done between the late 70s and the early 90s, there are concerns regarding their methodological quality. Allocation concealment was unclear in all of the studies included in the meta-analysis, while assessment of outcome measures was unclear in some. Publication bias is also suspected for all the efficacy outcomes. Overall certainty of evidence was graded low because of both the serious risks of bias that were noted amongst the critical efficacy outcomes and the small sample size. The Grade Evidence Profile summary is in Annex 10, Appendix C.

RECOMMENDATIONS FROM OTHER GROUPS

We reviewed the recommendations of the international guidelines that the Philippine medical community usually adopts or adapts (ACC-AHA, ESC, NICE)^{2,13,14} as well as two guidelines from the Asia-Pacific region (Malaysian and Australian).^{3,15} These international guidelines gave a strong recommendation for the use of diuretics for heart failure patients with congestion. Only the ESC gave a recommendation for the use of diuretics to improve exercise capacity and reduce HF-related hospitalization (Class I Level C).¹³ These recommendations were given although the randomized clinical trials

that investigated the use of diuretics in chronic heart failure were small and inadequately powered statistically to clearly demonstrate the effectiveness of diuretics in reducing morbidity and mortality rates.

Table 43. Summary of Key Recommendations from other groups on the use of diuretics in heart failure

GROUP	Recommendation	Strength of Recommendation and Certainty of Evidence
ACC AHA 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 2022	In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF ²	COR -1 (Strong) LOE B-NR (Moderate)
	For patients with HF and congestive symptoms, the addition of a thiazide (e.g. Metolazone) to loop diuretic treatment should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities ²	COR -1 (Strong) LOE B-NR (Moderate)
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2021	Loop Diuretics are recommended in patients with HFrEF who have signs and symptoms of congestion in order to alleviate HF symptoms, improve exercise capacity, and reduce HF-related hospitalizations. ¹³	Class I Level C
NICE UK Guidelines in chronic heart failure in adults: diagnosis and management 2018	Diuretics should be routinely used to relieve congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. ¹⁴	
National Heart Association of Malaysia Clinical Practice Guidelines on the Management of Heart Failure 2019	Diuretics are indicated in all patients with HF in whom there are signs and symptoms of fluid retention. ¹⁵	I, B
	The combination of thiazides and loop diuretics may also be used as these drugs that work synergistically to improve diuresis. However, this combination has been associated with hypokalemia, hyponatremia, worsening renal function, and increased mortality. ¹⁵	IIb, B
National Heart Foundation of Australia and Cardiac Society of	A diuretic should be considered in patients with heart failure and clinical symptoms or signs of congestion to improve symptoms and manage congestion. ³	Strong recommendation FOR, very low quality of evidence

ONGOING STUDIES

Optimization of guideline-directed medical therapy (GDMT) has been one of the guiding principles in the management of chronic heart failure patients. These efforts have been shown to improve long-term outcomes, particularly in the use of beta-blockers, RAAS inhibitors, and mineralocorticoid receptor antagonists. However, there has been little evidence to provide guidance on the optimal dose of loop diuretics.

The strategy for outpatient diuretic management will be evaluated in one pilot study that is to be conducted this 2023. The trial will evaluate whether a fixed diuretic dose or a flexible dosing regimen based on daily weight is more effective in preventing HF-related hospitalization and acute kidney injury for patients with heart failure being seen at ambulatory care facilities.¹⁶

With the advent of SGLT-2 inhibitors and Sacubutril-Valsartan, it may also be time to consider doing a “withdrawal trial” on the background of this current GDMT.¹⁷ The level of evidence for diuretic use in heart failure will remain low in the absence of a large, randomized clinical trial which has been a necessary proof for guideline development. However, performing a randomized-controlled trial on diuretic use for congestive heart failure may be akin to doing an RCT for parachutes at this point in time.¹⁷

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

Table 44. Cost implication for diuretics for chronic heart failure in the local setting

	Cost/dose (PHP)	Dosing	Annual Cost (PHP)
Furosemide	0.70 - 1.90 (20 mg) ¹⁶ 0.58 - 2.50 (40 mg) ¹⁶	20 to 40 mg OD	255.5 to 693.50 211.7 to 912.50
Consultation	500 - 1,000 per consult	4 consults in 1 year	2,000 – 4,000

Serum potassium	165* to 400** per test*	Baseline, After 1 week, 4 weeks and 6 months of initiation (estimate)	660 – 1,600
TOTAL Annual Cost per patient		20 mg OD 40 mg OD	2,916.5 to 6,293.5 2,871.7 to 6,512.5

* Price from PGH-OPD **Price from PHC OPD

The reviewer did not encounter published economic effectiveness studies on diuretics use for heart failure. The prices of diuretic use based on the following assumptions: the local price of furosemide, which is Php. 0.58 to Php 2.50 per 40-mg tablet ¹⁸; four serum potassium determinations per year, pegged at Php 165.00 to Php 400.00 per determination; and four consultations per year at Php 500 to Php 1,000 per consultation.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

There are no specific studies on the equity, acceptability, and feasibility of diuretic use for heart failure. Based on the International Congestive Heart Failure (INTER-CHF) study, around 45% of the South East Asian cohort in the INTER-CHF study was on loop diuretics, making it the third highest heart failure medication that patients received next to ACE-Inhibitor/ARB (73%) and beta blocker (66%).¹⁹

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9. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection fraction (HFrEF) at the outpatient clinic, what is the effect of beta-blockers on the incidence of cardiovascular mortality, heart failure-related hospitalization, and quality of life?

Recommendation 9

Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we recommend the use of beta-blockers (metoprolol succinate, carvedilol, bisoprolol or nebivolol).

(high level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- There is a wealth of evidence supporting the use of beta-blockers (metoprolol succinate, bisoprolol, carvedilol, nebivolol) in the treatment of HFrEF.

KEY FINDINGS

Fifteen randomized controlled trials compared the use of beta-blockers on top of standard of care (a diuretic and an angiotensin-converting enzyme inhibitor (ACEi) in the treatment of stable chronic heart failure (CHF) with an ejection fraction of less than or equal to 40% (HFrEF) with regards to the outcomes of cardiovascular mortality, heart failure-related hospitalization, and safety.

For the outcome on quality of life, one meta-analysis that included 13 studies (some studies are likewise present in the de novo meta-analysis) to examine the same intervention against placebo was included.

Results showed that compared to a placebo, the use of beta-blockers, specifically bisoprolol, carvedilol, metoprolol succinate and nebivolol, on top of standard of care decreased cardiovascular mortality, heart failure mortality, and heart failure-related

hospitalization. With regard to the quality of life outcome, there is a trend to benefit from the use of the aforementioned beta-blockers.

The frequency of the adverse events of dizziness, hypotension, and bradycardia were significantly higher among patients with HFrEF who were given beta-blockers compared to placebo. On the other hand, there is a significantly lower incidence of worsening heart failure and malignant ventricular arrhythmias among patients with HFrEF who were given beta-blockers as compared to placebo. The incidence of syncope was similar in both arms.

Most of the studies had a low risk of bias although some trials did not describe how allocation concealment was done. One study had significant drop-out rates. Moreover, heterogeneity was significant when all the beta-blockers with studies on heart failure were included, or when the studies comparing the different dosages of beta-blockers were included. The sensitivity analysis using only bisoprolol, carvedilol, and metoprolol succinate showed no significant heterogeneity. Nevertheless, significant heterogeneity was the reason for downgrading the certainty of evidence for the outcomes of heart failure mortality and heart failure-related hospitalization.

INTRODUCTION:

In a local study conducted in 2016 using PhilHealth hospitalization claims,¹ the prevalence rate for hospitalization due to congestive heart failure was 1.6% or 1,648 cases for every 100,000 patient claims for a medical condition. The burden of the disease in the outpatient setting can only be surmised. Likewise, a study published in 2018 was done to determine the economic burden of heart failure-related hospitalization using PhilHealth data.² It was found that the price of hospitalization ranged from PhP 19,340 to PhP 28,220 in government hospitals and from PhP 28,370 to PhP 41,800 in private hospitals. These are conservative estimates of the hospitalization costs for patients with congestive heart failure class III using the local setting.

The use of beta-blockers has long been part of the pillars of heart failure management in international clinical practice guidelines because of their effect on cardiovascular mortality, hospitalization, and quality of life. Several beta-blockers—metoprolol tartrate, metoprolol succinate, carvedilol, bisoprolol, bucindolol, atenolol and nebivolol—have been studied with regards to their effect on heart failure. Recent guidelines showed that the beta-blockers with benefits regarding cardiovascular mortality and heart failure-related hospitalization are carvedilol, bisoprolol, and metoprolol succinate. On the other hand, it was also shown that nebivolol is beneficial in reducing composite outcome of death or cardiovascular hospitalization but not in reducing mortality.

In a local study done in 2020, it was found that the prescription rate of beta-blockers among patients admitted for heart failure was 56.3%.³ Registry data suggested that the programme had significant impact in improving the rate of use of beta-blockers (from a 34% baseline to a rate of 51% by 2014) to 56.3% by 2018.

Because of the epidemiologic and economic burden of the disease, the importance of optimal management of heart failure with reduced ejection fraction, or of heart failure with an ejection fraction that was objectively assessed to be less than or equal to 40% in the outpatient setting has been highlighted, hence this undertaking.

REVIEW METHODS

A comprehensive and systematic search of local and international databases was done from database inception up to December 31, 2022 through MEDLINE, Cochrane CENTRAL, HERDIN, Google scholar, and clinicaltrials.gov using the combined MeSH and keywords of the following terms: “heart failure”, “congestive heart failure”, “left-sided heart failure”, “heart failure reduced ejection fraction”, “heart failure, depressed”, “adrenergic beta-antagonists”, “beta blockers”, “atenolol”, “bucindolol”, “bisoprolol”, “carvedilol”, “nebivolol”, “death”, “mortality”, “hospitalization”, “myocardial infarction”, “arrhythmia”, and “quality of life”. A filter was placed to include only clinical and human trials, randomized controlled trials (RCTs), and meta-analyses, and to include only studies with subjects aged 19 years and above. Only studies with the outcome of interest were included. The references of included studies, past meta-analyses, and the latest clinical practice guidelines were also hand-searched to identify additional studies that may not have appeared in the database search. No language restrictions were applied. Additional search was done for unpublished studies through communication with authors or known researchers. The full search strategy is presented in Annex 11, Appendix 1.

Studies that compared beta-blockers to one another, or beta-blockers to an active treatment (e.g., ACEi) were excluded. Although two relevant local meta-analyses were found—one was a meta-analysis published in 1998 in the journal of a local specialty hospital,⁴ while the other is an unpublished meta-analysis on the effect of beta-blockers on non-ischemic heart failure⁵—both studies were excluded because the 1998 meta-analysis did not include more recent studies while the unpublished meta-analysis focused solely on the population whose heart failure etiology is non-ischemic in nature.

A de novo meta-analysis of the outcomes of interest was performed for the outcomes of cardiovascular mortality, heart failure mortality, and heart failure-related hospitalization. This was because the latest meta-analysis done on these outcomes was published in 2001,⁶ before the publication of the other landmark trials regarding the effects of beta-blockers on heart failure. The more recent meta-analyses released from 2021 to

2022 that addressed the mentioned outcomes of interest and included all the relevant trials were either individual patient data meta-analysis or a network meta-analysis.⁷⁻¹⁰

The Cochrane Collaboration tool for the assessment of risk of bias was used to assess the quality of the RCTs included in the meta-analysis. The meta-analysis was done using Review Manager 5.4. For the meta-analysis on quality of life by Turgeon et al.,¹¹ AMSTAR2 was used to assess risk of bias.

RESULTS

Characteristics of included studies

There were fifteen RCTs¹²⁻²⁶ that included patients with stable symptomatic CHF (of varying etiologies) with an EF of less than or equal to 40% to evaluate the effect of beta-blockers on cardiovascular mortality, heart failure-related hospitalization, quality of life, and safety. Most of the RCTs included had low risk of bias although some of the studies had unclear allocation concealment—something which was not specifically mentioned in older trials. One of the studies done in 1997 had unclear allocation concealment and did not specify how the participants, personnel, and outcome assessors were blinded. Two studies had attrition bias.

For the outcome on quality of life, the meta-analysis done by Turgeon et al.¹¹ published in 2021 was used. It included 37 RCTs of the treatment regimens used in the management of HFrEF (ACEi, BB, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, and sodium-glucose co-transporter-2 inhibitors) to evaluate HFrEF treatment and report on health-related quality of life. Some of the BB studies included in the de novo meta-analysis were included in this systematic review. Appraisal of the quality of the meta-analysis on quality of life using AMSTAR2 showed that it was a review of moderate quality but only because the meta-analysis did not report on the sources of funding of the studies included in the review.

Efficacy Outcomes

Cardiovascular Mortality

The pooled analysis of seven RCTs^{17-22,26} for cardiovascular mortality showed that it was significantly reduced by 29% with the use of bisoprolol, carvedilol, metoprolol succinate and nebivolol (RR 0.71, 95%CI 0.61-0.81, p<0.00001, I²=36% p=0.16) on top of the standard of care at that time compared to placebo.

Hospitalization for heart failure

The pooled analysis of six RCTs^{14,17,18,20,22,24} for heart failure-related hospitalization showed that compared to placebo, heart failure-related hospitalization was significantly reduced by 23% with the use of bisoprolol, carvedilol, metoprolol succinate (RR 0.73, 95%CI 0.66-0.80, p<0.00001, I²=0%, p=0.74) on top of the standard of care at the time.

Quality of Life

The meta-analysis by Turgeon et al. on quality of life¹¹ showed that there was no significant difference in the QoL scores (standard mean difference 0.04 (95%CI -0.02 to 0.09, p<0.56, I²=0, p=0.85) with no observed heterogeneity.

Table 45. GRADE summary of findings table for the effect of beta-blockers on mortality, hospitalization, and quality of life outcomes

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Interpretation
		Without beta- blockers	With beta- blockers	Difference		
Cardiovascular Mortality № of participants: 12106 (7 RCTs)	RR 0.71 (0.61 to 0.81)	12.1%	8.6% (7.4 to 9.8)	3.5% fewer (4.7 fewer to 2.3 fewer)	⊕⊕⊕⊕ High ^a	BENEFIT
Heart Failure Hospitalization - Bisoprolol, Carvedilol, Metoprolol succinate № of participants: 8317 (6 RCTs)	RR 0.78 (0.66 to 0.80)	18.8%	13.7% (12.4 to 15)	5.1% fewer (6.4 fewer to 3.8 fewer)	⊕⊕⊕⊕ High	BENEFIT
Quality of Life № of participants: 4650 (13 RCTs)	-	The mean quality of Life was 0	-	MD 0.04 higher (0.02 lower to 0.09 higher)	⊕⊕⊕○ Moderat e ^{b,c}	EQUIVALENT

Outcome No of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Interpretation
		Without beta- blockers	With beta- blockers	Difference		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

EXPLANATIONS: a. SENIORS trial has attrition bias b. Unclear risk of bias mostly because of insufficient reporting of randomization and allocation concealment for trials published in the 1990s and early 2000s. For the ENECA study, no specific mention of how allocation was concealed [just that a number was allocated to a subject and that number determined whether the patient was given the treatment drug or a placebo].

Safety Outcomes

Pooled analysis of the RCTs with the reported adverse events^{12-17, 20,21,23-25} showed that dizziness (6 studies, OR 1.90, 95%CI 1.31-2.75, p=0.0007, I²=79%, p=0.0002), hypotension (10 studies, OR 1.74, 95%CI 1.08-2.81, p=0.02, I²=68%, p=0.001), and bradycardia (9 studies, OR 3.63, 95%CI 1.84-7.18, p=0.0002, I²=74%, p=0.0001) were more frequent among patients taking a beta-blocker, while worsening heart failure (7 studies, OR 0.69, 0.58-0.82, p<0.0001, I²=11%, p<0.0001) and malignant ventricular arrhythmias (4 studies, OR 0.40, 0.21-0.60, p<0.00001, I²=0%, p=0.67) were less frequently observed in the beta blocker arm. Rate of syncope was similar in both arms (4 studies, OR 1.00, 0.79-1.26, p=0.98, I²=0%, p=0.67). The outcome of dyspnea was examined by the RCTs that did not exclude patients on beta-agonists or those with chronic lung disease. Pooled analysis showed that dyspnea was less frequent among patients given beta-blockers (4 studies, OR 0.79, 0.63-0.98, p=0.03, I²=0%, p=0.99). However, the etiology of the dyspnea was not specified. Although the SENIORS study²⁷ analyzed safety outcomes, it was not included in the pooled analysis because the data for EF of ≤40% was unavailable.

Table 46. GRADE summary of findings table for serious adverse events of beta-blockers

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Interpretation
		Without beta- blockers	With beta- blockers	Difference		
Safety Outcomes - Dizziness Nº of participants: 5051 (6 RCTs)	OR 1.90 (1.31 to 2.75)	30.3%	45.2% (36.3 to 54.5)	14.9% more (6 more to 24.2 more)	⊕⊕⊕○ Moderate ^a	HARM
Safety Outcomes - Hypotension Nº of participants: 11054 (10 RCTs)	OR 1.74 (1.08 to 2.81)	6.4%	10.6% (6.9 to 16.1)	4.2% more (0.5 more to 9.7 more)	⊕⊕⊕○ Moderate ^b	HARM
Safety Outcomes - Bradycardia Nº of participants: 10628 (9 RCTs)	OR 3.63 (1.84 to 7.18)	2.1%	7.2% (3.8 to 13.3)	5.1% more (1.7 more to 11.2 more)	⊕⊕⊕○ Moderate ^c	HARM
Safety Outcomes - Worsening HF Nº of participants: 5181 (7 RCTs)	OR 0.69 (0.58 to 0.82)	20.0%	14.7% (12.7 to 17.1)	5.3% fewer (7.3 fewer to 3 fewer)	⊕⊕⊕⊕ High	BENEFIT
Safety Outcomes - Syncope Nº of participants: 5641 (4 RCTs)	OR 1.00 (0.79 to 1.26)	5.7%	5.7% (4.5 to 7)	0.0% fewer (1.1 fewer to 1.4 more)	⊕⊕⊕⊕ High	NOT SIGNIFICANT

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Interpretation
		Without beta- blockers	With beta- blockers	Difference		
Safety Outcomes - VT or VF № of participants: 5943 (4 RCTs)	OR 0.40 (0.27 to 0.60)	2.9%	1.2% (0.8 to 1.8)	1.7% fewer (2.1 fewer to 1.1 fewer)	⊕⊕⊕⊕ High	BENEFIT
Safety Outcomes - Dyspnea № of participants: 4027 (4 RCTs)	OR 0.79 (0.63 to 0.98)	9.7%	7.8% (6.3 to 9.5)	1.9% fewer (3.4 fewer to 0.2 fewer)	⊕⊕⊕⊕ High	BENEFIT

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence (Please refer to table 1 for the guide). a. I² for heterogeneity = 79, p-value of 0.0002; b. I² for heterogeneity = 68%, p-value = 0.0010; c. I² for heterogeneity = 74%, p-value = 0.0001

Certainty of Evidence

There is a high certainty of evidence for the outcomes of cardiovascular mortality and heart failure-related hospitalization. On the safety outcomes, certainty of evidence was high in worsening heart failure, syncope, malignant ventricular arrhythmias, and dyspnea but moderate for the rest because of significant heterogeneity.

RECOMMENDATIONS FROM OTHER GROUPS

Table 47. Existing recommendations from other groups on the use of beta-blockers in heart failure

GUIDELINES	RECOMMENDATION	Strength of Recommendation/ Certainty / Quality of Evidence
Canadian Cardiovascular Society/Canadian Heart failure Society (CCS/CHFS) Heart Failure Guidelines Update: Defining a New	Start beta-blockers as soon as the diagnosis of HF is made, and to give them with	Strong Recommendation / High Quality

Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction.(29) (2021)	ARNi/ARB/ACEi, MRA and SGLT2i	
	Stabilize NYHA IV prior to initiation	
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 (30)	Consider giving BB (EF 50%)	Strong Recommendation / (Low quality for EF \leq 50%)
	Recommended for \leq 40%	High quality for EF \leq 40%
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 (31)	Recommended to reduce mortality and HHF	I / A
Japanese Circulation Society/Japanese Heart Failure Society (JCS/JHFS) 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure (32)	Recommended to improve prognosis	I / A
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure European Heart Journal (33)	Recommended to reduce mortality and HHF	I / A
Clinical Practice Guidelines Management of Heart Failure 2019 National Heart Association of Malaysia (34)	Indicated in all patients with HF to improve survival and delay progression	I / A

Existing clinical practice guidelines on heart failure management recommend starting beta-blockers among patients with an ejection fraction of less than or equal to 40% with high quality certainty of evidence and strong strength of recommendation. The CCS/CHFS, ACC/AHA/HFSA, JCS/JHFS, and ESC define reduced ejection fraction as an ejection fraction of less than or equal to 40% while the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand define reduced ejection fraction as an ejection fraction of less than 50%.

The CCS/CHFS Heart Failure guideline recommends stabilizing symptoms prior to starting beta-blocker treatment (strong recommendation, high-quality evidence).

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand advise the use of the following beta-blockers: bisoprolol, carvedilol, controlled-release metoprolol, and nebivolol.

In the 2022 AHA/ACC/HFSA guideline, three beta-blockers—bisoprolol, carvedilol, and sustained-release metoprolol succinate—are recommended to reduce mortality and hospitalizations among patients with HFrEF.

The recommendations from the NICE 2010 heart failure guidelines in relation to beta-blockers are the same in the 2018 guidelines: beta-blockers licensed for heart failure should be used. For patients who were previously on a different beta-blocker for another disease entity (e.g. hypertension), the previous beta-blocker should be changed to a beta-blocker for heart failure. Beta-blocker treatment should be started in a ‘start low, go slow’ manner: heart rate, blood pressure, and clinical status should be checked during each dose adjustment (in relation to the usual adverse events such as dizziness, hypotension, and arrhythmia, that caused patient withdrawal during the run-in period of major clinical trials).

A more detailed table on the recommendations of international groups can be found in Annex 11, Appendix 11.

ONGOING STUDIES

An epidemiologic study may be done after implementation of these recommendations to evaluate its effect in the all-cause mortality, cardiovascular mortality, and heart failure hospitalization compared to those currently seen in the country (e.g. in the Heart Failure Registry being done, or compared to the 2014 epidemiologic burden of hospitalization study).

ADDITIONAL CONSIDERATIONS FOR EVIDENCE-TO-DECISION (EtD) PHASE

Comparing the prices of beta-blockers for heart failure (bisoprolol, carvedilol, metoprolol succinate)—approximately between Php 442.00 and Php 592.00 per month, depending on brand and on frequency of intake^{34,35}—and the price of hospitalization for heart failure²—the estimated price of hospitalization was already between Php 19,340.00 and Php 28,220.00 in a government hospital and between Php 28,370.00 and Php 41,800.00 in a private hospital in 2014. However, the reviewer did not encounter economic evaluation studies for the use of beta blockers in the local setting.

A cost-effectiveness study on the use of beta-blocker in patients with chronic HF was done in Japan in 2004 by Inomata et al.³⁶ The assumptions of the study are as follows: that patients were 60 years old and were of NYHA Class II to III; that the patients receive regular outpatient care and testing; and that the patients receive conventional treatment (which was, at the time, diuretics, ACEI and digitalis). Two groups were assessed: one group received conventional treatment while the other received carvedilol on top of conventional treatment. Itemized costs show a higher outpatient

cost for the carvedilol group, and that the carvedilol group spent a greater amount on medication costs because of a concomitantly longer life span. However, the carvedilol group also spent a smaller amount with regards to heart failure-related hospitalization. The use of carvedilol was more cost-effective compared to conventional treatment.

In another study done in the US in 2013 by Banka et al.³⁷ regarding the incremental cost-effectiveness ratio of different HF treatments which included beta-blockers, the comparisons were diuretics alone, versus other standards of care. The incremental cost-effectiveness ratio (ICER) of ACEi+BB+AldA versus ACEi+BB was \$501 and \$34 per life-year for the ACEi+BB+AldA versus ACEi+BB cohort. The use of beta blockers in the treatment of heart failure was more cost-effective compared to the other cohort.

It was found that the ACEi/beta-blocker group benefited from more quality-adjusted life years, less total healthcare cost, and more cost-savings per life-year lived compared to the diuretics alone group.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

No local studies were found. However, a study done in the United Kingdom was published last 2008 showed that among patients diagnosed with heart failure, women and patients living in areas with low socioeconomic status are less likely to be prescribed beta-blocker treatment by primary care physicians even in the absence of contraindications.³⁸ Moreover, there were patients who were prescribed other types of beta-blockers.

Given that the effect of beta-blockers in heart failure is not a class effect, and given that the intake of specific beta-blockers significantly decreased the incidence of cardiovascular mortality, heart failure mortality and heart failure-related hospitalization, it must be ensured that the specific beta-blockers that have been proven beneficial for heart failure be prescribed to all patients diagnosed with HFrEF as long as there are no contraindications with regards to blood pressure, heart rate, the presence of high grade AV block, history of severe bronchospasm, that are present.

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10. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of RAAS-blockers (ACEi/ARB or ARNis) on the incidence of cardiovascular mortality, heart failure- related hospitalization, and quality of life?

Recommendation 10A

Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we recommend the use of RAAS Blockers. (ACE-is or ARBs or ARNis)

(moderate level of evidence, strong recommendation)

Recommendation 10B

Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we suggest the use of ARNis over ACE-is or ARBs.

(low level of evidence, weak recommendation)

CONSIDERATIONS

The consensus panel (CP) considered the following when formulating these recommendations:

- There was a discussion regarding the network analysis which showed statistically significant benefit of ARNis on the hard outcomes compared to ARBs or ACEis. The panelists also compared the costs of ARNis against the costs of ACEis or ARBs, as well as the cost of the monthly use of ARNis against the cost of hospitalization. There was a unanimous vote on statement number 2.
- There were 3 cycles of voting regarding the strength of recommendation of the 2nd statement. The panelists who voted for a strong recommendation mentioned that patients who use ARNis have better symptom relief and hospitalization based on real life practice. On the other hand, medication cost was a major issue for those who voted for a weak recommendation for the 2nd statement as patients with low income usually end up shifting from ARNis to the much cheaper ACEis.

- Prior to the 3rd round of voting, the technical facilitator clarified to the CP that a strong recommendation for the 2nd statement will not be consistent with the evidence. A strong recommendation from the CP would mean that patients would universally choose the intervention over the comparator, physicians will choose to prescribe ARNis, the use of ARNis would become the standard for quality care, and can thus affect policy. The 2nd statement could be recommended as weak if the evidence is not as strong or if there are other factors such as cost, equity, or availability that could hinder the implementation of the recommendation despite its benefits.
- Ten votes were cast on the 3rd and final round of voting—9 in favor of a “weak” strength of recommendation, 1 in favor of a “strong” recommendation. The panelist who voted for a strong recommendation decided on the strength of the evidence from the meta-analysis regarding the benefit of ARNis—that ARNis prevent repeated hospitalization whereas the cost of hospitalization is bigger than the cost of spending for ARNis as maintenance medication.

KEY FINDINGS

ACE Inhibitors

ACEIs were associated with a statistically significant reduction in all-cause mortality, CV mortality, and hospitalization for heart failure in patients with heart failure with reduced ejection fraction. The benefits of ACE-Inhibitors were observed when compared to placebo treatment.

Angiotensin II Type 1-Receptor Blockers (ARBs)

Clinical trials show conflicting results regarding benefit as a class effect of ARBs on all-cause mortality, CV mortality, and hospitalization for heart failure in heart failure patients with reduced ejection fraction.

There are, however, identified ARBs with clear benefits on heart failure patient outcomes—candesartan, for instance, has been shown to reduce cardiovascular mortality while valsartan has been shown to have a positive effect on hospitalization for HF inpatients. There was no statistically significant difference in the critical outcomes of all-cause mortality, CV mortality, and hospitalization for heart failure between using ARBs and using ACE-Inhibitors.

Sacubitri/Valsartan

The use of Sacubitri/Valsartan decreases the risk of all-cause mortality, CV mortality, and hospitalization for heart failure compared to control (ACE-inhibitors or angiotensin receptor blockers) in patients with heart failure with reduced ejection fraction.

INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is one of the key regulatory mechanisms of the body responsible for maintaining arterial pressure homeostasis and regulating tissue perfusion. The inappropriate activation of the RAAS has been identified as a key pathophysiological mechanism involved in chronic heart failure. In HF, the heart fails to adequately fulfill its role as a pump, leading to renal hypoperfusion and sympathetic activation. Although the initial activation of the RAAS improves cardiac output, it becomes overwhelmed over time by the opposing vasodilator and natriuretic mediators, eventually propagating the heart failure syndrome. Three drugs targeting the RAAS are the angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and the angiotensin receptor-neprilysin inhibitors (ARNis),¹ the newest among the three.

Angiotensin-converting enzyme (ACE) inhibitors are part of first-line treatment in HFrEF.² Five molecules were recommended by the European Society of Cardiology in 2016 namely captopril, enalapril, lisinopril, ramipril, and trandolapril.³ Angiotensin II Type 1-Receptor Blockers (ARBs) work by inhibiting the angiotensin II receptors, causing systemic vasodilatation and blood pressure reduction. Earlier clinical trials have confirmed that suppression of the RAAS by ACE-Is and ARBs reduces cardiovascular (CV) events in patients with heart failure. Angiotensin receptor-neprilysin inhibitor (ARNi) is the latest drug targeting the RAAS. Sacubitri/Valsartan is the first drug of the class and is a novel therapy that has emerged from an improved understanding of the pathophysiology of heart failure and cardiac remodeling. Clinical trials show that sacubitri/valsartan has a beneficial effect on heart failure with reduced ejection fraction.⁴

Targeting the RAAS through these three drugs have been shown in clinical trials to have a consistent mortality benefit. Thus, the majority of international guidelines consider RAAS blockers as first line treatment, and have even recommended that ARNis replace ACE-is or ARBs with a class I recommendation.⁵⁻¹⁰

REVIEW METHODS

Electronic databases including Pubmed, Scopus, Medline, Google Scholar, and Cochrane reviews were searched. The investigation encompassed all published studies recruiting human participants, both local and international, until January 2023 to look for relevant controlled trials. Meta-analyses and randomized controlled trials that compared renin-angiotensin system inhibitors (RAS inhibitors) against placebo or standard care were included in this review. Outcomes of interest included the critical outcomes of all-cause mortality, cardiovascular mortality, hospitalization for heart failure, and adverse events (Annex 12, Figure 1). Excluded from the search were non-English journals, case reports, and series. To formulate the recommendations, meta-analyses and systematic reviews of studies carried out in individuals with heart failure with reduced ejection fraction were surveyed. Two investigators independently reviewed the literature, extracted data, and assessed the risk of bias. Disagreements were resolved by consensus. Revman5.3 software was used for statistical analysis. GRADE Pro was used for quantitative synthesis of clinical outcomes. The quality of evidence was assessed using the GRADE approach identifying study design, study limitations (lack of allocation concealment, lack of blinding, loss to follow-up, adherence to intention-to-treat analysis, failure to report outcomes), study inconsistencies (heterogeneity), indirectness of evidence (applicability of the studies), study imprecision, and other identified limiting characteristics. Standardized summary of evidence tables were used to present the quality of the evidence and key results in a transparent and reproducible fashion.

RESULTS

Characteristics of included studies

A network meta-analysis (NMA)¹¹ of 28 randomized controlled trials including 47,407 was used in this evidence summary. The NMA directly and indirectly compared ARNis, ARBs, ACE-is, and placebo in heart failure with reduced ejection fraction. The etiology of HFrEF was ischemic cardiomyopathy in most trials and most of the patients had mild to moderate symptoms. In only one trial, the LIFE trial,¹² were patients with severe (Class IV) symptoms included, making up one-third of the patient population. Different generic ACE inhibitor and ARB interventions were used but the only ARNi used was sacubitril/valsartan. No RAAS-inhibitors were used simultaneously in all trials. Comparators were either another class of RAAS-inhibitor or placebo. Critical outcomes measured include cardiovascular mortality, all-cause mortality, and hospitalization for heart failure. Adverse events were also measured in this NMA, namely hypotension, hyperkalemia, renal failure, and angioedema.

Efficacy outcomes

ACE-Inhibitors vs Placebo

Seven RCTs involving 7,518 patients looking at critical outcomes of cardiovascular mortality, all-cause mortality, and hospitalization for heart failure were included in this study. All critical outcomes showed a statistically significant benefit when ACEis were used with placebo on all-cause mortality, (RR 0.86, 95% CI 0.79-0.94), cardiovascular mortality (RR 0.83, 95% CI 0.74-0.93), and hospitalization for heart failure (RR 0.69, 95% CI 0.59-0.81).

Table 48. Summary of findings of ACE inhibitors compared to placebo based on 7 RCTs

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	RR 0.86 (0.79 to 0.84)	7518	⊕⊕⊕⊕ High	Benefit
Cardiovascular Mortality	RR 0.83 (0.74 to 0.93)	7518	⊕⊕⊕⊕ High	Benefit
Hospitalization for worsening Heart Failure	RR 0.69 (0.59 to 0.81)	7518	⊕⊕⊕⊕ High	Benefit
Hypotension	RR 1.77 (1.23 to 2.55)	7518	⊕⊕⊕⊕ High	Harm
Hyperkalemia	RR 1.98 (1.09 to 3.60)	7518	⊕⊕⊕⊕ High	Harm
Renal failure	RR 1.32 (0.96 to 2.06)	7518	⊕⊕⊕⊕ High	Inconclusive
Angioedema	RR 2.00 (0.53 to 7.51)	7518	⊕⊕⊕⊕ High	Inconclusive

Angiotensin Receptor Blockers

ARBs vs Placebo

Five randomized controlled trials with a total of 8,444 patients were analyzed in the network meta-analysis. Hospitalization for worsening heart failure was the only critical

outcome for which the use of ARBs showed a statistically significant benefit over placebo (RR 0.71, 95% CI 0.61-0.81). For the other critical outcomes, there was a trend toward benefit regarding the use of an ARB over placebo but it was not statistically significant for all-cause mortality (RR 0.92, 95% CI 0.84-1.01) and CV mortality (RR 0.90, 95% CI 0.79-1.01).

Table 49. Summary of findings of ARBs compared to placebo based on 5 RCTs

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	RR 0.92 (0.84 to 1.01)	8,444	⊕⊕⊕ High	Inconclusive
Cardiovascular mortality	RR 0.90 (0.79 to 1.01)	8,444	⊕⊕⊕ High	Inconclusive
Hospitalizations for worsening HF	RR 0.71 (0.61 to 0.81)	8,444	⊕⊕⊕ High	Benefit
Hypotension	RR 2.04 (1.43 to 2.92)	8,444	⊕⊕⊕ High	Harm
Hyperkalemia	RR 2.13 (2.12 to 4.03)	8,444	⊕⊕⊕ High	Harm
Renal Failure	RR 1.84 (1.35 to 2.51)	8,444	⊕⊕⊕ High	Harm
Angioedema	RR 1.18 (0.36 to 3.89)	8,444	⊕⊕⊕ High	Inconclusive

ARBs vs ACEis

Nine randomized controlled trials with 20,406 patients were used to analyze ARBs against ACEis in patients with HFrEF. There was no statistically significant difference between the two drug classes with regards to the critical outcomes of all-cause mortality, cardiovascular mortality, and hospitalization for worsening heart failure (see table 50).

Table 50. Summary of findings of ARBs compared to ACE inhibitors based on 9 RCTs

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	RR 1.07 (0.98 to 1.16)	20,406	⊕⊕⊕⊕ High	Inconclusive
Cardiovascular mortality	RR 1.08 (0.97 to 1.20)	20,406	⊕⊕⊕⊕ High	Inconclusive
Hospitalization for worsening HF	RR 1.02 (0.90 to 1.15)	20,406	⊕⊕⊕⊕ High	Inconclusive
Hypotension	RR 1.15 (0.88 to 1.52)	20,406	⊕⊕⊕⊕ High	Inconclusive
Hyperkalemia	RR 1.07 (0.67 to 1.91)	20,406	⊕⊕⊕⊕ High	Inconclusive
Renal failure	RR 1.40 (1.07 to 1.83)	20,406	⊕⊕⊕⊕ High	Harm
Angioedema	RR 0.59 (0.33 to 1.04)	20,406	⊕⊕⊕⊕ High	Inconclusive

Angiotensin receptor-neprilysin inhibitor

ARNi vs Placebo

There are no studies (RCTs or cohorts) that compared ARNis to placebo. Thus, the network meta-analysis was used to indirectly determine the benefit of the medication. Based on the analysis, the use of ARNis benefits has a benefit on the critical outcomes of all-cause mortality (RR 0.75, 95% CI 0.63-0.89), CV death (RR 0.71, 95% CI 0.57-0.89), and hospitalizations for worsening heart failure (RR 0.60, 95% CI 0.48-0.75). However, issues of indirectness (one study used inpatients) and imprecision downgraded the certainty of evidence, thus the low rating.

Table 51. Summary of Findings of ARNi compared to placebo based on NMA

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	RR 0.75 (0.63 to 0.89)	27 studies	⊕⊕○○ Low ^a	Benefit
Cardiovascular death	RR 0.71 (0.57 to 0.89)	16 studies	⊕⊕○○ Low ^a	Benefit
Hospitalization for worsening heart failure	RR 0.60 (0.48 to 0.75)	18 studies	⊕⊕○○ Low ^a	Benefit
Hypotension	RR 2.98 (1.91 to 4.67)	19 studies	⊕⊕○○ Low ^a	Harm
Hyperkalemia	RR 2.55 (1.32 to 4.90)	14 studies	⊕⊕○○ Low ^a	Harm
Renal Failure	RR 1.23 (0.82 to 1.84)	16 studies	⊕⊕○○ Low ^a	Inconclusive
Angioedema	RR 2.10 (0.46 to 9.50)	12 studies	⊕⊕○○ Low ^a	Inconclusive

ARNi vs ACEi or ARB

All clinical trials compared ARNI to either an ARB or an ACEi. Based on the seven (7) RCTs available, ARNi was associated with a lower risk of all-cause mortality (RR 0.75, 95% CI 0.63 to 0.89), cardiac death (RR 0.71, 95% CI 0.57 to 0.89), and hospitalization for heart failure (RR 0.60, 95% CI 0.48-0.75) when compared to ARBs and ACE inhibitors.

Table 52. Summary of Findings of ARNi compared to ARB/ACEi (See Annex 12)

Outcomes	ARNI	ARB	ACE-I
	Vs PLACEBO		
All-cause mortality	0.75 (0.63-0.89)	0.92 (0.84 to 1.01)	0.86 (0.79 to 0.84)
CV mortality	0.71 (0.57-0.89)	0.90 (0.79 to 1.01)	0.83 (0.74 to 0.93)
Hospitalizations	0.60 (0.48-0.75)	0.71 (0.61 to 0.81)	0.69 (0.59 to 0.81)
Hypotension	2.98 (1.91-4.67)	2.04 (1.43 to 2.92)	1.77 (1.23 to 2.55)
Hyperkalemia	2.55 (1.32 - 4.90)	2.13 (2.12 to 4.03)	1.98 (1.09 to 3.60)
Renal failure	1.23 (0.82 - 1.84)	1.84 (1.35 to 2.51)	1.32 (0.96 to 2.06)
Angioedema	2.10 (0.46 - 9.50)	1.18 (0.36 to 3.89)	2.00 (0.53 to 7.51)

Safety outcomes

On the network meta-analysis, four major adverse events were analyzed, namely hypotension, hyperkalemia, renal failure, and angioedema. For renal failure, there is a statistically significant benefit with the use of ARNi compared to ARBs (RR 0.67, 95% CI 0.47-0.96). For the outcome of hypotension, there is a statistically significant harm with the use of ARNi when compared to ACEis (RR 1.69, 95% CI 1.27- 2.34) or ARBs (RR 1.46, 95% CI 1.02 – 2.10). Meanwhile, there is no statistically significant difference between the use of an ARNi and of ARBs/ACEis for the outcomes of hyperkalemia and angioedema.

There is a statistically significant harm in terms of renal failure with the use of ARBs (RR 1.40, 95% CI 1.07 – 1.83) compared to ACE-is but there are no statistically significant differences for the outcomes of hypotension, hyperkalemia, and even angioedema. When compared to placebo, the use of ACE-Is is associated with a statistically significant increase in hypotension (RR 1.77, 95% CI 1.23 – 2.55) and hyperkalemia (RR 1.98, 95% CI 1.09 – 3.60) but it has no such effect on renal failure and angioedema. Similarly, indirect comparison of ARNi to placebo showed harm due to an increased risk for hypotension (RR 2.98, 95% CI 1.91-4.67) and hyperkalemia (RR 2.55, 95% CI 1.32 to 4.90) but not for renal failure or angioedema.

Certainty of Evidence

The ARNI vs ARB analysis included the LIFE trial, which included patients who were diagnosed with HF NYHA Class IV, so indirectness was downgraded to serious, resulting in a moderate certainty of evidence. The certainty of evidence for ARNi vs placebo was downgraded to low because it was an indirect analysis from the network meta-analysis (observational study). The rest of the GRADE Pro analyses of certainty of evidence were rated high. (Annex 12, Appendix tables 5 to 8)

RECOMMENDATIONS FROM OTHER GROUPS

All the international guidelines have already recommended that RAAS blockers be given to patients with HFrEF. They have also recommended that ARNis be given if a patient has not received ACEis or ARBs. The Canadian guidelines also mentioned that ARNis are the preferred choice over ACEis or ARBs.

Table 53. Summary of recommendations from various guidelines regarding use of ARNis in heart failure

Group or Agency	Recommendation	Strength of Recommendation
2019 ACC Expert Consensus Report ⁵	Recommends ARNi in patients who are ACEi/ARB-naive	Strong
2019 ESC Expert Consensus Report ⁶	Recommends ARNi in patients who are ACEi/ARB-naive	Strong
2019 Malaysian CPG on the Management of HF ⁷	ARNi should be considered as a replacement of ACEi/ARB in patients with HFrEF who remain symptomatic to decrease CV death, HF hospitalisations, and symptoms. ARBs are also indicated in HFrEF. There is no difference between ACEis and ARBs in terms of CV outcomes such as mortality and HF hospitalisation. ARBs are however better tolerated because of their better side effect profile.	Strong Recommendation IIa, B
2020 Spanish Consensus ⁸	Elevated ARNi ahead of ACEi/ARB	Strong
2021 ACC Expert Consensus Decision Pathway ⁹	Recommends ARNi as the preferred RAASI for all appropriate HFrEF patients	Strong
2021 Canadian CCS/CHFS HF Guidelines Updates ¹⁰	Elevated ARNi ahead of ACEi/ARB	Strong

2021 ESC HF Guidelines ²	Recommends ARNi in patients ACEi/ARB-naïve Recommends ARNi as a cornerstone therapy for HFrEF along with ACEi, BB, and MRA, and as replacement for ACEi in patients who remain symptomatic.	Strong
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ONGOING STUDIES AND RESEARCH GAPS

There are several ongoing studies on ARNis particularly with regards to decompensated HF,¹³ the different subsets of patients with CHF,¹⁴ LVAD recipients,¹⁵ and patients with pulmonary hypertension¹⁶ (www.clinicaltrials.gov).

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

Sacubitril/Valsartan

In the UK, the cost per quality-adjusted life-year (QALY) gained by using sacubitril/valsartan (using cardiovascular mortality) was £17,100 (€20,400) versus using enalapril. In Denmark, the ICER for sacubitril/ valsartan was Kr 174,000 (€22,600). In Colombia, the ICER was COP \$39.5 million (€11,200) per QALY gained. In all three countries, sacubitril/valsartan is likely to be more cost-effective compared to an ACEi (the current standard of care) in patients with HFrEF.¹⁷

In Indonesia, therapy with sacubitril/valsartan had an ICER of IDR 26,742,098 or USD 1,890 per QALY gained compared to enalapril based on a healthcare system perspective. When willingness to pay thresholds of GDP per capita was used, this result was considered cost-effective. Reductions in mortality, hospitalization, and the cost of sacubitril/valsartan also appeared to have the most influential impact on the ICER.¹⁸

Differences in “cost-effectiveness” in these two countries demonstrate that the results may vary depending on where the study is conducted. Thus, applying the results to another setting is problematic.

ACE-Inhibitors/Angiotensin II Type 1-Receptor Blockers (ARBs)

Based on the search conducted on economic evaluation for these drugs, the reviewer did not encounter economic evaluation studies of individual medications. It is important to note that majority of the drugs have already been included in the Philippine National Formulary.

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11. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of mineralocorticoid receptor antagonists on the incidence of cardiovascular mortality, heart failure- related hospitalization, and quality of life?

Recommendation 11

Among Filipino patients with chronic HFrEF, with estimated glomerular filtration rate (eGFR) >30ml/min/1.73 m², and serum potassium <5 mEq/L, we recommend the use of a MRA (spironolactone or eplerenone) on top of standard of care.

(low level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- Despite the overall low certainty of evidence, the CP gave a strong recommendation because there is moderate to high certainty of evidence in reducing critical outcomes of all-cause mortality, cardiovascular mortality, and hospitalizations for heart failure with the use of MRAs.
- Spironolactone is included in the Philippine National Drug Formulary; however, at the time of writing, eplerenone is not.

KEY FINDINGS

Six randomized trials were included in the evidence summary. These trials showed that there was an improvement in CV mortality and all-cause mortality, and a reduction in hospitalization from heart failure associated with MRA use. There was also a higher risk of hyperkalemia associated with the use of mineralocorticoid receptor antagonists (MRAs) compared to placebo. MRA use did not increase the risk of gynecomastia, renal impairment, worsening heart failure, hypotension, and death. There was no difference in quality of life with MRA use compared to placebo. The overall certainty of evidence is moderate.

INTRODUCTION

Activation of the mineralocorticoid receptor by both aldosterone and cortisol plays a central role in congestive heart failure. Consequently, mineralocorticoid receptors are overexpressed in the failing heart. Mineralocorticoid receptor antagonists (MRAs) have thus been incorporated in the treatment of congestive heart failure.¹

The diseases of the heart rank as the most common cause of mortality in the Philippines with 102,936 deaths noted.² The Heart Failure Registry of patients under the Philippine Heart Association's Council on Heart Failure showed that the majority of cases of heart failure with reduced ejection fraction was caused by ischemic heart disease, followed by hypertension, then by rheumatic heart disease. Most of the cases were also classified under NYHA FC III. Cardiac complications occurred during hospitalization in 13.2% of included patients with an overall mortality rate of 3.9%.³

REVIEW METHODS

A systematic search was done using Medline, Cochrane Library, and Google Scholar using the search terms “congestive heart failure”, “eplerenone”, and “spironolactone”. Studies comparing the use of eplerenone or spironolactone with placebo or standard-of-care which included adult patients were included. Relevant clinical practice guidelines were likewise retrieved and the references of these were also included. Studies which included patients with NYHA IV and acute, decompensated heart failure were excluded from the search.

Outcomes of interest included mortality, hospitalization from heart failure, quality of life, and adverse events. No limits were placed on age and on the dosing of the medications. The Risk of Bias Tool was used to determine the risk of bias among the studies. Relative risks for dichotomous outcomes and mean difference for continuous data were pooled whenever possible using Review Manager. Meanwhile, certainty of evidence was assessed using GRADEPRO.

RESULTS

Characteristics of included studies

Six randomized trials were included in the evidence review investigating the use of spironolactone and eplerenone among patients with HFrEF.^{1,4-10} Patients enrolled included NYHA I-III participants with cut-offs for ejection fraction ranging from less than 30% to 45%.

Evidence was available for all the critical outcomes: all-cause mortality, CV mortality, heart failure-related hospitalization, and quality of life. For the outcomes of all-cause mortality, CV mortality, and hospitalization from heart failure, two studies were included. Two studies investigated the quality of life among patients. The adverse events of treatment were reported in six studies. Four studies were deemed at high risk for bias due to low sample sizes and high attrition rates.

Efficacy outcomes

Based on two trials, the use of MRAs has a significant benefit on cardiovascular mortality, all-cause mortality, and hospitalizations from heart failure.^{1,8}

Table 54. Efficacy outcomes on the use of MRAs in HFrEF

Outcome (total number of patients)	Number of patients	Relative risk (RR), 95% CI	Interpretation	Certainty of evidence
Cardiovascular mortality	2867	0.78 [0.64, 0.96]	Benefit	Moderate
All-cause mortality	3164	0.81 [0.68, 0.97]	Benefit	Moderate
Hospitalizations from heart failure	2953	0.64 [0.54, 0.77]	Benefit	High

Quality of life

Based on one trial, there was no difference in quality of life scores after administration of MRAs using the visual analog scale.

Table 55. Effect of MRA on quality of life

Outcome	Number of patients	Mean difference (MD), 95% CI	Interpretation	Certainty of evidence
Quality of life	40	0.04 [-0.58, 0.66]	No significant difference	Low

Safety outcomes

Based on four randomized trials, there was a higher risk of hyperkalemia with the use of MRA compared to placebo. The use of spironolactone is associated with other adverse events such as hypotension, worsening of renal function, metabolic abnormalities (hyponatremia, hypomagnesemia, hypocalcemia, hypochloremic alkalosis, hyperuricemia, and hyperglycemia), precipitation of gout, gynecomastia, and impaired neurological function/ coma in patients with hepatic impairment, cirrhosis and ascites. (FDA) The use of eplerenone is associated with hyperkalemia, myocardial infarction, abnormal renal function, gynecomastia, mastodynia, and abnormal uterine bleeding. (FDA).

Table 56. Adverse events associated with MRA use

Outcome	Number of patients	Relative risk (RR), 95% CI	Interpretation	Certainty of evidence
Hyperkalemia	3204	2.31 [1.71, 3.12]	Harm	Low

Certainty of evidence

The outcomes on all-cause mortality and CV mortality were downgraded because of risk of bias. The adverse events outcomes were downgraded due to risk of bias and imprecision. The overall certainty of evidence is low.

RECOMMENDATIONS FROM OTHER GROUPS

Table 57. Recommendations from Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
AHA 2022 ¹¹	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 ² and serum potassium is <5.0 mEq/L.	(IA)

	Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize the risk of hyperkalemia and renal insufficiency. In patients taking an MRA whose serum potassium cannot be maintained at <5.5 mEq/L, the MRA should be discontinued to avoid life-threatening hyperkalemia.	(3B-NR)
ESC 2021¹²	An MRA is recommended for patients with HFrEF to reduce the risk of hospitalization and death.	(IA)
Australian Guidelines 2018¹³	Recommendation: An MRA is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%), unless contraindicated or not tolerated, to decrease mortality and decrease hospitalisation for heart failure.	(Strong recommendation FOR; high quality of evidence.)
CCS/CHFS Heart Failure Guidelines 2021¹⁴	We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including one evidence-based medication from each of the following categories: a. ARNI (or ACEI/ARB); b. b-blocker; c. MRA; and d. SGLT2 inhibitor.	(Strong Recommendation; Moderate-Quality Evidence).
NICE¹⁵	Offer a mineralocorticoid receptor antagonist (MRA), in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction.	

ONGOING STUDIES AND RESEARCH GAPS

There are no ongoing studies related to this research topic. Since the majority of studies included patients with acute heart failure, more studies investigating the use of MRAs on patients with chronic heart failure should be conducted.

COST

An economic evaluation study in the United States using MRA therapy was assessed in RALES and EPHESUS.¹⁶⁻¹⁷

Using a US-based Markov Model, the incremental cost-effectiveness ratio (ICER) on the use of combination treatment ACEI+BB, and Aldosterone antagonist was \$1,500 per

quality-adjusted life-year.¹⁶ In the economic study of the RALES study, spironolactone therapy was more cost-effective than placebo.¹⁷ Based on the search, the reviewer did not encounter local economic evaluation studies.

Table 58. A comparison of the monthly costs between spironolactone, eplerenone, medical consultations and serum potassium

	Cost/dose (PHP)	Dosing	Cost per month
Spironolactone*	4.71 - 15.00 (25 mg) 8.50 - 36.28 (50 mg)	25 to 50 mg	141.30 to 1088.40
Eplerenone*	29.50 (25 mg)	25 to 50 mg	P 885 to P 1770
Consultation	500 to 1000 per consult		P 1000
Serum potassium**	After 1 week, 4 weeks and 6 months of initiation	P 165 per testing	

*price from the Philippine National Drug Formulary or Watson's drugstore Cost per month after initiation: (eplerenone) 2,215 to 3,100 (spironolactone) 1471.3 to 2418.4

**price from the outpatient department of the Philippine General Hospital

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

In a Swedish Registry of heart failure with reduced ejection fraction patients, only 40% of patients were given MRAs. Factors associated with non-use of MRAs included lower creatinine clearance (<60 mL/min), no diuretic use, higher blood pressure, no digoxin use, higher ejection fraction, outpatient setting, older age, lower income, ischaemic heart disease, male sex, follow-up in primary vs. specialty care, lower NYHA class, and absence of hypertension.¹⁸

Guideline-directed therapy such as the use of beta blockers, ACE inhibitors, mineralocorticoid receptors antagonists, and ivabradine was underutilized. Only 26.5% of patients received an MRA as part of treatment.³

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12. Among adult Filipinos diagnosed with chronic heart failure (HFrEF) at the outpatient clinic, what is the effect of Sodium-Glucose co-transporter 2 (SGLT2) inhibitors on the incidence of cardiovascular mortality and heart failure- related hospitalization, and quality of life?

Recommendation 12

Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we recommend treatment with SGLT2 inhibitors.

(high level of evidence, strong recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- There was a unanimous vote on the recommendation for SGLT2i for the treatment of HFrEF considering the benefit from the use of the medication and the local study on its cost effectiveness.

KEY FINDINGS

There were four randomized controlled trials that assessed the efficacy and safety of sodium-glucose transport protein 2 (SGLT2) inhibition with dapagliflozin or empagliflozin compared to placebo in patients with heart failure and reduced ejection fraction (HFrEF). The use of SGLT2 inhibitors significantly reduced cardiovascular mortality, death from any cause, hospitalization from heart failure, and worsening of kidney function compared to placebo. There was also an improvement in the quality of life (QoL) as measured by the KCCQ score. There was no significant difference between SGLT2 inhibitors and placebo on the incidence of volume depletion, fractures, amputations, major hypoglycemia among those with diabetes, diabetic ketoacidosis, and complicated urinary tract infection. However, compared to placebo, there was an increase in the incidence of genital infections with the use of SGLT2 inhibitors.

Allocation concealment was not clear in one of the four trials but the overall risk of bias remained low. Cardiovascular mortality, death from any cause, hospitalization for heart failure, improvement in the quality of life, and worsening of kidney function had high certainty of evidence. Most of the safety outcomes had moderate certainty of evidence due to the small number of events obtained and the wide confidence interval.

Overall, SGLT2 inhibitors showed efficacy in the cardiovascular and renal outcomes without an increased risk of serious adverse events (except for genital infections) in HF patients with reduced EF.

INTRODUCTION

Measures to alleviate the epidemiologic^{1,2} and economic burdens³ in the Philippines are imperative, especially those that will reduce cardiovascular outcomes. A class of drugs that recently came out was the sodium-glucose transport protein 2 (SGLT2) inhibitors. Before the advent of the specific Heart Failure (HF) trials, the cardiovascular outcome trials using SGLT2 inhibitors (SGLT2is) were used among diabetics with a high cardiovascular risk profile or established atherosclerotic CVD^{4,5,6} and even on patients with chronic kidney disease (CKD).⁷ Findings showed significant reduction in death from cardiovascular causes,⁴ hospitalization for heart failure,^{4,5,6} and death from any cause.⁴ There was also benefit seen with the use of SGLT2 inhibitor in the composite endpoint of a sustained decline in estimated glomerular filtration rate of at least 50%, end-stage renal disease, or death from renal disease.^{5,6,7}

The mechanisms proposed could be due to its cardioprotection (eg. decrease heart rate, decrease fluid congestion), renoprotection (e.g. decrease sympathetic tone, decrease interstitial fluid), and direct SGLT2i effects (e.g. natriuresis).⁸

There are now completed trials on SGLT2is that focused on patients with HFrEF, regardless of diabetes status at baseline. Hence, it is the aim of this review to determine the direction and magnitude of the effects of SGLT2 inhibitors compared to placebo among patients with HRrEF when it comes to efficacy and safety outcomes. Other considerations like cost-effectiveness will also be reported. The data provided can hopefully help determine the recommendation of its use in the local setting.

REVIEW METHODS

The selection criteria for the included studies were randomized-controlled trials (RCTs) on patients with chronic heart failure with reduced ejection fraction ($EF \leq 40\%$) that enrolled patients on any sodium-glucose transport protein 2 (SGLT) inhibitors versus placebo and reported on at least one of the efficacy measures. For the efficacy outcomes, the trial must have investigated any of the following outcomes: cardiovascular mortality; death from any cause; hospitalization for heart failure; and change in the quality of life (QoL) based on Kansas City Cardiomyopathy Questionnaire (KCCQ) score. Selected safety endpoints were also included in the review, namely: worsening kidney function; volume depletion; fracture; amputation; major hypoglycemia among those with DM; diabetic ketoacidosis; complicated urinary tract infections (UTI); and genital infections.

Exclusion criteria included the following: Observational or nonrandomized trials; trials combining and comparing SGLT2 inhibitors with another pharmacological agent (e.g. ACE, ARB, ARNI, MRA); and trials reporting only on mechanistic or surrogate outcomes (e.g. change in the levels of NT-proBNP).

The search strategy (Annex 14, Appendix A) for the identification of studies used the Medline database of the National Institute of Medicine at Pubmed, Cochrane Library, and Herdin Plus from December 2022 to January 2023.

Key search terms were “Sodium-glucose transport protein 2 (SGLT) inhibitors”, “empagliflozin”, “dapagliflozin”, “canagliflozin”, “ertugliflozin”, “remoglitiflozin”, “luseogliflozin”, “cardiovascular mortality”, “all-cause death”, “death from any cause”, “hospitalization for heart failure”, “quality of life”, “adverse effects”, “safety profile”, “side effects”, “adults with chronic heart failure”, “adults with reduced ejection fraction”, “randomized, controlled”, and “placebo” as free text, MeSH terms, and a combination of the above. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Appendix B) summarized the search and study selection process.

To assess the potential for bias, the Cochrane risk of bias assessment criteria were used. Pooled risk ratio and 95% confidence intervals (CIs) were calculated for estimates using the Mantel-Haenszel and inverse variance for efficacy and safety outcomes, respectively. Review Manager 5.4.1 was used for all statistical analyses.

There were systematic review and meta-analysis papers comparing SGLT2is to placebo among patients with HFrEF.⁹⁻¹⁴ However, not all efficacy outcomes were evaluated quantitatively. Hence, a de novo meta-analysis was done and included other identified trials as well as specified safety outcomes.

RESULTS

Characteristics of included studies

Four randomized placebo-controlled trials were found including 9,052 patients with chronic heart failure with reduced ejection fraction. All trials compared SGLTis versus placebo in addition to guideline-directed treatment for HFrEF. Two studies used dapagliflozin (10 mg once a day)^{15,16} while two trials used empagliflozin (10 mg once a day)^{17,18} as treatment. Three studies^{15,16,17} reported on cardiovascular mortality, death from any cause, and hospitalization for heart failure. Four studies¹⁵⁻¹⁸ reported on the quality of life (QoL) based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. All four studies¹⁵⁻¹⁸ provided data on adverse events. All efficacy outcomes were considered critical while the safety outcomes were considered important.

The median follow-up was 18.2 months for DAPA-HF¹⁵ and 16 months for EMPEROR-Reduced.¹⁷ Both DEFINE-HF¹⁶ and EMPERIAL-Reduced¹⁸ were completed in 12 weeks. The mean age ranged from 61.3 years to 69.0 years and the mean EF was 26% to 31.1%. The mean GFR ranged from 62.2 mL/min/1.73m² to 69.0 mL/min/1.73m² [15,16,17] or a median of 55 mL/min/1.73m².¹⁸ Other details on the baseline characteristics of the included trials are in Annex 14, Appendix C.

DAPA-HF,¹⁵ EMPEROR-Reduced,¹⁷ and EMPERIAL-Reduced¹⁸ have low risk of bias on the following parameters: selection, performance, detection, attrition, and reporting bias. Allocation concealment was not mentioned in DEFINE-HF making the selection bias partially unclear. However, the other parameters all have low risk of bias. Moreover, DEFINE-HF contributed only a weight of 0.2% in the efficacy outcomes and a weight of 1.3 to 8.2% in the safety outcomes which implies that it may not have a major impact in the direction and magnitude of the results. Hence, DEFINE-HF can still be considered as having a low risk of bias.

Efficacy outcomes:

Table 59. GRADE summary of findings table: SGLT2 inhibitors vs placebo for HReRF on efficacy outcomes

CRITICAL Outcomes	BASIS (Number and Type of Studies; Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Cardiovascular Mortality	3 RCTs (N = 8737)	RR 0.87	0.77 to 0.99	Benefit*	High
Death from any cause	3 RCTs (N = 8737)	RR 0.88	0.79 to 0.99	Benefit*	High
Hospitalization for heart failure	3 RCTs (N = 8737)	RR 0.73	0.65 to 0.81	Benefit*	High
Change in QoL using KCCQ score (mean)** Scale from: 0 to 100	3 RCTs Dapa-HF (N = 4,744) Emperor-R (N = 3,730) Emperial-R (N = 312) Define-HF (N = 263)	MD 1.18 MD 1.7 MD 4.55 aOR 2.35	1.11 to 1.26 0.5 to 3.0 1.18 to 7.93 1.31 to 4.22	Benefit*	High

*favors intervention **individual study report

Cardiovascular mortality

Three studies^{15,16,17} reported on cardiovascular mortality. The pooled sample included 8,737 patients. Results showed that there was a significant 13% reduction in cardiovascular death (RR 0.87, 95% CI = 0.77-0.99, I² = 0%) with the use of SGLT2 inhibitors on top of recommended or guideline-directed treatment for HFrEF compared to placebo. The absolute effect (95% CI) was 14 fewer per 1,000 (from 25 fewer to 1 fewer). The certainty of evidence is high.

Death from any cause

Three studies [15,16,17] reported on death from any cause. The pooled sample included 8,737 patients. Results showed that there was a significant 12% reduction in death from any cause (RR 0.88, 95%CI 0.79-0.99, I² = 0%) with the use of SGLT2 inhibitors compared to placebo on top of recommended or guideline-directed treatment for HFrE. The absolute effect (95% CI) was 16 fewer per 1,000 (from 29 fewer to 1 fewer. The certainty of evidence is HIGH.

Hospitalization for heart failure

Three studies^{15,16,17} reported on hospitalization for heart failure. The pooled sample included 8,737 patients. The results showed that there was a significant 27% reduction in hospitalization for heart failure (RR 0.72, 95%CI 0.65-0.81, I² = 0%) with the use of SGLT2 inhibitors on top of recommended or guideline-directed treatment for HFrEF compared to placebo. The absolute effect (95% CI) was 41 fewer per 1,000 (from 54 fewer to 29 fewer). The certainty of evidence is high.

Quality of Life (QoL)

Four studies¹⁵⁻¹⁸ reported on the quality-of-life score using the Kansas City Cardiomyopathy Questionnaire or KCCQ. The KCCQ is a 23-item, self-administered instrument that “quantifies physical function, symptoms (frequency, severity, and recent change), quality of life, and social function.”¹⁶ The score ranged from 0 to 100 and a higher score indicated fewer symptoms. An increase of 5 points from baseline is considered a clinically important change and translates to better quality of life.^{16,19} The domain of KCCQ-total symptom score (KCCQ-TSS) included a symptom frequency score and a symptom burden score. Meanwhile, the domain of KCCQ-clinical summary score (KCCQ-CSS) covered the physical limitation score and the KCCQ-TSS. Both the DAPA-HF¹⁵ and the EMPERIAL-Reduced¹⁸ trials measured mean change in the KCCQ-TSS while the EMPEROR-Reduced trial¹⁷ reported on the mean change in the KCCQ-CSS. The DEFINE-HF¹⁶ reported on the proportion of patients with ≥5 point improvement in KCCQ-CSS.

Of the four studies that reported on QoL outcome, it was the DEFINE-HF study¹⁶ that showed a clinically meaningful improvement of ≥ 5 points in KCCQ-clinical summary score domain at 12 weeks with the use of dapagliflozin compared to placebo (aOR 2.35. 95%CI 1.31-4.22).

Three studies reported on the mean change of KCCQ score from baseline.^{15,17,18} Combining the three trials (Appendix D, Figure 4A) yielded an inconclusive result (Std. MD 2.71 95% CI --0.50-5.93, $I^2 = 100\%$) with a significant test for heterogeneity. This could be attributed to the different scoring systems used and the different timelines during which the scores were re-measured.

A sensitivity analysis (Appendix D, Figure 4B) was done and pooled only the trials^{15,18} that measured the same domain: KCCQ-TSS. There was, however, an increase in the mean total symptom score by almost four points (MD 3.73 95% CI 2.08-5.39, $I^2 = 89\%$) which translated to an improvement in symptoms. The test for heterogeneity was still significant; this can be attributed to the different timelines or periods of observation for getting the KCCQ-TSS scores. DAPA-HF and EMPERIAL-Reduced were taken at the 8th month and the 12th week, respectively. The longer follow-up may have had a different impact on the magnitude of symptom improvement as compared to a shorter follow-up.

Another sensitivity analysis (Appendix D, Figure 4C) was done and pooled only the trials^{15,17} that measured KCCQ scores after a longer observation period, on the 8th to 13th month. The result was inclusive (MD 2.20 95% CI -1.82-6.22, $I^2 = 100\%$) and the test for heterogeneity was significant.

In this regard, the three studies could not be combined. Instead, the results of the individual studies would be reported. Both DAPA-HF¹⁵ and EMPERIAL-Reduced¹⁸ showed an improvement in the KCCQ-TSS domain with resulting mean differences of MD 1.18 (95% CI 1.11 to 1.26) and MD 4.55 (95CI 1.018-7.93), respectively. EMPEROR-Reduced¹⁷ used the KCCQ-CCS domain and likewise showed an improvement (MD 1.7 95% 0.5 to 3.0).

All four trials have low risk of bias; the certainty of evidence remains high.

For the efficacy outcomes, the detailed forest plots are in Annex 14, Appendix D. The detailed GRADEPRO table is in Annex 14, Appendix E.

Safety Outcomes

The safety outcomes investigated were: 1) Worsening renal function; 2) Volume depletion; 3) Fractures; 4) Amputations; 5) Major hypoglycemia among those with

diabetes; 6) Diabetic ketoacidosis; 7) Complicated UTI; and 8) Genital infections. All the safety outcomes were considered important.

Among the eight safety outcomes, only worsening of renal function was reduced (by 39%) with the use of SGLT2 inhibitors compared to placebo (RR 0.61, 95% CI = 0.45-0.84, $I^2 = 0\%$). The pooled sample was from four trials¹⁵⁻¹⁸ consisting of 9,049 patients. The absolute effect (95% CI) was 9 fewer per 1,000 (from 13 fewer to 4 fewer).

No significant difference in effect was observed between SGLT2 inhibitors and placebo for the six other safety outcomes: volume depletion^{15,16,17} (RR 1.10, 95%CI = 0.95-1.26, $I^2 = 0\%$); fractures^{15,17,18} (RR 1.03, 95% CI = 0.78-1.37, $I^2 = 0\%$); amputations^{15,16,17} (RR 0.18, 95% CI = 0.67-2.08, $I^2 = 0\%$); major hypoglycemia among those with diabetes¹⁵⁻¹⁸ (RR 1.16, 95% CI = 0.53-0.256, $I^2 = 0\%$), diabetic ketoacidosis¹⁵⁻¹⁸ (RR 7.01, 95%CI = 0.36-135.61 $I^2 = 20\%$); and complicated UTI^{17,18} (RR 1.20, 95%CI = 0.62-2.32, $I^2 = 0\%$). The wide confidence intervals for amputations, major hypoglycemia among those with diabetes, diabetic ketoacidosis, and complicated UTI were due to the small number of events per group. Diabetic ketoacidosis in particular was based on only one trial (DAPA-HF)¹⁵ because the other three trials^{16,17,18} reported zero events in both the SGLT2 inhibitor and placebo groups.

However, there was a significant increase in the incidence of genital infections^{17,18} (RR 2.47, 95% CI = 1.30-04.69, $I^2 = 0\%$). Based on two studies,^{17,18} the incidence of genital infections for SGLT2 was 1.6% and 0.6% for placebo. The absolute effect (95% CI) was 9 more per 1,000 (from 2 more to 24 more). The wide confidence interval was also due to paucity of events.

The tests for heterogeneity for all the eight safety outcomes were not significant. Below is the table containing a summary of findings on the safety outcomes described above. For the safety outcomes, the detailed forest plots are in Annex 14, Appendix D. The detailed GRADEPRO table is in Annex 14, Appendix E.

Table 60. GRADE summary of findings table: safety outcomes of SGLT2 Inhibitors vs placebo for HReRF

IMPORTANT OUTCOMES	BASIS (Number and Type of Studies; Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Worsening renal function	3 RCTs (N= 8737)	RR 0.61	(0.45 to 0.84)	Benefit (favors intervention)	High
Volume depletion	3 RCTs (N = 8737)	RR 1.10	(0.95 to 1.26)	Inconclusive	High

Fracture	3 RCTs (N = 8737)	RR 1.03	(0.78 to 1.37)	Inconclusive	High
Amputation	3 RCTs (N = 8786)	RR 1.18	(0.67 to 2.08)	Inconclusive	Moderate
Major hypoglycemia among those with DM	3 RCTs (N = 8737)	RR 1.16	(0.53 to 2.56)	Inconclusive	Moderate
Diabetic Ketoacidosis	3 RCTs (N = 8737)	RR 7.01	(0.36 to 135.61)	Inconclusive	Moderate
Complicated Urinary Tract Infection	3 RCTs (N = 8737)	RR 1.20	(0.62 to 2.32)	Inconclusive	Moderate
Genital Infections	3 RCTs (N = 8737)	RR 2.47	(1.30 to 4.69)	Harm (favors placebo)	Moderate

Certainty of evidence

The certainty of evidence was **HIGH** for the following outcomes: 1) cardiovascular mortality; 2) death from any cause; 3) hospitalization for heart failure; 4) change in the quality of life using KCCS score; 5) worsening renal function; 6) volume depletion; and 7) fracture. The certainty of evidence was **MODERATE** for the following outcomes: 1) amputation; 2) major hypoglycemia among those with DM; 3) diabetic ketoacidosis; 4) complicated UTI; and 5) genital infections. The reason for downgrading the certainty of evidence to moderate was imprecision (Annex 14, Appendix E), since these outcomes were not primary outcomes and were assessed using frequency reports. Based on the results, the numbers of obtained events were small with a wide confidence interval.

RECOMMENDATIONS FROM OTHER GROUPS

Most of the recommendations of different task forces and groups added SGLT2 inhibitors to the management of patients with chronic heart failure. Four out of seven guidelines²⁰⁻²³ gave a class I or strong level of recommendation and a Level A or high quality of evidence for the use of SGLT2is among patients with HFrEF. The NICE guidelines²⁴ recommended its use as an option but did not mention the level of evidence or the strength of recommendation. The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018,²⁵ the 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the management of Heart Failure,²⁶ and the JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure²⁷ recommended the use of SGLT2is for the prevention of heart failure-related outcomes among type 2 diabetes mellitus (DM) patients with

cardiovascular disease. The trials on SGLT2 inhibitor use among patients with heart failure with reduced ejection fraction came out in 2019 (Dapagliflozin) and in 2020 (Empagliflozin).

Table 61. Recommendations from various guidelines regarding the use of SGLT2 inhibitors for the treatment of heart failure

Groups	Recommendation	Strength of Recommendation and Certainty of Evidence
JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure [20] Accepted April 27, 2021	Dapagliflozin* or empagliflozin**is recommended to reduce the risk of worsening heart failure and of cardiovascular death in patients with symptomatic heart failure with reduced ejection fraction (LVEF < 40%) despite optimum pharmacologic therapy (b-blockers, ACE inhibitors [or ARB] and MRA at either the maximum dose or the maximum tolerable dose). *approved in Japan **not approved in Japan	Class of Recommendation: I Level of evidence: A Grade of Recommendation (MINDS) A (strongly recommended and supported by strong evidence) Level of Evidence (MINDS) I (Systematic review/meta-analysis of randomized controlled trials)
CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction [21] Accepted January 16, 2021	We recommend the use of an SGLT2 inhibitor such as dapagliflozin or empagliflozin on patients with HFrEF with or without concomitant type 2 diabetes to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality.	Strong Recommendation; High-Quality Evidence
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [22] Online publish-ahead-of-print August 27, 2021	Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	Class of recommendation: I Level of evidence: A

<p>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 [23]</p> <p>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)</p>	<p>In patients with symptomatic, chronic HFrEF, SGLT2is are recommended to reduce HF-related hospitalization and cardiovascular mortality, irrespective of the presence of type 2 diabetes.</p> <p>In patients with symptomatic, chronic HFrEF, SGLT2i therapy provides intermediate economic value.</p>	<p>Class (Strength) of Recommendation: I (Strong)</p> <p>Level (Quality) of Evidence: A</p> <p>Value Statement: Intermediate Value (A)</p>
<p>Chronic heart failure in adults: diagnosis and management [24]</p> <p>NICE guideline Published: 12 September 2018 www.nice.org.uk/guidance/ng106</p>	<p>Dapagliflozin is recommended as an option for treating symptomatic, chronic heart failure with reduced ejection fraction in adults only if it is used as an add-on to optimized standard care with:</p> <ul style="list-style-type: none"> • Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs); or • Sacubitril/valsartan, with beta blockers, and, if tolerated, MRAs. <p>Start the treatment of symptomatic heart failure with reduced ejection fraction with dapagliflozin on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.</p> <p>Empagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults only if it</p>	<p>Chronic heart failure in adults: diagnosis and management [26]</p> <p>NICE guideline Published: 12 September 2018 www.nice.org.uk/guidance/ng106</p>

	<p>is used as an add-on to optimized standard care with:</p> <ul style="list-style-type: none"> • an angiotensin-converting enzyme (ACE) inhibitor or angiotensin 2 receptor blocker (ARB), a beta blocker, and, if tolerated, a mineralocorticoid receptor antagonist (MRA); or • Sacubitril/valsartan, a beta blocker and, if tolerated, an MRA. <p>Start empagliflozin to treat symptomatic heart failure with reduced ejection fraction on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.</p>	
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 [25]	<p>Prevention of heart failure—pharmacological</p> <p>Sodium-glucose cotransporter 2 (SGLT2) inhibitors are recommended in patients with type 2 diabetes mellitus associated with cardiovascular disease and insufficient glycaemic control despite metformin to decrease the risk of cardiovascular events and of heart failure-related hospitalisation.</p>	Strong Recommendation FOR High-Quality Evidence
2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. [26] Accepted August 28, 2017	<p>Authors suggested “that the use of empagliflozin, an SGLT-2 inhibitor, be considered for patients with type 2 diabetes and established CVD for the prevention of HF-related outcomes.”</p>	GRADE standards: Weak Recommendation; Low-Quality Evidence

<p>JCS 2017/JHFS 2017 Guideline on the Diagnosis and Treatment of Acute and Chronic Heart Failure - Digest Version [27]</p> <p>Advance publication released online September 10, 2019</p>	<p>From the CPG: "Among currently available SGLT2 inhibitors, empagliflozin and canagliflozin have been demonstrated to reduce the composite endpoint of major adverse cardio-vascular events including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, and the number of hospitalizations for heart failure in patients with type 2 diabetes mellitus and high cardiovascular risk, and are expected to improve the cardiovascular prognosis of patients with type 2 diabetes mellitus and high cardiovascular risk regardless of the presence or absence of heart failure. However, as patients complicated with heart failure account for only 10 to 15% of patients enrolled in these large-scale clinical studies of SGLT2 inhibitors, further studies are necessary to clarify the beneficial effects of these drugs on heart failure. Also, as there has been no evidence indicating that these results reflect class effects of SGLT2 inhibitors, the results of large-scale clinical studies of other SGLT2 inhibitors are awaited. In addition, further studies should be conducted to clarify the efficacy of SGLT2 inhibitors in patients aged 75 and above."</p>	<p>Class of Recommendation: I Level of evidence: A</p> <p>Grade of Recommendation (MINDS) B (recommended with moderately strong supporting evidence)</p> <p>Level of Evidence (MINDS) II (one or more randomized controlled trials)</p>
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ONGOING STUDIES AND RESEARCH GAPS

There is one ongoing study with trial number NCT04249778 that is currently recruiting patients with HFrEF (N = 392) comparing Dapagliflozin to placebo. It is a randomized controlled trial that is to be held for a period of 26 weeks. The primary outcomes are a composite of HF hospital admissions, HF emergency department visits, HF urgent clinic visits, and death after acute decompensated HF admission. The secondary outcomes include KCCQ score, CHQ-SAS score, NT-proBNP, 6MWT, and HbA1C. The primary completion is estimated to be in December 2025.⁸

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

A local cost-utility study that measured the economic value of one intervention over another in terms of the cost necessary to provide benefit was conducted by Mendoza, et al.²⁸ The study utilized the public healthcare provider's perspective and determined the cost-effectiveness of giving dapagliflozin to patients with HFrEF on top of the standard treatment.

Using the lifetime Markov model to factor in the following: the efficacy results of the study on Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction trial¹⁵; the cost of the drug; Philippine age-related mortality (55 years old among Filipinos); and utilities from other studies, the incremental cost per quality-adjusted life year (ICER) was estimated. The threshold ICER in 2019 was PHP 180,500. This was equivalent to the gross domestic product per capita of the Philippines in 2019.

The results showed that the ICER was PHP 177,868 for the drug price of PHP 44.00 and PHP 160,983 for drug price of PHP 40.00. These costs were considered cost-effective since both were below the threshold ICER of PHP 180,500.

A sub-group analysis was done among diabetic patients with HFrEF and the ICERS were even much lower—PhP 132,585 for the drug price of PHP 44.00 and PHP 120,249 for the drug price of PHP 40.00. Based on the cost-effectiveness acceptability curve, 76% of the ICERs are below the threshold ICER of PhP 180,500. Based on the cost-utility analysis²⁸ and the current prevailing market prices, especially for Dapagliflozin, an SGLT2 inhibitor can be considered cost-effective when added to standard therapy for HFrEF.

In the Philippines, the prevailing market prices of Dapagliflozin and Empagliflozin are PHP 44.20 and PHP 55.31, respectively, for non-seniors. For seniors, the market prices are PHP 36.00 and PHP 44.25 for Dapagliflozin and Empagliflozin, respectively. The discounts provided to senior citizens is important. However, the discounted price cannot be used in the analysis since this is not applicable to all patients who will take the drug.

On March 7, 2023, HTAC has recommended the inclusion of dapagliflozin in the Philippine National Formulary. The accompanying evidence summary mentioned that as of February 2023, four local manufacturers have already been issued a product registration certificate by the Philippine FDA. It also mentioned that the patent of the innovator drug was “expected to expire by May 2023”. Although the exact generic cost is not yet certain, a 40% reduction in the maximum wholesale price (PHP19.44) was included in HTAC’s costing analysis apart from the drug’s maximum wholesale price as

mandated in EO No. 104 [HTAC, March 2023]. In view of this development, the unit cost of PHP19.44 may be used in the sensitivity analysis.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Advances in the management of patients with chronic heart failure, particularly those with reduced ejection fraction, have been proven to reduce clinical outcomes (e.g. cardiovascular mortality and hospitalization for heart failure). Clinical benefit has been shown with the addition of SGLT2 inhibitors to the standard of care. Moreover, the cost-effectiveness of using SGLT2 inhibitors has also been demonstrated. It is a challenge especially to health care providers and health care policy makers to make the treatment available, accessible, and sustainable.

The reviewer did not come across local studies based on the search done on the use of SGLT2is among patients with HFrEF that looked into the patient's values and preferences, equity, acceptability, and feasibility.

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13. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of a timely referral to a cardiovascular specialist on the incidence of cardiovascular mortality, heart failure-related hospitalization, and quality of life?

Recommendation 13

Among adult Filipinos diagnosed with chronic HFrEF at the outpatient clinic, we suggest referral of patients with high risk features* and recurrent hospitalizations** to higher levels of care.***

***High Risk features:** older age, lower BMI, lower SBP, NYHA Class III or IV, presence of pulmonary or peripheral congestion, third heart sound, aortic stenosis, atrial fibrillation, peripheral vascular disease, renal dysfunction, and absence of an implantable cardioverter defibrillator (ICD)

****Recurrent Hospitalizations:** The suggested definition is ≥ 2 hospitalizations in the past year.

******"Higher levels of care"** refers to secondary or tertiary care.

(low level of evidence, weak recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- Clinical clues to advanced heart failure that will benefit from referral to higher levels of care were captured in the mnemonic "I NEED HELP," as indicated in the AHA and ESC guidelines on HF. These included I-inotropes, N-NYHA class and natriuretic peptides, E-end organ dysfunction, E- LV ejection fraction $\leq 25\%$, D-defibrillator shock, H-one hospitalization in the prior 12 months, E-edema and escalating diuretics, L-low blood pressure, P-prognostic medications. These items were raised during the CP discussion to serve as guide for deliberation but were ultimately not included in the data review.

- Although the evidence review only mentioned aortic valve stenosis as a high risk feature, the consensus panel deemed that the presence of any significant valvular lesion and/or cardiac congenital abnormality should serve as a trigger for referral to higher levels of care.
- The consensus panelists agreed to define recurrent hospitalization as 2 or more hospitalizations per year.
- Other high risk features such as arrhythmia (ventricular tachycardia) and QRS duration of >0.15 ms were discussed but ultimately not included based on the evidence presented.
- The consensus panel also emphasized the need to further elaborate clinical services that are unique to higher levels of care.

KEY FINDINGS

- There are no studies that directly answer the question of timely referral to higher levels of care at the outpatient setting. Because of this, the timeliness of a referral could be indicated by the presence of certain factors associated with increased morbidity and mortality among patients with chronic heart failure.
- Two studies on the presence of prognostic factors such as chronic heart failure with high-risk features and recurrent hospitalization that affect morbidity and mortality among patients with heart failure were included.^{1,2}
- “Higher levels of care” refers to secondary or tertiary care. In this review, the levels of care used by the Department of Health, namely, the “Intermediate Hospital” category (enhanced Level 2 hospitals) and the “Specialty Hospital” category (National Cardiovascular Center and Level 3 hospitals) will be adopted.³
 - Intermediate Category – Enhanced Level 2 hospitals have at least 1 specialization, preferably an IM Department with an ICU.
 - Specialty Category – National Specialty Center (PHC) or Level 3 Hospitals with Basic or Advanced Cardiovascular Centers (National, Subnational or Regional medical centers which offer teaching and training facilities).
- The closest evidence in literature that investigates escalation of care to secondary and tertiary care would be studies regarding referral to Multidisciplinary teams that shows an impact on outcomes. There are several

studies pertaining to referral to multidisciplinary heart failure disease management programs in the outpatient setting.

- Four RCTs that studied referrals to Multidisciplinary HF DMTs versus usual care and their impact on mortality as well as five RCTs that looked at the impact of referrals on hospitalization were analyzed.⁴⁻⁷ Though there were more events in terms of mortality in the HF MDT group and more HF-related hospitalizations in the usual care group, referral to multidisciplinary HF DMTs did not show any significant reduction in the two outcomes.
- Three studies included quality-of-life questionnaires but the questionnaires used varied. One study⁶ made use of several questionnaires that measured the disease-specific QoL, as well as physical and mental components but there were no significant improvements found in generic and disease-specific QoL. However, a recent study in India⁷ demonstrated an improvement in QoL in the intervention group. In the study of Kalter-Leibovici et al.,⁵ there was significant improvement in generic QoL and depression scores in the group that was being managed by Multidisciplinary DMTs compared to usual care.
- All studies had risk of bias issues as there were concerns about allocation concealment, blinding, and selective reporting of outcomes. Most of the studies were done in countries where healthcare system referrals are in place, nor were there studies involving Filipinos; furthermore, the evidence that was analyzed did not directly answer the clinical question. As such, there is an issue of directness. The risk of bias contributed to the downgrading of the evidence to low certainty of evidence for the outcome of mortality, hospitalization, and quality of life.

INTRODUCTION

Heart Failure is an important and growing health problem with a large impact on the quality of life of patients as well as on healthcare costs. Effective treatments that have greatly improved patient survival have been developed in the past years. Despite these breakthroughs, however, heart failure still has a large impact on the quality of life of patients as well as on healthcare costs.

Patients with heart failure are treated by a range of healthcare providers including primary care physicians, family medicine specialists, internists, cardiologists, and recently, disease management teams. The follow-up of heart failure patients in the outpatient setting plays a crucial role in their long-term prognosis.

The escalation of care provides many additional diagnostic and therapeutic components that are beneficial in managing patients with complex or refractory HF, including expert

disease management teams, the optimization of conventional therapies, and the resources for the definitive treatment for patients who ultimately require advanced therapies.

Higher levels of care pertain to secondary and tertiary hospitals. The Department of Health under the UHC program developed resource-stratified frameworks that determine the service capability that must be available to be able to manage cardiovascular diseases. For heart failure, the cardiovascular care centers that are relevant to the clinical question refer to Intermediate Level 2 hospitals and Specialty Hospitals. Intermediate Level 2 hospitals capable of providing cardiovascular care are the enhanced Level 2 hospitals which should have at least one relevant specialty, preferably an IM Department with an ICU. Similarly, Level 3 Hospitals capable of providing cardiovascular care must have a Basic or Advanced Comprehensive Cardiovascular Center.¹ A component of Level 3 hospitals, both basic and advanced, is the capacity to manage all simple and some complex cardiovascular cases and requires specialized multidisciplinary teams.

Full clinical services management is the process of care coordination for patients with a chronic condition across different healthcare settings. This has been proposed as a model of care for complex chronic conditions such as heart failure. The majority of HF patients have multiple medical, social, and behavioral challenges; their care thus requires a multidisciplinary systems approach that can help them navigate and address these issues and concerns. A multidisciplinary disease management program (DMT) is the model that has been adopted in the care of heart failure (HF) patients in order to provide coordinated care within the healthcare system.⁸ DMT includes close coordination with and involvement of healthcare workers specially trained in heart failure management (primarily, cardiologists, HF nurses, and general practitioners) and other experts including pharmacists, dieticians, physiotherapists, psychologists, palliative care providers, and social workers through structured follow-up. Other aspects of DMT include patient education, optimization of medical treatment, psychosocial support, and improved access to care.⁹

Several guidelines have recommended that referral to heart failure multidisciplinary teams either in secondary or tertiary care should be done for heart failure patients with high-risk features and recurrent hospitalizations.

Heart failure disease management teams/MDTs vary in their content but the core specialist in a heart failure multidisciplinary team (MDT) should work in collaboration with the primary care team, and should include¹⁰ a lead physician with a subspecialty interest in heart failure (usually a consultant cardiologist), a specialist heart failure nurse, or a healthcare professional with an expertise in prescribing for heart failure. The specialist heart failure MDT should directly involve, or refer people to, other services, including rehabilitation services, and tertiary and palliative care, as needed.

Several systematic reviews have demonstrated that multidisciplinary disease management reduces all-cause mortality and hospitalizations in heart failure patients discharged from the hospital.^{11,12} As such, heart failure DMTs are part of the recent guidelines.^{13,14} The evidence that was reviewed regarding DMTs was limited to patients in the outpatient setting where patients with Heart Failure with reduced ejection fraction (HFrEF) are referred to DMTs.

REVIEW METHODS

A comprehensive literature search was done from the date of the last search December 2022 until April 2023 using Medline, Cochrane Library, Google Scholar and, HERDIN plus with a combined MeSH and free text search using the terms “chronic heart failure”, “timely referral to secondary, tertiary hospitals”, “cardiology”, and “outpatient setting”.

Unfortunately, there were no studies that would likely answer the question of the timely referral of patients with heart failure with reduced ejection fraction (HFrEF) seen in the outpatient setting to a higher level of care. The search was then revised to include factors that affect prognosis using the search terms “chronic heart failure”, “HFrEF”, “prognostic factors”, “indicators”, and “mortality”; as well as referrals to heart failure multidisciplinary teams (MDTs) and disease management programs using the following search terms: “HFrEF in the outpatient setting”, “disease management programs”, “multidisciplinary teams”, “mortality”, “heart failure hospitalizations”, “hospitalizations”, and “quality of life”.

Because of limited evidence with regards to poor prognostic factors that prompt referral to higher levels of care, prospective cohort and retrospective cohort studies were included in this review. Bibliographic references of selected studies were also searched. After a review of the titles and abstracts, relevant studies were obtained and the full reports evaluated. All studies meeting the explicit inclusion and exclusion criteria were retained. A de novo meta-analysis of the five studies was conducted to determine the pooled estimate of the effect of referral to HF DMTs/MDTS versus usual care for explicit outcomes. A description of the studies on quality of life was also done.

The outcomes of interest include mortality, rehospitalization, quality of life, and worsening symptoms of heart failure.

RESULTS

Two studies looking at poor prognostic factors among patients with chronic heart failure were included. One prospective observational registry by the European Society of Cardiology analyzed 7,173 chronic heart failure patients with a median follow-up time of

a year.² The study showed that **older age, lower BMI, lower SBP, geographical region (Southern vs. North European), NYHA class (III or IV), the presence of pulmonary or peripheral congestion, third heart sound, aortic stenosis, atrial fibrillation, peripheral vascular disease, renal dysfunction, and the absence of an implantable cardioverter defibrillator (ICD)** to be independent predictors of 1-year all-cause mortality. (Table 62)

Table 62. Prognostic factors predicting one-year all-cause mortality for chronic heart failure (CHF)

CHF outpatient	HR (95% CI)	P value
Age (every 5 years: IQR 55–60)	1.11 (1.04–1.18)	0.0007
BMI (every 1 kg/m ² : IQR 25–26)	0.95 (0.93–0.98)	0.0005
SBP (every 5 mmHg: IQR 110–115)	0.94 (0.91–0.97)	0.0001
Region (N: S)*	0.47 (0.25–0.90)	0.0204
NYHA III–IV (yes vs. no)	1.93 (1.50–2.49)	<0.0001
Third heart sound (yes vs. no)	1.54 (1.07–2.20)	0.0186
Aortic stenosis (yes vs. no)	1.70 (1.12–2.59)	0.0135
Atrial fibrillation (yes vs. no)	1.45 (1.13–1.86)	0.0033
PAD (yes vs. no)	1.62 (1.19–2.19)	0.0019
Renal dysfunction (yes vs. no)	1.41 (1.09–1.83)	0.0080
ICD (yes vs. no)	0.67 (0.46–0.98)	0.0414

Another study is a retrospective review of a health care utilization database involving 14,374 patients hospitalized for HF of which 7,401 died during the four years of follow-up.¹ Of 14,374 patients, 3,358 patients had second, 1,123 had third, and 417 had fourth hospitalizations for HF during the study period. Mortality significantly increased after each HF hospitalization. Results showed that after adjusting for age, sex, and major comorbidities, the **number of HF hospitalizations** was a strong predictor of all-cause death. Median survival times after the first, second, third, and fourth hospitalization were 2.4 (95% CI 2.3–2.5), 1.4 (95% CI 1.2–1.5), 1.0 (95% CI 0.9–1.1), and 0.6 (95% CI 0.5–0.9) years.

For the definition of higher levels of care, we refer to the Department of Health 2021-0001 designation of hospitals as specialty centers. In this document, the DOH

developed resource-stratified frameworks that determine the service capability of each level of facility across the care continuum. Table 63 summarizes the levels of care for cardiovascular care.³ Higher levels of care will refer to Enhanced Intermediate cardiovascular care centers (Level 2 Hospitals) and Specialty cardiovascular care centers (Level 3 hospitals capable of Basic and Advanced comprehensive cardiovascular care delivery, and the National Cardiovascular Specialty Center, the Philippine Heart Center).

Table 63. Resource stratified framework for cardiovascular care centers (excerpt adapted from Annex B in DOH DEPARTMENT ORDER 2021-0001)³

Level of Care	Specialty			Intermediate
	National Specialty Center (NSC) Philippine Heart Center (PHC)	Center of Excellence	Maximal	Enhanced
		Level 3 Hospital (Advanced Comprehensive Cardiovascular Care)	Level 3 Hospital (Basic Comprehensive Cardiovascular Center)	Level 2 Hospital
Current Licensing Standard	Designated Hospitals	Level 2 plus teaching and training facility	Level 2 plus teaching and training facility	At least 1 Internal Medicine Department plus Departments of Pediatrics, Obstetrics, and Surgery with accredited programs AND an Intensive Care Unit (ICU)
General Description of Service Capability	<ul style="list-style-type: none"> > Capacity of managing ALL cardiovascular cases <ul style="list-style-type: none"> -End referral -Policy-making and protocol development > Highest level of clinical service, training and research > Clinical Practice Guidelines (CPG) development 	<ul style="list-style-type: none"> > Capacity of managing all simple and some complex cardiovascular cases > Second opinion center > May have the highest level of clinical service, training and research 	<ul style="list-style-type: none"> > Capacity of managing all simple and some complex cardiovascular cases with option for PHC assistance > Requires specialized multidisciplinary teams > Full clinical services 	<ul style="list-style-type: none"> > Management of higher/advanced stages of medical cardiovascular care > Management requiring intensive care

We included five RCTs with a total of 890 patients with HF with reduced ejection fraction seen at the outpatient clinic who have been referred to multidisciplinary Heart Failure DMTs and followed up for at least three months. Disease management by multidisciplinary teams includes some if not all the following aspects: coordination of

care; empowerment; patient education; monitoring of symptoms and adherence to medications; titration of medications; and use of information systems and technology such as telemonitoring of weight and vital signs. A recent study in India⁷ compared the outcomes of follow-up at a multidisciplinary heart failure clinic vs. usual care, while a study in Germany⁶ looked at the effect of structured case management by a trained doctor's assistant with feedback and follow-up with their primary care physician. One study in Israel⁵ involved six monthly visits to heart failure centers with cardiologist evaluation while being regularly monitored by a nurse in between visits. Meanwhile, there are two RCTs in the UK looking at the impact of referring to a specialist or to a multidisciplinary team in both primary and secondary care.

The usual care used in the studies involves follow-up with primary care physicians or cardiologists.

Outcomes measured include all-cause mortality, all-cause hospitalization, and quality of care. In terms of quality of life, most of the studies made use of were patient-reported outcomes. Since most of the questionnaires were varied, the results cannot be pooled together to come up with definite evidence. The characteristics of included studies are summarized in Annex 15, Appendix 2.

Table 64: GRADE summary of findings table on efficacy outcomes of referral to HF multidisciplinary disease teams

Critical Outcomes	Basis (No. and Type Of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Cardiovascular Mortality	4 RCTs (n=878)	OR 1.08	(0.87 to 1.35)	Inconclusive	Low
Heart Failure Hospitalization	5 RCTs (n=890)	OR 0.85	(0.69 to 1.03)	Inconclusive	Low

Three studies included quality-of-life questionnaires but these were patient-reported outcomes. One study⁶ made use of several questionnaires that measure the disease-specific QoL, as well as the physical and mental components. However, there was no significant improvement in generic and disease-specific QoL. The study used the SF-36 scale and showed that between-group differences (95%CI) at the 12th month follow-up of the physical and mental component scale of SF-36 were minimal: -0.3 (-3.0; 2.5) and -0.1 (-3.4; 3.1).

In the study of Kalter-Leibovici et al.,⁵ there was a significant improvement in generic QoL [SF-36 physical component 1.531 (1.165 to 2.011), mental component (1.253 to 1.971), and depression scores [PHQ-9 0.688 (0.528 to 0.897)] in the group that was being managed by Multidisciplinary DMTs vs usual care. Another study in India⁷ showed that quality of life as assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was better in the intervention group than in the usual care group (MLHFQ score 21.44+/-9 vs 49 +/- 12.6 p<0.01).

Efficacy outcomes/Certainty of Evidence

Based on the 4 RCTs included, referral to HF multidisciplinary disease teams did not show any significant difference to standard of care in reducing all-cause mortality (OR 1.08, 95% CI 0.87-1.35, p=0.48, I²=0%). There also appears to have no significant reductions in heart failure hospitalizations compared to usual care based on 5 RCTs reviewed (OR 0.85 95% CI 0.69-1.03 p=0.10 I²=64%).(Table 64)

All of the studies had an overall high risk of bias due to lack of blinding leading to selection, performance and detection bias. Moreover, for heart failure hospitalization, there appears to be moderate heterogeneity with an I² of 64%. Over-all Certainty of Evidence was then downgraded to moderate because of these serious risks of bias across the different critical outcomes. In terms of quality of life, majority of the studies were patient-reported outcomes, and since most of the questionnaires were varied, the results cannot be pooled together to come up with definite evidence.

Safety outcomes

There was no direct evidence of harm as this issue involves the coordination of care across healthcare settings and is not a pharmacologic intervention. The caveat is that because the multidisciplinary teams are properly trained in heart failure management and there must be close coordination across the continuum of care, lack of communication and coordination may lead to medical errors.

RECOMMENDATIONS FROM OTHER GROUPS

The Australian guidelines summarized the practical indicators present in patients with heart failure that were associated with an increased risk of premature morbidity and mortality. There is an increased risk of premature morbidity and mortality if two or more of the following factors are present: age >65 years; NYHA Class III or IV symptoms; Charlson Index of comorbidity Score of ≥2; an LVEF of ≤30%; living alone or remote from specialist cardiac services; depression; language barrier; (e.g. non-English speaking); lower socioeconomic status; and significant renal dysfunction (GFR <60mL/min/1.73m²).¹⁵

The Canadian guidelines recommend that all patients with recurrent HF hospitalizations, irrespective of age, multimorbidity, or frailty, should be referred to a HF disease management program.¹⁵

According to the scientific statement of the American Heart Association as guidance for timely and appropriate referral of patients with advanced heart failure, poor prognostic factors in patients with advanced heart failure include: recurrent hospitalizations, defined as two prior HF-related admissions in a 12 month period; inability to tolerate GDMT; increasing burden of arrhythmias; and worsening renal function.¹⁶

Many major and international guidelines recommend referral to heart failure disease management teams. However, the evidence for this comes from RCTs where referrals are done after hospitalization. There are few studies that look into referrals to HF DMTs in the outpatient setting.

Table 65. Summary of recommendations from various guidelines regarding multidisciplinary management of heart failure

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
ESC Guidelines for the diagnosis and management of acute and chronic heart failure (2021)(14)	<ul style="list-style-type: none">• Recommends that HF patients be enrolled in a multidisciplinary HF management program to reduce the risk of HF hospitalization and mortality.• Either home-based and/or clinic-based programs to improve outcomes, specifically, to reduce the risk of HF hospitalization and mortality.	<ul style="list-style-type: none">• Both given Class I Level A

AHA/ACC/HFSA Guideline for the Management of Heart Failure 2022 (13)	<ul style="list-style-type: none"> Recommends that timely referral for HF specialty care to review HF management and assess suitability of advanced HF therapies (eg, LVAD, cardiac transplantation, palliative care, and palliative inotropes) for patients with advanced HF, when consistent with the patient's goals of care. 	<ul style="list-style-type: none"> Class I recommendation Level of evidence CLD- Limited data
NICE UK Guidelines in chronic heart failure in adults, diagnosis and management, 2018 (10)	<ul style="list-style-type: none"> Recommends that a core specialist heart failure multidisciplinary team (MDT) should work in collaboration with the primary care team, and should include: <ul style="list-style-type: none"> a lead physician with subspecialty training in heart failure (usually a consultant cardiologist) who is responsible for making the clinical diagnosis a specialist heart failure nurse a healthcare professional with expertise in specialist prescribing for heart failure. 	<ul style="list-style-type: none"> No grading for strength and quality of evidence
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 (17)	<ul style="list-style-type: none"> Referral to a multidisciplinary heart failure disease management program is recommended for patients with heart failure that is associated with high-risk features (orthopnea, PND, syncope, ischemic chest pain, tachycardia, bradycardia, hypoxemia, gallop rhythm, significant heart murmur, evidence of ischemia or infarction on 12L ECG, pulmonary edema on CXR, raised cardiac troponin level, moderator or severe valvular heart disease on 2D echocardiography, LVEF of <= 40 and ischemia on stress testing) to decrease mortality and re-hospitalization. In areas where access to a face-to-face multidisciplinary heart failure disease-management program after discharge is limited, patients should be followed up with a multidisciplinary telemonitoring or telephone support program. 	<ul style="list-style-type: none"> Strong recommendation, high quality of evidence Strong recommendation, moderate quality of evidence
2017 Comprehensive Update of the Canadian Cardiovascular	<ul style="list-style-type: none"> Recommends that specialized outpatient HF clinics or disease management programs provide access to an interprofessional team ideally including a physician, a nurse, and a 	<ul style="list-style-type: none"> Strong Recommendation;

Society Guidelines for the Management of Heart Failure(15)	<p>pharmacist with experience and expertise in HF</p> <ul style="list-style-type: none"> • Recommends that all patients with recurrent HF hospitalizations, irrespective of age, multimorbidity, or frailty, should be referred to a HF disease management program 	<p>High-Quality Evidence).</p> <ul style="list-style-type: none"> • (Strong Recommendation; High-Quality Evidence).
Malaysian Guidelines for the Management of Heart Failure 2019(18)	<ul style="list-style-type: none"> • Recommends that HF care should ideally take place in a multidisciplinary system, allowing for shared care between the hospital (secondary or tertiary settings) and community (primary setting). • The multidisciplinary team consists of cardiologists and/or general physicians, HF nurses, pharmacists, dieticians, physiotherapists, primary care providers, social workers, as well as geriatricians, psychologists, occupational therapists, and, when necessary, palliative care specialists. It can be done in two settings: the patient's home or in heart failure clinics • HF patients with stable symptoms may be managed at the primary care level. Referral to the cardiologist should be considered in certain situations: <ul style="list-style-type: none"> ◦ De novo HF for a comprehensive workup to confirm the diagnosis, determine the etiology, and devise a management plan. ◦ Episodes of acute decompensation. ◦ Worsening HF symptoms despite appropriate therapy. ◦ HF complicated by symptomatic hypotension, excessive bradycardia, or limiting uptitration of pharmacotherapy. ◦ Symptomatic stable CAD and/or acute coronary syndrome in consideration for revascularization (PCI or CABG). ◦ Resuscitated cardiac arrest. ◦ Documented or suspected significant arrhythmias, e.g. AF, VT. ◦ Significant valvular disease not previously assessed, or worsening valvular dysfunction. 	<ul style="list-style-type: none"> • No grading for strength and quality of evidence

	<ul style="list-style-type: none"> o Preconception assessment and counselling of women with significant structural heart disease or past history of HF or LV dysfunction. o Complex congenital cardiac lesions and/or Eisenmenger's syndrome. 	
JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure(19)	<ul style="list-style-type: none"> • Education and support to improve adherence and self-care using a multidisciplinary team approach are recommended. 	<ul style="list-style-type: none"> • Class I, A

ONGOING STUDIES

There are no direct studies looking into timely referrals to higher centers of care. Most of the studies involving referrals to HF DMTs are about patients who were hospitalized. There is a paucity of studies looking into the impact of referring to HF MDT's in the primary care setting.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

The reviewer did not encounter local studies but since this involves training multidisciplinary HF DMTs that primarily involve cardiologists, HF nurses, general practitioners, and other experts, including pharmacists, dieticians, physiotherapists, psychologists, palliative care providers and social workers, costs may be high during the initial phase.

In a 2008 study in Canada, the cost of care in HF clinics was \$52 per 30 patient-days.²⁰ The projected life-expectancy of HF clinic patients was 3.91 years, compared to 3.21 years in standard care. The 12-year cumulative cost per patient in the HF clinic group was \$66,532 versus \$53,638 in the standard care group. The ICER was \$18,259/life-year gained.

In a study that looked at the impact of a HF management program among Medicare advantage population, the results suggest that engagement in a multidimensional HF management program has the potential to positively influence patient outcomes through

the earlier identification of HF exacerbations, thus prompting attention to potentially harmful condition episodes, thereby reducing cost of care.²¹

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Currently, there are only four heart failure clinics in the country. It is not yet clear, however, if the clinics have multidisciplinary teams in place that can take care of patients at every step of the patient's journey. As this involves training not only physicians but also allied health care workers, the diaspora of Filipino nurses and other health care workers might be a significant limitation in terms of organizing these HF multidisciplinary care teams. Limitations in technology can also be a hindrance in using technology to compensate for a lack in manpower.

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14. Among adult Filipinos diagnosed with chronic heart failure with reduced ejection (HFrEF) at the outpatient clinic, what is the effect of palliative care on quality of life and on the incidence of cardiovascular mortality and heart failure-related hospitalization?

Recommendation 14

Among adult Filipinos diagnosed with chronic HFrEF, with NYHA class III-IV, at the outpatient clinic, we suggest the early integration of palliative care for holistic management.

(low level of evidence, weak recommendation)

CONSIDERATIONS

The consensus panel considered the following when formulating these recommendations:

- It should be understood that a referral to the palliative care service would mean that the patient shall be managed by a multidisciplinary team, including the current attending physician of the patient.
- In 2015, the Department of Health issued an Administrative Order which considered the training of primary care physicians in palliative care to address the palpable need for palliative care services, particularly in the Visayas and Mindanao regions.
- Through patient education, the palliative care physicians are able to communicate the full spectrum and benefits derived from palliative care, particularly if such is considered early in the holistic approach of patient management of patients who are chronically severely ill.
- Palliative care is primarily aimed at the alleviation of suffering and improvement in the quality of life of these patients.
- Palliative and hospice care is one of the foundational courses in Family Medicine. Thus, the Philippine Academy of Family Physicians is advocating for all family physicians to become knowledgeable in palliative care, including the development of the appropriate skills for its implementation.

- Palliative care is not necessarily a hospital/hospice-based care. The palliative care specialists can do telehealth and/ or perform home visits for patients who prefer staying at home.
- The ERE clarified that hospice care specifically deals with dying patients who have less than 6 months to live, whereas, palliative care is more of a collaborative supportive care that can be applied even during the early part of the disease process (e.g. the first decompensation). Thus, palliative care is not limited only for the dying patients or those who are already in an advanced state of disease.
- The early referral to palliative care service allows for other domains of palliative care (psychological, cultural) to become part of the holistic approach to HF management, and not stopping other interventions. Thus, an early integration of palliative care at the point of diagnosis may enhance patient care, and lead to medical improvement, too.
- It was highlighted in the en banc meeting that the clinical course of HF patients has varying illness trajectories. A concern that has been raised is the readiness of the present palliative care specialists to cater to these HF patients. Reassurance, however, was given by the palliative care specialist who explained that the training curriculum for palliative care includes a wide array of diseases and, hence, they would be ready to take care of HF patients. The group hopes that the inclusion of palliative care in the guidelines would encourage further capacity-building for the care of HF patients and for the DOH to provide more training for primary care physicians in basic palliative care.

KEY FINDINGS

1. There were five RCTs included in this analysis which looked into the effect of palliative care in the outpatient setting compared to the usual care among patients with heart failure.
2. Referral to a palliative care team led to a significant reduction in rehospitalization and an improvement in quality of life, with no significant reduction in mortality within a period of three to six months. Only one RCT reported a reduction in the worsening of heart failure symptoms albeit it was not significant.
3. The certainty of evidence was low due to the serious risk of bias issues. The presence of performance and detection bias stemmed from the impossibility of blinding patients, caregivers, and some of the outcome assessors due to the nature of the intervention. There was also a serious issue of imprecision regarding the worsening heart failure outcome due to a small sample size.

INTRODUCTION

Palliative care, as defined by the World Health Organization, is an approach that improves the quality of life of patients and families through the prevention and relief of suffering.¹ Its framework is composed of eight domains, namely: structure and processes; physical; psychological and psychiatric; social; spiritual; cultural; ethical and legal; and lastly, care of the patient nearing the end of life.² A palliative care team may consist of family medicine—palliative care specialists, general cardiologists, heart failure specialists, nurses, counselors, and social workers.

Palliative care is a well-established part of management among cancer patients and other chronic illnesses, especially among those in the advanced stage of their disease. Multiple studies have shown that palliative care interventions are associated with improvements in quality of life and symptom burden.³ Therefore, we will review the evidence regarding its role among heart failure patients in the outpatient setting.

REVIEW METHODS

A systematic search was done using Pubmed, Google scholar, Cochrane review, and HERDIN plus using the following keywords: “congestive heart failure”, “palliative care”, “mortality”, “hospitalization”, “quality of life”, “outpatient”, “randomized controlled trials”, “meta analysis” and “systematic review” with a combined MeSH and free text search for the past 10 years.

Only randomized controlled trials (RCTs) comparing palliative care against usual care among heart failure patients in the outpatient setting were included in this review. Each included RCT was assessed for risk of bias using the Cochrane risk of bias assessment. The outcomes of interest included mortality, rehospitalization, quality of life, and worsening symptoms of heart failure.

RESULTS

Characteristics of included studies

We included five RCTs (Table 65) with a total of 371 patients. These studies included patients in an advanced stage of heart failure, with New York Heart Association (NYHA) class III-IV, who were mostly recruited prior to hospital discharge and for transitional care to their homes. The teams were composed of primary palliative care specialists, general cardiologists, psychiatrists, occupational therapists, physiotherapists, and nurses; some teams also had volunteer social workers. Two RCTs were conducted in the USA^{4,5}; one RCT was from Sweden⁶; one RCT from China⁷; and one RCT was from

Hong Kong.⁸ Most studies had six out of the eight domains for the ideal framework for palliative care. The mean follow-up period was six months.

The palliative care (PC) intervention arm of these trials can be described into 5Ss—structured, systematic, scheduled, synergistic, and sustained. PC is structured patient centered care which entails a multidisciplinary approach involving a team composed of clinicians (palliative care specialists, cardiologists, HF specialists, psychiatrists) and other health providers (nurses, social workers, physiotherapists, occupational therapists) whose support can vary over time.

It is systematic and reproducible; the intervention starts prior to discharge or immediately after discharge during which the goals of care and a review of a patient's prognosis are discussed with the patient, family and caregiver. Weekly or even more frequent home visits/ telephone calls are scheduled for the monitoring of symptoms and end-organ function. There is a synergistic approach among the various specialties as to which of them may take a more central role in the coordination of patient care at different times of the disease span. The included providers are likely partial, and other team members may exist in individual teams to support patients as best as able. This is sustained care that spans throughout the disease process and extends to the bereavement phase for their family and caregivers.

The usual care intervention arm of these trials was provided mainly by clinicians (cardiologist, general practitioners) and/or nurse-led heart failure clinics. Discharge instructions were given by clinicians and, in one study,⁴ even printed materials containing information on advance care planning, prior to discharge. Unstructured home visits and phone calls of varying intervals were done depending on the clinical status of the patient. Sometimes, social calls were made consisting of light conversation topics unrelated to clinical issues.

Efficacy outcomes/ Certainty of Evidence

Palliative care intervention was associated with a significant reduction in the number of rehospitalizations [OR 0.48, 95% CI,(0.3-0.77), p = 0.002, I² = 2%] (Annex 16, Figure 2) and an improvement in the quality of life measure using the Kansas City Cardiomyopathy questionnaire or the McGill quality of life questionnaire [Standard mean difference 0.37, 95% CI, (0.16-0.57), p = 0.0004, I² = 0%] (Annex 16, Figure 3). The certainty of the level of evidence for both outcomes was moderate because it was downgraded by one level for risk of bias (i.e. performance and detection bias).

There was no benefit for mortality among the 4 RCTs with a total of 356 patients with substantial heterogeneity [OR 0.93, 95% CI,(0.4-2.16), p = 0.87, I² = 58%] (Annex 16, Figure 4). However, the study by Wong et al.⁹ was excluded due to its outlying result. There were no issues of heterogeneity seen [OR 1.32, 95% CI, (0.77-2.27), p = 0.32, I²

= 0%] (Fig.5 Appendix). The significant reduction in mortality seen in the study by Wong et al could be due to its shorter follow-up time of 84 days compared to the other studies with a longer follow-up period of six months. There was moderate certainty regarding the level of evidence due to issues with the risk of bias.

Only one RCT⁶ looked into worsening of heart failure symptoms; the study showed no significant difference between the two intervention arms [OR 0.42, 95% CI,(0.07-2.33), p = 0.32]. It also showed low certainty regarding the level of evidence due to issues with the risk of bias and inconsistency (low population size).

Table 66. Summary of findings table on effect of palliative care in chronic heart failure

Palliative care compared to Usual care for adult Filipinos with chronic heart failure						
Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Interpretation
		Usual Care	Palliative Care	Difference		
Mortality Nº of participants: 356 (4 RCTs)	OR 0.97 (0.60 to 1.57)	25.0%	24.4% (16.7 to 34.4)	0.6% fewer (8.3 fewer to 9.4 more)	⊕⊕○○ <small>Low^{a,b}</small>	Not significant
Rehospitalization Nº of participants: 306 (3 RCTs)	OR 0.48 (0.30 to 0.77)	63.2%	45.1% (34 to 56.9)	18.0% fewer (29.2 fewer to 6.3 fewer)	⊕⊕⊕○ <small>Moderate^a</small>	Significantly beneficial
Quality of Life assessed with: Mc Gill QoL and KCCQ follow-up: mean 1-6 months Nº of participants: 371 (5 RCTs)	-	-	-	SMD 0.37 SD higher (0.16 higher to 0.57 higher)	⊕⊕⊕○ <small>Moderate^a</small>	Significantly beneficial
Worsening heart failure Nº of participants: 60 (1 RCT)	OR 0.42 (0.07 to 2.33)	15.6%	7.2% (1.3 to 30.1)	8.4% fewer (14.3 fewer to 14.5 more)	⊕⊕○○ <small>Low^{a,b}</small>	Not significant

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; SMD: standardised mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Safety outcomes

There are no direct safety issues since this is a non-pharmacologic intervention. Training of staff members is of utmost importance. Poorly competent staff may lead to medication errors and miscommunication between them, the patients and the patients' caregivers, leading to worsened symptoms, disrupted dying, serious injury, and hastened death.⁹

RECOMMENDATIONS FROM OTHER GROUPS

Many international guidelines (Canada, Australia, New Zealand, Europe, and the USA) gave a strong recommendation to provide palliative care for the advanced stage of heart failure despite low quality of evidence. The guidelines mention that the involvement of a palliative care team should be part of the early trajectory of the disease based on a thorough assessment of needs and symptoms, rather than on individual estimates of patient's remaining life expectancy.

All available guidelines unanimously recommend referral to a palliative care team for patients in the advanced stage of heart failure who are refractory to guideline medical therapy in order to alleviate symptoms, decrease rehospitalization and assist in advance care planning for end of life and extend bereavement care to the caregiver/family..

Among these guidelines, Japan has the most detailed description of what constitutes a palliative care team and of the importance of training the staff. The Japanese guidelines have also extended medical coverage to include not only hospital-based palliative care but also outpatient palliative care, such as outpatient service and in-home medical care.

Table 67. Summary of recommendations from various guidelines regarding palliative care for patients with heart failure

Group or Agency	Recommendation	Strength of Recommendation/Certainty/Quality of Evidence (If available)
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the	Referral to palliative care should be considered in patients with advanced heart failure to alleviate end-stage symptoms, improve quality of life, and decrease rehospitalization. The involvement of palliative care should be considered early in the trajectory towards end stage heart failure.	Strong recommendation, high quality of evidence

Prevention, Detection, and Management of Heart Failure in Australia 2018 [10]		
Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure 2017 [11]	Recommends that the provision of palliative care to patients with HF should be on the basis of a thorough assessment of needs and symptoms, rather than on individual estimates of remaining life expectancy.	Strong recommendation, very low quality of evidence
NICE UK Guidelines in chronic heart failure in adults: diagnosis and management 2018 [12]	<p>These are the following statements for palliative care in heart failure:</p> <ul style="list-style-type: none"> • Do not use prognostic risk tools to determine whether to refer a person with heart failure to palliative care services. • If the symptoms of a person with heart failure are worsening despite optimal specialist treatment, discuss their palliative care needs with the specialist heart failure multidisciplinary team and consider a needs assessment for palliative care. • People with heart failure and their families or carers should have access to professionals with palliative care skills within the heart failure team. • The specialist heart failure MDT should directly involve, or refer people to, other services, including rehabilitation, services for older people, and palliative care services, as needed. 	No grading for strength of recommendation and quality of evidence
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2021 [13]	<p>Palliative care was not explicitly stated in their recommendation but it was one of the common issues identified in which there are still gaps in the evidence to determine specific options for palliative care.</p> <p>They stated in one of their recommendations that it is recommended for heart failure patients to be enrolled in a multidisciplinary heart failure</p>	Referral to MD-HF program was given class I recommendation with level A evidence.

	(MD-HF) management program to reduce the risk of hospitalization and mortality.	
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 2022 [14]	<p>For all patients with HF, palliative and supportive care, including high-quality communication, conveyance of prognosis, clarification of care goals, shared decision-making, symptom management, and caregiver support should be provided to improve QOL and relieve suffering.</p> <p>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.</p>	<p>Class I recommendation, Level of Evidence C – Limited data</p> <p>Class IIa recommendation, Level of Evidence B – Randomized (moderate quality)</p>
Malaysia Clinical Practice Guidelines Management of Heart Failure 2019 [15]	Patients with refractory symptoms despite guideline-directed medical therapy should be considered for palliative and end of life care.	No grading for strength of recommendation and quality of evidence
Japanese Circulation Society/Japanese Heart Failure Society Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure 2021 [16]	<p>As part of the cardiac rehabilitation of advanced heart failure, they recommend the introduction of palliative care early in stage C to improve overall quality of life and support for decision-making in selecting the treatment method.</p> <p>The Palliative care Emphasis program on symptom management and Assessment for Continuous medical Education (PEACE) was developed and implemented mainly by the Japanese Society for Palliative Medicine. It underscores the need for educating and training medical staff for the care of circulatory disease patients since their early experiences were with cancer patients.</p>	No grading for strength of recommendation and quality of evidence

ONGOING STUDIES

The treatment gap in heart failure still exists since all studies included patients in the advanced stage of their illness (i.e. stage C or D). There is an ongoing study—the early

palliative care in heart failure (EPC-HF)—which will enroll patients at NYHA class II or higher. This will answer the limited evidence that exists from RCTs supporting the use of interdisciplinary palliative care in the progressive course of heart failure.¹⁷

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (EtD) PHASE

COST

The reviewer did not encounter any local economic evaluation studies. In a study conducted in Hong Kong by Wong et al, the total cost of pre-program training for the palliative care team staff is HK\$ 17,349. This study also showed that over an 84-day period, the total cost of health care utilization per case was significantly less, at HK\$ 10,123 for the intervention group, compared to that of the control group, at HK\$ 36,206.¹⁸

The Palliative Care in Heart Failure (PAL-HF) study in the USA showed that the intervention resulted in an incremental gain of 0.033 QALYs and an incremental payment of \$964 per patient, for an incremental cost-effectiveness ratio (ICER) of \$29,041 per quality adjusted life year (QALY) after 36 months. This ICER was well within the ICER threshold of \$50,000 adopted by the ACC-AHA which makes it a clinically attractive intervention.¹⁹

The Palliative advanced home-caRE and heart FailurE caRe (PREFER) study conducted in Sweden revealed a reduced cost of €59,412 for the intervention group as compared to the control group. This was due to reduced hospital and emergency care.²⁰

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

The clinical course of heart failure is unpredictable. It is described as having short-term improvement after an acute decompensation event, followed by the gradual decline of function over time with no complete recovery.²¹ Therefore, achieving care alignment through shared decision-making with palliative care for personalized treatment should be enacted earlier in the disease process than at the very end of life. In a study done in Ontario, Canada on advanced heart failure, patients who received home-based palliative care led to changes in their treatment preferences to avoid hospitalization and focus on comfort at home with an eventual increase in out-of-hospital death.²²

Ethical issues often arise in those patients with advanced heart failure in treatment decision-making (e.g. device implantation, heart transplant, advanced care, near end of life care) and integrating palliative care will aid in these dilemmas. Discussing goals and

plans in preparing for death is mostly considered inappropriate and culturally insensitive, like here in the Philippines.²³ The beliefs of the patients and their family have to be contemplated before approaching individuals with poor prognosis. The patient and the family should be included in the decision-making process for better communication. Therefore, these are challenges ahead that need to be overcome in order for palliative care to become an acceptable and integral part of the management of heart failure.

Last 2015, the Department of Health (DOH) enacted the National Policy on Palliative and Hospice Care in the Philippines, integrating it into our health care delivery system to provide holistic health care ranging from promotive and preventive to curative and rehabilitative. Its general objective is to set overall policy directions and identify the roles and functions of DOH and its partner agencies in the provision of palliative care in hospitals, health facilities, communities, and homes.²⁴

Currently, there are 64 certified palliative care physicians according to the Philippine Society of Hospice and Palliative Medicine. They are mostly situated in Luzon. These physicians are trained to handle patients with chronic debilitating illnesses, mostly cancer and stroke. They also handle some heart failure patients but these patients usually only have heart failure as a comorbidity. Tertiary government hospitals such as the National Kidney and Transplant Institute and the Philippine Heart Center have recently come up with focused palliative care programs for end-stage kidney disease and for cardiovascular patients, respectively. A more comprehensive listing of palliative care specialists in the country is available via the official website of the Philippine Society of Hospice and Palliative Medicine (<https://www.pshpm.org/fellows>).

Like in most countries, the starting point of referral is usually at the hospital as part of transition care prior to discharge, in order to help transition the patient to home-based palliative care. The structure for an outpatient or home-based palliative care service is still lacking. There is still a need to identify and train nurses, barangay health workers, social workers (volunteers), and even physicians to recognize heart failure patients in need of palliative care and make outpatient palliative care a viable reality.

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Applicability Issues

The Heart Failure Task Force accentuates some caveats of this CPG using equity and applicability lenses. Comprehensive history taking, physical examination, and monitoring are essential in the evaluation of patients suspected or confirmed to have heart failure. These mandatory clinical processes must be emphasized to all primary care providers, regardless of their geographic or logistical setting. The unavailability or inaccessibility of recommended diagnostic tests, medications, and services in selected areas in the country is, however, a real-world concern that must be carefully reviewed and addressed by concerned policy-makers and stakeholders at the local (e.g. municipal health offices, rural health units, private medical facilities) and national levels (e.g. Department of Health, PhilHealth). The CPG task force is cognizant of the fact that not all ideal diagnostic tools are at the disposal of the patient and primary care provider, owing to cost and access issues. Moreover, some evidence-based and guideline-recommended therapeutics are included in the Philippine National Formulary (PNF), such as ACEis and ARBs, ARNi (Sacubitril/Valsartan), beta-blockers (Bisoprolol and Carvedilol), diuretics (Furosemide) and MRA (spironolactone). On March 2023, a SGLT2 inhibitor (dapagliflozin) was approved for inclusion in the PNF (DOH department circular 2023-0169), albeit as an add-on drug to Metformin for adult patients with Type 2 diabetes mellitus who have or are at high risk for cardiovascular disease and diabetic nephropathy.¹ Other heart failure drugs like Empagliflozin (SGLT2 inhibitor), Metoprolol Succinate and Nebivolol (beta-blockers), and Eplerenone (MRA) have not yet been approved for inclusion.

The task force looks forward to proactive efforts from concerned sectors in order to update guidance documents (e.g. PNF) and policies (e.g. PhilHealth) as well as pursue more capacity-building initiatives (e.g. Department of Health and professional medical societies).²

Finally, this CPG does not necessarily supersede the various stakeholders' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances. Although this CPG is intended to guide administrators in setting the general direction of health policies for the general population, it should not be the sole basis for reinforcing, recreating or abolishing certain health practices and procedures linked to the care of patients with heart failure.

¹Department of Health Circular 2021-0169. April 11, 2023

²https://www.philhealth.gov.ph/partners/providers/pdf/PNF-EML_11022022.pdf

Barriers and Facilitators to Guideline Implementation

A holistic approach to the care of patients with heart failure entails that the patient be granted ample opportunity to benefit from the necessary diagnostic procedures and appropriate treatment. As a low-middle-income country, our limited resources need to be allocated and used efficiently. The cost of the tests and interventions being done for Heart Failure management was one important consideration discussed in the panel meetings/health technology assessment; it should be a key gatekeeping mechanism to ensure that all payments made by the government (through PhilHealth) are cost-effective. The task force is cognizant of the reality that certain diagnostic tests and therapeutic interventions may not be readily available in rural areas and limited-resource settings. In fact, some of the medications recommended in this guideline unfortunately are not yet part of the Philippine National Formulary, effectively restricting access in government hospitals. As such, the evidence-based recommendations in this guideline are hoped to shape policy and practice in the Philippines, to ensure equitable and timely access to diagnostic and therapeutic resources for all Filipino patients with heart failure.

Meanwhile, the task force also recognizes some factors that can help facilitate the application and implementation of the guidelines, such as heightened awareness campaigns, greater access to low-cost yet evidence-based diagnostic and therapeutic options, and incentivization of adherence to guidelines.

The effective use and implementation of the HF guidelines will rest heavily on the mandate coming from the Department of Health. The task force hopes that such guideline recommendations will be properly cascaded to intended users through close collaboration between the national government, the implementing agency, the Philippine Heart Center, key professional societies, and local health administrators. Strategies may be developed to determine real-world use of such guidelines, looking into adherence to key recommendations and impact of their application, whether through scorecard metrics or coordinated research using rapid assessment methods and quality of care analysis. Such evaluations may be planned based on pre-specified intervals, depending on the current need of the health industry.

Monitoring and Evaluation

Dissemination

The SC will submit the full-text manuscript of this CPG to the Department of Health. The Disease Prevention and Control Bureau of DOH will transmit copies of this CPG to PhilHealth, health maintenance organizations, and pharmaceutical industry partners. DOH will release a memorandum to notify all stakeholders of the publication.

This CPG will be presented during conferences and annual conventions of medical societies. Copies of this CPG with the endorsement of relevant medical institutions will be sent to medical schools and libraries to integrate the recommendations in their training curricula, with the support of faculty members and the heads of hospital-based departments, including but not limited to surgery, radiology, pathology, and internal medicine.

An executive paper as well as the full paper will be submitted for publication in reputable, peer-reviewed cardiology and medical journals. Once the article is published, the CPG will be made available on the websites of DOH, the Philippine Heart Center, different medical societies and organizations such as PMA, PAFP, PCP, PHA and NHFN. Other forms of dissemination will include press conferences, social media sites, and professional society conventions.

All strong recommendations in this guideline can be used for monitoring and auditing practices in institutions. These can be converted to key performance indicators and can also be used to create clinical pathways.

The DOH planned to develop a simplified version of this CPG and make it available in the format that will be most ready for reproduction and dissemination to patients in different health care settings. It will also be available for all interested parties by visiting the DOH website. (For more details, see pp 31-32)

Updating of the guidelines

Considering the level of certainty in the body of evidence found for each guideline question, it is anticipated that these guidelines will need regular updating. Guidelines will be updated after three years or earlier should new important evidence become available. (For more details, see page 36-37)

Research Implications/Gaps

An exhaustive search of existing literature and investigative work on all clinical questions uncovered some key gaps worth looking into:

- Signs and symptoms: paucity of robust local studies on the diagnostic accuracy of symptoms and signs of heart failure in patients seen at a primary care or general practice outpatient clinic;
- Chest X-ray: paucity of studies on accuracy, cost-effectiveness, feasibility and prognostic value of the chest X-ray as a diagnostic tool for heart failure;
- 12L ECG: absence of local studies on the diagnostic utility of the electrocardiogram for heart failure in the outpatient setting; lack of local data on availability of the 12L ECG in primary care centers; absence of local studies looking into physician proficiency in interpreting a 12L ECG;
- Echocardiogram: lack of local studies looking into the real-world utility of cardiac point-of-care ultrasonography (POCUS) particularly for heart failure screening and diagnosis in the outpatient or community setting;
- Baseline serum electrolytes and serum creatinine: need for studies on the impact of determining the baseline serum electrolytes and serum creatinine on mortality among patients with chronic heart failure
- Dietary sodium and fluid restriction: lack of studies on dietary sodium and fluid restriction among patients outside the hospital setting and those who are not in acute decompensation, as well as studies specifically looking into the optimal amount of sodium and fluid intake beneficial for patients with chronic heart failure at the outpatient setting;
- Diuretics: paucity of studies providing guidance regarding optimal dose of loop diuretics as well as diuretic dosing strategies amidst newer GDMTs for outpatients with chronic heart failure;
- ARNI: lack of local studies looking into cost-effectiveness of ARNIs in the treatment of patients with heart failure at the primary care setting, and their impact on reduction of unnecessary testing and interventions;
- MRA: lack of studies investigating the use of MRAs on patients with chronic heart failure;
- SGLT2i: lack of real-world data on patients' preference and acceptability regarding the use of SGLT2 inhibitors as one of the recommended treatment modalities for HF with reduced ejection fraction;
- Referral to higher levels of care: paucity of studies directly looking into timely referral of patients with heart failure seen at the primary care setting to multidisciplinary teams and higher centers of care.

Other general recommendations include the following:

- Creation of a heart failure pathway that incorporates recommendations that have proven clinical benefit;
- Development of monitoring and evaluation tools that will examine the effects of these guideline recommendations on the quality of patient care across various institutions;
- Conduct of an updated epidemiological study on patients with heart failure in both in-patient and out-patient settings across the spectrum of ejection fractions (HFrEF, HFmrEF and HFpEF);
- The need for economic evaluation studies that include not only cost-effectiveness analyses, but also cost-utility and cost-benefit analyses. These studies can be used as tools in prioritizing cost-effective and cost-saving tests and interventions.
- Conduct of additional studies on budget impact analysis (BIA) that can be used by health policy makers to improve the Philhealth coverage of patients hospitalized for heart failure;
- Conduct of studies looking into performance metrics on the management of patients with HFrEF (e.g. adherence to GDMT; timeliness of interventions, appropriateness of referral)
- For future guideline updates, conduct of patient focus group discussions prior to development of the CPG, inclusion of representatives of Hospital administrators, Philhealth and DOH to ensure more representation of all stakeholders

Finally, with the advancements in the field of heart failure, exploring the role of precision medicine can spur the development of practice-changing research. These studies can provide answers to current questions which can influence the recommendations for updating this guideline.

Recommendations for Future Guideline Development

Despite the methodological rigor with which this CPG was created, the task force still recognizes some areas for improvement and consideration for the formulation of the succeeding set of guidelines. These include the following:

- Use of tailored surveys and focused group discussions involving a wider range of end-users (e.g. patient groups) to more effectively capture their values and preferences;

- Creation of a document intended for patient education that shall accompany the clinical practice guideline;
- Dialogue with representatives from various stakeholders and policy makers, such as the Philippine Health Corporation (PhilHealth), hospital administrators and health economists, to obtain their insights on local laws, the guideline impact on future health directions, and their perspectives on the socioeconomic value of testing and therapy;
- Conduct of local cost-effectiveness or cost evaluation and budget impact analyses as well as health economic outcomes research.

Ultimately, the CPG task force hopes that the approval and effective dissemination and implementation of these guidelines will translate to the adoption of more enabling health policies, higher quality standards in physician practice, and better clinical outcomes for the Filipino patient with chronic heart failure.

APPENDICES

Annex 1 : Members of the CPG Task Force

PHILIPPINE CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION FOR PRIMARY CARE PHYSICIANS 2023

Task Force Steering Committee

Chair: Gilbert C. Vilela, MD, FPCP, FPCC, FACC, FESC, FAsCC

Co-chair: Maria Teresa B. Abola, MD, FPCP, FPCC, FACC, FPSVM, MSVM

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Maria Victoria Concepcion Pilares-Cruz, MD, DFM, FPAFP

Milagros L. Estrada-Yamamoto, MD, FPCP, FPCC, FACC

Eden A. Gabriel, MD, FPCP, FPCC

Maria Encarnita Blanco - Limpin, MD, FPCP, FPCCP, FPSCCM, FPSSM

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April Ann Bermudez-delos Santos, MD, FPCP, FPCC

Lourdes Ella Gonzalez-Santos, MD, FPCP, FPCC

Elmer Jasper B. Llanes, MD, FPCP, FPCC

Marie T. Magno, MD, FPCP, FPCC

Leahdette O. Padua, MD, FPCP, FPCC

Noemi S. Pestaño, MD, FPCP, FPCC

Miriam Roxas Timonera, MD, FPCP

Alexander A. Tuazon, MD, FPCP, FPCC

Rogelio N. Velasco, Jr., MD, FPCP, FPSMO

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Arnelia C. Bersales-Masendo, MD, FPCP, FPSN

Leandro C. Bongosia, MA, MD, FPCP, FPCC, FCRSP, FACC

Francis B. Cabatingan, MD, FPAFP , FPSHPM

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Wilbert Allan G. Gumatay, MD, FPCP, FPCC , IFPSCCI

Sunny Ku (Heart Failure Patient)

Adillah Latiph, MD, RMT, DFM

Maaliddin B. Biruar, MD, FPCP, FPSN

Marian E. Manalo, MD, FPCP, FPCC

Lariza Z. Rendon, RN

Nathania N. Salazar-Fajardo, MD, FPCP, FPCC, FCRSP

Ian Jonathan N. Tiotangco, RN, MD, DFM

Edwin S. Tucay, MD, FPCP, FPCC, FPSE, FAsCC, FASE

Liberty O. Yaneza, MD, FPCP, FPCC

Julie Rubite, MD, DOH Representative (Non-voting Observer, Resource Person from Funding Agency)

Consensus Panel Meeting Technical Facilitator: Carlo Irwin Panelo, MD, MA

Technical Writer: Lauren Kay M. Evangelista, MD, FPCP, FPCC

Administrative Officer: Princess Marie T. Sulit, RN

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Maria Belen O. Carisma, MD, FPCP, FPCC

Marcellus Francis L. Ramirez, MD, MA, FPCP, FPCC, FACC

Norbert Lingling D. Uy, MD, MSPH, FPCP, FPCC, FPSE, FACC, FACP

Annex 2: Summary of COI Declarations

Name/ Discipline	Society and Institutional Affiliation	Summary of Declared Conflict of Interest	Assess- ment
Dr. Maria Teresa B. Abola	Philippine Heart Association, Philippine Heart Center	Lead investigator for 2 HF Trials	C
Dr. Michael Joseph F. Agbayani	Philippine Heart Association	Speaker Honoraria from pharmaceutical companies with interests in Heart Failure such as Boehringer Ingelheim, Novartis, and Astra Zeneca. Sponsorships to attend international conferences	C
Dr. Lorraine Almelor- Sembrana	Philippine Heart Association, Philippine Heart Center	Employed by J and J with products used for HF (Xarelto)	B
Dr. Florido Atibagos, Jr.	Philippine Society of Pathologists, Inc., Philippine Heart Center	None	A
Dr. Irene S. Bandong	Philippine College of Radiology, Philippine Heart Center	None	A

Dr. Arnelia Bersales-Masendo	Philippine College of Physicians	None	A
Dr. Maaliddin B. Biruar	Philippine College of Physicians	Speaker and Advisory Board member for Astra Zeneca and Boehringer Ingelheim	C
Dr. Leandro C. Bongosia	Philippine Heart Association, Philippine Heart Center	None	A
Dr. Erlyn Cabanag-Demerre	Philippine Heart Association	Lecturer for 4 pharmaceutical companies with HF drugs	C
Dr. Francis B. Cabatingan	Philippine Academy of Family Physicians	None	A
Dr. Minerva P. Calimag	Philippine Medical Association	None	A
Dr. Deborah Ignacia Abad David-Ona	Philippine College of Physicians	Speaker and travel grant recipient from pharmaceutical companies with HF drugs	C
Dr. Karen A. De Leon	Philippine Heart Association	None	A
Dr. April Ann Bermudez-delos Santos	Philippine Heart Association	Involved in SGD with Boehringer; with shares in hospitals	C

Dr. Milagros Estrada-Yamamoto	Philippine Heart Association	Lecturer for UMED	B
Dr. Lauren Kay M. Evangelista	Philippine Heart Association	Recipient of training grant for HF training from pharmaceutical company	C
Dr. Eden A. Gabriel	Philippine Heart Association, Philippine Heart Center	Co-author of published papers related to economic burden, epidemiologic burden of diseases warranting devices	B
Dr. Lourdes Ella Gonzalez-Santos	Philippine Heart Association	Speaker for 4 pharmaceutical companies with HF drugs	C
Dr. Wilbert Allan G. Gumatay	Philippine Heart Association	Speaker for 5 pharmaceutical companies with HF drugs	C
Mr. Sunny Sy Ku	Lay Sector	None	A
Dr. Adillah Latiph	Philippine Academy of Family Physicians	Brother and sister own a hospital in Marawi; brother is former health minister of BARMM	B
Dr. Maria Encarnita Blanco-Limpin	Philippine College of Physicians	None	A

Dr. Elmer Jasper B. Llanes	Philippine Heart Association	Speaker for pharmaceutical companies with HF drugs	C
Dr. Jose Donato A. Magno	Philippine Heart Association	Unrestricted grant from 4 pharmaceutical companies with HF drugs; administrator and co-owner of outpatient cardiovascular diagnostic laboratory with heart failure clinic	C
Dr. Marie T. Magno	Philippine Heart Association, Philippine Heart Center	Speaker for pharmaceutical company with HF drug	C
Dr. Marian E. Manalo	Philippine Heart Association	Speakers Bureau member- Astra Zeneca, Boehringer, Novartis, Zydus, Pfizer, Getz Pharma, Sanofi, LRI-Thera Pharma, Ajanta Pharma, Merck	C
Dr. Florian R. Nuevo	Philippine Society of Cardiothoracic Anesthesiologists	None	A
Dr. Raymond V. Oliva	Philippine College of Physicians	Head of Medical Affairs of Astellas Pharma; products are unrelated to the CPG topic	B

Dr. Leahdette O. Padua	Philippine Heart Association, Philippine Heart Center	None	A
Dr. Carlo Irwin Panelo	Department of Clinical Epidemiology, University of the Philippines Manila, College of Medicine	Speaker for pharmaceutical companies with HF drug	C
Dr. Noemi S. Pestaño	Philippine Heart Association	Co-author in heart failure studies	B
Dr. Maria Victoria Concepcion Pilares-Cruz	Philippine Academy of Family Physicians	None	A
Dr. Felix Eduardo R. Punzalan	Philippine Heart Association	Lecturer for Astra Zeneca	C
Ms. Lariza Z. Rendon	Philippine Heart Center, Cardiac Rehabilitation Section, Division of Preventive Cardiology	None	A

Dr. Nathania Salazar-Fajardo	Philippine Heart Association	Speakers bureau and lecturer for Astra Zeneca, Novartis and Servier (Currently not bound with any contract). All that were presented were evidence-based without any intention to promote off label use of the drugs/compound.	C
Dr. Antonio S. Sibulo, Jr.	Philippine Heart Association	Lecturer for 2 pharmaceutical companies with HF drugs	C
Ms. Princess Marie T. Sulit, RN		None	A
Dr. Miriam Roxas Timonera	Philippine Heart Association	None	A
Dr. Ian Jonathan N. Tiotangco	Philippine Academy of Family Physicians	None	A
Dr. Alexander A. Tuazon	Philippine Heart Association, Philippine Heart Center	Travel grant from pharmaceutical companies	C
Dr. Edwin S. Tucay	Philippine Heart Association,	None	A

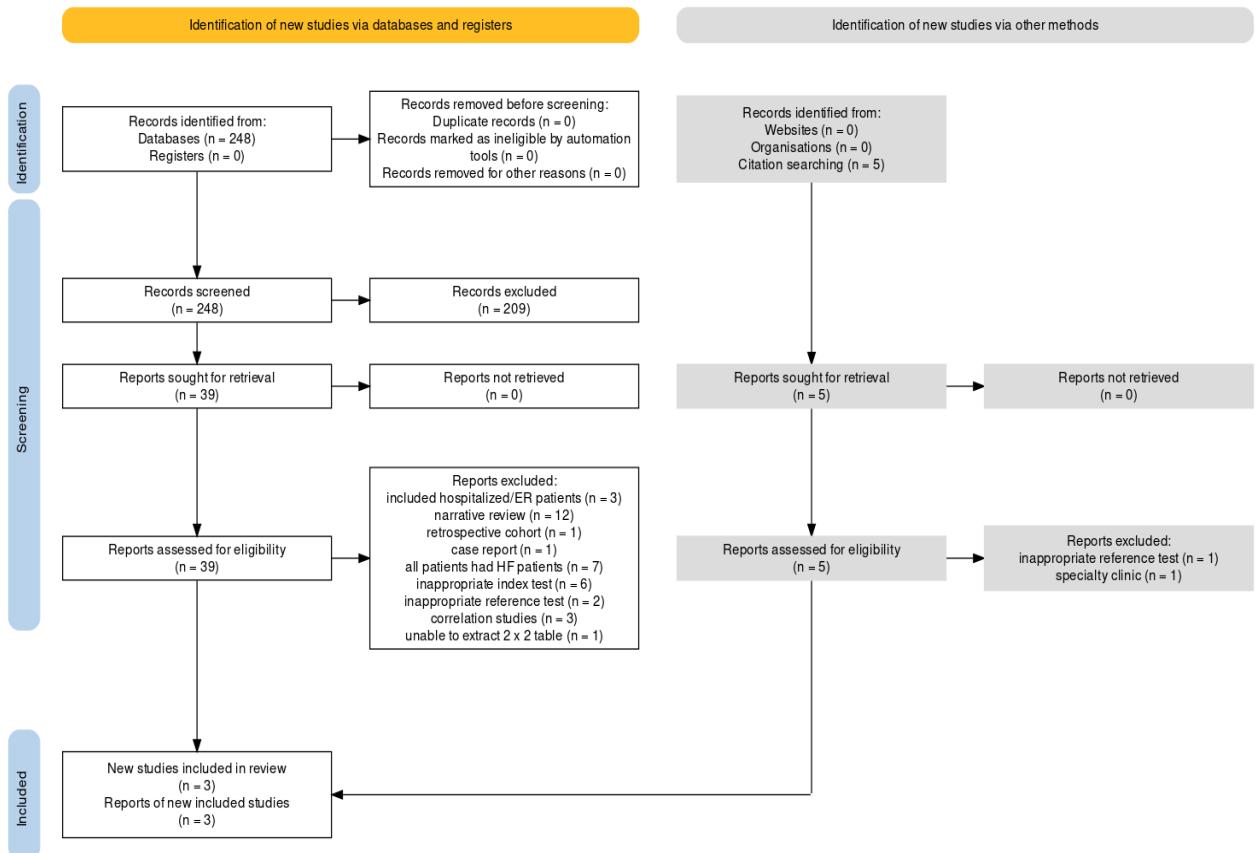
	Philippine Heart Center		
Dr. Rogelio N. Velasco, Jr.	Philippine Heart Association, Philippine Heart Center	None	A
Dr. Gilbert C. Vilela	Philippine Heart Association, Philippine Heart Center	Speaker for 3 pharmaceutical companies with HF drugs	C
Dr. Liberty O. Yaneza	Philippine Heart Association, Philippine Heart Center	Speaker on Dapagliflozin	C

Annex 3: Signs and symptoms of heart failure

1. SEARCH STRATEGY AND YIELD (06 December 2022 7:39:59)

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS																																																	
			Yield	Eligible																																																
Medline	<table border="1"> <tbody> <tr><td>#1</td><td>heart failure</td><td>302,074</td></tr> <tr><td>#2</td><td>dyspnea</td><td>68,021</td></tr> <tr><td>#3</td><td># 1 and # 2</td><td>7,592</td></tr> <tr><td>#4</td><td>#3 AND easy fatigability</td><td>11</td></tr> <tr><td>#5</td><td>#3 AND orthopnea</td><td>244</td></tr> <tr><td>#6</td><td>#3 AND paroxysmal nocturnal dyspnea</td><td>509</td></tr> <tr><td>#7</td><td>#3 AND elevated jugular venous pressure</td><td>30</td></tr> <tr><td>#8</td><td>#3 AND rales</td><td>120</td></tr> <tr><td>#9</td><td>#3 AND peripheral edema</td><td>195</td></tr> <tr><td>#10</td><td>#4 OR #5 OR #6 OR #7 OR #8 OR #9</td><td>931</td></tr> <tr><td>#11</td><td>#10 AND sensitivity</td><td>185</td></tr> <tr><td>#12</td><td>#10 AND specificity</td><td>91</td></tr> <tr><td>#13</td><td>#10 AND diagnostic accuracy</td><td>14</td></tr> <tr><td>#14</td><td>#10 AND predictive value</td><td>43</td></tr> <tr><td>#15</td><td>#10 AND likelihood ratio</td><td>26</td></tr> <tr><td>#16</td><td>#11 OR #12 OR #13 OR #14 OR # 15</td><td>248</td></tr> </tbody> </table>	#1	heart failure	302,074	#2	dyspnea	68,021	#3	# 1 and # 2	7,592	#4	#3 AND easy fatigability	11	#5	#3 AND orthopnea	244	#6	#3 AND paroxysmal nocturnal dyspnea	509	#7	#3 AND elevated jugular venous pressure	30	#8	#3 AND rales	120	#9	#3 AND peripheral edema	195	#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	931	#11	#10 AND sensitivity	185	#12	#10 AND specificity	91	#13	#10 AND diagnostic accuracy	14	#14	#10 AND predictive value	43	#15	#10 AND likelihood ratio	26	#16	#11 OR #12 OR #13 OR #14 OR # 15	248	December 6, 2022 7:39:59 pm	248	3
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2. PRISMA



3. Table of the characteristics of included studies

Study ID	Type of study, n	Setting	Mean age, years (\pm SD)	Population	Index test	Reference standard
Hobbs et al 2002	Prospective cohort n=273	Primary care/ general practice	66 \pm 11	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	rales, peripheral edema	ESC criteria
Fonseca et al. 2004	cross-sectional study n=1058	Primary care/ general practice	68 \pm 15	Randomly selected patients (stratified by age)	orthopnea, PND, JVP, rales, edema	ESC criteria
Rutten et al. 2005	cross-sectional study n=405	Primary care/ general practice	73 \pm 5	COPD patients with no previous diagnosis of heart failure	orthopnea, PND, JVP, rales, edema	Clinical consensus
Ekundayo et al. 2009	Prospective cohort n=5771	Primary care/ general practice	73 \pm 6.0	community dwelling patients with orthopnea and PND	orthopnea, PND	clinical consensus
Kelder et al. 2011	cross-sectional study n=721	Primary care/ general practice	75. 5 \pm 9.7	Patients presenting with symptoms and signs of heart failure with no previous diagnosis of heart failure	EF, orthopnea, PND, JVP, rales, peripheral edema	ESC criteria
van Riet et al. 2016	cross-sectional study n=585	Primary care/ general practice	74.1 \pm 6 .3	patients with non acute shortness of breath	rales, peripheral edema	ESC criteria

4. GRADE EVIDENCE PROFILE TABLES

EASY FATIGABILITY

Author(s): Miriam Roxas Timonera, M.D.

Question: Should Easy fatigability be used to diagnose heart failure in adult patients with dyspnea?

Setting: primary care/general practice

Bibliography:

[6] Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011 Dec 20;124(25):2865-73. doi: 10.1161/CIRCULATIONAHA.111.019216. Epub 2011 Nov 21. PMID: 22104551

Sensitivity	0.72 (95% CI: 0.66 to 0.79)	Prevalences	1.6%	30%	0%
Specificity	0.44 (95% CI: 0.40 to 0.48)				

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	pre-test probability of 0%	
True positives (patients with heart failure)	1 studies 207 patients	cross-sectional (cohort type accuracy study)	very serious ^a	serious ^b	not serious	not serious	none	12 (11 to 13)	217 (199 to 236)	0 (0 to 0)	⊕○○○ Very low
False negatives (patients incorrectly classified as not having heart failure)								4 (3 to 5)	83 (64 to 101)	0 (0 to 0)	
True negatives (patients without heart failure)								433 (390 to 475)	308 (278 to 338)	440 (397 to 483)	⊕○○○ Very low

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	pre-test probability of 0%	

Explanations

a. Incorporation bias - signs and symptoms of HF (index test) were included in the diagnosis of HF (reference standard)

b. Indirectness - easy fatigability was referred to as dyspnea on climbing 1 flight of stairs. There is no generally accepted definition of easy fatigability but this is usually a perception of tiredness rather than dyspnea.

Orthopnea

Author(s): Miriam Roxas Timonera, M.D.

Question: Should orthopnea be used to diagnose heart failure in adult patients with dyspnea?

Setting: primary care/general practice

Bibliography:

[1]	Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011 Dec 20;124(25):2865-73. doi: 10.1161/CIRCULATIONAHA.111.019216. Epub 2011 Nov 21. PMID: 22104551.
[2]	Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, Ceia F; EPICA Investigators. The diagnosis of heart failure in primary care: value of symptoms and signs. Eur J Heart Fail. 2004 Oct;6(6):795-800, 821-2. doi: 10.1016/j.ejheart.2004.08.002. PMID: 15542419.
[3]	Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuijthoff NP, Lammers JW, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ. 2005 Dec 10;331(7529):1379. doi: 10.1136/bmj.38664.661181.55. Epub 2005 Dec 1. PMID: 16321994; PMCID: PMC1309648.

Question: Should orthopnea be used to diagnose heart failure in adult patients with dyspnea?

Sensitivity	0.32 (95% CI: 0.25 to 0.39)	Prevalences	1.6%	30%	0%
Specificity	0.86 (95% CI: 0.77 to 0.92)				

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	pre-test probability of 0%	
True positives (patients with heart failure)	4 studies 1113 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^b	not serious	none	5 (4 to 6)	95 (76 to 117)	0 (0 to 0)	
False negatives (patients incorrectly classified as not having heart failure)								11 (10 to 12)	205 (183 to 224)	0 (0 to 0)	
True negatives (patients without heart failure)	4 studies 6870 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^c	not serious	none	846 (755 to 905)	602 (537 to 644)	860 (767 to 920)	
False positives (patients incorrectly classified as having heart failure)								138 (79 to 229)	98 (56 to 163)	140 (80 to 233)	

Explanations

a. Incorporation bias - signs and symptoms of HF (index test) were included in the diagnosis of HF (reference standard)

b. Heterogeneity $I^2=0.886$ but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill

c. Heterogeneity $I^2=0.963$ but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill

Paroxysmal Nocturnal Dyspnea

Author(s): Miriam Roxas Timonera, .M.D.

Question: Should Paroxysmal Nocturnal Dyspnea be used to diagnose heart failure in adult patients with dyspnea?

Bibliography:

[1]	Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. <i>Circulation</i> . 2011 Dec 20;124(25):2865-73. doi: 10.1161/CIRCULATIONAHA.111.019216. Epub 2011 Nov 21. PMID: 22104551.
[2]	Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, Ceia F; EPICA Investigators. The diagnosis of heart failure in primary care: value of symptoms and signs. <i>Eur J Heart Fail</i> . 2004 Oct;6(6):795-800, 821-2. doi: 10.1016/j.ejheart.2004.08.002. PMID: 15542419.
[3]	Ekundayo OJ, Howard VJ, Safford MM, McClure LA, Arnett D, Allman RM, Howard G, Ahmed A. Value of orthopnea, paroxysmal nocturnal dyspnea, and medications in prospective population studies of incident heart failure. <i>Am J Cardiol</i> . 2009 Jul 15;104(2):259-64. doi: 10.1016/j.amjcard.2009.03.025. Epub 2009 May 14. PMID: 19576357; PMCID: PMC2787196

Question: Should Paroxysmal Nocturnal Dyspnea be used to diagnose heart failure in adult patients with dyspnea?

Sensitivity	0.31 (95% CI: 0.26 to 0.36)	Prevalences	1.6 %	30%
Specificity	0.86 (95% CI: 0.82 to 0.90)			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	
True positives (patients with heart failure)	3 studies 1030 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^b	not serious	none	5 (4 to 6)	93 (79 to 108)	
False negatives (patients incorrectly classified as not having heart failure)								11 (10 to 12)	207 (192 to 221)	
True negatives (patients without heart failure)	3 studies 6608 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^c	not serious	none	849 (810 to 881)	604 (576 to 627)	
False positives (patients incorrectly classified as having heart failure)								135 (103 to 174)	96 (73 to 124)	

Explanations

a. Incorporation bias - signs and symptoms of HF (index test) were included in the diagnosis of HF (reference standard)

b. I²=0.757 but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill

c. I²=0.942

Elevated Jugular Venous Pressure

Author(s): Miriam Roxas Timonera, .M.D.

Question: Should Elevated Jugular Venous Pressure be used to diagnose heart failure in adult patients with dyspnea?

Bibliography:

[1]	Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. <i>Circulation</i> . 2011 Dec 20;124(25):2865-73. doi: 10.1161/CIRCULATIONAHA.111.019216. Epub 2011 Nov 21. PMID: 22104551.
[2]	Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, Ceia F; EPICA Investigators. The diagnosis of heart failure in primary care: value of symptoms and signs. <i>Eur J Heart Fail</i> . 2004 Oct;6(6):795-800, 821-2. doi: 10.1016/j.ejheart.2004.08.002. PMID: 15542419.
[3]	Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuijthoff NP, Lammers JW, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. <i>BMJ</i> . 2005 Dec 10;331(7529):1379. doi: 10.1136/bmj.38664.661181.55. Epub 2005 Dec 1. PMID: 16321994; PMCID: PMC1309648.

Question: Should Elevated Jugular Venous Pressure be used to diagnose heart failure in adult patients with dyspnea?

Sensitivity	0.27 (95% CI: 0.19 to 0.36)	Prevalences	1.6%	30%
Specificity	0.93 (95% CI: 0.81 to 0.98)			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	
True positives (patients with heart failure)	3 studies 841 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^b	not serious	none	4 (3 to 6)	81 (58 to 108)	
False negatives (patients incorrectly classified as not having heart failure)								12 (10 to 13)	219 (192 to 242)	

Outcome	No of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	
True negatives (patients without heart failure)	3 studies 1343 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^c	not serious	none	919 (797 to 963)	654 (567 to 685)	
False positives (patients incorrectly classified as having heart failure)								65 (21 to 187)	46 (15 to 133)	

Explanations

- a. Incorporation bias - signs and symptoms of HF (index test) were included in the diagnosis of HF (reference standard)
- b. Heterogeneity $I^2=0.878$ but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill
- c. Heterogeneity $I^2=0.98$ but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill

RALES OR LUNG CREPITATIONS

Author(s): Miriam Roxas Timonera, M.D.

Question: Should Rales (Lung crepitations) be used to diagnose heart failure in adult patients with dyspnea?

Bibliography:

[1]	Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011 Dec 20;124(25):2865-73. doi:
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	10.1161/CIRCULATIONAHA.111.019216. Epub 2011 Nov 21. PMID: 22104551.
[2]	Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, Ceia F; EPICA Investigators. The diagnosis of heart failure in primary care: value of symptoms and signs. <i>Eur J Heart Fail.</i> 2004 Oct;6(6):795-800, 821-2. doi: 10.1016/j.ejheart.2004.08.002. PMID: 15542419.
[3]	Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuijhoff NP, Lammers JW, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. <i>BMJ.</i> 2005 Dec 10;331(7529):1379. doi: 10.1136/bmj.38664.661181.55. Epub 2005 Dec 1. PMID: 16321994; PMCID: PMC1309648.
[4]	Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK. Reliability of N-terminal proBNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. <i>Heart.</i> 2004 Aug;90(8):866-70. doi: 10.1136/heart.2003.014258. PMID: 15253955; PMCID: PMC1768355.
[5]	van Riet EE, Hoes AW, Limburg A, Landman MA, Kemperman H, Rutten FH. Extended prediction rule to optimise early detection of heart failure in older persons with non-acute shortness of breath: a cross-sectional study. <i>BMJ Open.</i> 2016 Feb 15;6(2):e008225. doi: 10.1136/bmjopen-2015-008225. PMID: 26880668; PMCID: PMC4762114.

Question: Should Rales (Lung crepitations) be used to diagnose heart failure in adult patients with dyspnea?

Sensitivity	0.31 (95% CI: 0.25 to 0.37)	Prevalences	1.6%	30%
Specificity	0.84 (95% CI: 0.73 to 0.91)			

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence						Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%		
True positives (patients with heart failure)	5 studies 950 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^b	not serious	none	5 (4 to 6)	92 (75 to 111)		
False negatives (patients incorrectly classified as not having heart failure)								11 (10 to 12)	208 (189 to 225)		

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	
True negatives (patients without heart failure)	5 studies 2092 patients	cross-sectional (cohort type accuracy study)	very serious ^a	not serious	not serious ^c	not serious	none	825 (718 to 893)	587 (511 to 636)	
False positives (patients incorrectly classified as having heart failure)								159 (91 to 266)	113 (64 to 189)	

Explanations

a. Incorporation bias - signs and symptoms of HF (index test) were included in the diagnosis of HF (reference standard)

b. Heterogeneity I²=0.619 but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill

c. Heterogeneity I²=0.965

PERIPHERAL EDEMA

Author(s): Miriam Roxas Timonera, M.D.

Question: Should peripheral edema be used to diagnose heart failure in adult patients with dyspnea?

Bibliography:

[1]	Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011 Dec 20;124(25):2865-73. doi: 10.1161/CIRCULATIONAHA.111.019216. Epub 2011 Nov 21. PMID: 22104551.
[2]	Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, Ceia F; EPICA Investigators. The diagnosis of heart failure in primary care: value of symptoms and

	signs. Eur J Heart Fail. 2004 Oct;6(6):795-800, 821-2. doi: 10.1016/j.ejheart.2004.08.002. PMID: 15542419.
[3]	Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuijthoff NP, Lammers JW, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ. 2005 Dec 10;331(7529):1379. doi: 10.1136/bmj.38664.661181.55. Epub 2005 Dec 1. PMID: 16321994; PMCID: PMC1309648.
[4]	Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK. Reliability of N-terminal proBNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. Heart. 2004 Aug;90(8):866-70. doi: 10.1136/heart.2003.014258. PMID: 15253955; PMCID: PMC1768355.
[5]	van Riet EE, Hoes AW, Limburg A, Landman MA, Kemperman H, Rutten FH. Extended prediction rule to optimise early detection of heart failure in older persons with non-acute shortness of breath: a cross-sectional study. BMJ Open. 2016 Feb 15;6(2):e008225. doi: 10.1136/bmjopen-2015-008225. PMID: 26880668; PMCID: PMC4762114.

Question: Should peripheral edema be used to diagnose heart failure in adult patients with dyspnea?

Sensitivity	0.44 (95% CI: 0.34 to 0.55)	Prevalences 1.6 % 30%
Specificity	0.79 (95% CI: 0.68 to 0.87)	

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	
True positives (patients)	5 studies 950 patients	cross-section-al (cohort type)	very serious ^a	not serious	not serious ^b	not serious	none	7 (5 to 9)	132 (102 to 165)	⊕⊕○○ Low ^a

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 30%	
with heart failure)		accuracy study)								
False negatives (patients incorrectly classified as not having heart failure)								9 (7 to 11)	168 (135 to 198)	
True negatives (patients without heart failure)	5 studies 2092 patients	cross-section-al (cohort type accuracy study)	very serious ^a	not serious	not serious ^c	not serious	none	777 (669 to 856)	553 (476 to 609)	⊕⊕○○ Low
False positives (patients incorrectly classified as having heart failure)								207 (128 to 315)	147 (91 to 224)	

Explanations

- a. Incorporation bias - signs and symptoms of HF (index test) were included in the diagnosis of HF (reference standard)
- b. I²=0.876 but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill
- c. I²=0.966 but this could be explained by differences in the definition and elicitation of these symptom which is highly dependent on experience and skill

5. FOREST PLOTS

Figure 1. Orthopnea

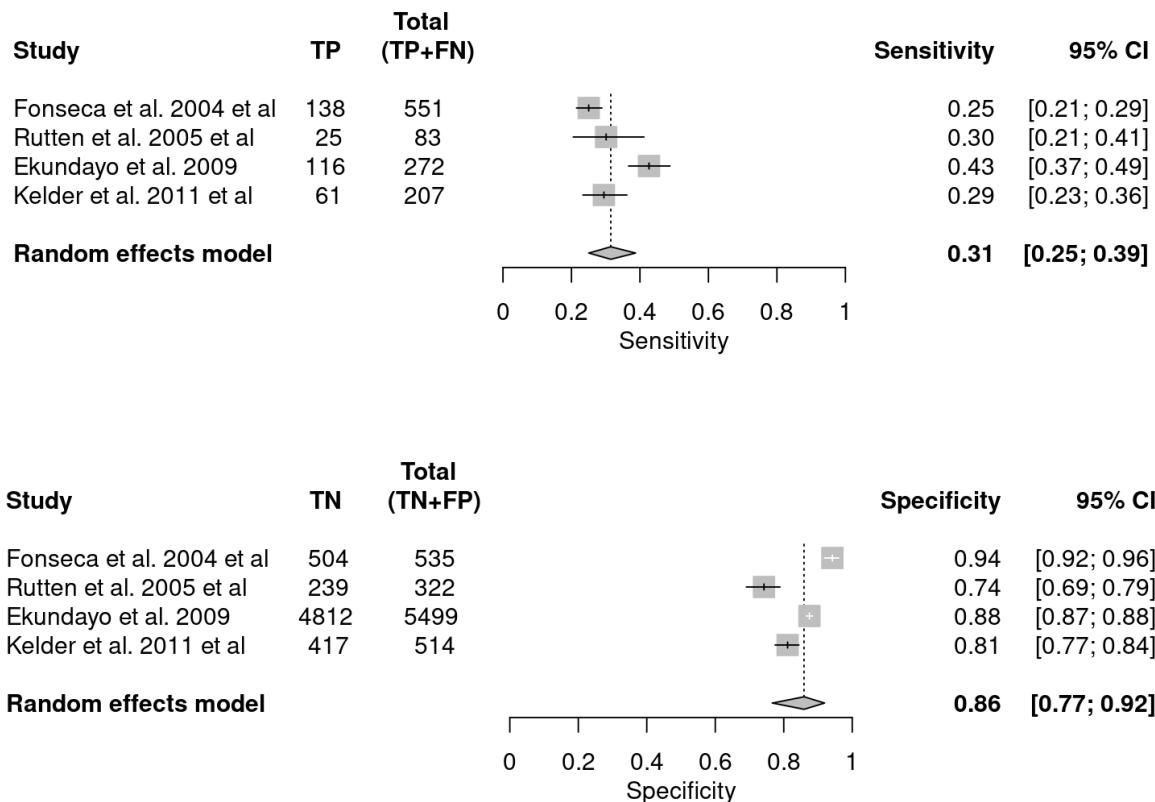
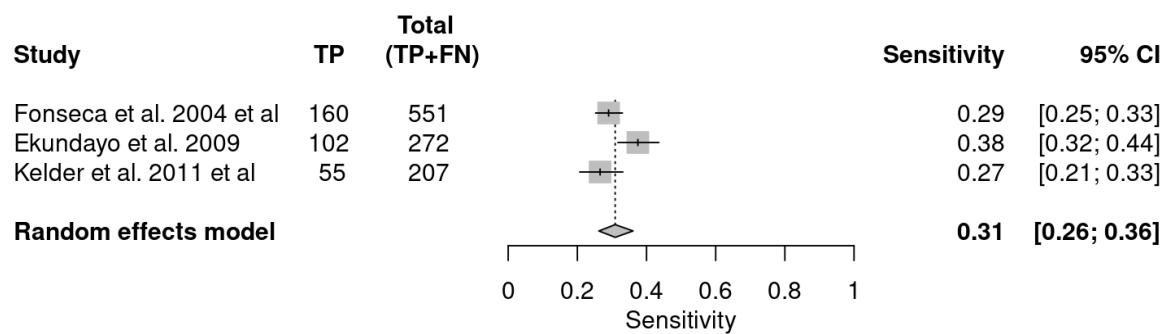


Figure 2. Paroxysmal Nocturnal Dyspnea



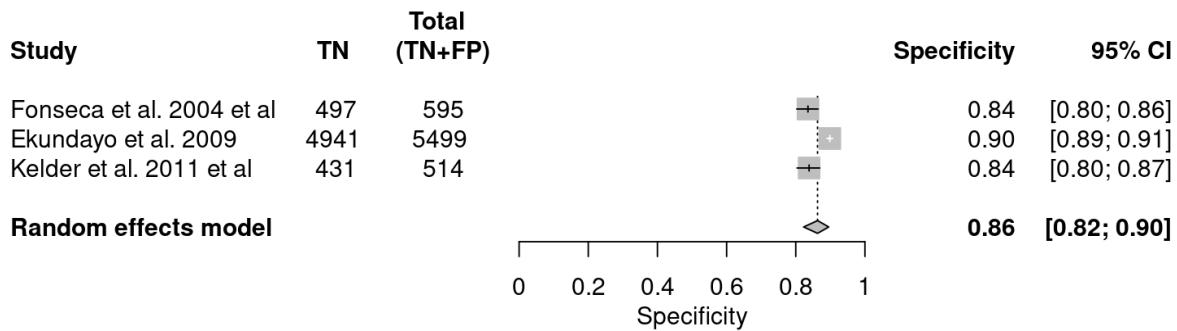


Figure 3. Elevated Jugular Venous Pressure

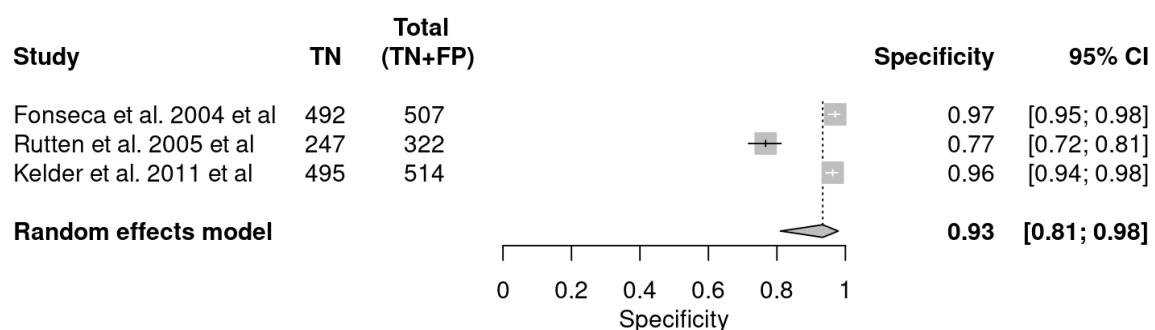
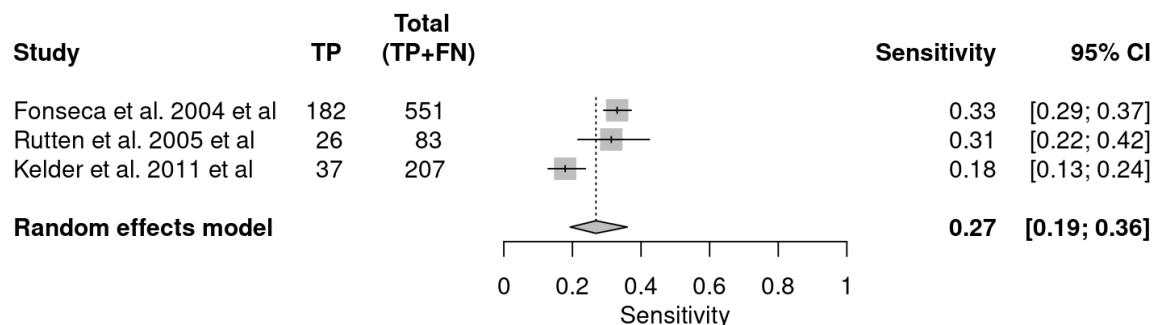


Figure 4. Rales or lung crepitations

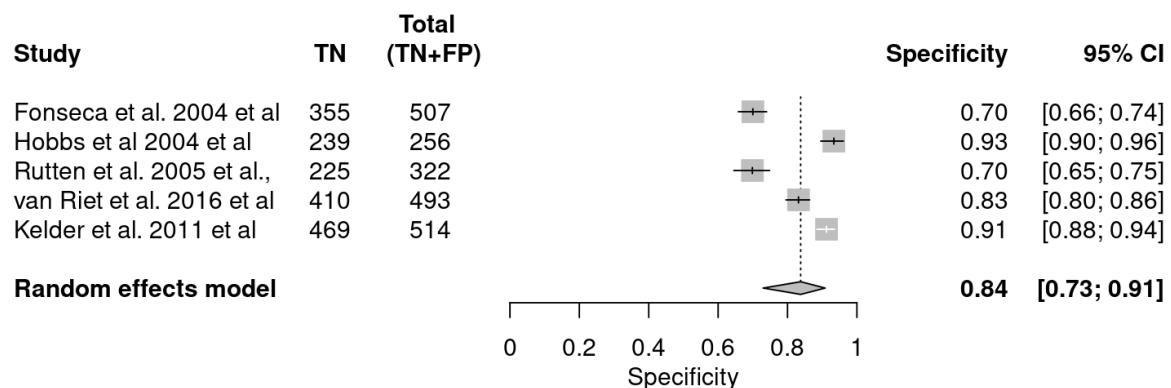
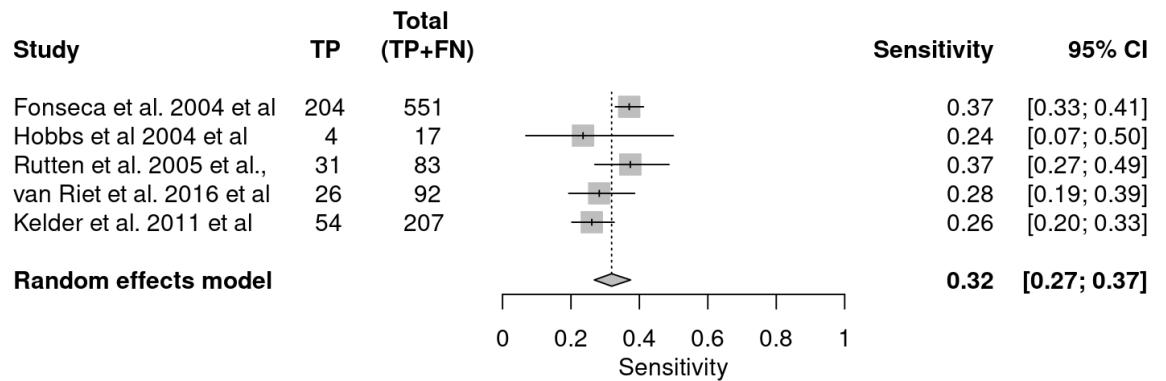
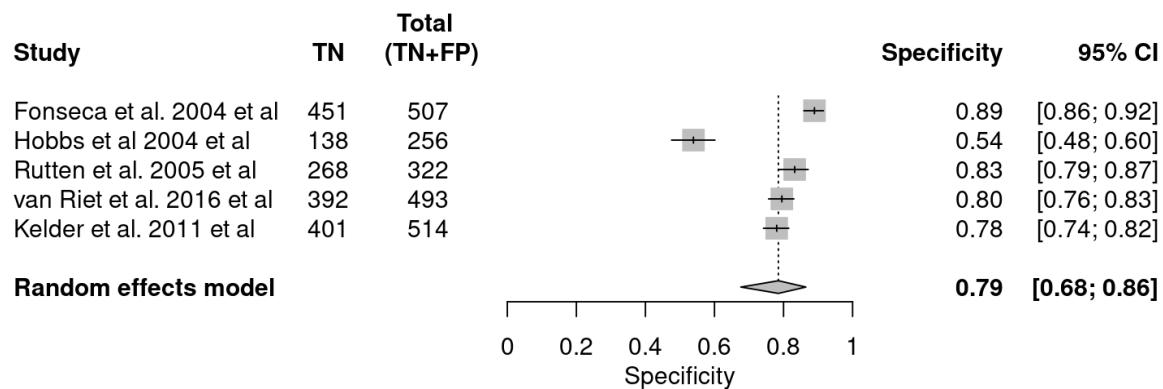
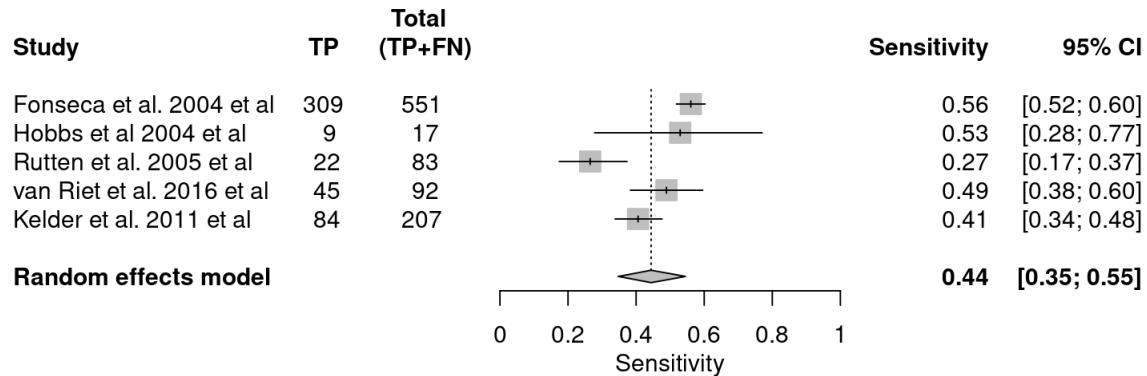


Figure 5. Peripheral Edema

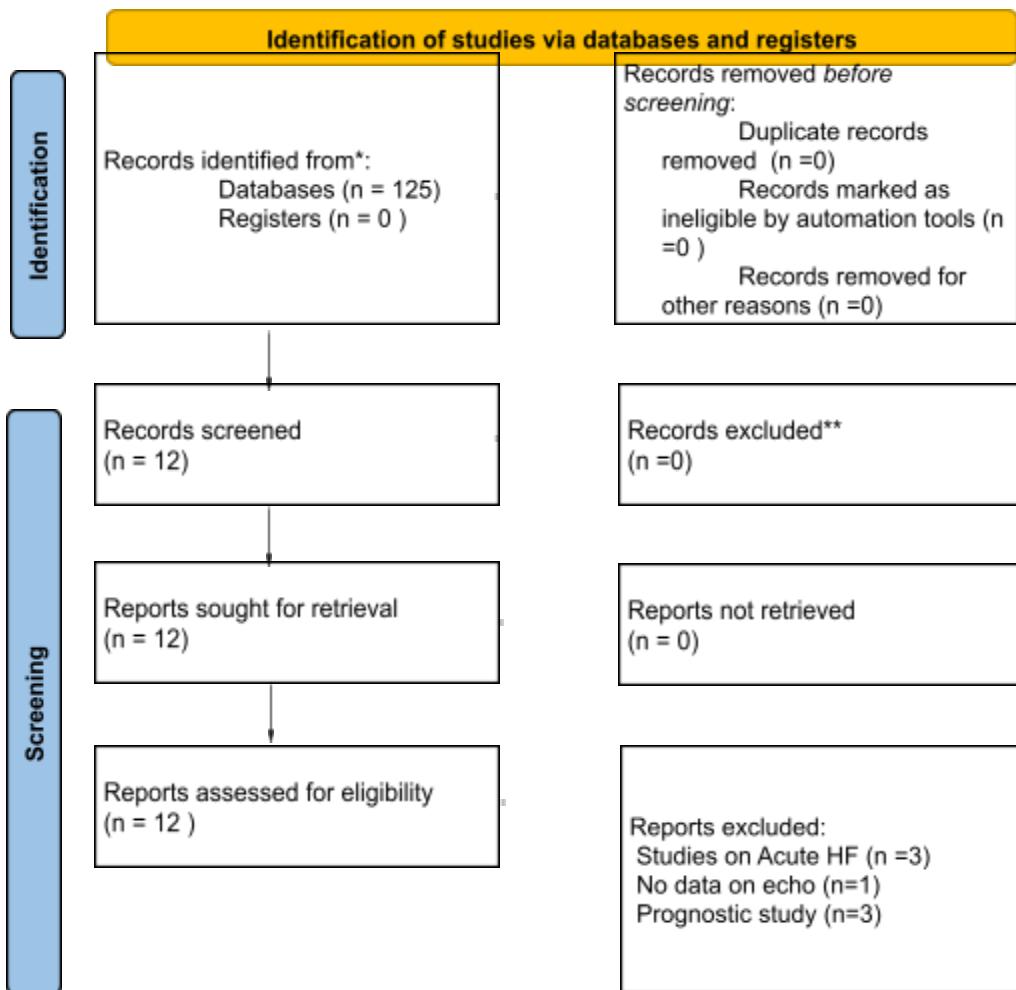


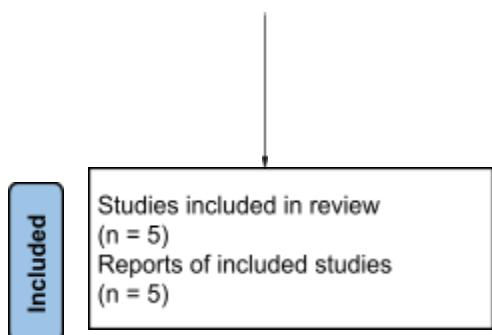
SEARCH STRATEGY and yield (31 December 2022)

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(chronic heart failure) OR (congestive heart failure)) OR (congestive heart failure[MeSH Terms])) OR (chronic heart failure[MeSH Terms])) AND (diagnostic accuracy)) OR (diagnostic accuracy[MeSH Terms])) OR (diagnosis)) AND (echocardiogram)) OR (2d echocardiogram)) OR (echocardiogram[MeS	December 31, 2022 11:00AM	117	12

Cochrane	H Terms)))) OR(echocardiography[MeSH Terms])))	December 2022 31, 12:00PM	8	0
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Appendix II: PRISMA Flow Diagram





Appendix III: Characteristics of Included Studies

Table 1. Summary of included studies

STUDY ID	SETTING	POPULATION	SAMPLE SIZE	INDEX TEST	REFERENCE STANDARD
SHARIFOV 2016 <small>(Systematic Review and meta-analysis)</small>	In Hospital	Adult patients (≥ 18 years old) with HFrEF undergoing left heart catheterization (24 studies)	24 studies, 1198	Tissue Doppler Imaging	invasive measures of LVFP via left heart catheterization.
JONES 2020 <small>(Systematic Review and meta-analysis)</small>	In Hospital	Adult patients (≥ 18 years old)	27 Studies, 2058 patients	Echocardiographic measures of LVFP	invasive measures of LVFP via left heart catheterization.
LANCELOTI 2017	In Hospital	Adult patients undergoing clinically indicated coronary angiography (159 patients)	159 patients	Echocardiographic measures of LVFP (2009 and 2016 ASE Recommendations)	invasive measures of LVFP (LVEDP)
ANDERSON 2017	In Hospital	Adult patients undergoing left or right heart catheterization	450 patients	Echocardiographic measures of LVFP	invasive measures of LVFP (PCWP)
BALANEY 2017	In Hospital	Adult patients undergoing left or right heart catheterization	90 patients	Echocardiographic measures of LVFP (2009 and 2016 ASE Recommendations)	invasive measures of LVFP (LV pre-A pressure)

- Evidence to decision survey prior to voting showed that the 100% of the CP considered this clinical question as a priority problem—accurate for easy fatigability (53%), orthopnea (61.5%), PND (61.5%), elevated JVP (46.2%), rales (69.2%), and peripheral edema (46.2%); 61.5% voted for unknown for desirable and undesirable anticipated effects. For the certainty of test accuracy, 84.6% voted for low for easy fatigability, 92.3% for moderate for orthopnea, 92.3% for moderate for PND, 69.2% moderate for elevated JVP, 84.6% moderate for rales, 76.9% moderate for peripheral edema. 46.2% voted for moderate and 46.2% voted for no included studies on overall certainty of evidence for any critical or important direct benefits, adverse effects of burden of the test. 46.2% voted that there are no included studies on the certainty of evidence of effects of the management that is guided by the test results. 46.2% voted that there are no included studies on the certainty of the link between test results and management decisions and overall certainty of the evidence of effects of the test. 53.8% voted that it is possibly important uncertainty or variability in how much people value the main outcomes. For balance between desirable and undesirable effects, 46.2% probably favors the intervention. As to resources required, 46.2% voted for large costs while 30.8% voted for moderate savings and 23.1% voted for negligible costs and savings. Majority (46.2%) voted for no included studies on the certainty of costs. 61.5% voted for no included studies on the cost- effectiveness. On the impact of testing on health equity, 30.8% voted for probably increased impact and 30.8% voted for increased. The panelists voted for acceptability to key stake holders at 61.5% and that it is feasible to implement at 92.3%. Majority of the CP (92.3%) voted for screening with strong strength of recommendation (61.5%)

Annex 4: Chest Radiography for the diagnosis of heart failure

APPENDIX I

REVMAN META-ANALYSIS FOREST PLOTS

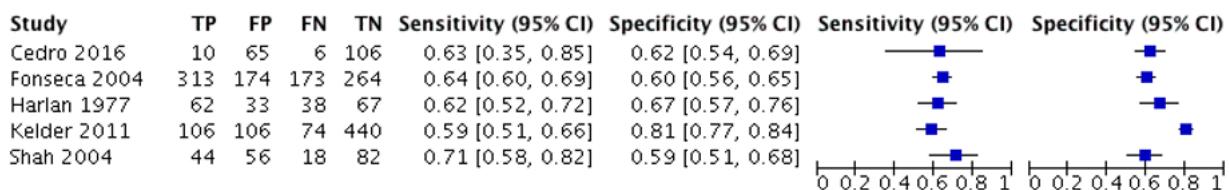


Figure 1. Forest Plot of Cardiomegaly on CXR

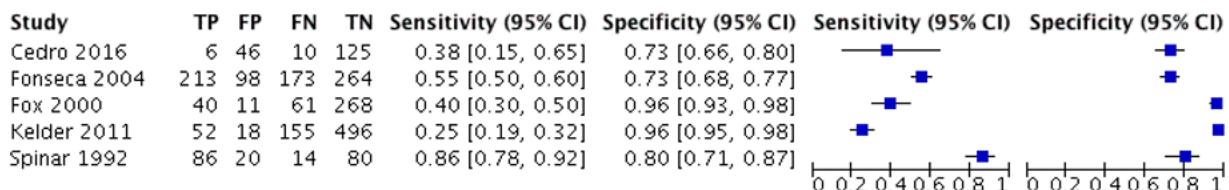


Figure 2. Forest Plot of Pulmonary Congestion on CXR

APPENDIX II

SYSTEMATIC LITERATURE SEARCH STRATEGY

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE OF SEARCH	RESULTS	
			Yield	Eligible
Medline	"Heart Failure"[MeSH Terms] AND ("Mass Chest X-Ray"[MeSH Terms] OR "Radiography"[MeSH Terms] OR "radiography, thoracic"[MeSH Terms]) AND ("sensitivity"[Title/Abstract] OR "specificity"[Title/Abstract])	January 2, 2023	147	4
	"Heart Failure"[MeSH Terms] AND ("Mass Chest X-Ray"[MeSH Terms] OR "Radiography"[MeSH Terms] OR "radiography, thoracic"[MeSH Terms]) AND ("Primary Health Care"[MeSH Terms] OR ("Ambulatory Care"[MeSH Terms] OR "outpatient clinics, hospital"[MeSH Terms]))	January 2, 2023	23	3
HERDIN Plus	All fields / Completed Studies: "chest x-ray" AND sensitivity OR specificity	January 2, 2023	35	1

	All fields / Ongoing Studies: "heart failure"		9	0
Google Scholar	AND "chest x ray" AND "primary care" AND sensitivity OR specificity "heart failure" -acute	January 2, 2023	496	3
Cochrane Database for Systematic Reviews	(heart failure*):ti,ab,kw AND ("X-ray"):ti,ab,kw (Word variations have been searched) 431	January 2, 2023	2	0

APPENDIX III

PRISMA FLOW DIAGRAM FOR THE META-ANALYSIS

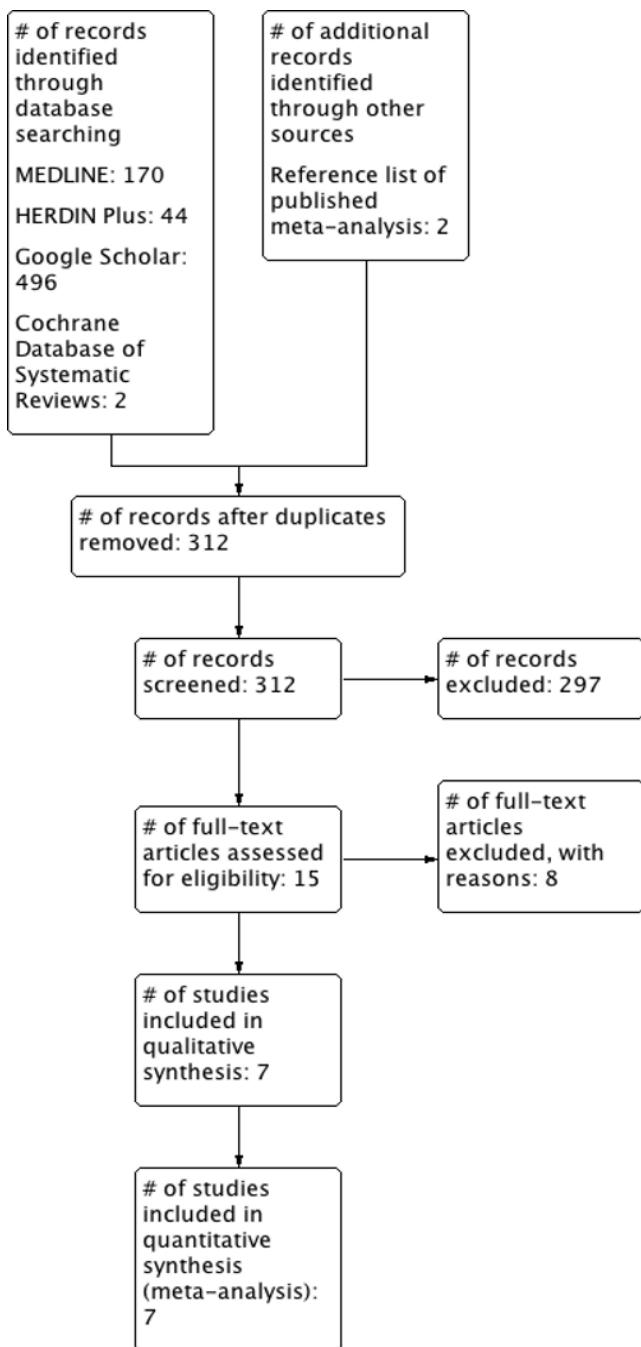


Figure 3. Study flow diagram.

APPENDIX IV

TABLE OF CHARACTERISTICS OF INCLUDED STUDIES

	Study Population	Index Test	Reference Standard	Study Design
Cedro 2016 (11)	<p>Consecutive patients referred for echocardiography.</p> <p>Presence of signs and symptoms of HF in the study sample were not specified.</p> <p>N cardiomegaly = 187</p> <p>N pulmonary congestion = 187</p>	<p>Cardiomegaly = CT ratio >0.5</p> <p>Pulmonary congestion = pulmonary blood flow redistribution, equalization, cephalization, interstitial edema, or alveolar edema</p> <p>CXR views - postero-anterior and lateral</p>	echocardiographic LV EF <0.45	<p>Analysis: Cross-sectional observational</p> <p>Data collection: Prospective</p>
Fonseca 2004 (12)	<p>Randomly selected general practice patients with symptoms and/or signs of HF, or taking diuretics for HF</p> <p>N cardiomegaly = 924</p> <p>N pulmonary congestion = 748</p>	<p>Cardiomegaly = Cardiomegaly and CT ratio >0.5</p> <p>Pulmonary congestion = pulmonary vessel cephalisation or lung interstitial oedema or alveolar pulmonary oedema</p> <p>CXR view – postero-anterior upright</p>	clinical HF diagnosis (clinical syndrome and/or anti-congestive medical therapy for HF, together with echocardiographic evidence of cardiac dysfunction at rest)	<p>Analysis: Cross-sectional observational</p> <p>Data collection: Prospective</p>

Fox 2000 (16)	Consecutive patients with suspected new onset HF referred to a rapid access heart failure clinic by their GP, or by the ED (did not require admission) N = 380	Pulmonary congestion – Kerley B lines, interstitial or alveolar shadowing on chest X-ray CXR view – postero-anterior	clinical HF diagnosis by MD (symptoms with clinical signs of fluid retention (pulmonary or peripheral) in the presence of abnormal cardiac structure or function) or beneficial response to HF therapy	Analysis: Cross-sectional observational Data collection: Prospective
Harlan 1977 (13)	Patients with at least one >70% arteriosclerotic coronary artery narrowing on elective coronary angiography. Most patients had signs and symptoms of heart failure. N = N/A	Cardiomegaly = CT ratio >0.48 CXR views - postero-anterior and lateral	LV end diastolic pressure > 15 mm Hg or angiographic EF ≤40%	Analysis: Cross-sectional observational Data collection: Prospective
Kelder 2011 (14)	Consecutive patients with symptoms and signs of HF that were referred to a rapid access outpatient clinic N cardiomegaly = 726 N pulmonary vascular redistribution = 721	Cardiomegaly = CT ratio >0.5 Pulmonary congestion = pulmonary vascular redistribution CXR view – not specified	clinical HF diagnosis by MD (confirmation of cardiac dysfunction with signs and symptoms suggestive of HF, or response to HF treatment)	Analysis: Cross-sectional observational Data collection: Prospective

Shah 2004 (15)	Consecutive patients with symptoms and signs of HF or with factors associated with increased risk of developing HF/ asymptomatic LV systolic dysfunction, who were referred to an open access HF clinic N = N/A	Cardiomegaly = CT ratio >0.5 CXR view – postero-anterior	echocardiographic LV EF <50%	Analysis: Cross-sectional observational Data collection: Prospective
Spinar 1992 (17)	Patients with chronic congestive HF N = N/A	Pulmonary congestion = definition not available CXR view – not specified	invasive pulmonary artery wedge pressure >18 mmHg	Cross-sectional observational

APPENDIX V

QUADAS-2 TOOL RISK OF BIAS SUMMARY

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Cedro 2016	+	+	+	+	?	+	+
Fonseca 2004	+	+	+	+	+	+	+
Fox 2000	+	?	+	+	+	+	+
Harlan 1977	+	?	+	+	+	+	+
Kelder 2011	+	+	+	+	+	+	+
Shah 2004	+	+	+	?	+	+	+
Spinar 1992	?	?	+	+	+	+	+

- High
 ? Unclear
 + Low

Figure 4. Risk of bias and applicability concerns summary: review author's judgements about each domain for each included study

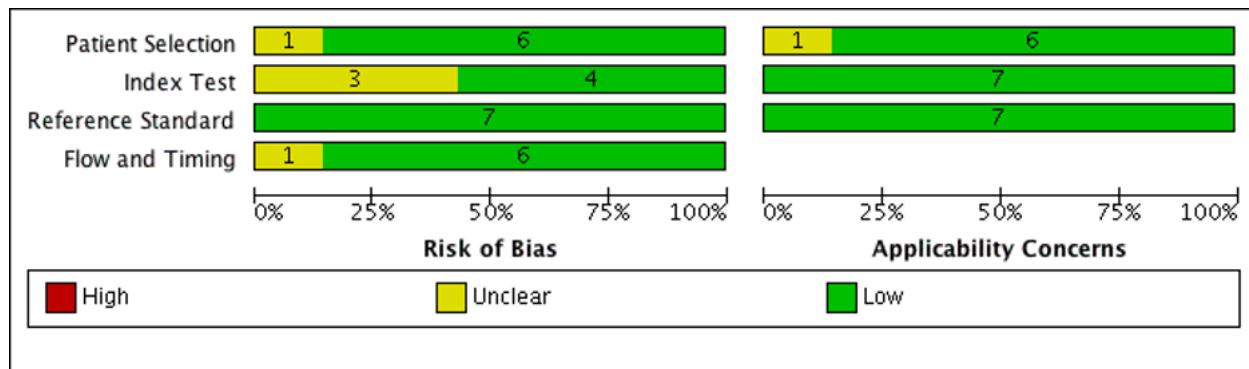


Figure 5. Risk of bias and applicability concerns graph: review author's judgements about each domain presented as percentages across included studies

APPENDIX VI

QUADAS-2 TOOL RISK OF BIAS ASSESSMENTS FOR INCLUDED STUDIES

1. Cardiomegaly

	Cedro 2016	Fonseca 2004	Harlan 1977	Kelder 2011	Shah 2004
1. Patient Selection					
A. Risk of Bias					
Patient Sampling	Prospective consecutive patient sampling.	Random patient sampling from a prospectively collected study database (EPICA study).	Prospective consecutive patient sampling.	Prospective consecutive patient sampling.	Prospective consecutive patient sampling.
Was a consecutive or random sample of patients enrolled?	Yes	Yes	Yes	Yes	Yes
Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	Low risk	Low risk	Low risk	Low risk	Low risk
B. Concerns regarding applicability					

Patient characteristics and setting	Adults referred for echocardiography. Presence of signs and symptoms of heart failure in the study patient sample were not specified.	General practice patients with symptoms and/or signs of heart failure, or taking diuretics for heart failure, who were enrolled in the EPICA study, an epidemiological study of the prevalence of heart failure in Portugal.	Patients with at least one >70% arteriosclerotic coronary artery narrowing on elective coronary angiography. Most patients had signs and symptoms of heart failure.	Patients presenting with symptoms and signs suggestive of heart failure (typically dyspnea, fatigue, signs of fluid retention) that were referred to a rapid access outpatient clinic by primary care physicians.	Patients with symptoms and signs of heart failure or with factors associated with increased risk of developing heart failure/asymptomatic left ventricular systolic dysfunction, who were referred to an open access heart failure clinic by their general practitioner.
Are there concerns that the included patients and setting do not match the review question?	Unclear concern	Low concern	Low concern	Low concern	Low concern
2. Index Test					
A. Risk of Bias					
Index test	Chest x-ray postero-anterior and lateral views. Independently read by 3 radiologists who were unaware of the clinical data and 2D echocardiogram results.	Chest x-ray postero-anterior view. Interpretation by radiology specialists who were unaware of the specific clinical findings of the patients.	Chest x-ray postero-anterior and lateral views. Interpreted by physician observers.	Chest x-ray, view not specified. Interpreted by the local specialist.	Chest x-ray postero-anterior view. Interpreter not specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Unclear	Yes	Unclear
If a threshold was used, was it pre-specified?	Yes	Yes	Yes	Yes	Yes

Could the conduct or interpretation of the index test have introduced bias?	Low risk	Low risk	Low risk	Low risk	Low risk
B. Concerns regarding applicability					
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern	Low concern	Low concern	Low concern	Low concern
3. Reference Standard					
A. Risk of Bias					
Target condition and reference standard(s)	Left ventricular dysfunction defined as a transthoracic echocardiographic LV EF <0.45. Left ventricular ejection fraction (LVEF) results taken from the official report (M-mode and modified Simpson's methods).	Clinical heart failure diagnosis by attending general practitioner based on Guidelines on Diagnosis of Heart Failure of the European Society of Cardiology (clinical syndrome and/or anti-congestive medical therapy for HF, together with echocardiographic evidence of cardiac dysfunction at rest).	Left ventricular end diastolic pressure > 15 mm Hg or angiographic left ventricular ejection fraction ≤40% on invasive hemodynamic study.	Clinical heart failure diagnosis by a multidisciplinary consensus panel based on the Guidelines on Diagnosis of Heart Failure of the European Society of Cardiology (confirmation of cardiac dysfunction with signs and symptoms suggestive of heart failure, or response to heart failure treatment).	Left ventricular dysfunction defined as a transthoracic echocardiographic left ventricular ejection fraction <50% (based on fractional shortening or Simpson's rule; or eyeball estimation for suboptimal echocardiographic views).
Is the reference standards likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the	Yes	Unclear	Yes	Unclear	Yes

results of the index tests?					
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	Low risk	Low risk	Low risk	Low risk
B. Concerns regarding applicability					
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern	Low concern	Low concern	Low concern	Low concern
4. Flow and Timing					
A. Risk of Bias					
Flow and timing	All recruited patients underwent chest radiograph and 2D echocardiogram within the same day or at most 24 hours apart.	All recruited patients underwent chest radiograph, 2D echocardiogram, and clinical assessment by the attending general practitioner. Timing not specified.	All recruited patients underwent chest radiograph and invasive hemodynamic study during the same admission for elective coronary angiography.	All recruited patients underwent chest radiograph, 2D echocardiogram, and clinical assessment by the consensus panel. Timing not specified.	All recruited patients underwent chest radiograph and 2D echocardiogram. Timing not specified.
Was there an appropriate interval between index test and reference standard?	Yes	Unclear	Yes	Unclear	Unclear
Did all patients receive the same reference standard?	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes	Yes	Yes	Yes	Yes

Could the patient flow have introduced bias?	Low risk	Low risk	Low risk	Low risk	Unclear risk
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2. Pulmonary Congestion

	Cedro 2016	Fonseca 2004	Fox 2000	Kelder 2011	Spinar 1992
1. Patient Selection					
A. Risk of Bias					
Patient Sampling	Prospective consecutive patient sampling	Random patient sampling from a prospectively collected study database (EPICA study)	Prospective consecutive patient sampling	Prospective consecutive patient sampling	Not mentioned
Was a consecutive or random sample of patients enrolled?	Yes	Yes	Yes	Yes	Unclear
Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes	Yes	Yes	Yes	Unclear
Could the selection of patients have introduced bias?	Low risk	Low risk	Low risk	Low risk	Unclear risk
B. Concerns regarding applicability					

Patient characteristics and setting	Adults referred for echocardiography. Presence of signs and symptoms of heart failure in the study patient sample were not specified	General practice patients with symptoms and/or signs of heart failure, or taking diuretics for heart failure, who were enrolled in the EPICA study, an epidemiological study of the prevalence of heart failure in Portugal.	Suspected new onset heart failure patients referred to a rapid access heart failure clinic by their general practitioner, or by the Emergency Department with the same diagnosis but who did not require hospital admission.	Patients presenting with symptoms and signs suggestive of heart failure (typically dyspnea, fatigue, signs of fluid retention) that were referred to a rapid access outpatient clinic by primary care physicians.	Patients with chronic congestive heart failure.
Are there concerns that the included patients and setting do not match the review question?	Low concern	Low concern	Low concern	Low concern	Low concern
2. Index Test					
A. Risk of Bias					
Index test	Chest x-ray postero-anterior and lateral views. Independently read by 3 radiologists who were unaware of the clinical data and 2D echocardiogram results.	Chest x-ray postero-anterior view. Interpretation by radiology specialists who were unaware of the specific clinical findings of the patients.	Chest x-ray postero-anterior view. Interpreter not specified.	Chest x-ray, view not specified. Interpreted by the local specialist.	Chest x-ray, view not specified. Interpreter not specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Unclear	Yes	Unclear
If a threshold was used, was it pre-specified?	Yes	Yes	Yes	Yes	Yes

Could the conduct or interpretation of the index test have introduced bias?	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
B. Concerns regarding applicability					
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern	Low concern	Low concern	Low concern	Low concern
3. Reference Standard					
A. Risk of Bias					
Target condition and reference standard(s)	Left ventricular dysfunction defined as a transthoracic echocardiographic LV EF <0.45. Left ventricular ejection fraction (LVEF) results taken from the official report (M-mode and modified Simpson's methods).	Clinical heart failure diagnosis by attending general practitioner based on Guidelines on Diagnosis of Heart Failure of the European Society of Cardiology (clinical syndrome and/or anti-congestive medical therapy for HF, together with echocardiographic evidence of cardiac dysfunction at rest).	Clinical HF diagnosis by rapid access heart failure clinic cardiology registrar based on Guidelines on Diagnosis of Heart Failure of the European Society of Cardiology (symptoms with clinical signs of fluid retention (pulmonary or peripheral) in the presence of abnormal cardiac structure or function), or a beneficial response to therapy for heart failure.	Clinical heart failure diagnosis by a multidisciplinary consensus panel based on the Guidelines on Diagnosis of Heart Failure of the European Society of Cardiology (confirmation of cardiac dysfunction with signs and symptoms suggestive of heart failure, or response to heart failure treatment).	Invasive pulmonary artery wedge pressure >18 mmHg on invasive hemodynamic study.
Is the reference standards likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	Unclear	Unclear	Unclear	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	Low risk	Low risk	Low risk	Low risk
B. Concerns regarding applicability					
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern	Low concern	Low concern	Low concern	Low concern
4. Flow and Timing					
A. Risk of Bias					
Flow and timing	All recruited patients underwent chest radiograph and 2D echocardiogram within the same day or at most 24 hours apart.	All recruited patients underwent chest radiograph, 2D echocardiogram, and clinical assessment by the attending general practitioner. Timing not specified.	All recruited patients underwent chest radiograph, 2D echocardiogram, and clinical assessment by the cardiology registrar on the same day.	All recruited patients underwent chest radiograph, 2D echocardiogram and clinical assessment by the consensus panel. Timing not specified.	All recruited patients underwent chest radiograph and invasive hemodynamic study. Timing not specified.
Was there an appropriate interval between index test and reference standard?	Yes	Unclear	Yes	Unclear	Unclear
Did all patients receive the same reference standard?	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes	Yes	Yes	Yes	Yes

Could the patient flow have introduced bias?	Low risk				
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3. Cardiomegaly OR Pulmonary Congestion

	Landray et al, 2000
1. Patient Selection	
A. Risk of Bias	
Patient Sampling	Prospective patient sampling.
Was a consecutive or random sample of patients enrolled?	Not mentioned.
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk
B. Concerns regarding applicability	
Patient characteristics and setting	General practice patients suspected of heart failure.
Are there concerns that the included patients and setting do not match the review question?	Low concern
2. Index Test	
A. Risk of Bias	
Index test	Chest x-ray, view not specified. Interpreter not specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

3. Reference Standard	
A. Risk of Bias	
Target condition and reference standard(s)	Left ventricular systolic dysfunction as indicated by a brain natriuretic peptide immunoradiometric assay level > 17.9 pg/ml.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
4. Flow and Timing	
A. Risk of Bias	
Flow and timing	All recruited patients underwent chest radiograph and brain natriuretic peptide immunoradiometric assay. Timing not specified.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

APPENDIX VII

GRADEPRO Summary of Findings Tables

1. Cardiomegaly on CXR

Summary of Findings	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 1.6%*	pre-test probability of 29%**	
True positives (patients with heart failure)	5 studies	cross-section-al (cohort type accuracy study)	not serious	not serious	not serious	not serious - some included studies only reported computed sensitivity and specificity percentages	9 to 11	171 to 206	HIGH Although imprecision in reporting of study results in 2 included studies was a concern, this was unlikely to lower the confidence in the accuracy of the test.
False negatives (patients incorrectly classified as not having heart failure)							5 to 7	84 to 119	
True negatives (patients without heart failure)	5 studies	cross-section-al (cohort type accuracy study)	not serious	not serious	not serious	not serious - some included studies only reported computed sensitivity and specificity percentages	581 to 797	419 to 575	HIGH Although imprecision in reporting of study results in 2 included studies was a concern, this was unlikely to lower the confidence in the accuracy of the test.
False positives (patients incorrectly classified as having heart failure)							187 to 403	135 to 291	

* The pre-test probability of 1.6% is taken from the reported prevalence of hospitalization due to CHF among adult patients aged 19 years and above in the Philippines last 2014. (34)

** The pre-test probability of 29% is taken from the post-test probability of heart failure in the presence of dyspnea, paroxysmal nocturnal dyspnea, and high jugular venous pressure (from HF CPG Question #1).

2. Pulmonary Congestion on CXR

Summary of Findings	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	pre-test probability of 1.6%*	pre-test probability of 29%**	
True positives (patients with heart failure)	5 studies	cross-sectional (cohort type accuracy study)	not serious	not serious	serious - significant visual heterogeneity in the forest plot	not serious	4 to 14	73 to 249	LOW There is heterogeneity among the study methods and significant visual heterogeneity in the forest plot.
False negatives (patients incorrectly classified as not having heart failure)							2 to 12	41 to 217	
True negatives (patients without heart failure)	5 studies	cross-sectional (cohort type accuracy study)	not serious	not serious	serious - significant visual heterogeneity in the forest plot	not serious	718 to 945	518 to 682	LOW There is heterogeneity among the study methods and significant visual heterogeneity in the forest plot.
False positives (patients incorrectly classified as having heart failure)							39 to 266	28 to 192	

* The pre-test probability of 1.6% is taken from the reported prevalence of hospitalization due to CHF among adult patients aged 19 years and above in the Philippines last 2014. (34)

** The pre-test probability of 29% is taken from the post-test probability of heart failure in the presence of dyspnea, paroxysmal nocturnal dyspnea, and high jugular venous pressure (from HF CPG Question #1).

- The evidence to decision survey prior to voting showed that the majority of the CP considered it a priority problem and CXR is accurate for cardiomegaly and pulmonary congestion. There were moderately desirable effects; undesirable effects were unknown. There was a high certainty of evidence test accuracy for cardiomegaly and a low certainty of test accuracy for pulmonary congestion. There were no studies on the overall certainty of effects, certainty of evidence test, management and test result/management effects. Probably favors intervention and comparison for balance of effects. There is possibly no important uncertainty/variability in values. There are moderate costs and negligible cost and savings. There are no studies on the certainty of evidence of required resources. Favors intervention for cost effectiveness. The use of chest radiographs are acceptable and feasible, with probably increased equity. The majority of the CP (91.7%) voted to recommend chest X-ray for diagnostic testing with a strong recommendation (91.7%).

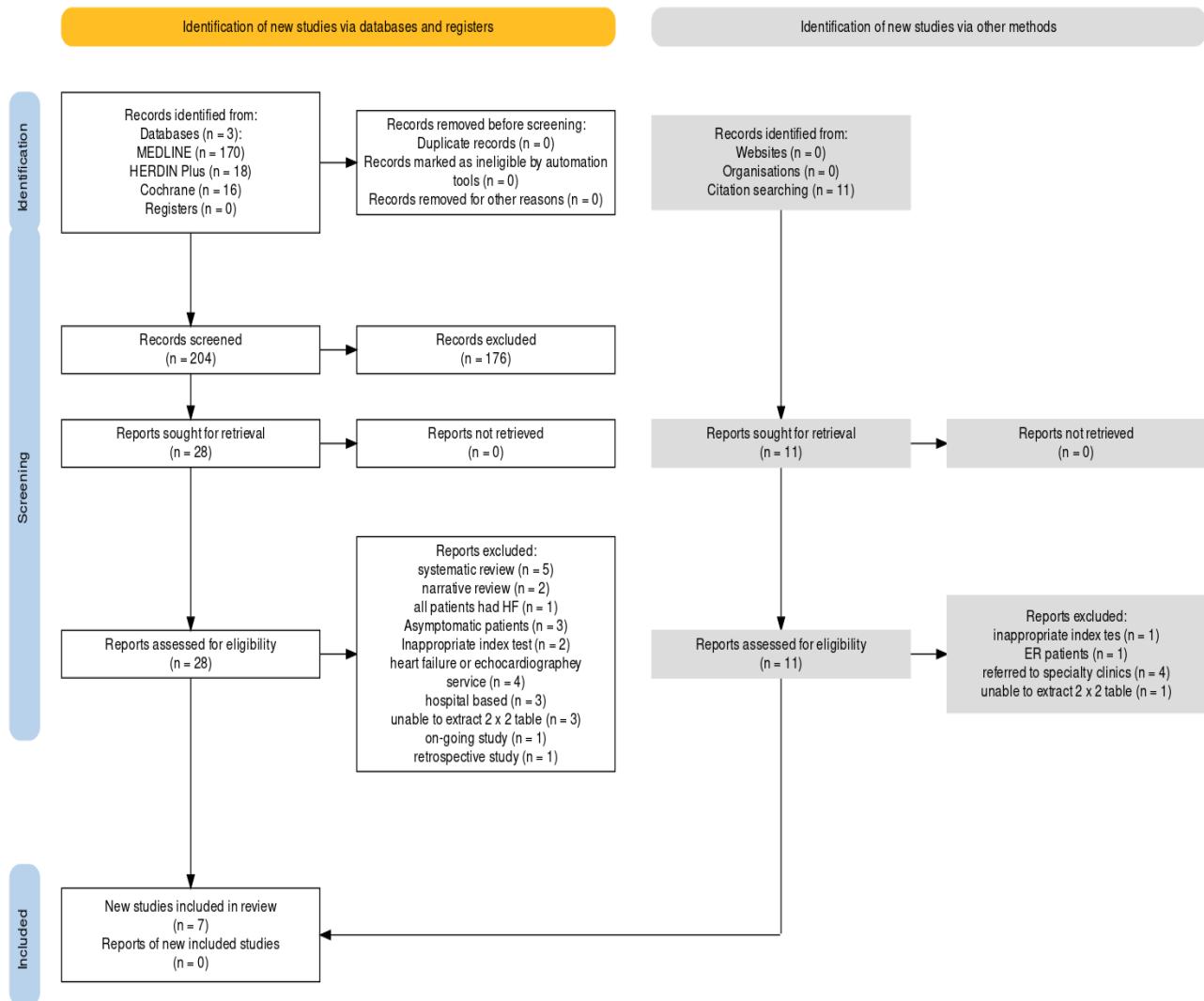
Annex 5: 12-lead ECG for diagnosis of heart failure

APPENDIX I LITERATURE SEARCH STRATEGY

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(((((heart failure) AND (diagnosis)) AND (electrocardiogram)) AND (sensitivity)) OR (((heart failure) AND (diagnosis)) AND (electrocardiogram)) AND (specificity))) AND (primary care)) OR (((((heart failure) AND (diagnosis)) AND (electrocardiogram)) AND (sensitivity)) OR (((heart failure) AND (diagnosis)) AND (electrocardiogram)) AND (specificity))) AND (general practice))	March 23, 2023	170	3
HERDIN Plus	Electrocardiogram and heart failure	April 19, 2023	18	0
Cochrane Database for Systematic Reviews	Electrocardiogram	April 19, 2023	16	0
Citation search	Hand search references	April 1, 2023	11	4

APPENDIX II

PRISMA [30]

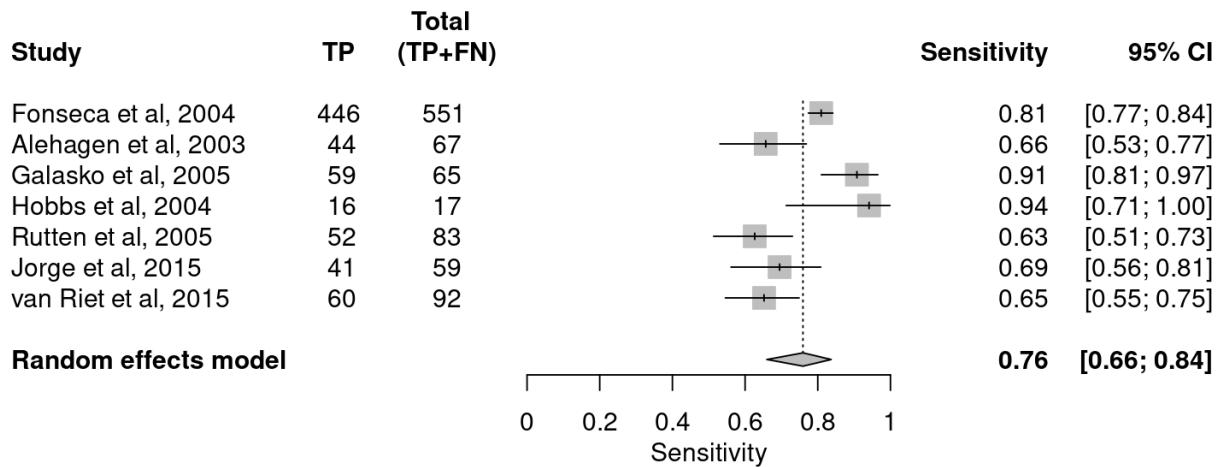


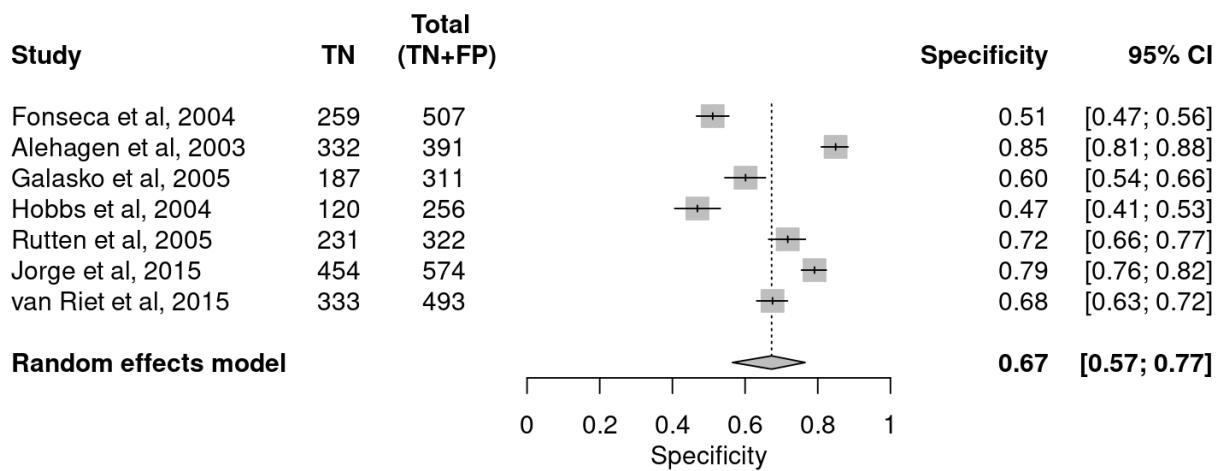
APPENDIX III
TABLE OF CHARACTERISTICS OF INCLUDED STUDIES

Study ID (study design)	Study Population (setting)	Index Test (reader)	Sample Size	Reference Standard
Fonseca et al., 2004 (cross-sectional study)	Randomly selected patients (general practice setting)	12L ECG - Abnormal rhythm, atrial abnormalities, conduction disturbances, presence of abnormal Q waves, poor R-wave progression in precordial leads, LVH, abnormal ST-segment T-wave changes (read by cardiologist)	1058	ESC criteria (one clinician)
Alehagen et al, 2003 (cross-sectional study)	Patients presenting with symptoms and signs of heart failure with no previous diagnosis of HF (primary health care setting)	ECG not in sinus rhythm or atrial fibrillation or sign of past ischaemic myocardial damage (read by cardiologist)	415	LVEF < 40% or atrial fibrillation and symptoms of heart failure
Galasko et al, 2005 (cross-sectional study)	Patients with symptoms of heart failure or on loop diuretics (community practice)	Abnormal ECG (reader not reported)	376	LVEF < 40% or atrial fibrillation and symptoms of heart failure
Hobbs et al, 2004 (cross-sectional study)	Patients presenting with symptoms and signs of heart failure (community setting)	Abnormal ECG (read by cardiologist)	273	ESC criteria (panel of three clinicians in equivocal cases)
Rutten et al, 2005 (cross-sectional study)	patients with stable chronic obstructive pulmonary disease (COPD) and no previous Dx of HF (primary care setting)	Abnormal ECG (Suggesting diagnosis of (previous) myocardial infarction (abnormal Q waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T wave abnormalities, and sinus tachycardia (read by cardiologist)	405	consensus diagnosis
Jorge et al, 2015 (cross-sectional study)	randomly selected patients (primary care program)	LVH, LAE, RBBB, LBBB by ECG (reader not reported)	633	ESC criteria for HF

Study ID (study design)	Study Population (setting)	Index Test (reader)	Sample Size	Reference Standard
van Riet et al (cross-sectional study)	patients with non-acute shortness of breath and no previous diagnosis of heart failure (primary care practice)	Abnormal ECG -(‡Atrial fibrillation, sinus tachycardia (heart rate >100 bpm), left and right bundle branch block (complete or incomplete), left anterior and posterior fascicular block, left ventricular hypertrophy, Q-waves suspected for previous myocardial infarction, P-wave abnormalities compatible with left atrial enlargement or P-pulmonale, or any ST segment/T-wave abnormalities. (reader not reported)	585	ESC criteria for HF

APPENDIX IV Forest Plot





APPENDIX V

GRADE pro EVIDENCE PROFILE [31]

Question: Should 12L ECG be used to diagnose chronic heart failure in primary care?

Sensitivity	0.76 (95% CI: 0.66 to 0.83)	Prevalences	1.6%	29%
Specificity	0.67 (95% CI: 0.56 to 0.77)			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.6%	pre-test probability of 29%	
True positives (patients with chronic heart failure)	7 studies 934 patients	cross-sectional (cohort type accuracy study)	very serious ^a	serious ^b	serious ^c	serious ^c	none	12 (11 to 13)	219 (191 to 241)	 Very low
								4 (3 to 5)	71 (49 to 99)	

heart failure)										
True negatives (patients without chronic heart failure)	7 studies 2854 patients	cross-sectional (cohort type accuracy study)	very serious ^a	serious ^b	serious ^c	serious ^c	none	661 (555 to 753)	477 (400 to 543)	 Very low
False positives (patients incorrectly classified as having chronic heart failure)								323 (231 to 429)	233 (167 to 310)	

Explanations

- a. Incorporation bias
- b. ECG reading done by cardiologists or by automatic reading
- c. studies differed widely in the criteria for abnormal ECG

APPENDIX VI OTHER INFORMATION

Estimated sensitivity and specificity of ECG variables for the diagnosis of heart failure in the primary care setting [4]

Characteristics	Sensitivity	Specificity
	%	%
Abnormal ECG	81.14	51.01
Atrial flutter	3.66	99.31
Abnormal atrial rhythm, other	1.58	99.07
Atrial fibrillation	13.45	95.66
Right atrial enlargement	10.14	98.82
Left atrial enlargement	17.88	91.97
Left ventricular hypertrophy	29.77	89.24

Left ventricular strain	26.13	89.18
Abnormal Q wave	3.4	98.11
Poor R wave progression	9.49	96.01
Ischemic ST-T changes	15.21	93.11
Nonspecific ST-T abnormalities	41.83	74.52
2nd degree AV block, Mobitz I	0.68	99.87
Left bundle branch block	6.52	98.1
1st degree AV block	9.85	97.18
IV conduction defect	10.96	95.97
Left anterior fascicular block	8.79	94.22
Right bundle branch block	6.69	92.82

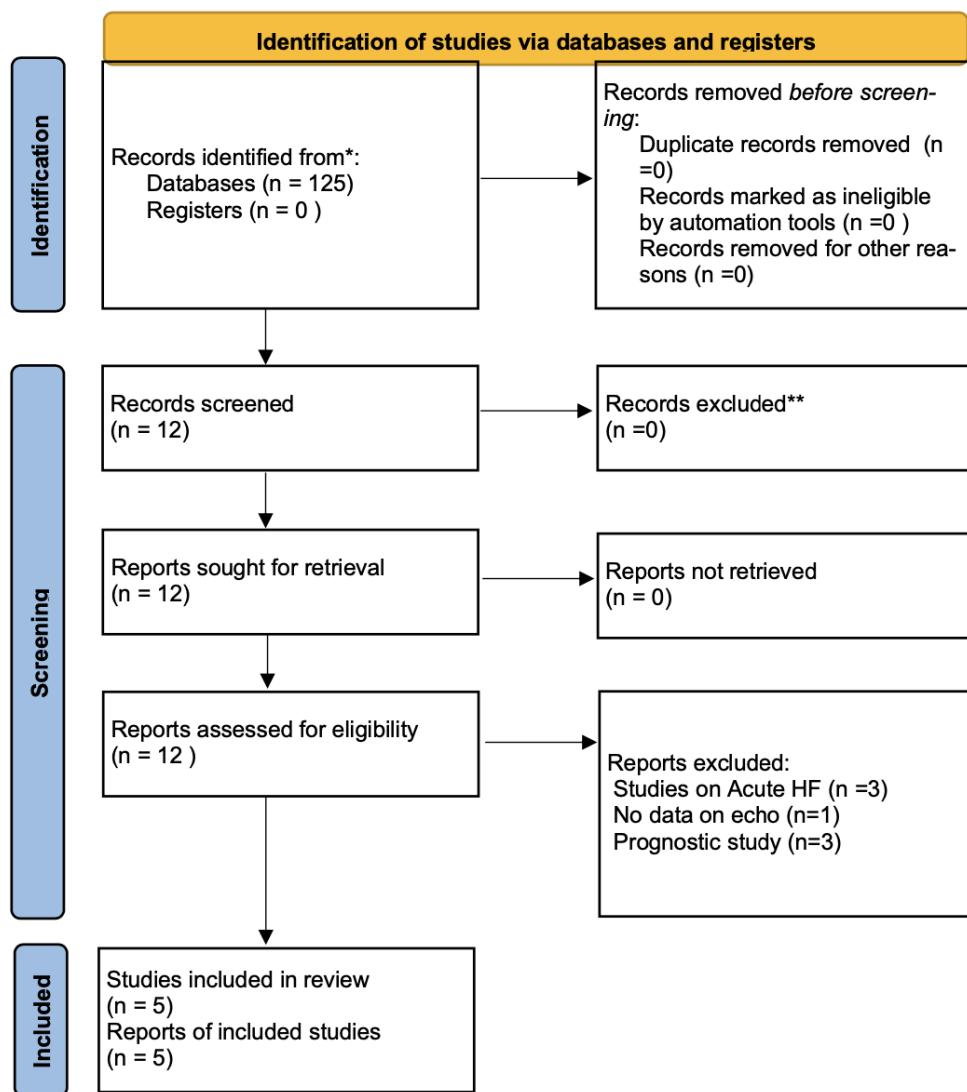
- The Evidence to Decision survey prior to voting showed that the majority of the CP considered it as a priority problem. The 12L ECG is accurate, with moderate desirable effects and small undesirable effects. The 12L ECG has high certainty of evidence test accuracy for cardiomegaly and very low certainty of test accuracy. There were no studies on overall certainty of effects, certainty of evidence test, and test result/management effects. There is low certainty of evidence of management. There is a split vote between “probably favors intervention” and “favors intervention” comparison for balance of effects. There is also a split vote on “possibly important uncertainty/variability” and “probably no important uncertainty/variability in values.” There is negligible cost and savings. There were no studies on the certainty of evidence of required resources and cost-effectiveness. There was also a divided vote between “probably no impact” and “probably increased equity.” Majority of the CP voted that it is acceptable and feasible. Sixty percent (60%) voted for diagnostic testing with weak strength of recommendation (60%)

Annex 6: Echocardiogram for the diagnosis of heart failure

Appendix I: SEARCH STRATEGY and yield (31 December 2022)

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	((((((((chronic heart failure) OR (congestive heart failure)) OR (congestive heart failure[MeSH Terms])) OR (chronic heart failure[MeSH Terms]))) AND (diagnostic accuracy)) OR (diagnostic accuracy[MeSH Terms])) OR (diagnosis)) AND (echocardiogram)) OR (2d echocardiogram)) (echocardiogram[MeSH Terms])) OR(echocardiography[MeSH Terms]))	December 31, 2022 11:00AM	11 7	12
Cochrane		December 31, 2022 12:00PM	8	0

Appendix II: PRISMA Flow Diagram



Appendix III: Characteristics of Included Studies

Table 1. Summary of included studies

STUDY ID	SETTING	POPULATION	SAMPLE SIZE	INDEX TEST	REFERENCE STANDARD
SHARIFOV 2016 <small>(Systematic Review and meta-analysis)</small>	In Hospital	Adult patients (≥ 18 years old) with HFrEF undergoing left heart catheterization (24 studies)	24 studies, 1198	Tissue Doppler Imaging	invasive measures of LVFP via left heart catheterization.
JONES 2020 <small>(Systematic Review and meta-analysis)</small>	In Hospital	Adult patients (≥ 18 years old)	27 Studies, 2058 patients	Echocardiographic measures of LVFP	invasive measures of LVFP via left heart catheterization.
LANCELOTI 2017	In Hospital	Adult patients undergoing indicated coronary angiography (159 patients)	159 patients	Echocardiographic measures of LVFP (2009 and 2016 ASE Recommendations)	invasive measures of LVFP (LVEDP)
ANDERSON 2017	In Hospital	Adult patients undergoing left or right heart catheterization	450 patients	Echocardiographic measures of LVFP	invasive measures of LVFP (PCWP)
BALANEY 2017	In Hospital	Adult patients undergoing left or right heart catheterization	90 patients	Echocardiographic measures of LVFP (2009 and 2016 ASE Recommendations)	invasive measures of LVFP (LV pre-A pressure)

Appendix IV: GRADE Evidence Profile table

A. Author(s): De Leon, Karen

Question: Should echocardiography be used to diagnose chronic heart failure in patients with signs and symptoms of HF?

Setting: in-hospital

Bibliography:

1. A. Andersen , O et al. Estimating Left Ventricular Filling Pressure by Echocardiography. JACC VOL. 69, NO. 15, 2017
2. P. Lancellotti et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. European Heart Journal - Cardiovascular Imaging (2017) 18, 961–968

3. Balaney B, Medvedovsky D, Mediratta A, Singh A, Ciszek B, Kruse E, Shah AP, Addetia K, Lang RM, Mor-Avi V. Invasive Validation of the Echocardiographic Assessment of Left Ventricular Filling Pressures Using the 2016 Diastolic Guidelines: Head-to-Head Comparison with the 2009 Guidelines. *J Am Soc Echocardiogr.* 2018 Jan;31(1):79-88. doi: 10.1016/j.echo.2017.09.002. Epub 2017 Oct 27. PMID: 29111121; PMCID: PMC5756671.

B. A. Author(s): De Leon, Karen

Question: Should echocardiography be used to diagnose heart failure with reduced Ejection Fraction in patients with signs and symptoms of HF?

Setting: in-hospital

Bibliography:

1. P. Lancellotti et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. *European Heart Journal - Cardiovascular Imaging* (2017) 18, 961–968

2. Balaney B, Medvedovsky D, Mediratta A, Singh A, Ciszek B, Kruse E, Shah AP, Addetia K, Lang RM, Mor-Avi V. Invasive Validation of the Echocardiographic Assessment of Left Ventricular Filling Pressures Using the 2016 Diastolic Guidelines: Head-to-Head Comparison with the 2009 Guidelines. *J Am Soc Echocardiogr.* 2018 Jan;31(1):79-88. doi: 10.1016/j.echo.2017.09.002. Epub 2017 Oct 27. PMID: 29111121; PMCID: PMC5756671.

B. Author(s): Sharifov et al.

Question: Should echocardiography be used to diagnose chronic heart failure

Setting: in-hospital

Question: Should E/e lateral in the diagnosis of HF be used to diagnose diagnosing Heart Failure in adult patients?

Sensitivity	0.30 (95% CI: 0.09 to 0.48)	Prevalences	1.6%		
Specificity	0.92 (95% CI: 0.82 to 1.00)				

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with diagnosing Heart Failure)	6 studies 142 patients	cohort & case-control type studies	not serious	very serious ^a	not serious	serious ^b	none	5 (1 to 8)	 Very low
False negatives (patients incorrectly classified as not having diagnosing Heart Failure)								11 (8 to 15)	
True negatives (patients without diagnosing Heart Failure)	6 studies 154 patients							905 (807 to 984)	-
False positives (patients incorrectly classified as having diagnosing Heart Failure)								79 (0 to 177)	

Explanations

a. studies only included patients with HFP EF

b. significant heterogeneity

Bibliography: Sharifov OF et al. Diagnostic Accuracy of Tissue Doppler Index E/e' for Evaluating Left Ventricular Filling Pressure and Diastolic Dysfunction/Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016 Jan 25;5(1):e002530

Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016 Jan 25;5(1):e002530.

Question: Should E/e septal in the diagnosis of HF be used to diagnose diagnosing Heart Failure in adult patients?

Sensitivity	0.24 (95% CI: 0.06 to 0.46)	Prevalences	0%		
Specificity	0.98 (95% CI: 0.92 to 1.00)				

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with diagnosing Heart Failure)	4 studies 95 patients	cohort & case-control type studies	not serious	very serious ^a	not serious	serious ^b	none	0 (0 to 0)	 Very low
False negatives (patients incorrectly classified as not having diagnosing Heart Failure)								0 (0 to 0)	
True negatives (patients without diagnosing Heart Failure)	4 studies 106 patients							980 (920 to 1000)	-
False positives (patients incorrectly classified as having diagnosing Heart Failure)								20 (0 to 80)	

Explanations

a. studies only included patients with HFP EF

b. significant heterogeneity

Question: Should E/e mean in the diagnosis of HF be used to diagnose diagnosing Heart Failure in adult patients?

Sensitivity	0.37 (95% CI: 0.13 to 0.61)	Prevalences	1.6%	
Specificity	0.91 (95% CI: 0.80 to 0.99)			

Outcome	N _t of studies (N _p of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with diagnosing Heart Failure)	6 studies 188 patients	cohort & case-control type studies	not serious	very serious ^a	not serious	serious ^b	none	6 (2 to 10)	⊕0000 Very low
False negatives (patients incorrectly classified as not having diagnosing Heart Failure)								10 (6 to 14)	
True negatives (patients without diagnosing Heart Failure)	6 studies 98 patients							895 (787 to 974)	-
False positives (patients incorrectly classified as having diagnosing Heart Failure)								89 (10 to 197)	

Explanations

- a. studies only included patients with HFpEF
- b. significant heterogeneity

Appendix V: Diagnostic Accuracy Results

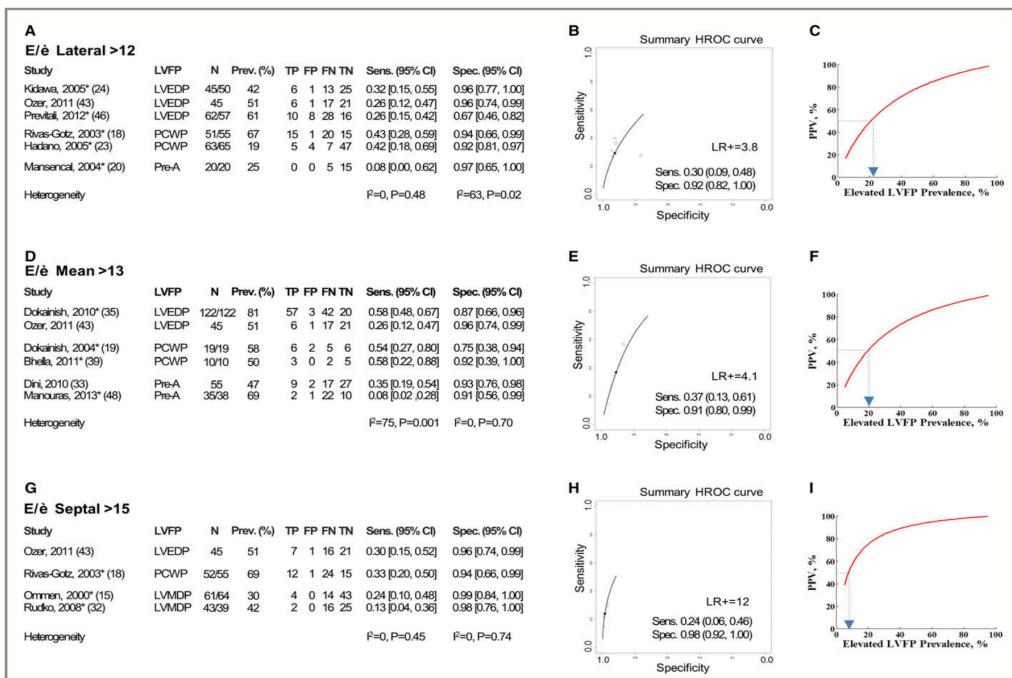


Table 4. Correlation (r) Between Invasive Measurements of LVFP and E/ \dot{e}

E/ \dot{e}		LVFP, mm Hg			
Location	Measure	LVEDP	PCWP	Pre-A	LVMDP
All primary studies					
Lateral	r (95% CI) Studies Heterogeneity Total patients	0.44 (0.30–0.57) (N=23,24,26,37,43,46,48,50); ($I^2=61$, $P=0.013$) (n=419)	0.46 (0.19–0.73) (N=4 ^{16,18,23,42}); ($I^2=79$, $P=0.003$) (n=188)	0.23 (0.10–0.36) (N=4 ^{20,40,46,48}); ($I^2=0$, $P=0.56$) (n=215)	0.4 (N=1 ¹⁵ ; N/A (n=64))
Septal	r (95% CI) Studies Heterogeneity Total patients	0.28 (0.08–0.49) (N=4 ^{24,43,46,48}); ($I^2=54$, $P=0.09$) (n=190)	0.48 (0.26–0.70) (N=3 ^{18,42,51}); ($I^2=42$, $P=0.18$) (n=113)	0.24 (0.09–0.40) (N=3 ^{40,46,48}); ($I^2=15$, $P=0.31$) (n=195)	0.47 (0.30–0.64) (N=2 ^{15,32}); ($I^2=0$, $P=1.00$) (n=103)
Mean	r (95% CI) Studies Heterogeneity Total patients	0.38 (0.11–0.65) (N=4 ^{35,43,46,48}); ($I^2=81$, $P=0.001$) (n=262)	0.49 (0.25–0.73) (N=4 ^{18,29,39,42}); ($I^2=51$, $P=0.10$) (n=122)	0.31 (0.07–0.55) (N=5 ^{30,34,40,46,48}); ($I^2=82$, $P=0.001$) (n=349)	0.45 (N=1 ¹⁵); N/A (n=64))
Primary studies with simultaneous measurements of echocardiographic and invasive parameters					
Lateral	r (95% CI) Studies Heterogeneity Total patients	0.51 (0.36–0.67) (N=2 ^{24,26,48}); ($I^2=0$, $P=0.40$) (n=143)	0.7 (0.51–0.89) (N=1 ¹⁸); N/A (n=55)	0.4 (0.19–0.61) (N=1 ⁴⁸); N/A (n=38)	0.4 (N=1 ¹⁵); N/A (n=64))
Septal	r (95% CI) Studies Heterogeneity Total patients	0.18 (-0.08 to 0.43) (N=2 ^{24,48}); ($I^2=31$, $P=0.23$) (n=88)	0.55 (0.32–0.78) (N=1 ¹⁸); N/A (n=55)	0.02 (-0.30 to 0.34) (N=1 ⁴⁸); N/A (n=38)	0.47 (0.30–0.64) (N=2 ^{15,32}); ($I^2=0$, $P=1.00$) (n=103)
Mean	r (95% CI) Studies Heterogeneity Total patients	0.18 (-0.14 to 0.50) (N=1 ⁴⁸); N/A (n=38)	0.6 (0.42–0.78) (N=3 ^{18,29,39}); ($I^2=0$, $P=0.91$) (n=86)	0.21 (-0.11 to 0.53) (N=1 ⁴⁸); N/A (n=38)	0.45 (N=1 ¹⁵); N/A (n=64))

Heterogeneity among the studies was estimated by using the I^2 statistic, and the corresponding P values are provided. N indicates number of studies; n, total patients N/A, not applicable.

Figure1. Diagnostic accuracy of E/e recommended by the American Society of Echocardiography to identify elevated left ventricular filling pressure (LVFP) (Sharifov, 2016)

Figure 2. Summary estimates of linear regression coefficient (r) for TDI and LVFP for primary studies. (Sharifov, 2016).

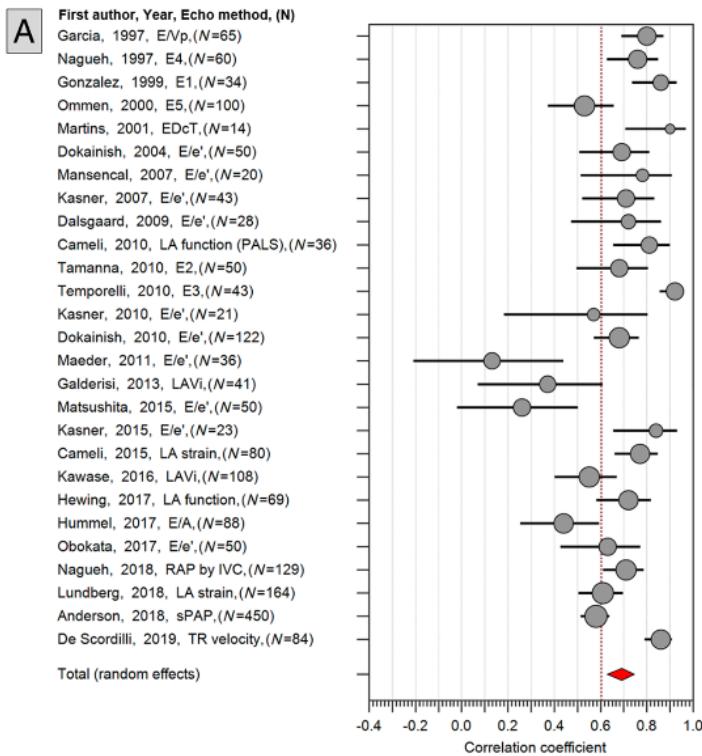
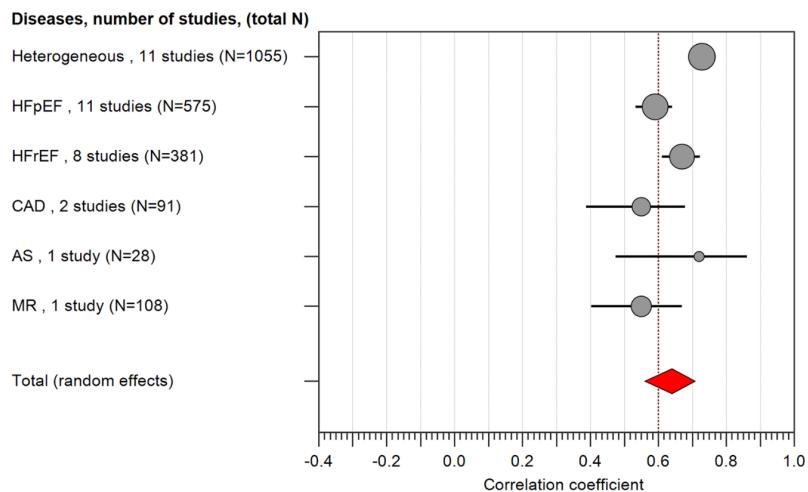


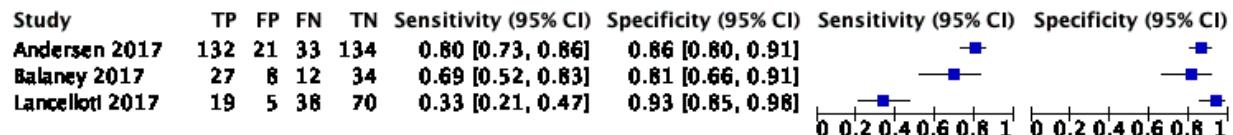
Figure 3. Forest plot of included studies evaluated in the meta-analysis for non-invasive assessment of left ventricular filling pressure (Jones, 2020).



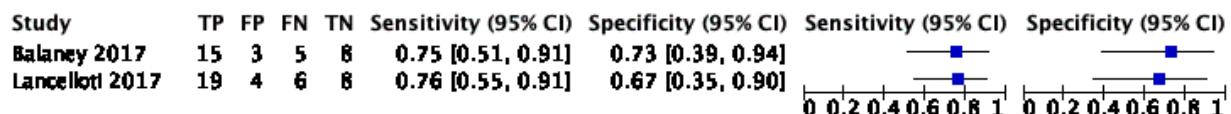
Disease state, number of studies, (total N)	N	R	95% CI	z	P	Weight (%)
Heterogeneous , 11 studies (N=1055)	1055	0.73	0.698 to 0.755			22.16
HFpEF , 11 studies (N=575)	575	0.59	0.534 to 0.641			21.24
HFrEF , 8 studies (N=381)	381	0.67	0.611 to 0.722			20.29
CAD , 2 studies (N=91)	91	0.55	0.388 to 0.679			14.13
AS , 1 study (N=28)	28	0.72	0.474 to 0.862			7.08
MR , 1 study (N=108)	108	0.55	0.403 to 0.669			15.1
Total (fixed effects)	2238	0.672	0.649 to 0.694	38. 4	<0.0 1	100
Total (random effects)	2238	0.64	0.560 to 0.708	11.9	<0.0 1	100
Test for heterogeneity						
Q	31					
DF	5					
Significance level	P<0.01					
I ² (inconsistency)	83.91 %	95% CI	66.50 to 92.27			

Abbreviations: CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CAD, coronary artery disease; AS, aortic stenosis; MR, mitral regurgitation; DF, degrees of freedom

Figure 5. Correlation between echocardiographically estimated LVEDP and invasive measurements in different disease states. (Jones, 2020).



A. All Patients with Heart Failures



B. Patients with Reduced Ejection Fraction.

Figure 6. Diagnostic accuracy of 2016 ASE/EACVI echocardiography guidelines in the diagnosis of elevated left ventricular filling pressures.

- The evidence to decision survey prior to voting showed that the majority of the CP considered the question as a priority problem. 2D Echocardiogram with doppler is accurate, with moderate to large desirable effects and unknown undesirable effects. 2D Echocardiogram has moderate certainty of evidence test accuracy for cardiomegaly and very low certainty of test accuracy. There are no studies on overall certainty of effects, certainty of evidence test, management and test result/management effects. The votes were split between “probably favors intervention” and “probably favors comparison for balance of effects.” The CP noted its possibly important uncertainty/variability. It has a moderate cost. There are no studies on certainty of evidence of required resources and cost-effectiveness. With probably increased equity, acceptable and probably feasible. All members of the CP (100%) were for diagnostic testing with strong strength of recommendation (91.7%).

Annex 7: Cardiac biomarkers (BNP or NT-proBNP for the diagnosis of heart failure)

APPENDIX:

Table of characteristics of included studies: Taylor KS (3)

Table 1 Included studies, study design and setting, and population characteristics						
Studies	Design	No of participants	Prevalence of heart failure (%)*	Setting	Age (years)†	Men (%)
Studies included in analysis						
Ajuluchukwu 2009	Case-control	72 (42 inpatients+30 controls)	58 - high	Inpatients and controls were staff and escorts, Nigeria	>14	Not stated
Alibay 2005	Cross sectional/ cohort	160	38 - low	Emergency department, France	80.1 (13.5)	78
Blondé-Cynober 2011	Cross sectional/ cohort	64	41 - low	Inpatients, France	84.3 (7.4)	31
Breathing not properly study:						
Maisel 2002	Cross sectional/ cohort	1586	47 - low	Emergency department, International	64 (17)	56
Maisel 2003	Cross sectional/ cohort	1586	47 - low	Emergency department, International	64 (17)	56
Pahle 2009‡	Cross sectional/ cohort	1583 (740 elevated blood pressure-843 normal blood pressure)	47 - low	Emergency department, International	Elevated: 67 (54-78); normal: 64 (49-76)	Elevated: 51.8; normal: 60
Chcrevier-Gobeaux 2010	Cross sectional/ cohort	378	30 - low	Emergency department, France	78 (12)	50
Dao 2001	Cross sectional/ cohort	250	39 - low	Emergency and urgent care departments, USA	63 (0.86)	94
De Vecchis 2016	Cross sectional/ cohort	111§	44 - low	Outpatients, Italy	58 (47-65)	65
Dokarish 2004	Cross sectional/ cohort	122	57 - high	Inpatients, USA	56 (13)	51
Fischer 2001	Cross sectional/ cohort but similar to case-control	145 (9% cardiac+50 healthy)	29 - low	Unclear, Germany	Cardiac: 61.9 (20-60); healthy range: 19-86	Cardiac: 67.4; healthy: 60
Fuat 2006	Cross sectional/ cohort	297	38 - low	One-stop diagnostic clinics in 2 hospitals and general practices, England	73.8 (34-94)¶	37
Gorissen 2007	Cross sectional/ cohort	80	50 - low	Emergency department, Netherlands	74 (10)	55
Gruson 2009	Cross sectional/ cohort	97	20 - low	Emergency department, Belgium	71 (30-95)	57

(Continued)

Table 1 | Included studies, study design and setting, and population characteristics

Studies	Design	No of participants	Prevalence of heart failure (%)*	Setting	Age (years)†	Men (%)
Jungbauer 2012	Case-control	222 (151 confirmed+71 healthy)	16, 24, 22, or 38‡ - low	Outpatients and controls were healthy hospital employees, Germany	Confirmed: 62.9 (12.1); healthy: 39.7 (15.1)	Confirmed: 71.5; healthy: 40.8
Knudsen 2004	Cross sectional/ cohort	155	48 - low	Emergency department, Norway	Men: 74 (66-79); women: 78 (71-84)	44.5
San Diego veterans' study:						
Krishnaswamy 2001	Cross sectional/ cohort	400	63 - high	Outpatients and inpatients, USA	65.7 (12.2)	96
Lubien 2002	Cross sectional/ cohort	294	40 - low	Outpatients and inpatients, USA	64.5 (5.5)	90
Lainchbury 2003	Cross sectional/ cohort	205	34 - low	Emergency department, New Zealand	70 (14)	49
Logeart 2002**	Cross sectional/ cohort	163	71 - high	Inpatients, France	67.4 (14.8)	67
Maisel 2001	Cross sectional/ cohort	200	48 - low	Inpatients and outpatients, USA	65.3 (0.9)	95
Mak 2004	Cross sectional/ cohort	100	16 - low	Inpatients and outpatients, USA	64 (13)	97
Monfort 2015	Cross sectional/ cohort	163§	69 - high (class II-IV)	Cardiac rehabilitation, France	Median 58	81
Prontera 2005	Cross sectional/ cohort but similar to case-control	284 (214 confirmed+91 healthy)	57 - high (of 213)	Unclear, Italy	Confirmed 62 (13); healthy 43.2 (13.4)	Confirmed 77; healthy 44
Prosen 2011	Cross sectional/ cohort	218	59 - high	Prehospital emergency, Slovenia	63.3 (16.1)	71
Ro 2011	Cross sectional/ cohort	250	43 - low	Emergency department, USA	70.7 (13.8)	57.8
Shao 2005	Cross sectional/ cohort	103	61 - high	Unclear, China	Not stated	Not stated
Storti 2004	Cross sectional/ cohort but similar to case-control	296 (202 cardiac+94 healthy)	59 - high (of 227)	Cardiac inpatients, Italy	Cardiac: 59.3 (20.5); healthy: 43.5 (14)	Cardiac: 70.3; healthy: 39.4
Su 2015	Cross sectional/ cohort	268	56 - high (of 203)	Emergency department, China	All 74.1 (7.9)	All 56.3
Tang 2005	Case-control	348 (241 confirmed+107 healthy)	69 - high	Secondary care, USA	Confirmed: male 69.4, female 69.1; Normal: male 44.0, female 44.9	Not stated
Taylor 2017	Cross sectional/ cohort	304	34 - low	Primary care, England	73.9 (8.8)	40.8
Tomonaga 2011	Cluster randomised controlled trial	369 (218 in POCT group)	44 - low (of 70 from POCT group)	Primary care, Switzerland	POCT group 65 (16)	POCT group 57.9
Verdu 2012	Cross sectional/ cohort	220	24 - low	Primary care, Spain	73.2 (19.2)	34.5
Villacorta 2002	Cross sectional/ cohort	70	51 - high	Emergency department, Brazil	72.4 (15.9)	47
Watson 2016	Cross sectional/ cohort	1368 (966 diabetes, 402 no diabetes)	19 - low	Primary care, Ireland	Diabetes: 65.7 (58.6-71.6); no diabetes: 67.9 (59.5-74.4)	Diabetes: 64.9; no diabetes: 47.0
Weekes 2016	Cross sectional/ cohort	116	22 - low	Emergency department, USA	59 (26)	51
Wei 2005	Cross sectional/ cohort	135	45 - low	Outpatients, China	67.8 (11.9)	63
Wieczorek 2002	Case-control	1050 (409 cardiac+641 controls)	39 - low	Inpatients and outpatients, USA	Not stated	Not stated
Zapata 2014	Cross sectional/ cohort	86	58 - high	Inpatients, Spain	63.8 (12.7)	66.3
Zhao 2008	Cross sectional/ cohort	195	69 - high	Inpatients, China	72.1 (8.3)	51.8
Eligible studies not included in analysis						
Morrison 2002	Cross sectional/ cohort	321	42 - low	Emergency department, USA	Not stated	Not stated
Vanderheyden 2006	Cross sectional/ cohort	72	56 - high	Inpatients, Belgium	65 (12)	71

POCT=point-of-care testing.

*As defined by reference standard, which, if based on clinical assessment, could use a single test or multiple tests.

†Mean (SD), or median (interquartile range) unless stated otherwise.

‡Reported baseline characteristics in groups based on blood pressure and hypertension history—numbers refer to patients with blood pressure status recorded.

§All with confirmed heart failure.

**Mean (range).

**Arrivals at emergency department, but 90% were later admitted to intensive care.

††Evaluated diagnostic accuracy using four different definitions of heart failure: New York Heart Association classes III and IV, left ventricular ejection fraction <40%, fluid retention, and American College of Cardiology/American Heart Association stages C and D, respectively.

Table 2 | Included studies, point-of-care tests and thresholds, and reference tests

Studies	Point-of-care tests*	Thresholds (pg/mL)	Reference tests
Studies included in analysis			
Ajuluchukwu 2009	Cardiac Reader (NTproBNP)	95, 100, 105, 110, 113, 115, 200, 122, 124, 125, 126, 127, 130, 135, 140, 145	Clinical evaluation and echocardiography. Evaluation of cases and controls by study assistant, senior registrar, or investigator
Alibay 2005	Triage (BNP)	50, 100, 150, 200	Retrospective review by two senior cardiologists
Blondé-Cynober 2011	Triage (BNP)	18, 100, 129, 400, 635	Retrospective review by cardiologist and geriatrician
Breathing not properly study:			
Maisel 2002	Triage (BNP)	50, 80, 100, 125, 150	Retrospective review by two cardiologists
Maisel 2003	Triage (BNP)	Additional 200, 300, 400	Retrospective review
Pahle 2009	Triage (BNP)	Additional 120, 140, 160, 180	Retrospective review
Chenevier-Gobeaux 2010	Triage (BNP)	100	Retrospective review by two senior emergency physicians
Dao 2001	Triage (BNP)	80, 100, 115, 120, 150	Retrospective review by two cardiologists
De Vecchis 2016	Alere (BNP)	412	New York Heart Association classification
Dokanish 2004	Triage (BNP)	250	Retrospective review by cardiologist
Fischer 2001	Triage (BNP)	130	Echocardiography
Fuat 2006	Triage (BNP)	40, 100	Echocardiography
Gorissen 2007	Triage (BNP)	78, 225, 260, 309	Retrospective review by cardiologist and pulmonologist
Gruson 2009	Biosite SOB panel (BNP)	100	Retrospective review
Jungbauer 2012	Cardiac Reader (NTproBNP); Triage (BNP)	410; 117	Based on clinical signs, physical examination, and echocardiography
Knudsen 2004	Triage (BNP)	50, 100, 150, 200	Retrospective review by two cardiologists
San Diego veterans' study:			
Krishnaswamy 2001	Triage (BNP)	49, 62, 75, 110, 160, 345	Retrospective review of echocardiography, admission treatment for heart failure, and visits to the emergency department for heart failure
Lubien 2002	Triage (BNP)	Additional 17.5, 62, 92, 130	Echocardiography
Lainchbury 2003	Triage (BNP)	69, 104, 208, 277, 346	Retrospective review by two cardiologists, with third cardiologist as adjudicator
Logeart 2002	Triage (BNP)†	80, 100, 150, 200, 250, 300, 400	Retrospective review by two cardiologists and pneumologist
Maisel 2001	Triage (BNP)	38.5, 46, 55, 65, 75	Echocardiography
Mak 2004	Triage (BNP)	90, 173, 279, 402	Echocardiography
Monfort 2015	Alere (BNP)	159	New York Heart Association classification
Prontera 2005	Triage (BNP)	5.1, 29	Retrospective review
Prosen 2011	Cardiac Reader (NTproBNP)	1000	Retrospective review by cardiologists or intensive care physicians, or both
Ro 2011	Triage (BNP); Abbott i-STAT (BNP)	100; 100	Based on discharge diagnosis, echocardiography (when available), and assessment of a consulting cardiologist
Shao 2005	Triage (BNP)	100	Echocardiography, and cardiac catheterization
Storti 2004	Triage (BNP)	40.7	Based on clinical (presence of suggestive symptoms), and echocardiographic evidence
Su 2015	RAMP (NTproBNP)	600	Retrospective review
Tang 2005	Triage (BNP)	52, 74, 100	Retrospective review
Taylor 2017	Cardiac Reader (NTproBNP)	125, 400	Retrospective review by expert panel
Tomonaga 2011	Cardiac Reader (NTproBNP)	125	Retrospective review
Verdu 2012	Cardiac Reader (NTproBNP)	125, 280, 400	Retrospective review by one cardiologist
Villacorta 2002	Triage (BNP)	200	Retrospective review by one cardiologist
Watson 2016	Triage (BNP)	10, 15, 25, 30, 50	Echocardiography
Weekes 2016	Abbott i-STAT (BNP)	90	Echocardiography
Wei 2005	Triage (BNP)	40	Retrospective review by two cardiologists
Wieczorek 2002	Triage (BNP)	100	Retrospective review by one physician
Zapata 2014	Triage (BNP)	125, 100	Echocardiography
Zhao 2008	Triage (BNP)	50, 80, 100, 130, 150	Cardiac catheterisation
Eligible studies not included in analysis			
Morrison 2002	Triage (BNP)	94, 105, 135, 195, 240	Retrospective review by two cardiologists
Vanderheyden 2006	Triage (BNP)	29.3, 50, 100, 139	Cardiac catheterisation

NTproBNP=N terminal fragment pro B-type natriuretic peptide; BNP=B-type natriuretic peptide; SOB=shortness of breath.

*Point-of-care devices: Cardiac Reader/Cobas h 232 (Roche Diagnostics); Triage (Biosite Diagnostics); RAMP (Response Biomedical Corporation); Abbott i-STAT (Abbott Point of Care); Alere™ Heart Check (Alere).

†Two point-of-care tests (Triage, to measure BNP, and Hewlett Packard Sonos 1500, to provide Doppler echocardiography) were compared with the same reference test to indirectly compare BNP with Doppler echocardiography. Only point-of-care test is listed in table.



Figure 1: QUADAS-2 summary of risk of bias and applicability concerns showing review authors' judgments about each domain for each included study. Based on 42 publications (39 studies), Taylor KS (3)

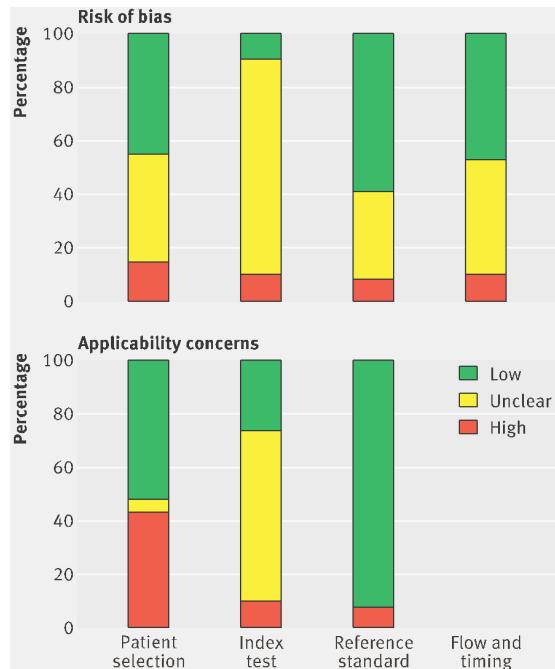


Fig 2 | QUADAS-2 risk of bias and applicability concerns graph showing review authors' judgments about each domain as percentages of included studies. Based on 42 publications (39 studies) , Taylor KS (3)

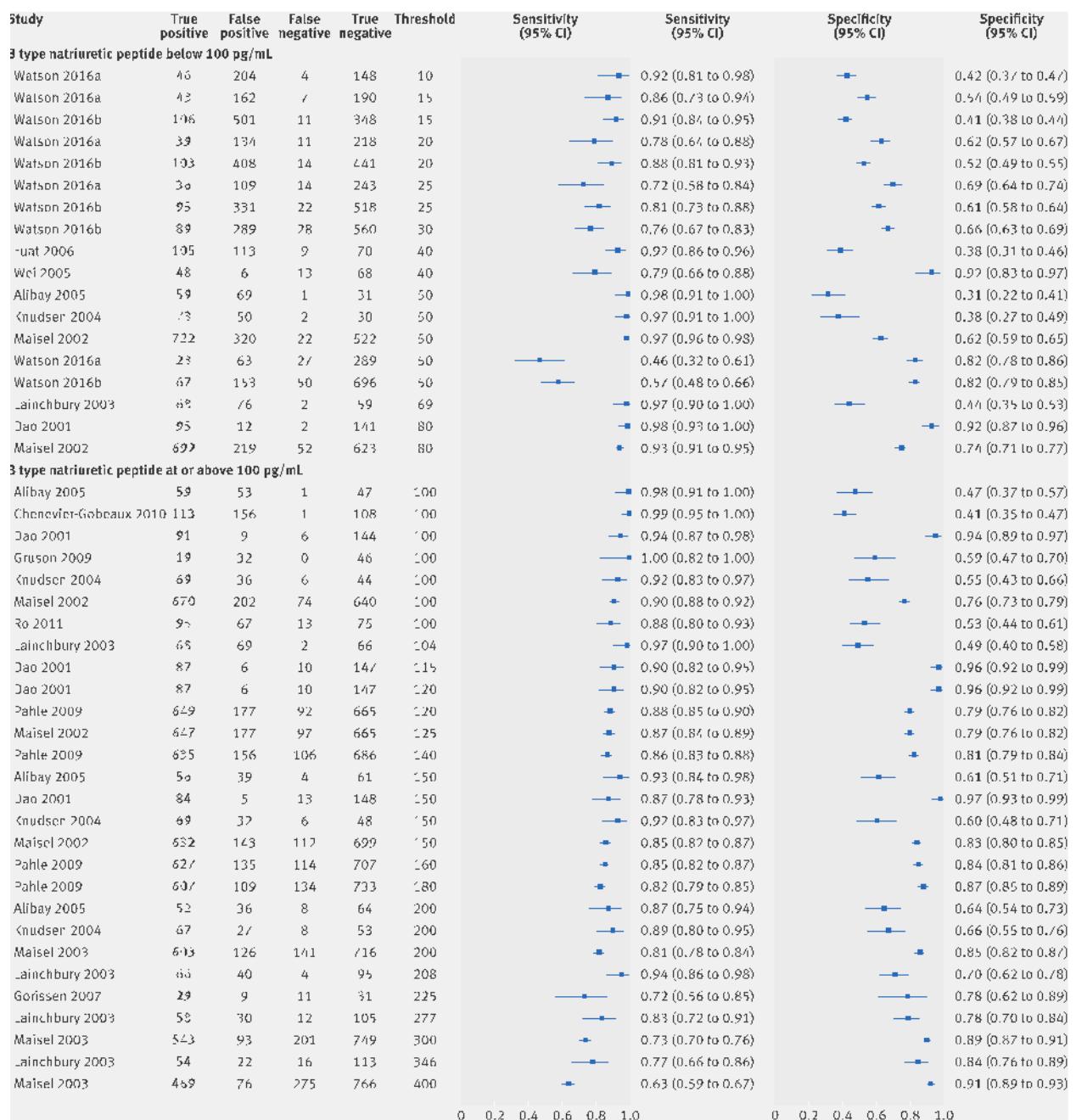


Figure 3: Paired sensitivity and specificity plots at two threshold levels for B-type natriuretic peptide compared with clinical assessment, for cross sectional/cohort studies with populations of low prevalence of chronic heart failure in ambulatory care settings , Taylor KS (3)

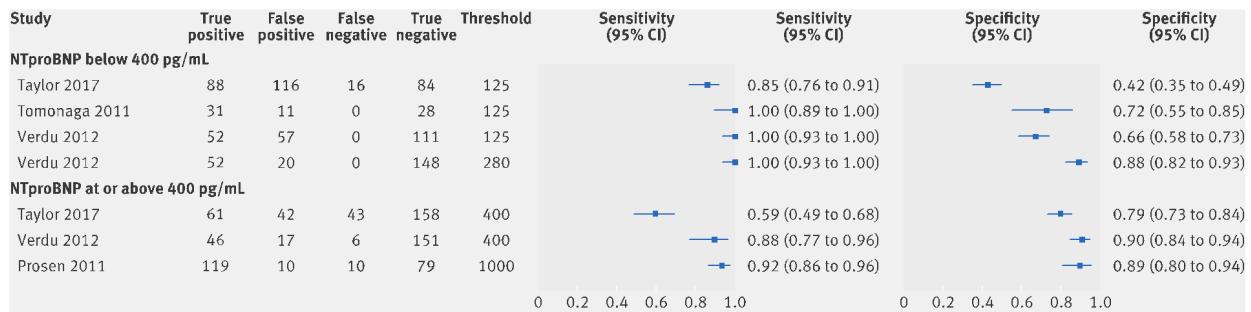


Figure 4. Paired sensitivity and specificity plots at two thresholds levels for N terminal fragment pro B-type natriuretic peptide compared with clinical assessment, for cross sectional/cohort/randomised controlled trial studies . Taylor KS (3)

Table 1 : GRADE evidence profile table with a BNP threshold less than 100 pg/ml

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence0% Typically seen in	Prevalence1.6% Typically seen in	Prevalence29% Typically seen in		
True positives	0 to 0	7 to 16	133 to 284	18 (2509)	 Low ^{a,b,c}
False negatives	0 to 0	0 to 9	6 to 157		
True negatives	310 to 980	305 to 964	220 to 696		
False positives	20 to 690	20 to 679	14 to 490		
Inconclusive*				(0)	-
Complications**				(0)	-

Table 2 : GRADE evidence profile table with a BNP threshold of more than 100 pg/ml

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence0% Typically seen in	Prevalence1.6% Typically seen in	Prevalence29% Typically seen in		
True positives	0 (0 to 0)	16 (14 to 16)	290 (261 to 290)	7305 (28)	 Low ^{a,b,c}
False negatives	0 (0 to 0)	0 (0 to 2)	0 (0 to 29)		
True negatives	970 (950 to 1000)	954 (935 to 984)	689 (675 to 710)		
False positives	30 (0 to 50)	30 (0 to 49)	21 (0 to 35)		

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0% Typically seen in	Prevalence 1.6% Typically seen in	Prevalence 29% Typically seen in		
Inconclusive*				(0)	-
Complications**				(0)	-

Table 3 : GRADE evidence profile table with an NT pro BNP threshold less than 400 pg/ml

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0% Typically seen in	Prevalence 1.6% Typically seen in	Prevalence 29% Typically seen in		
True positives	0 (0 to 0)	16 (9 to 16)	287 (165 to 290)	223 (4)	⊕⊕○○ Low ^{a,b,c}
False negatives	0 (0 to 0)	0 (0 to 7)	3 (0 to 125)	388 (4)	⊕⊕○○ Low ^{d,e,f}
True negatives	600 (440 to 740)	590 (433 to 728)	426 (312 to 525)		
False positives	400 (260 to 560)	394 (256 to 551)	284 (185 to 398)		
Inconclusive*				(0)	-
Complications**				(0)	-

Table 4 GRADE evidence profile table with an NT pro BNP threshold more than 400 pg/ml

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0% Typically seen in	Prevalence 1.6% Typically seen in	Prevalence 29% Typically seen in		
True positives	0 (0 to 0)	9 (8 to 11)	171 (142 to 197)	226 (3)	⊕⊕○○ Low ^{a,b,c,d}
False negatives	0 (0 to 0)	7 (5 to 8)	119 (93 to 148)	388 (3)	⊕⊕○○ Low ^{e,f,g}
True negatives	790 (730 to 840)	777 (718 to 827)	561 (518 to 596)		
False positives	210 (160 to 270)	207 (157 to 266)	149 (114 to 192)		
Inconclusive*				(0)	-
Complications**				(0)	-

Subgroup analysis on studies with patients presenting with dyspnea alone

Table 5: GRADE pro evidence profile of NT pro-BNP with a threshold of more than 400 pg/ml (Worster et al)

Should NT pro BNP be used to diagnose chronic congestive heart failure in OPD/primary care/ambulatory care?

Patient or population: OPD/primary care/ambulatory care

Setting: OPD/primary care/ambulatory care

New test: [comparator test] |Cut-off value:

Reference test: any relevant reference standard including echocardiography , clinical examination or combination of these
|Threshold: more than 400 pg/ml

Single study sensitivity:0.96 (95% CI: 0.89 to 0.99)|Single study specificity:0.74 (95% CI: 0.44 to 0.92)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence1.6% Typically seen in	Prevalence29% Typically seen in	Prevalence29% Typically seen in		
True positives	15 (14 to 16)	278 (258 to 287)	278 (258 to 287)	74 (1)	 Low ^{a,b,c}
False negatives	1 (0 to 2)	12 (3 to 32)	12 (3 to 32)		
True negatives	728 (433 to 905)	525 (312 to 653)	525 (312 to 653)	15 (1)	 Low ^{d,e,f}
False positives	256 (79 to 551)	185 (57 to 398)	185 (57 to 398)		

CI: confidence interval

Explanations

- a. it was not clear if the index test used prespecified thresholds using the prescribed thresholds or the interpretation of the index test was done without knowing the results of the reference standards
- b. it was not clear if the index test used prespecified thresholds using the prescribed thresholds
- c. there was a difference of accuracy results along different brands of POCT and is largely dependent on the prevalence of the condition

d. it was not clear if the index test used prespecified thresholds using the prescribed thresholds or the interpretation of the index test was done without knowing the results of the reference standards

e. it was not clear of the index test used prespecified thresholds using the prescribed thresholds

f. different brands of POCT reported different accuracy results and the accuracy is dependent on the prevalence of the condition

Table 6: GRADE pro evidence profile of BNP with a threshold of more than 100 pg/ml (McCullough et al)

Should BNP be used to diagnose chronic congestive heart failure in [health problem and/or population]?

Patient or population: [health problem and/or population]

Setting: OPD/primary care/ambulatory care

New test: [comparator test] |Cut-off value:

Reference test: any relevant reference standard including echocardiography and clinical examination or combination of these |Threshold: more than 100 pg/ml

Single study sensitivity:0.94 (95% CI: 0.87 to 0.98)|Single study specificity:0.94 (95% CI: 0.89 to 0.97)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence1.6% Typically seen in	Prevalence29% Typically seen in	Prevalence29% Typically seen in		
True positives	15 (14 to 16)	273 (252 to 284)	273 (252 to 284)	98 (1)	 Low ^{a,b,c}
False negatives	1 (0 to 2)	17 (6 to 38)	17 (6 to 38)		
True negatives	925 (876 to 954)	667 (632 to 689)	667 (632 to 689)	162 (1)	 Low ^{d,e,f}
False positives	59 (30 to 108)	43 (21 to 78)	43 (21 to 78)		

CI: confidence interval

Explanations

a. it was not clear for the index test if the threshold used have been prespecified using the prescribed thresholds or those who interpreted the index test was blinded to the results of the reference standard

- b. it was not clear for the index test if the threshold used have been prespecified using the prescribed thresholds
- c. some of the POCT devices used have higher accuracy results and was highly dependent on the prevalence of the condition
- d. it was not clear for the index test if threshold used was prespecified using prescribed thresholds or those who interpreted the index test truly blinded to the results of the reference standard
- e. it was not clear for the index test if the threshold used have been prespecified using prescribed thresholds
- f. some of the POCT devices have higher accuracy resulys and was highly affected by the prevalence of the condition

Table 6: GRADE pro evidence profile of BNP with a threshold of more than 100 pg/ml (McCullough et al)

- The evidence to decision survey prior to voting showed that the majority of the CP considered this question as a priority problem. The use of BNP or NT-proBNP to diagnose or rule out chronic heart failure is accurate, with moderate desirable and small undesirable effects, but with low certainty of evidence of test accuracy. There were no studies on overall certainty of effects, certainty of evidence test, management effects, and test result/management effects. Probably favors comparison for balance of effects. The CP noted it as possibly important uncertainty/variability. There was a split vote between large cost and unknown. There was high certainty of evidence of required resources but no study on cost-effectiveness. Equity was unknown, probably acceptable, and there was a split vote between probably feasible and not feasible. Seventy five percent (75%) of the CP voted for diagnostic testing with weak strength of recommendation (75%).

Annex 8: Electrolytes and creatinine in confirmed heart failure

A. Quality of included studies using Newcastle Ottawa Scale (NOS)

1. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum sodium** (135-144 mEq/L vs <135 mEq/L)

Study	Selection	Comparability	Outcome	Quality
Alem 2020	****	*	***	Good
Balling 2014	****	*	***	Good
Bavishi 2018	****	*	***	Good
DeWolfe 2008	****	*	***	Good

2. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum potassium** (4 mEq/L vs <4 mEq/L)

Study	Selection	Comparability	Outcome	Quality
Ahmed 2007	****	*	***	Good
Alper 2009	****	*	***	Good

3. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum creatinine** (1.2 mg/dl vs <1.2 mg/dl)

Study	Selection	Comparability	Outcome	Quality
Hillege 2006	****	*	***	Good
Mahon 2002	****	*	***	Good

B. Characteristics of Included studies

1. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum sodium of <135 mEq/L (hyponatremia)**

Authors, Country Study design	Population	Exposure	Outcome	Comments
Alem 2020 Saudi Arabia Retrospective cohort	241 patients with chronic heart failure Mean age: 60.6 ± 12.6 65.1% male	Serum Na <135 mEq/L N= 207 Serum Na 135-144 mEq/L N= 34	All cause mortality Serum Na <135 mEq/L 87/207 = 42% Serum Na 135-145 mEq/L 17/ 34 = 50% RR: 1.19 (95%CI: 0.82, 1.73)	Mixed in patients and outpatients diagnosed with chronic heart failure 24-month follow-up (from the time serum Na measurements were taken)
Balling 2014 Denmark 18 Danish HF clinics Retrospective cohort	3465 patients with heart failure Mean age: 68 73% male	Serum Na <136 mEq/L N= 2863 Serum Na 136-144 mEq/L N= 602	All cause mortality Serum Na <136 mEq/L 429/2863 = 15% Serum Na 136-145 mEq/L 147/602 = 24.4% RR: 1.63 (95% CI: 1.38, 1.92)	A baseline measurement of serum Na obtained at the initial clinic visit All endpoints were obtained from The Danish National Patient Registry Median follow-up time was 495 (1–1660) days
Bavishi 2018 USA ambulatory clinics of US Dept of Veterans Affairs (VA) medical center Retrospective cohort	6158 patients with heart failure Mean age: 70 95% male	Serum Na ≤135 mEq/L N= 847 Serum Na 136-144 mEq/L N= 5311	Serum Na ≤135 mEq/L 292/847 = 34.5% Serum Na 136-145 mEq/L 1307/5311 = 24.6% RR: 1.40 (95% CI: 1.26, 1.55)	Variables with >20% missing values were excluded 2 year follow-up
DeWolfe 2008 Louisiana, USA Heart Failure Disease Management Program (HFDMP) Prospective Cohort	364 patients with heart failure Mean age: 55 Majority were male	Serum Na <135 mEq/L N= 48 Serum Na 135-144 mEq/L N= 316	Serum Na <135 mEq/L 8/48 = 17% Serum Na 135-144 mEq/L 31/316 = 9.8% RR: 1.70 (95% CI: 0.83, 3.27)	Mortality information was obtained through the Social Security Death Index 40 month follow-up

2. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum sodium of >145 mEq/L (hypernatremia)**

Authors, Country Study design	Population	Exposure	Outcome	Comments
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Patel 2018 USA national Veterans Affairs (VA) patient database Cohort	Mean age: 70.8 ±11.5 Majority were male	Serum Na >144 mEq/L N= 1660 Serum Na 135-143 mEq/L N= 20140	Serum Na >144 mEq/L 1009/1660 = 60.7% Serum Na 135-143 mEq/L 11204 / 20140 = 55.6% RR: 1.09 (95% CI: 1.05, 1.14)	Out-patient Participants serum entered the analysis at the time of their first sodium measurement, In-patient the last serum sodium measurement in the series was used as the baseline value under the assumption that the most stable serum sodium value would be on the day of hospital discharge Mean follow-up: 3.6 years
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3. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum potassium of <3.5 mEq/L (hypokalemia)**

Authors, Country Study design	Population	Exposure	Outcome	Comments
Ahmed 2008 USA 302 centres (186 in the United States and 116 in Canada) cohort	6845 HF patients in the Digitalis Investigation Group trial Mean age: 63 ±11 69% were male	Serum K < 4 mEq/L N = 1187 Serum K 4-4.9 mEq/L N = 1187	Serum K < 4 mEq/L 441/1187 = 37.2% Serum K ≥ 4 mEq/L 379 / 1187 = 31.9% RR: 1.16 (95% CI: 1.07, 1.25)	a median follow-up of 36.7 months
Alper 2009 USA Cohort	2231 HF patients in the Digitalis Investigation Group trial Mean age: 72 ± 6 71% were male	Serum K < 4 mEq/L N = 561 Serum K 4-4.9 mEq/L N = 1670	Serum K < 4 mEq/L 242 / 561 = 43.1% Serum K 4-4.9 mEq/L N = 625 / 1670 = 37.4% RR: 1.15 (95%CI: 1.03, 1.29)	32 month follow-up

4. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum potassium of >5 mEq/L (hyperkalemia)**

Authors, Country Study design	Population	Exposure	Outcome	Comments
Collins 2017 USA de-identified EMR data from multiple US integrated health delivery network Cohort	Mean age: 57.4 ± 17.6 58% were female	Serum K ≥5 mEq/L N = 4548 Serum K 3.5-4.9 mEq/L N = 43589	Serum K ≥5 mEq/L 275 / 4548 = 6% Serum K 3.5-4.9 mEq/L 1577 / 43589 = 3.6% RR:1.71 (95% CI:1.50, 1.96)	outpatient and hospital data from medical care Deaths were identified from the United States Social Security Death Index The average follow-up was approximately 18 months and ranged from 12 to 48 months

5. Among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline creatinine of >1.1 mg/dl**

Authors, Country Study design	Population	Exposure	Outcome	Comments
Hillege 2006 Candesartan in Heart Failure:Assessment of Reduction in Mortality and Morbidity (CHARM)-Overall program Cohort	1087 were enrolled from CHARM-Preserved, 931 from CHARM-Added, and 662 from CHARM-Alternative	Serum crea >1.2 mg/dl N=996 Serum crea ≤ 1.2 mg/dl N=1714	Serum crea >1.2 mg/dl 330/996= 33.1% Serum crea ≤ 1.2 mg/dl 295/1714= 17.2% RR: 1.93 (95%CI: 1.68, 2.21)	median follow-up of 34.4 months (range, 1 day to 45.2 months)
Mahon 2002 Ohio, USA Digitalis investigation group (DIG) trial Cohort	585 participants of the 6-min walk substudy of the Digitalis Investigation Group (DIG) trial. Mean age: 65±12 Majority are male	Serum crea >1.2 mg/dl N=291 Serum crea ≤ 1.2 mg/dl N=294	Serum crea >1.2 mg/dl 97/291 = 33.3% Serum crea ≤ 1.2 mg/dl 56/294 = 19% RR: 1.75 (95% CI: 1.31, 2.33)	Follow-up for up to five years (median 3.2 years)

C. Forest plots

Figure 1. Baseline serum sodium (135-144 mEq/L vs <135 mEq/L), outcome: mortality

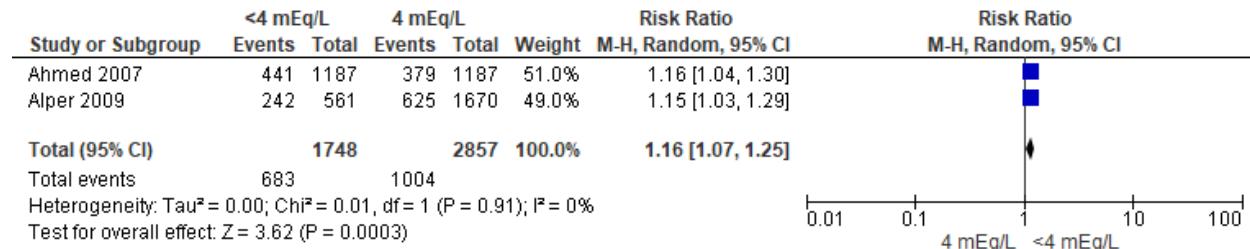


Figure 2. Baseline serum potassium (4 mEq/L vs < 4 mEq/L) outcome: Mortality

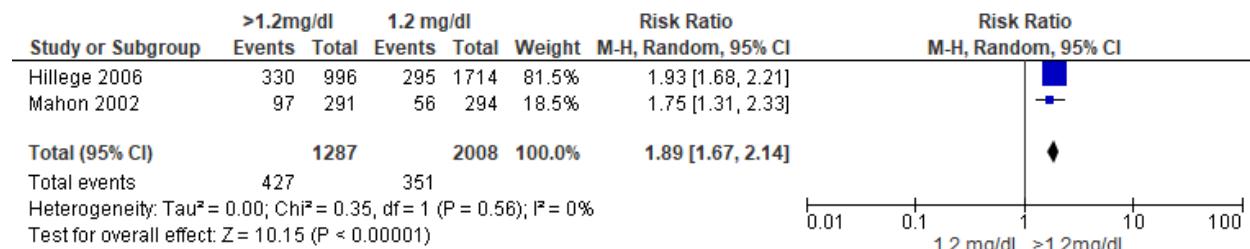


Figure 3. Baseline serum creatinine (1.2 mg/dl vs >1.2 mg/dl), outcome: Mortality

Risk of mortality among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum sodium of <135 mEq/L (hyponatremia)**

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With normal serum sodium	With Low		Risk with normal serum sodium	Risk difference with Low

Mortality

10228 (4 observational studies)	serious	not serious	serious	not serious	none	⊕○○○ Very low	1854/8697 (21.3%)	464/1531 (30.3%)	RR 1.46 (1.31 to 1.62)	213 per 1,000	98 more per 1,000 (from 66 more to 132 more)
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CI: confidence interval; RR: risk ratio

Risk of mortality among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum sodium of >145 mEq/L (hypernatremia)**

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With normal serum sodium	With High		Risk with normal serum sodium	Risk difference with High

Mortality

21800 (1 observational study)	serious	not serious	serious	not serious	none	⊕○○○ Very low	11204/20140 (55.6%)	1009/1660 (60.8%)	RR 1.09 (1.05 to 1.14)	556 per 1,000	50 more per 1,000 (from 28 more to 78 more)
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CI: confidence interval; RR: risk ratio

Risk of mortality among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum potassium of <3.5 mEq/L (hypokalemia)**

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With normal serum potassium	With Low		Risk with normal serum potassium	Risk difference with Low

Mortality

4605 (2 observational studies)	serious	not serious	serious	not serious	none	⊕○○○ Very low	1004/2857 (35.1%)	683/1748 (39.1%)	RR 1.16 (1.07 to 1.25)	351 per 1,000	56 more per 1,000 (from 25 more to 88 more)
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CI: confidence interval; RR: risk ratio

Risk of mortality among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline serum potassium of >5 mEq/L (hyperkalemia)**

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With normal serum potassium	With High		Risk with normal serum potassium	Risk difference with High
Mortality											
48137 (1 observational study)	serious	not serious	serious	not serious	none	⊕○○○ Very low	1577/43589 (3.6%)	275/4548 (6.0%)	RR 1.67 (1.48 to 1.89)	36 per 1,000	24 more per 1,000 (from 17 more to 32 more)

CI: confidence interval; RR: risk ratio

Risk of mortality among patients diagnosed with chronic heart failure at the outpatient clinic with **baseline creatinine of >1.1 mg/dl**

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With normal serum creatinine	With High		Risk with normal serum creatinine	Risk difference with High
Mortality											
3295 (2 observational studies)	serious	not serious	serious	not serious	none	⊕○○○ Very low	351/2008 (17.5%)	427/1287 (33.2%)	RR 1.89 (1.67 to 2.14)	175 per 1,000	156 more per 1,000 (from 117 more to 199 more)

CI: confidence interval; RR: risk ratio

- The evidence to decision survey prior to voting showed that the majority of the CP considered it as a priority problem. Determining serum electrolyte and creatinine levels has moderate desirable and unknown undesirable effects. It has moderate certainty of evidence of test accuracy. The vote was split between “probably favors intervention” and “favors intervention.” There were no studies on the certainty of evidence of required costs. Costs were moderate, with no study on cost effectiveness. Probably no important/uncertainty/variability, increased equity, probably acceptable and feasible. All members of the CP (100%) voted to recommend diagnostic testing with strong strength of recommendation (60%)

Annex 9: Nonpharmacologic interventions in confirmed heart failure

EVIDENCE TO DECISION FRAMEWORK WORKSHEET (THERAPY)

Guideline Question : Among adult Filipinos diagnosed with chronic heart failure and reduced ejection fraction at the outpatient clinic, what is the effect of nonpharmacologic interventions (dietary sodium and fluid restriction, exercise prescription) on the incidence of mortality and heart failure hospitalization, and on quality of life?

(1) Problem : Is the problem a priority?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Don't know	<p>Heart failure is a major cause of mortality and morbidity globally. Although pharmacologic treatment of heart failure has been dynamic and effective in improving quality of life, non pharmacologic aspect of treatment remains important. Dietary salt re remains a and water restriction have been historically part of heart failure treatment. This strategy became controversial with studies coming out where the intervention was shown to not have the expected effect on clinical outcomes. There is also evidence that sodium restriction may lead to detrimental renal and neurohormonal effects that worsen clinical outcomes .</p> <p>Physical deconditioning in patients with heart failure is believed to be the main cause of fatigue that stems from decreased nutritive blood flow to the muscle and alterations in metabolism. Exercise rehabilitation has been promoted to counteract this but studies have not shown consistent benefit and some safety concerns for patients with reduced ejection fraction have come up.</p>				
(2) Desirable Effects : How substantial are the desirable anticipated effects?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
<input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Don't know	Dietary sodium AND fluid restriction <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <th>Outcomes</th> <th>Relative Effect (95% CI)</th> <th>Absolute Effects (95% CI)</th> </tr> </table>	Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)	
Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)			

	<table border="1"> <tr> <td>HF Hospitalization No. of participants: 259 2 studies</td><td>RR 3.76 (1.85 to 7.63)</td><td>23.5% more (8.9 more to 40.9 more)</td></tr> <tr> <td>All cause Death No. of participants: 232 1 study</td><td>OR 2.83 (1.06 to 7.67)</td><td>8.1% more (0.3 more to 23.8 more)</td></tr> </table>	HF Hospitalization No. of participants: 259 2 studies	RR 3.76 (1.85 to 7.63)	23.5% more (8.9 more to 40.9 more)	All cause Death No. of participants: 232 1 study	OR 2.83 (1.06 to 7.67)	8.1% more (0.3 more to 23.8 more)							
HF Hospitalization No. of participants: 259 2 studies	RR 3.76 (1.85 to 7.63)	23.5% more (8.9 more to 40.9 more)												
All cause Death No. of participants: 232 1 study	OR 2.83 (1.06 to 7.67)	8.1% more (0.3 more to 23.8 more)												
	Dietary sodium restriction alone													
	<table border="1"> <thead> <tr> <th>Outcomes</th><th>Relative Effect (95% CI)</th><th>Absolute Effects (95% CI)</th></tr> </thead> <tbody> <tr> <td>HF Hospitalization No. of participants: 872 2 studies</td><td>OR 0.72 (0.48 to 1.10)</td><td>3.4% fewer (6.6 fewer to 1.2 more)</td></tr> <tr> <td>All cause Death No. of participants: 806 1 study</td><td>OR 1.58 (0.83 to 3.02)</td><td>2.1% more (0.6 fewer to 7 more)</td></tr> </tbody> </table>	Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)	HF Hospitalization No. of participants: 872 2 studies	OR 0.72 (0.48 to 1.10)	3.4% fewer (6.6 fewer to 1.2 more)	All cause Death No. of participants: 806 1 study	OR 1.58 (0.83 to 3.02)	2.1% more (0.6 fewer to 7 more)				
Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)												
HF Hospitalization No. of participants: 872 2 studies	OR 0.72 (0.48 to 1.10)	3.4% fewer (6.6 fewer to 1.2 more)												
All cause Death No. of participants: 806 1 study	OR 1.58 (0.83 to 3.02)	2.1% more (0.6 fewer to 7 more)												
	Dietary sodium and/or fluid restriction													
	<table border="1"> <thead> <tr> <th>Outcomes</th><th>Relative Effect (95% CI)</th><th>Absolute Effects (95% CI)</th></tr> </thead> <tbody> <tr> <td>Quality of Life No. of participants: 93 2 studies</td><td>OR 0.72 (0.48 to 1.10)</td><td>3.4% fewer (6.6 fewer to 1.2 more)</td></tr> </tbody> </table>	Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)	Quality of Life No. of participants: 93 2 studies	OR 0.72 (0.48 to 1.10)	3.4% fewer (6.6 fewer to 1.2 more)							
Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)												
Quality of Life No. of participants: 93 2 studies	OR 0.72 (0.48 to 1.10)	3.4% fewer (6.6 fewer to 1.2 more)												
	Exercise based cardiac rehabilitation													
	<table border="1"> <thead> <tr> <th>Outcomes</th><th>Relative Effect (95% CI)</th><th>Absolute Effects (95% CI)</th></tr> </thead> <tbody> <tr> <td>HF Hospitalization No. of participants: 1114 14 studies</td><td>RR 0.59 (0.42 to 0.84)</td><td>4.6% less (6.5 less to 1.8 less)</td></tr> <tr> <td>All cause Death (12mos) No. of participants: 2596 27 studies</td><td>RR 0.89 (0.66 to 1.21)</td><td>0.6% less (2 less to 1.2 more)</td></tr> <tr> <td>Quality of life MLWHF No. of participants: 1995 17 studies</td><td></td><td>Mean 7.11 lower (10.49 lower to 3.73 lower)</td></tr> </tbody> </table>	Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)	HF Hospitalization No. of participants: 1114 14 studies	RR 0.59 (0.42 to 0.84)	4.6% less (6.5 less to 1.8 less)	All cause Death (12mos) No. of participants: 2596 27 studies	RR 0.89 (0.66 to 1.21)	0.6% less (2 less to 1.2 more)	Quality of life MLWHF No. of participants: 1995 17 studies		Mean 7.11 lower (10.49 lower to 3.73 lower)	
Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)												
HF Hospitalization No. of participants: 1114 14 studies	RR 0.59 (0.42 to 0.84)	4.6% less (6.5 less to 1.8 less)												
All cause Death (12mos) No. of participants: 2596 27 studies	RR 0.89 (0.66 to 1.21)	0.6% less (2 less to 1.2 more)												
Quality of life MLWHF No. of participants: 1995 17 studies		Mean 7.11 lower (10.49 lower to 3.73 lower)												

(3) Undesirable Effects : How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE			ADDITIONAL CONSIDERATIONS
<input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input type="radio"/> Don't know	Use your abbreviated SoF without the certainty of evidence column, including only outcomes on adverse events/ harm			
	Outcomes	Relative Effect (95% CI)	Absolute Effects (95% CI)	
	change in SBP		MD 4.27 lower (6.9 lower to 1.63 lower)	
	change in crea	-	MD 0.17 lower (0.19 lower to 0. 15 lower)	
			-	

(4) Certainty of effects : What is the overall certainty of the evidence of effects of the intervention?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	<table border="1"> <thead> <tr> <th>Outcomes</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Dietary sodium AND fluid HF hospitalization</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Dietary sodium AND fluid All cause death</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Dietary sodium restriction alone HF hospitalization</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Dietary sodium restriction alone All cause death</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Exercise- based cardiac rehabilitation HF hospitalization</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Exercise- based cardiac rehabilitation All cause death (12 mos)</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Exercise- based cardiac rehabilitation Quality of life MLWHF</td> <td>⊕⊕○○ LOW</td> </tr> </tbody> </table>	Outcomes	Certainty of the evidence (GRADE)	Dietary sodium AND fluid HF hospitalization	⊕⊕○○ LOW	Dietary sodium AND fluid All cause death	⊕⊕○○ LOW	Dietary sodium restriction alone HF hospitalization	⊕⊕○○ LOW	Dietary sodium restriction alone All cause death	⊕⊕⊕○ MODERATE	Exercise- based cardiac rehabilitation HF hospitalization	⊕⊕○○ LOW	Exercise- based cardiac rehabilitation All cause death (12 mos)	⊕⊕○○ LOW	Exercise- based cardiac rehabilitation Quality of life MLWHF	⊕⊕○○ LOW	
Outcomes	Certainty of the evidence (GRADE)																	
Dietary sodium AND fluid HF hospitalization	⊕⊕○○ LOW																	
Dietary sodium AND fluid All cause death	⊕⊕○○ LOW																	
Dietary sodium restriction alone HF hospitalization	⊕⊕○○ LOW																	
Dietary sodium restriction alone All cause death	⊕⊕⊕○ MODERATE																	
Exercise- based cardiac rehabilitation HF hospitalization	⊕⊕○○ LOW																	
Exercise- based cardiac rehabilitation All cause death (12 mos)	⊕⊕○○ LOW																	
Exercise- based cardiac rehabilitation Quality of life MLWHF	⊕⊕○○ LOW																	

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APPENDICES

Table 1.1 SEARCH STRATEGY AND YIELD for Dietary sodium and water restriction

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PUBMED	(((((heart failure[MeSH Major Topic]) OR (chronic heart failure[MeSH Major Topic])) OR (stable heart failure[MeSH Major Topic]))) OR (compensated heart failure[MeSH Major Topic]))) AND (((((dietary sodium intake) OR (dietary sodium restriction)) OR (salt intake)) OR (fluid restriction))) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND (((((mortality) OR (hospitalization)) OR (quality of life)) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])))	Jan 2023	65	6
HERDIN	Sodium restriction	Dec 2022	0	0
Cochrane library	Title abstract keyword: dietary sodium AND heart failure	Dec 2022	2	0
Google scholar	In Title: heart failure ; in text : sodium restriction	Dec 2022	23	3

Table 1.2 SEARCH STRATEGY AND YIELD for exercise

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PUBMED	(((((heart failure[MeSH Major Topic]) OR (chronic heart failure[MeSH Major Topic])) OR (stable heart failure[MeSH Major Topic]))) OR (compensated heart failure[MeSH Major Topic]))) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND (((((exercise[MeSH	Jan 2023	88	5

	Major Topic]) OR (aerobic exercise[MeSH Major Topic])) OR (exercise rehabilitation[MeSH Major Topic])) OR (exercise program[MeSH Major Topic])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND (((((mortality) OR (quality of life)) OR (hospitalization)) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])))			
HERDIN	Heart failure and exercise	Dec 2022	0	0
Cochrane library	Title abstract keyword: heart failure AND exercise	Dec 2022	40	1

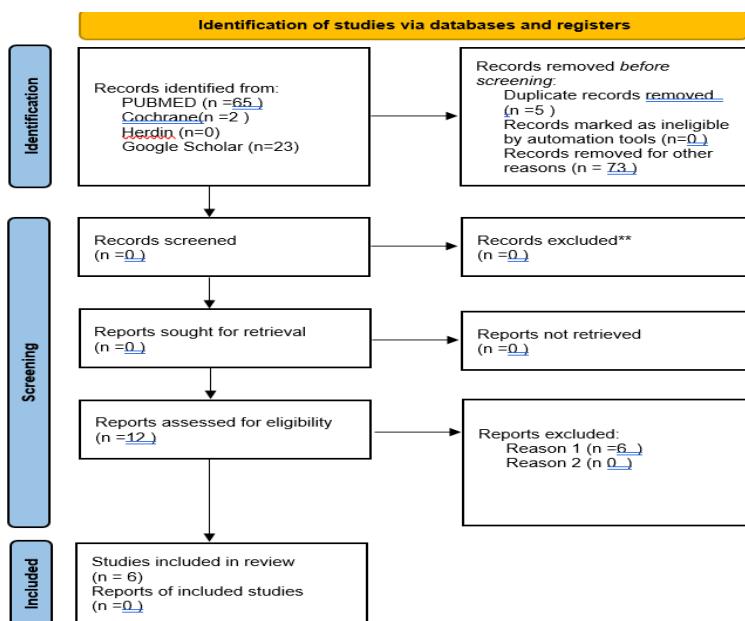


Figure 1. PRISMA Flow Diagram for dietary sodium and water restriction

Pubmed : 65 hits, 12 screened, 6 included in patients, 5 studies included : 1 for fluid, 4 for sodium

Google scholar: 23 hits, 3 included but same as pubmed hits

Herdin: no hits

Reason 1 : meta analysis including studies for in patients and out patients

Table 2. Characteristics of included studies for dietary sodium and water restriction

Title/Author	Study design	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Kalogeropoulos A, Papadimitriou L 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	RCT	27	Post discharge from HF; EF less than 40%	1500mg sodium meals	3000mg sodium meals	Study retention; hospitalization QoL KCCQ
Hummel SL, Karmally W, Gillespie BW, et al. 2018 Home-delivered meals post discharge from heart failure hospitalization. (GOURMET-HF)	RCT	66	Age above 65yo HF pxs 64% with Ef less than 50%	Sodium restricted DASH diet	Usual care	Death All cause hospitalization HF hospitalization QoL KCCQ
<u>Justin A</u> <u>Ezekowitz</u> ¹ <u>Eloisa</u> <u>Colin-Ramirez</u> ^{2et al} <u>SODIUM-HF</u> <u>Investigators</u> Reduction of dietary sodium to less than 100 mmol in heart	RCT	808	Ambulatory pxs with chronic CHF	100 mmol sodium diet	Usual care	All cause death, er visit and hospitalization

failure (SODIUM-HF): an international, open-label, randomised, controlled trial						
Paterna,S; P gaspare et al Normal sodium diet compared with low sodium diet in Compensated heart failure	RCT	232	Compensated CHF patients post discharge	80mmol sodium diet	120 mmol sodium diet	All cause Mortality HF readmission
Holst M, a. Stromberg et al Liberal vs restricted fluid restriction in stabilized	RCT	64	Stable CHF patients	1500ml water per day	30-35 ml per kg water per day	QoL Median score of MLWHFQ

Table 3. GRADE evidence profile table for dietary sodium restriction with fluid restriction in patients with stable heart failure and reduced ejection fraction for outcomes of all cause death and HF hospitalization

Author(s): Marie t. Magno

Question: Dietary sodium restriction compared to usual care for chronic heart failure with reduced EF

Setting: out patient clinics

Summary of findings:

Low sodium and fluid compared to usual care for chronic heart failure

Patient or population: chronic heart failure

Setting:

Intervention: low sodium and fluid

Comparison: usual care

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
hospitalizati on rate № of participants: 259 (2 RCTs)	OR 3.76 (1.85 to 7.63)	13.5%	37.0% (22.5 to 54.4)	23.5% more (8.9 more to 40.9 more)	⊕⊕○○ LOW ^a	
death № of participants: 232 (1 RCT)	OR 2.83 (1.06 to 7.57)	5.1%	13.2% (5.4 to 28.9)	8.1% more (0.3 more to 23.8 more)	⊕⊕○○ LOW ^b	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 4. GRADE evidence profile table for dietary sodium alone in patients with stable heart failure and reduced ejection fraction for outcomes of all cause death and HF hospitalization

Summary of findings:

Low sodium alone compared to usual care for chronic heart failure

Patient or population: chronic heart failure

Setting:

Intervention: low sodium alone

Comparison: usual care

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
hospitaliza- tion rate Nº of participants: 872 (2 RCTs)	OR 0.72 (0.48 to 1.10)	13.6%	10.2% (7 to 14.7)	3.4% fewer (6.6 fewer to 1.2 more)	⊕⊕○○	Low ^{a,b,c}
death Nº of participants: 806 (1 RCT)	OR 1.58 (0.83 to 3.02)	3.9%	6.0% (3.3 to 10.9)	2.1% more (0.6 fewer to 7 more)	⊕⊕⊕○	Moderate ^d

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 5. GRADE evidence profile table for dietary sodium alone in patients with stable heart failure and reduced ejection fraction for Quality of Life and safety outcomes

Summary of findings:

Low sodium and/or fluid compared to usual care for chronic heart failure

Patient or population: chronic heart failure

Setting:

Intervention: low sodium and/or fluid

Comparison: usual care

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
quality of life using KCCQ scores № of participants: 93 (2 RCTs)	The mean quality of life using KCCQ scores was 0	-	-	MD 10.75 higher (9.26 higher to 12.25 higher)	⊕⊕⊕ ○	Moderate ^a
change in SBP № of participants: 93 (2 studies)	The mean change in SBP was 0	-	-	MD 4.27 lower (6.9 lower to 1.63 lower)	-	-
change in creatinine № of participants: 93 (2 studies)	The mean change in creatinine was 0	-	-	MD 0.17 lower (0.19 lower to 0.15 lower)	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 6. GRADE evidence profile table for exercise-based cardiac rehabilitation in patients with stable heart failure and reduced ejection fraction for outcomes of all cause death , HF hospitalization and quality of life

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Exercise-based cardiac rehabilitation compared to usual care for heart failure

Exercise-based cardiac rehabilitation compared to usual care for heart failure

Patient or population: adults with heart failure

Setting: hospital-based, community-based, and home-based settings

Intervention: exercise-based cardiac rehabilitation

Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with all exercise interventions				
All-cause mortality up to 12 months' follow-up (all studies) Range: 6 to 12 months	58 per 1000 (38 to 70)	52 per 1000 (38 to 70)	RR 0.89 (0.66 to 1.21)	2596 (27 RCTs, 28 comparisons)	⊕⊕⊕ LOW ^{a,b}	Overall, exercise-based CR may make little or no difference in all-cause mortality in the short term (up to 12 months). Six studies had no events in either the intervention arm or the control arm Sensitivity analysis from studies at low risk of bias show similar treatment effects (RR 0.9, 95% CI 0.6 to 1.34; participants = 1651; studies = 16; $I^2 = 0\%$). From these studies, exercise-based cardiac rehabilitation probably makes little or no difference in all-cause mortality in the short term. Studies were downgraded due to imprecision (small number of events < 300)
Hospital admission heart failure only (all studies) Range: 6 months to 6.2 years	111 per 1000 (46 to 93)	65 per 1000 (46 to 93)	RR 0.59 (0.42 to 0.84)	1114 (14 RCTs, 15 comparisons)	⊕⊕⊕ LOW ^{b,f}	Overall, exercise-based CR may improve hospital admissions for heart failure only in the medium term (over 12 months) Sensitivity analysis from studies at low risk of bias was higher (RR 0.61, 95% CI 0.36 to 1.04; participants = 588; studies = 6; $I^2 = 10\%$) Based on low risk of bias studies, exercise-based CR may make little or no difference in hospital admissions for heart failure only. Studies were downgraded due to imprecision (small number of events < 300 and confidence intervals including potential for no benefit and important benefit, as 95% CI crosses RR of 0.75)
Health-related quality of life - MLWHF up to 12 months' follow-up (all studies) Range: 6 to 12 months	Mean 18 to 56 (10.49 lower to 3.73 lower)	MD 7.11 lower (6.95 lower to 0.19 higher)	-	1995 (17 RCTs, 18 comparisons)	⊕⊕⊕ LOW ^{f,g}	Overall, exercise-based CR may improve health-related quality of life in the short term (up to 12 months) Sensitivity analysis from studies at low risk of bias was lower (MD 3.38 lower, 95% CI 6.95 lower to 0.19 higher; participants = 1101; studies = 9; $I^2 = 71\%$) Based on low risk of bias studies, exercise-based cardiac rehabilitation may confer little or no benefit for health-related quality of life in the short term (up to 12 months) Studies were downgraded due to imprecision (confidence intervals including potential for no benefit and important clinical benefit) and inconsistency ($I^2 = 71\%$)

Forest plots for de novo meta-analysis for dietary sodium and water restriction

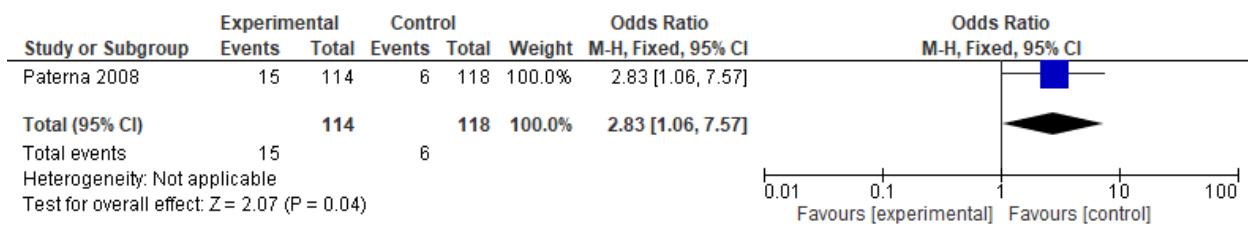


Figure 2. Forest Plot of comparison of sodium and fluid restriction vs usual care on all cause death rate

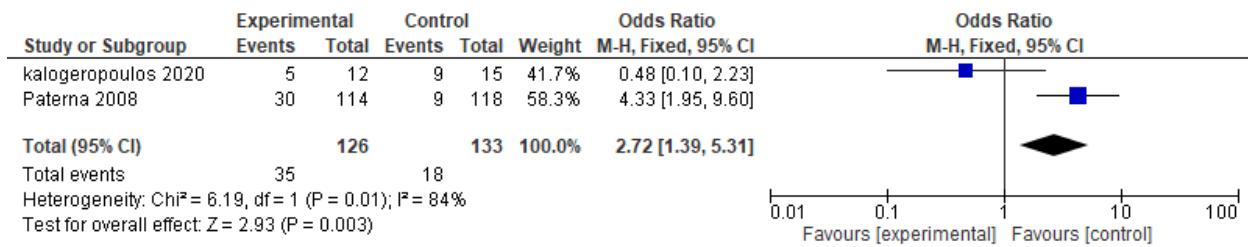


Figure 3. Forest Plot of comparison of sodium and fluid restriction vs usual care on HF hospitalization rate

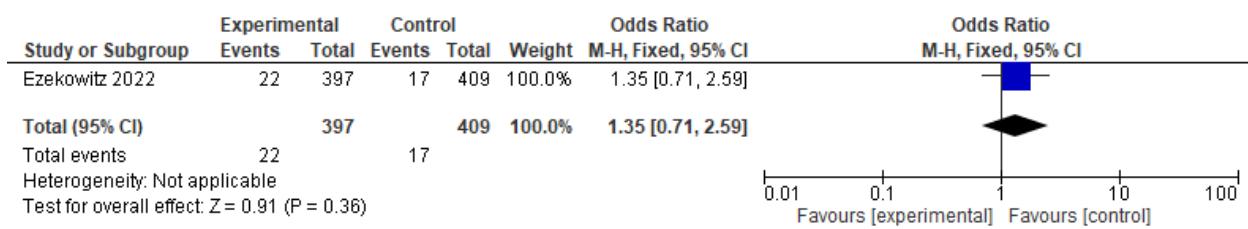


Figure 4. Forest Plot of comparison of sodium restriction vs usual care on death rate

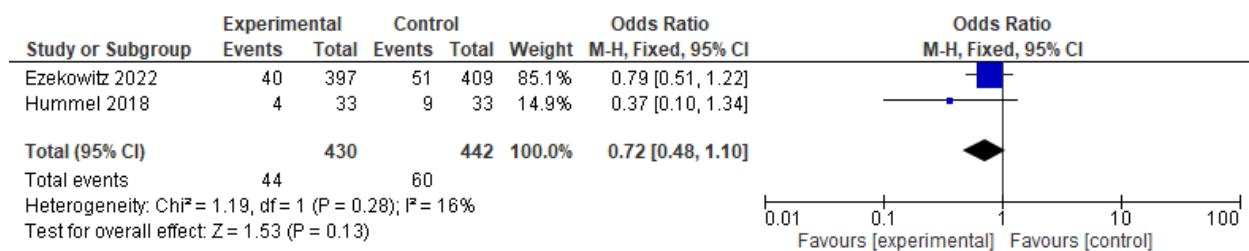


Figure 5. Forest Plot of comparison of sodium restriction vs usual care on HF hospitalization rate

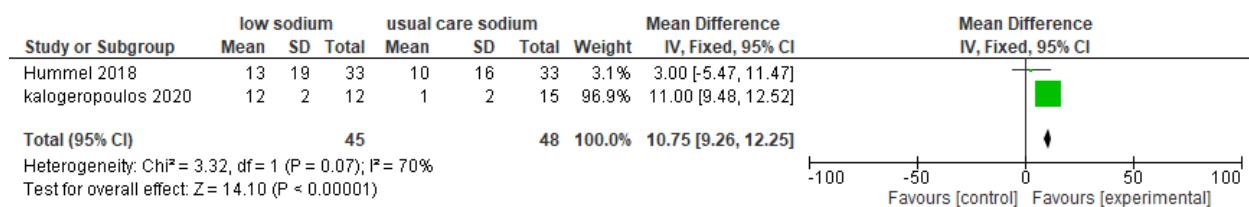


Figure 6. Forest Plot of comparison of sodium and /or fluid restriction vs usual care on quality of life

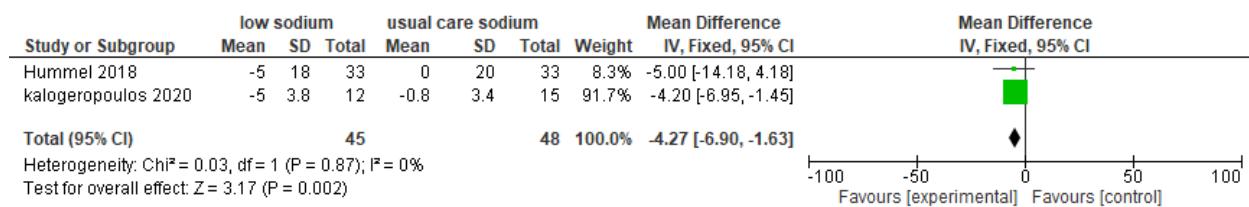


Figure 7. Forest Plot of comparison of sodium and /or fluid restriction vs usual care on safety outcome (change in SBP)

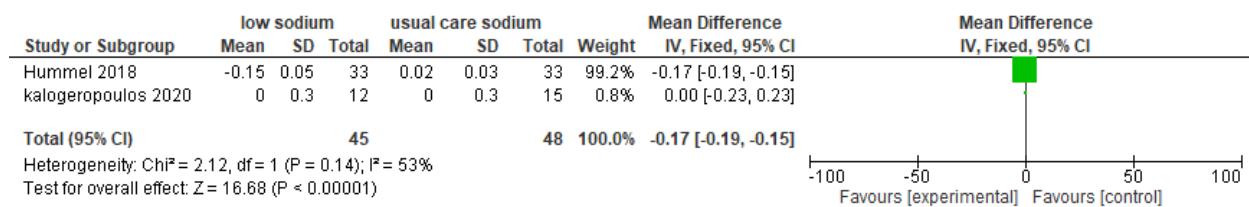


Figure 8. Forest Plot of comparison of sodium and /or fluid restriction vs usual care on safety outcome(change in creatinine)

- The evidence to decision survey prior to voting showed that the majority of the CP considered it as a priority problem. There was a split vote between small and

large desirable effects of exercise, and salt and water restriction. Majority voted for small undesirable effects of salt and water restriction and exercise, with low certainty of evidence, probably favors intervention. No included studies on certainty of evidence for required costs, with moderate cost and no study on cost effectiveness. There was a split vote on possibly important uncertainty/variability and probably no important uncertainty/variability. Unknown equity, probably acceptable and split vote between probably feasible and feasible. For recommendation A, 66.7% voted for treatment with a split vote of 50%-50% for weak vs strong recommendation. For recommendation B, 91.7% voted for treatment and 58.3% for a strong recommendation.

Annex 10: Diuretics for the treatment of confirmed heart failure

APPENDIX A. Search Strategy (last search on Jan. 20, 2023)

Database/ Sources	Time Period Searched	Inclusion Criteria	Exclusion Criteria, if any	Search terms	Full Search Strategy
Main Databases: -Medline PubMed -Google Scholar -HERDIN plus	Inception up to 20 Jan 2023	P> patients with chronic heart failure	P> Pediatric; Acute HF; Decompensated HF	MESH and free-text search for the following: "Heart Failure" OR "Congestive Heart Failure" OR "CHF"	["Heart Failure" OR "Congestive Heart Failure" OR "CHF"] AND
Clinical Trials -ClinicalTrials.gov -International Clinical Trials Registry Platform (WHO)		I> Diuretics	I> Spironolactone; Mineralocorticoid Receptor Antagonist (MRA)	"Diuretics" OR "Loop diuretics" OR "Furosemide" OR "Bumetanide" OR "Thiazides" OR "Potassium-sparing diuretics"	["Diuretics" OR "Loop diuretics" OR "Furosemide" OR "Bumetanide" OR "Thiazides" OR "Potassium-sparing diuretics"] AND
Systematic Reviews/ Meta-analysis: -Cochrane Reviews -PROSPERO		O> mortality; CV mortality; hospitalizations due to heart failure; quality of life; exercise capacity; adverse events	O> hemodynamic effects; neuroendocrine effects	"mortality" OR "Cardiovascular-related mortality" OR "CV mortality" OR "hospitalizations due to heart failure" OR "readmissions" OR "heart failure hospitalizations" OR "quality of life" OR "exercise capacity" OR "effect on symptoms"	["mortality" OR "Cardiovascular-related mortality" OR "CV mortality" OR "hospitalizations due to heart failure" OR "readmissions" OR "heart failure hospitalizations" OR "quality of life" OR "exercise capacity" OR "effect on symptoms"]

GUIDELINES -Guidelines International Network		M> meta-analysis, systematic review, RCT or cohort studies	M> case-reports; case series; non- randomized and uncontrolled clinical trials;		Limits: English Language or with English Translation
Gray Literature					

[Appendix B: Characteristics of Included Studies](#)

Table 1. Study characteristics of included studies in published metaanalysis [5]

Study ID Design	Participants	Intervention	Control	Outcomes
Boconelli, 1986 RCT - parallel	n=15 patients, 13 completed study, NYHA II-IV Follow-up: 13 weeks	Eurosemide	Captopril	Worsening heart failure (0/8 vs 1/7); exercise tolerance 43.2% vs 76.8% ; NYHA functional class improvement 8/8-vs-5/7; LV performance 17%-vs-30%
Burr, 1977 RCT- double blind withdrawal, parallel	n=106 89 completed the study Mean age 82 NYHA not available treatment diuretics 49% Follow-up 12 weeks	Diuretic agents	Placebo	Mortality 3/54-vs-1/52 Worsening heart failure 6/54-vs- 0/52
Cowley, 1986 RCT double blind cross-over	n=10 all patients completed the study mean age= 57.5 NYHA II-III Follow-up: 4 weeks	Eurosemide	Captopril	Exercise tolerance: 11.2% -vs-15.7%
De Jong, 1994 RC, open, withdrawal	n=63, 55 completed the study mean age 75 NYHA not available treatment diuretics 100% Follow-up 8 weeks	Diuretics	Placebo	Worsening heart failure 8/34-vs- 0/29

Haener, 1989 RCT, double blind parallel	n=28, all patients completed the study NYHA II-III	Furosemide	Digitalis	Exercise tolerance: 60%-vs-104% Hemodynamic improvement
Myer, 1982 RCT- double blind, withdrawal	n=77 58 had completed Mean age = 82 Chronic heart failure NYHA not available Follow-up 52 weeks	Various diuretics	Placebo	Mortality: 7/29 -vs- 2/29 Worsening heart failure: 2/29 -vs- 6/29
Richardson. 1987 RCT double blind cross-over	n=14, 10 patients completed the study mean age 54 NYHA II-III follow-up: 8 weeks	Frumil	Captopril	Worsening heart failure: 28.6%-vs 0 Exercise tolerance: 1.1%-vs. 2.2%
Sherman. 1986 RCT- double blind, parallel	n=38, 36 completed the study mean age: 59.5 NYHA I-IV Follow-up: 4 weeks	Piretanide	Placebo	Mortality: 2/18 vs- 0/20

Appendix C: GRADE Evidence Profile table

Question: Diuretics compared to Placebo for patients with chronic heart failure

Setting: Outpatient

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diuretics	Placebo	Relative (95% CI)	Absolute (95% CI)		
All Cause Mortality												
3	randomised trials	serious ^a	not serious	Serious ^b	not serious	publication bias strongly suspected ^c	3/101 (3.0%)	12/101 (11.9%)	RR 0.28 (0.09 to 0.87)	86 fewer per 1,000 (from 108 fewer to 15 fewer)	⊕⊕○○ Low	CRITICAL
Hospitalization due to worsening heart failure												
2	randomised trials	serious ^a	not serious	Serious ^b	not serious	publication bias strongly suspected ^c	0/81 (0.0%)	13/88 (14.8%)	RR 0.08 (0.01 to 0.59)	136 fewer per 1,000 (from 146 fewer to 61 fewer)	⊕⊕○○ Low	CRITICAL
Exercise Capacity												
4	randomised trials	serious ^a	not serious	Serious ^b	not serious	publication bias strongly suspected ^c	46	45	-	MD 0.76 higher (0.44 higher to 1.09 higher)	⊕⊕○○ Low	IMPORTANT
Hyponatremia												
2	observational studies	serious ^d	not serious	not serious	not serious		6413/31784 (20.2%)	3031/16394 (18.5%)	RR 1.10 (1.05 to 1.14)	18 more per 1,000 (from 9 more to 26 more)	⊕⊕○○ Low	IMPORTANT
Hypokalemia												

Nº of studies	Study design	Certainty assessment						Nº of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diuretics	Placebo	Relative (95% CI)	Absolute (95% CI)			
3	observational studies	serious ^d	not serious	not serious	not serious		5180/872 99 (5.9%)	1867/639 10 (2.9%)	RR 1.57 (1.49 to 1.65)	17 more per 1,000 (from 14 more to 19 more)		IMPORTANT	
Arrhythmia related to electrolyte abnormality													
1	observational studies	serious ^d	not serious	not serious	not serious		241/2901 (8.3%)	183/3896 (4.7%)	RR 1.77 (1.47 to 2.13)	36 more per 1,000 (from 22 more to 53 more)		IMPORTANT	

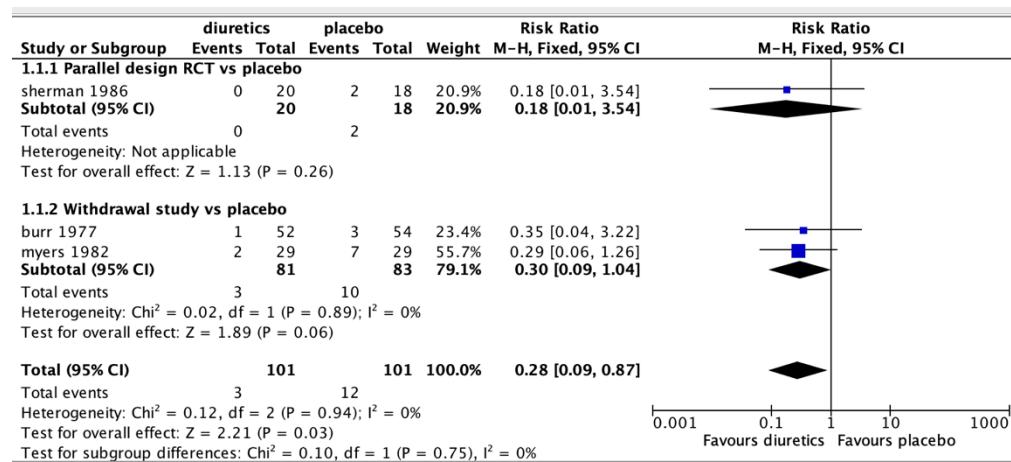
CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Unclear allocation concealment for all studies; unclear blinding of outcome assessment in some studies
- b. No data on ejection fraction. May have included patients that do not have reduced ejection fraction
- c. authors did not do statistical analysis for publication bias
- d. Some confounders may have not been accounted for: dose of diuretics, severity of heart failure

APPENDIX D. Forest plots from the published metaanalysis of diuretics on heart failure [5]

Analysis 1.1 Comparison 1 Diuretic versus placebo, Outcome 1 Mortality

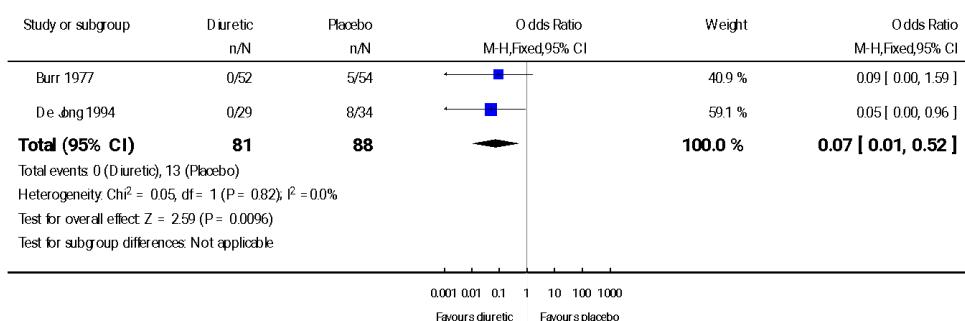


Analysis 1.2. Comparison 1 Diuretic versus placebo, Outcome 2 Heart failure worsening: Withdrawal study versus placebo.

Review: Diuretics for heart failure

Comparison: 1 Diuretic versus placebo

Outcome: 2 Heart failure worsening Withdrawal study versus placebo

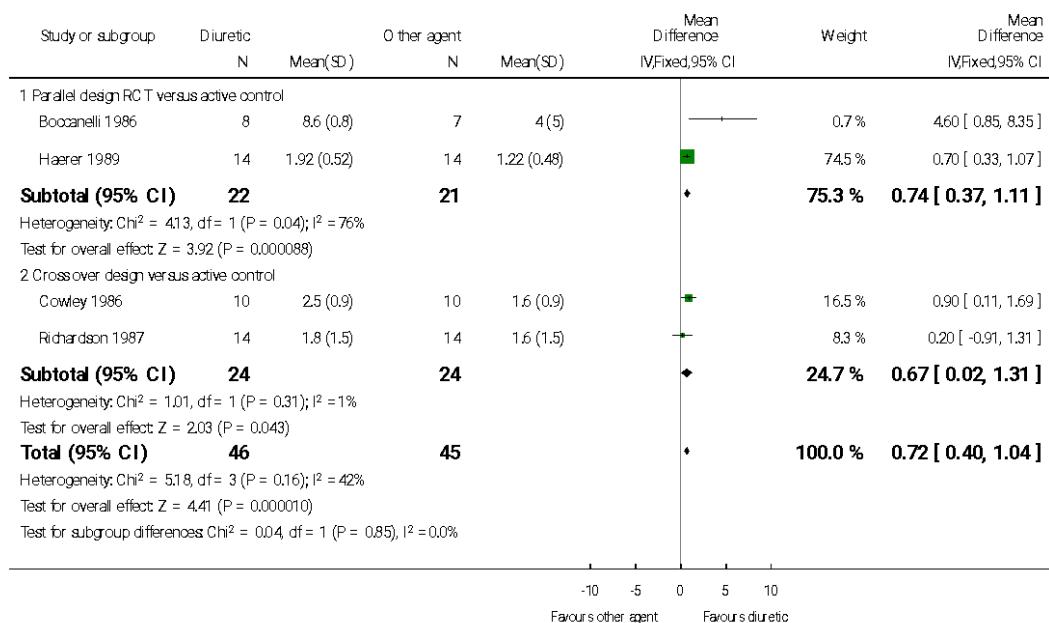


Analysis 2.1. Comparison 2 Diuretic versus other active agent, Outcome 1 Exercise capacity (positive outcome).

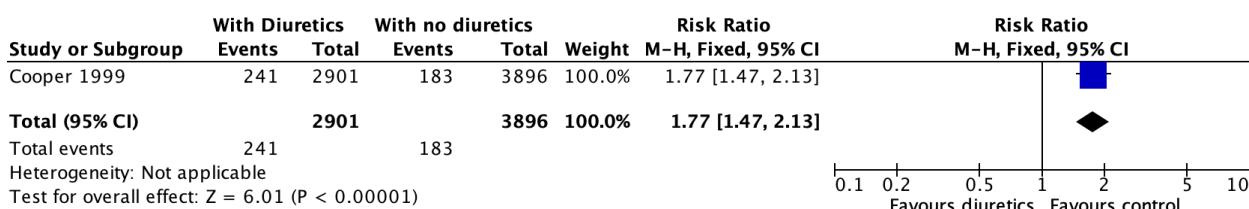
Review: Diuretics for heart failure

Comparison: 2 Diuretic versus other active agent

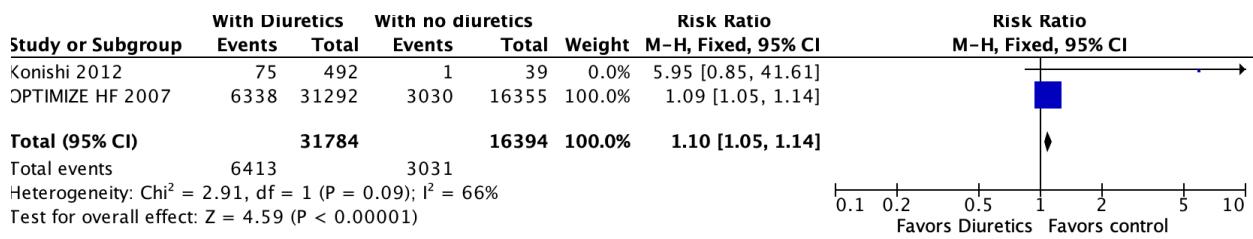
Outcome: 1 Exercise capacity (positive outcome)



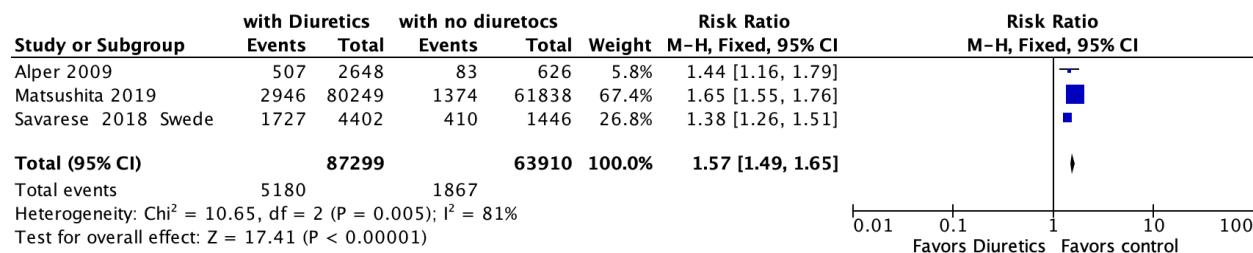
Analysis Comparison: Diuretics vs. Placebo Outcome: Arrhythmia related deaths



Analysis Comparison: Diuretics vs. Placebo Outcome: Hyponatremia



Analysis Comparison: Diuretics vs. Placebo Outcome: Hypokalemia



- The Evidence to Decision survey conducted prior to voting showed that the majority of the CP considered the question as a priority problem. With large desirable effects of diuretics. The majority voted for moderate undesirable effects with low certainty of evidence, favoring intervention. There were no included studies regarding the certainty of evidence for required costs, with moderate cost and no study on evidence of required costs. There was negligible cost and savings with no study of cost effectiveness. There was a divided vote on equity of probably no important/uncertainty/variability with probably increased equity among the CP. Diuretic treatment was considered acceptable and feasible by the CP. One hundred percent (100%) voted for treatment with 91.7% voting for strong strength recommendation.

Annex 11: Beta-blockers for the treatment of confirmed heart failure

APPENDIX 1. SEARCH STRATEGY AND DATABASES INCLUDED

Search strategy and yield (as of December 31, 2022), MEDLINE (PUBMED)

#	Query	Results
1	"heart failure"[MeSH Terms] OR heart failure[Text Word] OR congestive heart failure[Text Word] OR heart failure, diastolic[Text Word] OR Heart failure, systolic[Text Word] OR congestive heart failure[Text Word] OR heart failure, congestive[Text Word] OR left sided heart failure[Text Word] OR left-sided heart failure[Text Word] OR heart failure, left-sided [Text Word] OR heart failure, left sided[Text Word] OR right sided heart failure[Text Word] OR right-sided heart failure[Text Word] OR heart failure, right sided[Text Word] OR heart failure reduced ejection fraction[Text Word] OR heart failure, depressed[Text Word]	246,948
2	"adrenergic beta-antagonists"[MeSH Terms] OR "adrenergic beta-antagonists"[All Fields] OR "adrenergic beta-antagonists"[MeSH Terms] OR adrenergic beta-antagonist[Text Word] OR beta-blockers[Text Word] OR atenolol[Text Word] OR Bucindolol[Text Word] OR S-atenolol[Text Word] OR Bisoprolol[Text Word] OR Metoprolol[Text Word] OR Carvedilol[Text Word] OR Nebivolol[Text Word]	104,260
3	"mortality"[MeSH Terms] OR "mortality"[Text Word] OR "death"[MeSH Terms] OR "death"[Text Word] OR "hospitalization"[MeSH Terms] OR "hospitalization"[Text Word] OR "myocardial infarction"[MeSH Terms] OR "myocardial infarction"[Text Word] OR "arrhythmia"[Text Word] OR "quality of life"[MeSH Terms] OR "quality of life"[Text Word]	3,049,642
4	((("heart failure"[MeSH Terms] OR heart failure[Text Word] OR congestive heart failure[Text Word] OR heart failure, diastolic[Text Word] OR Heart failure, systolic[Text Word] OR congestive heart failure[Text Word] OR heart failure, congestive[Text Word] OR left sided heart failure[Text Word] OR left-sided heart failure[Text Word] OR heart failure, left-sided [Text Word] OR heart failure, left sided[Text Word] OR right sided heart failure[Text Word] OR right-sided heart failure[Text Word] OR heart failure, right sided[Text Word] OR heart failure reduced ejection fraction[Text Word] OR heart failure, depressed[Text Word])) AND ("adrenergic beta-antagonists"[MeSH Terms] OR "adrenergic beta-antagonists"[All Fields] OR "adrenergic beta-antagonists"[MeSH Terms] OR adrenergic beta-antagonist[Text Word] OR beta-blockers[Text Word] OR atenolol[Text Word] OR Bucindolol[Text Word] OR S-atenolol[Text Word] OR Bisoprolol[Text Word] OR Metoprolol[Text Word] OR Carvedilol[Text Word] OR Nebivolol[Text Word])) AND ("mortality"[MeSH Terms] OR mortality[Text Word] OR "death"[MeSH Terms] OR death[Text Word] OR "hospitalization"[MeSH Terms] OR hospitalization[Text Word] OR "myocardial infarction"[MeSH Terms] OR myocardial infarction[Text Word] OR arrhythmia[Text Word] OR "quality of life"[MeSH Terms] OR quality of life[Text Word])	6486
5	"adult"[MeSH Terms] OR "adult"[Text Word] AND ("heart failure"[MeSH Terms] OR "heart failure"[Text Word] OR "congestive heart failure"[Text Word] OR "heart failure diastolic"[Text Word] OR "heart failure systolic"[Text Word] OR "congestive heart failure"[Text Word] OR "heart failure congestive"[Text Word] OR "left sided heart failure"[Text Word] OR "left sided heart failure"[Text Word] OR "heart failure left sided"[Text Word] OR "heart failure left sided"[Text Word] OR "right sided heart failure"[Text Word] OR "right sided heart failure"[Text Word] OR "heart failure right sided"[Text Word] OR "heart failure reduced ejection fraction"[Text Word] OR ((("heart failure"[MeSH Terms] OR ("Heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND "depressed"[Text Word])) AND ("adrenergic beta-antagonists"[MeSH Terms] OR "adrenergic beta antagonist"[Text Word] OR "beta-blockers"[Text Word] OR "atenolol"[Text Word] OR "Bucindolol"[Text Word] OR "S-atenolol"[Text Word] OR "Bisoprolol"[Text Word] OR "Metoprolol"[Text Word] OR "Carvedilol"[Text Word] OR "Nebivolol"[Text Word]) AND ("mortality"[MeSH Terms] OR "mortality"[Text Word] OR "death"[MeSH Terms] OR "death"[Text Word] OR "hospitalization"[MeSH Terms] OR "hospitalization"[Text Word] OR "myocardial infarction"[MeSH Terms] OR "myocardial infarction"[Text Word] OR "arrhythmia"[Text Word] OR "quality of life"[MeSH Terms] OR "quality of life"[Text Word]) Translations heart failure: "heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]	3194
6	((((("adult"[mesh terms] or adult[text word]))) and (((("heart failure"[mesh terms] or heart failure[text word] or congestive heart failure[text word] or heart failure, diastolic[text word] or heart failure, systolic[text word] or congestive heart failure[text word] or heart failure, congestive[text word] or left sided heart failure[text word] or left-sided heart failure[text word] or heart failure, left-sided [text word] or heart failure, left sided[text word] or right sided heart failure[text word] or right-sided heart failure[text word] or heart failure, right sided[text word] or heart failure reduced ejection fraction[text word] or heart failure, depressed[Text Word])))) and (((("adrenergic beta-antagonists"[mesh terms] or "adrenergic beta-antagonists"[all fields] or "adrenergic beta-antagonists"[mesh terms] or adrenergic beta-antagonist[text word] or beta-blockers[text word] or atenolol[text word] or bucindolol[text word] or s-atenolol[text word] or bisoprolol[text word] or metoprolol[text word] or carvedilol[text word] or nebivolol[text word])))) and (((("mortality"[mesh terms] or mortality[text word] or "death"[mesh terms] or death[text word] or	3146

	"hospitalization"[mesh terms] or hospitalization[text word] or "myocardial infarction"[mesh terms] or myocardial infarction[text word] or arrhythmia[text word] or "quality of life"[mesh terms] or quality of life[text word])) Filters: Adult: 19+ years	
7	(("heart failure"[MeSH Terms] OR heart failure[Text Word] OR congestive heart failure[Text Word] OR heart failure, diastolic[Text Word] OR Heart failure, systolic[Text Word] OR congestive heart failure[Text Word] OR heart failure, congestive[Text Word] OR left sided heart failure[Text Word] OR left-sided heart failure[Text Word] OR heart failure, left-sided [Text Word] OR heart failure, left sided[Text Word] OR right sided heart failure[Text Word] OR right-sided heart failure[Text Word] OR heart failure, right sided[Text Word] OR heart failure reduced ejection fraction[Text Word] OR heart failure, depressed[Text Word])) AND ("adrenergic beta-antagonists"[MeSH Terms] OR "adrenergic beta-antagonists"[All Fields] OR "adrenergic beta-antagonists"[MeSH Terms] OR adrenergic beta-antagonist[Text Word] OR beta-blockers[Text Word] OR atenolol[Text Word] OR Bucindolol[Text Word] OR S-atenolol[Text Word] OR Bisoprolol[Text Word] OR Metoprolol[Text Word] OR Carvedilol[Text Word] OR Nebivolol[Text Word])) AND ("mortality"[MeSH Terms] OR mortality[Text Word] OR "death"[MeSH Terms] OR death[Text Word] OR "hospitalization"[MeSH Terms] OR hospitalization[Text Word] OR "myocardial infarction"[MeSH Terms] OR myocardial infarction[Text Word] OR arrhythmia[Text Word] OR "quality of life"[MeSH Terms] OR quality of life[Text Word])) Filters: Adult: 19+ years	3146

Nota Bene: an email prompt was set for these search terms. Notifications were continuous as of this writing. No further additional RCT or meta-analysis was added.

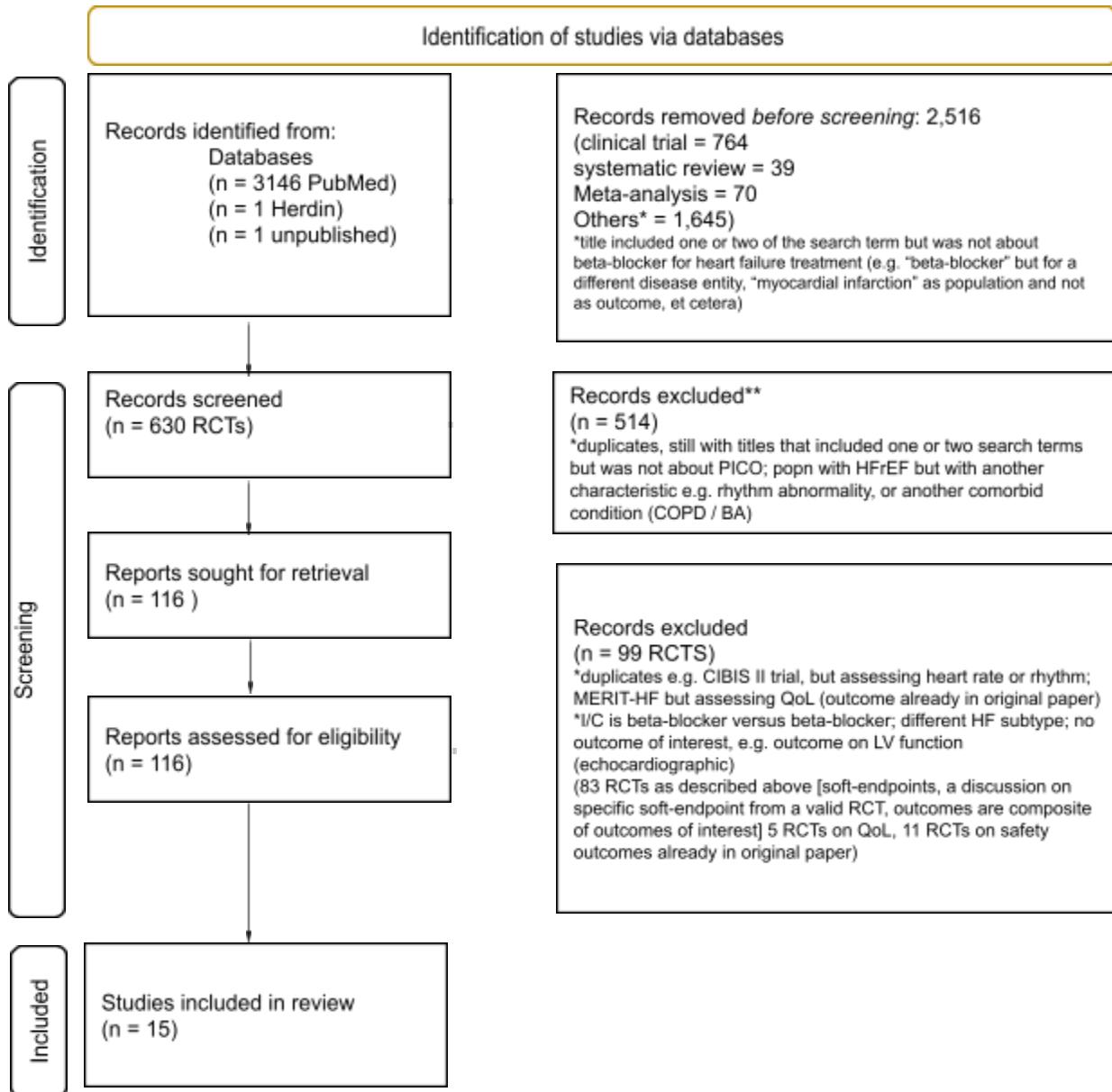
HERDIN

Guadana YD, Tolentino MCR. "Beta blockers in heart failure: A meta-analysis of large randomized trials." Philippine Heart Center Journal

UNPUBLISHED, LOCAL

Delos Santos J, Pines AA, Punzalan FER, Pestano NS. Beta Blockers on Non-Ischemic Heart Failure: What's the Evidence? A Meta-Analysis on the Randomized Clinical Trials on the efficacy of Beta Blockers on Non-Ischemic Heart failure. Unpublished. Oral presentation, Philippine College of Physicians Annual Convention 2013.

Appendix 2. PRISMA Flow Diagram for Systematic Reviews



APPENDIX 3A. TABLE OF CHARACTERISTICS OF INCLUDED STUDIES (FOR DE NOVO META-ANALYSIS)

Trial (drug), year	n total	Population	Intervention	Inclusion Criteria	Exclusion criteria	Background treatment	Endpoints Primary Secondary	Withdrawal / Lost to follow-up	Study period / Follow-up period
MDC 1993 Waagstein et al	383 189 pl 194 bb	Symptomatic IDC	Metoprolol tartrate Wk 1 10mg Wk 2 15mg Wk 3 30mg Wk 4 50mg Wk 5 75mg Wk 6 100mg Wk 7 onwards 150mg Mean dose at 3 months after randomization 108±51mg	EF < 40% Symptomatic IDC Aged 16 to 75 y/o SBP ≥90mmHg HR ≥ 45bpm NYHA Class III (80%)	Treatment with Bblockers, CCB, inotropic agents except digitalis; high dose of TCA; significant CAD (>50% obstruction); myocarditis; obstructive lung disease requiring B2-agonists; drug abuse; IDDM; phaeochromocytoma;, thyroid disease	Digitalis, diuretics, ACEI, nitrates	Combined fatal (all-cause mortality) and non-fatal (need for cardiac transplantation) endpoint 1°: Need for heart transplantation defined as: a decrease EF by ≥10 units, increase in mean right atrial pressure >5mmHg or mean PWP of > 10mmHg or both, fall in cardiac index of 30%, continuous need to be in hospital dt HF 2°: assess effect of metoprolol on cardiac function, exercise capacity, QoL, hospital admissions or emergency visits dt HF	12% metoprolol 16% placebo 1 lost During test dose: 17 had intolerance to metoprolol, ie, hypoTN, hypoTN with extreme fatigue, inc congestive sx, or both	18 months (12 after 1990) And additional 3 year data

CIBIS 1994 Lechat et al	641 321 pl 320 bb	Symptomatic HF	Bisoprolol 1.25mg/d increased to 48hours later to 2.5mg/d and 1month after to 5mg/d Prereq: clinically stable within 6 wks before study entry	EF <40% Aged 18 and 75 years old NYHA Class III (95%) NYHA Class IV (5%)	HOCM, restrictive CMP, untreated VHD, pending CABG, MI in previous 3mos, on heart transplat list, IDDM, BA, crea >300umol/l, thyroid disease, CA, SBP<85 or > 160mmHg, HR < 65 bpm	Digitalis, vasodilator therapy (ACEI)	1' all-cause mortality 2' bisoprolol tolerability: analyzed by premature tx withdrawals, NYHA class of patients, number of nonlethal events incl nonCV events	23% bisoprolol 26% placebo 1 lost Reason for withdrawal: tx failure or intercurrent pathological events: HF deterioration or being in a transplantation program (57), sinus bradycardia (2), AV block (2, Bisoprolol group)	Mean 23 mos
US-HF 1996 Packer et al	1,094 398 pl 696 bb	Symptomatic HF	Carvedilol 6.25mg, 12.5mg or 25mg bid Gradually adjusted upward to target level 50mg bid of 2 to 10 weeks	EF <35% With sx of HF for at least 3 mos despite tx with diuretic and ACEI	Major CV event/sx w/in 3mos, uncorrected VHD, myocarditis, VT / heart block, clinically important hepatic or renal dse, conditions limiting exercise or survival, tx with BB, CCB or Class 1 c antiarrhythmic, SBP <85mmHg or > 160mmHg, HR <68	Diuretic, ACEI Digoxin, hydralazine, nitrates permitted	All-cause mortality hospitalization	5.7% carvedilol 7.8% placebo No lost to ffup	Median 6.5 mos

PRECISE 1996 Packer et al	278 145 pl 133 bb	Symptomatic HF	Carvedilol Target 25 to 50mg bid	EF \leq 35% Dyspnea or fatigue at rest or on exertion for \geq 3mos	Uncorrected 1' VHD, active myocarditis, obstructive or restrictive CMP; MI, CVD, UA or CABG w/in 3 mos; sx or sust VT; SSS or adv HB w/o pacemaker; anything that could limit exercise; SBP >160mmHg or <85mmHg; HR <68; sign hepatic, renal or endocrine disease; drug or alcohol abuse,	Diuretic and ACEI allowed: digoxin, hydralazine, nitrates	1': exercise tolerance (6MWT, (min TST) 2' global assessments, NYHA fxnal class, EF, QoL scores Frequency of hospitalization for CV causes	23% 17 patients AE 6 patients administrative Dizziness 3 patients	6 mos
Colluci et al 1996	366 134pl 232 bb	Symptomatic HF	Carvedilol 12.5mg bid then uptitrated weekly up to 25mg bid (50mg bid for >85kbw pts)	LVEF \leq 35% 18 to 85 y/o	Uncorrected 1' VHD; nondilated or HCM; symp or uncontrolled sust VT; ICD w/in 3 mos; MI; UA; CABG w/in 3 mos; likelihood of PTCA, CABG or heart transplant in 12mos; SSS or 2' or 3' HB; anything that can limit exercise; SBP < 85mmHg or > 160mmHg, DBP >100mmHg; clinically significant hepatic or renal dse; illness or do that could preclude participation; women with HF w/in 12mos pp;	Diuretics, ACEI Digoxin, hydralazine, nitrates allowed but not required	1' progression of HF (death, HHF, need for sustained increase in HF meds) (pts with more than 1 endpoint is counted only once) 2' LVEF; NYHA score; HF score; physician global assessment; QoL; distance walked in 9mins TST; heart size on radiograph	2 lost 15.9% did not complete open label phase 13 AE: dizziness, hypotension (see results table)	Mean 15 mos

MOCHA 1996 Bristow et al	345 84 pl 261 bb	Symptomatic HF	Carvedilol Groups: Carvedilol 6.25mg Carvedilol 12.5mg Carvedilol 25mg	EF \leq 35% Mild to moderate stable CHF with sx for \geq 3 mos, with no change in NYHA class or HHF withing 1 mo of rando 18-85 yo Resting HR \geq 68	Uncorrected VHD, HCM, PPCM, sx or uncontrolled VT, AMI within 3 mos, CABG or PTCA in 6 mos, SSS, 2' or 3' AVB, PAD limiting walking, SBP <85mmHg or > 160mmHg, CVA w/in 3mos, cor pul, COPD on bronchodilator, crea >2.5mg/dL, SGOT or SGPT >3x normal, chronic biliary do, any terminal illness, thyroid dse, IDDM, alcohol intake >100g/d, pregnancy, lactation, plt <100, wbc >3000, hx of AE to BB; concomitant use of MAOI, CCB, flec, disopyramide, encainade, sotalol, propafenone, moricizine, amiodarone	Diuretic ACEI Allowed but not required: digoxin, hydralazine, nitrates	1': impvt in submaximal exercise (6MWT, self-powered treadmill) 2': changes in QoL with MLWHF, changes in NYHA class, changes in EF, HHF	11% group 17% group 7% 25mg group 25% placebo	6.25mg	Mean 6 mos
AUS / ANZ HF 1997 McMahon et al	415 207 pl 208 bb	Symptomatic HF dt CAD	Carvedilol 3.125mg bid with 2 to 5 wk dose titration period, maximum 25mg bid or to the highest dose tolerated	EF <45% NYHA II or III (70%) or previous II to IV	NYHA Class IV, HR < 50 bp, SSS, 2' or 3' AVB, BP < 90mmHg or >160/100mmHg, TST less than 2min or > 18 min (mod Naughton prot); MI, UA, CABG, or coronary angioplasty w/in past 4 wks; primary myocardial or VHD; current tx with BB, B agonist or verapamil; IDDM, COPD; serum aminotransferase >3x normal; crea >250umol/L; any other life-threatening non-cardiac dse.	ACEI	1': changes in LVEF, treadmill exercise duration 2': LVD, 6MWTT, sx of HF described by NYHA class and specific activity scale, frequency of death, hospital admission or worsening HF	20% carvedilol 14% placebo No lost to ffup		Mean 19 mos

CIBIS II 1999 Lechat et al	2,647 1320 pl 1327 bb	Symptomatic HF	Bisoprolol Started at 1.25mg until 10mg maximum dose reached **no run-in period	EF \leq 35% NYHA III or IV 18-80yo	MI/UA w/l 3mos; revasc w/l 6mos; prior or schedule heart transplat; uncontrolled 2' or 3' AVB; crea >300umol/L; reversible COPD; tx with BB, CCB or antiarrhythmic drugs other than amiodarone; SBP <100mmHg or uncontrolled HPN; HR <60	Diuretics, ACEI	1': All-cause mortality 2': All-cause hospital admissions, CV mortality, CV mortality + CV admission, *permanent premature tx withdrawal *medical need for BB arose Intolerance to study medication despite increases in baseline tx, study-drug dose was decreased or temporarily withdrawn, patients experienced intolerance to first dose, for all other circumstances in which study drug was permanently stopped	15% bisoprolol 15% placebo 6 lost	Mean 15 mos
MERIT HF 1999 Hjalmarson et al	3,991 2001 pl 1990 bb		Metoprolol XL 12.5mg od (for NYHA III to IV) or 25mg od	EF \leq 40% Aged 40 to 80 yo NYHA III to IV	MI/UA win 28 days; BB win 6wks; CCB or amio win 6 mos; Planned or performed transplantation or ICD; CABG or PCI planned or win 4mos; uncorrected 2' or 3' HB; other serious diseases; SBP <100mmHg; HR <68		1': All-cause mortality 2': All-cause mortality + all-cause hospitalization	14% metoprolol, 15% placebo 0 lost	Mean 12 mos

RESOLVD 2000 White et al	426 214 bb 212 pl	Severe HF	Metoprolol XL Metoprolol 12.5mg od up titrated every 2 weeks to maximum 200mg od (12.5mg, 50mg, 75mg, 100mg, 200mg)	EF <40% NYHA II to IV, 6MWT <500m HF of any cause		Candesartan or Enalapril or ACEI+ARB	1' endpoint: determine efficacy and safety of the administration Metoprolol CR in terms of 6MWT and neurohumoral parameters 1' safety endpoint: combination of AE (sx hypoTN, worsening CHF, sx bradycardia), tolerability 2' objectives: ventricular volumes and fxn, NYHA fxnal class, QoL		24 weeks total
COPERN- ICUS 2001 Packer et al	2,289 1156 bb 1133 pl	Severe HF	Carvedilol Initial dose 3.125mg bid, increased to 2 week intervals (if tolerated) 6.25mg then 12.5mg then 25mg bid	EF <25% NYHA III or IV	Uncorrected VHD or reversible cause; prior or planned cardiac transplant; 1' pulmonary or hepatic dse; crea >247.5umol/L; K <3.5 or >5.2mmol/L; coronary revasc, MI; CVD or vent arrhythmia w/in 2mos; tx with BB w/in 2mos or alpha-blocker, CCB or class I antiarrhyth w/in 4wks; SBP <85mmHg; HR <68 Tx with intravenous vasodilators or IV inotropes w/in 4 days of screening	Diuretic, ACEI	1': All-cause mortality 2': combined death or hospitalization	15% carvedilol 19% placebo 0 lost	Mean 10.4 mos

CAPRI- CORN 2001 Dargie et al	1,959 975 bb 984 pl	Severe HF	Carvedilol 6.25mg progressively increased to 25mg in 4-6 wks	EF \leq 40% 18 yo and above, stable, definite MI 3 to 21 days before rando, receipt of concurrent ACEI for at least 48h and stable dose for more than 24h.	Inotropic support, uncontrolled HF, UA, SBP <90 mmHg, uncont hypertension, HR <60 bpm, Uns IDDM, BB for any clinical indication other than HF, those on inhaled B2-agonists or steroids	ACEI Diuretics	1' all-cause mortality + hospital admission, all-cause mortality 2' sudden death, HHF, recurrent nonfatal MI, all-cause mort + recurrent nonfatal MI		Mean 1.3 years
BEST 2001 Eichhorn et al	2,708 1354 bb 1354 pl	Severe HF	Bucindolol 3mg bid x 1wk then inc weekly to 6.25mg, 12.5mg, 25mg, 50mg, and 100mg (if >75 kgs)	LVEF \leq 35% NYHA III and IV 1' or 2' DCM 18 yo and above	Reversible cause of HF, uncorrected 1' VHD, untx thyroid dse, obstructive or HCM, pericardial disease, amyloidosis, active myocarditis, malfunctioning artificial heart valve, hx of MI win 6 mos, candidate for heart trans, PCI or CABG win 60 days, UA, HR <50 bpm, tx with other investigational agents, life expectancy less than 3 years, active liver dse, crea >265 umol/L or 3mg/dL, hematologic, GI, immune, endo, metabolic or CNS dse, decomp HF, active abusers of alcohol, illicit drug use, intake of CCB, theophylline, TCA, MAO _i or beta agonists win 1 week of eval, BB win 30 days before eval, flec, encainide, propafenone, disopyramide win 2 wks before rando, amio win 8 wks before eval	ACEI	1' all-cause mortality 2' cv mortality (death dt HF, ischemic event, or sudden death); all-cause hospitalization; HHF; death + heart transplantation, EF, MI, QoL	Lost to ffup 3 pl 5 bb	

ENECA 2005 Edes et al	260 Bb 134 PI 126	Severe HF	Nebivolol 1.25mg titrated q 14 days up to maximum 10mg.day (after 8wks)	LVEF \leq 35% NYHA II to IV Stable clinical course Stable basic medication for CHF 65 and above y/o ** study included hospitalized patients	ACS, MI w/in 3mos, PTCA or CABG w/in 1 mo, obs or HCM, hemodynamically relevant CHD or VHD, HR >100/min resistant to tx, HR <50bpm. BB w/in 4 wks prior to trial, intolerance or hypersensitivity to nebivolol	ACEI \pm ARB \pm diuretics \pm digitalis	1': improvement of LVEF 2': change in NYHA functional class, QoL, hospitalization rate, survival rate, safety parameters	10 withdrawn bb 14 withdrawn pl Lost to ffup 1 (placebo group)	10 mos
Van Veldhuisen et al 2009 (Data from SENIORS 2005 but delineated into impaired and preserved EF;)	1359 EF \leq 35% Bb 678 PI 681		Nebivolol 1.25mg uptitrated every 1 – 2wks, 2.5mg, 5mg, up to 10mg at 16 th week	LVEF \leq 35% Aged \geq 70 yo Documented hospital admission within the previous 12mos with dc dx of CHF or documented EF as above w/in prev 6 mos	New drug tx for CHF w/in 6 wks, any change in CV drug tx in 2 wks, HF dt uncorrected VHD, Cl or prev BB intolerance, HR <60, SBP <90, current use of BB, significant hepatic or renal dse, CVD within 3 mos, waitlisted on PCI or cardiac sx or other major medical conditions that may reduce survival during study period	Diuretic, ACEI,	1' all-cause mortality or CV hospitalization 2' all-cause mortality, composite of all-cause mortality or all cause hospitalization, all cause hospitalization, CV mortality, composite of CV mortality or CV admission, functional capacity by NYHA, 6MWT at 6mos	Lost to ffup 16 bb 21 pl	Mean 21 mos

APPENDIX 3B. TABLE OF OUTCOMES OF INCLUDED STUDIES (FOR DE NOVO META-ANALYSIS)

Trial, Year, Intervention	Intervention n	Placebo n	Outcomes of interest (Intervention / Placebo, n (%))					Safety profile / Other notes
			All-cause mortality	Cardio-vascular Mortality	Heart Failure Mortality	Heart Failure Hospitalization	Quality of life	
MDC 1993 Metoprolol Waagstein et al	194	189	23 (11.8) 21 (11.1)		5 (2.6) 5 (2.6)		Within the metoprolol group, exercise capacity was significantly greater than at baseline at 6 months' follow-up (mean increase 80 [SD 216] s, p = 0.0006) and at 12 months (76 [214] s, p = 0.0007). In the placebo group, there was a significant improvement at 6 months (47 [189] s, p = 0.0007) but not at 12 months (15 [178] s, p = 0.46). Thus, the difference between the groups in exercise capacity improvement was significant at 12 months (0.046) but not at 6 months.	Before randomization: Hypotension alone: 3 Hypotension + extreme fatigue + increased congestive symptoms or both: 9 Extreme fatigue + congestive symptoms: 5 Withdrawal after randomization, before completing a primary endpoint: 23 patients Progressive HF: 7 AE: 4 31 patients Progressive HF: 13 AE: 7 Administrative difficulties (12 patients, 11 patients)

CIBIS 1994 Bisoprolol Lechat et al	320	321	53 (16.5) 67 (20.9)	40 (12.5) 59 (18.3)	11 (3.4) 22 (6.8)	61 (19) 90 (28)	No assessment of QoL by questionnaire Assessed by improvement in functional class Patients with improved fxnal class: Bb 68 (21%) Pl 48 (15%) P < 0.03 Deterioration of fxnal status BB 41 (13%) PI 35 (11%)	Withdrawal: 75 bb (23%, NS) 82 pl (26%) Reasons: HF deterioration being in a pretransplantation program (57) 2 sinus bradycardia bb group 2 AV block bb group Critical events recorded were per patient (ie, several critical events may be recorded in a single subject) Nonlethal critical events VT or fib: Bb 5 14 pl AF Bb 13 PI 14 2' or 3' avb: Bb 2 PI 0 HypoTN Bb 5 PI 3 Bradycardia Bb 8 PI 2 MI 2 2
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US HF 1996 Carvedilol Packer et al	696	398	22 (3.2) 31 (7.8)	20 (2.9) 31 (7.8)	5 (0.72) 13 (3.3)	Combined hospitalization cause	<p>Run-in period 5.6% not able to complete Worsening HF 1.4% Death 0.6%</p> <p>HR 12.6+12.8bpm bb 1.4+12.2 pl P<0.001 Neither group had significant changes in BP</p> <p>Most common side effect: dizziness during initiation of tx or during dose-adjustment period, but with spontaneous resolution 5.7% carvedilol (1.1% dt cardiac trans) 7.8% of the pl (1.5% dt cardiac trans)</p> <p>Dizziness 233 bb (33) 80 pl (20)</p> <p>Fatigue 177 bb (25) 93 pl (23)</p> <p>Dyspnea 150 bb (22) 101 pl (25)</p> <p>hypoTN 60bb (9) 15 pl (4)</p> <p>Bradycardia 65 bb (9) 4 pl (1)</p> <p>HF Bb 111 (16) Pl 84 (21)</p>
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PRECISE 1996 Carvedilol Packer et al	133	145	6 (4.5) 11 (7.6)				<p>Global assessment of dse severity (symptomatic improvement) 81% bb 53% pl</p> <p>Clinical deterioration 2% bb 12% pl</p>	<p>AE Dizziness</p> <p>HR decreased BB -16.3 PI -1.9 P 0.0001</p> <p>SBP BB -5.8 -0.7 P 0.002</p> <p>DBP BB -4.7 PI -0.3 P 0.002</p> <p>HypoTN BB 12.8% (17 pts) PI 4.1% (6 pts)</p> <p>Bradycardia BB 8.3% (11) PI 0.7% (1)</p> <p>Dizziness BB 60 PI 27</p> <p>HBlock BB 0 PI 2</p> <p>HF Bb 24 PI 37</p> <p>MI Bb 0</p>
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							PI 3 Syncope 6 3 Fatigue Bb 60 PI 27
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Colucci et al 1996	232	134	2 (0.9) 5 (4)		0 (0) 4 (3)	9 (4) 8 (6)	-4.9 -2.4	Adverse Experiences Open-label phase Dizziness 15%; Fatigue 12%; Dyspnea 12%
Carvedilol								Blinded phase Dizziness Bb 79 34% Pl 27 20% fatigue bb 55 23.7% + 2 (0.9) pl 32 24% + 2 (1.5) dyspnea bb 46 19.8 + 1 (0.4) pl 32 23.9 + 1 (0.7) Bradycardia Bb 30 12.9 Pl 1 0.7 hypoTN bb 21 9.1 pl 0.4 3.0 cardiac failure BB 26 (11.2) + 2 (0.9) PI 22 (16.4) + 4 (3) MI Bb 1 (0.4) Pl 1 (0.7) Syncope BB 2 (0.9) Pl 0 (0) VT Bb 0 (0) Pl 2 (1.5)

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MOCHA 1996 Carvedilol Bristow et al	261	84	12 13			13 8			During challenge period: 8% did not undergo random bec of orthostatic hypoTN or myocardial depression Vs placebo Bradycardia (p 0.03). Dizziness BB 6.25 20 (24) 12.5 29 (33) 25 34 (38) PI 19 (23) Bradycardia BB as above 1 (1) 10 (11) 10 (11) PI 1 (1) HypoTN BB as above 5 (6) 6 (7) 6 (7) PI 4 (5) HF BB as above 11 (13) 23 (26) 22 (25). PI 19 (23)
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							Fatigue BB as above 15 (18) 31 (35) 22 (25) PI 26 (31)
AUS/ANZ 1997 Carvedilol McMahon	HF 280	207	20 (7.1) 26 (12.5)	18 (6.4) 20 (9.7)	14 (5) 15 (7.2)	23 (8.2) 33 (15.9)	Continuous data on safety endpoint baseline to 12 months, supine and maximum exercise heart rates fell by 6.8 bpm and 20.2 bpm, respectively (both 2p<0.0001), in the carvedilol group compared with the placebo group. Supine and maximum exercise blood pressures declined by 5.2/3.7 mm Hg (2p=0.008/0.006) and 10.8/3.0mm Hg (2p<0.0001/0.07) respectively, in the carvedilol group compared with the placebo group during the same period. The fall in maximum exercise-rate/pressure product from baseline to 12 months was 4201 mm Hg bpm (22%; 2p<0.0001). Between the 6-month and 12-month visits, there was no evidence of any attenuation of the differences between the groups in heart rate or blood pressure (all 2p>0.1, except maximum exercise heart rate 2 ~ 0 . 0 8

CIBIS II 1999 Carvedilol Lechat et al	1327	1320	156 (11.8) 228 (17.3)	119 (9) 161 (12)	36 (3) 47 (4)	159 (12) 232 (18)		VT or Fib BB 6 PI 20 HypoTN BB 3 PI 11 Bradycardia BB 14 PI 2
MERIT HF 1999 Metoprolol XL Hjalmarson et al	1990	2001	145 217	128 203	30 58			HR decrease 14 bpm (bb); 3bpm (pl) SBP decrease -2.1 in bb, 3.5mmHg pl No safety, just Kaplan Meier
RESOLVD 2000 Metoprolol XL White et al	214	212	8 17			15 5	6MWT Bb 398 ± 84 to 397 ± 95 m PI 399 ± 85 to 396 ± 102	Symptomatic hypoTN Bb 4+4 PI 1+2 Symptomatic bradycardia 0 for both groups Worsening CHF Bb 6+7 PI 3+5

COPERNI- 2001	CUS	1156	1133	130 190			198 (17.1) 268 (23.7)		AE happened in total 451 (39) 516 (45.5)
Carvedilol									Worsening HF 192 (16.6) 273 (24.1)
Packer et al									Sudden death 45 (3.9) 69 (6.1)
									Dyspnea 19 (1.6) 26 (2.3)
									VT 12 (1.0) 26 (2.3)
									VF 12 (1.0) 23 (2.0)
									HypoTN 22 (1.9) 18 (1.6)
									CShock 5 (0.4) 19 (1.7)
									Syncope 19 (1.6) 17 (1.5)
									Bradycardia 17 (1.5) 14 (1.2)

CAPRICORN 2001 Carvedilol Dargie et al	975	984	116 (12) 151 (15)	104 (11) 139 (14)	18 (2) 30 (2)	118 (12) 138 (14)		No safety endpoints
BEST 2001 Bucindolol Eichhorn et al	1354	1354	411 (30) 449 (33)	342 (25) 389 (29)	122 (9) 140 (10)	476 (35) 569 (42)		Dizziness 583 (43) 524 (39) HypoTN 279 (21) 272 (20) Syncope 131 (10) 137 (10) Bradycardia 156 (12) 68 (5)
ENECA 2004 Nebivolol Edes et al	134	126	7 (5.2) 7 (5.6)				BB -9.13 \pm 13.78 PI -11.01 \pm 14.66 NYHA improvement in class Bb 35 PI 37 Worsened by NYHA 1 class BB 2 PI 1	Bradycardia Bb 9 PI 2 hypoTN bb 8 pl 4 Dizziness Bb 5 PI 2

Nebivolol Van Veldhuisen et al 2009 (Data from SENIORS 2005 study, but delineated into impaired and preserved. In this table: data for EF ≤35%)	678	681	88 (12.9) 104 (15.2)					SAFETY OUTCOMES DATA for the SENIORS 2005 (Flathers et al) study ARE FOR ALL RANGES OF EF; NO DATA DELINEATED FOR EF ≤35%
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APPENDIX 4A. GRADE Evidence Profile for Cardiovascular Mortality, Heart Failure Hospitalization and Quality of Life

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-blockers	placebo	Relative (95% CI)	Absolute (95% CI)		
N_Cardiovascular Mortality - Bisoprolol, Carvedilol, Metoprolol succinate, Nebivolol												
7	randomised trials	not serious ^a	not serious	not serious	not serious	none	517/6194 (8.3%)	717/5912 (12.1%)	RR 0.71 (0.61 to 0.81)	35 fewer per 1,000 (from 47 fewer to 23 fewer)	⊕⊕⊕⊕ High	CRITICAL
N_Heart Failure Hospitalization - Bisoprolol, Carvedilol, Metoprolol succinate												
6	randomised trials	not serious	not serious	not serious	not serious	none	568/4218 (13.5%)	770/4099 (18.8%)	RR 0.73 (0.66 to 0.80)	51 fewer per 1,000 (from 64 fewer to 38 fewer)	⊕⊕⊕⊕ High	CRITICAL
Quality of Life												
13	randomised trials	serious ^{b,c}	not serious	not serious	not serious	none	2396	2254	-	MD 0.04 higher (0.02 lower to 0.09 higher)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio;; EXPLANATIONS: a. SENIORS trial has attrition bias; b. Unclear risk of bias mostly because of insufficient reporting of randomization and allocation concealment for trials published in the 1990s and early 2000s. For the ENECA study, no specific mention of how allocation was concealed [just that a number was allocated to a subject and that number determined whether the patient will be given the treatment drug or a placebo]; c. 6/13 studies have unclear attrition bias

APPENDIX 4B. GRADE Evidence Profile for the Safety Outcomes

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty assessment		№ of patients	Effect		Certainty	Importance
							beta-blockers	placebo		Relative (95% CI)	Absolute (95% CI)		
Safety Outcomes - Dizziness													
6	randomised trials	not serious	not serious	not serious	serious ^a	none	1043/2810 (37.1%)	679/2241 (30.3%)	OR 1.90 (1.31 to 2.75)	149 more per 1,000 (from 60 more to 242 more)		Moderate	IMPORTANT
Safety Outcomes - Hypotension													
10	randomised trials	not serious	not serious	not serious	serious ^b	none	440/5827 (7.6%)	334/5227 (6.4%)	OR 1.74 (1.08 to 2.81)	42 more per 1,000 (from 5 more to 97 more)		Moderate	IMPORTANT
Safety Outcomes - Bradycardia													
9	randomised trials	not serious	not serious	not serious	serious ^c	none	331/5613 (5.9%)	105/5015 (2.1%)	OR 3.63 (1.84 to 7.18)	51 more per 1,000 (from 17 more to 112 more)		Moderate	IMPORTANT
Safety Outcomes - Worsening HF													
7	randomised trials	not serious	not serious	not serious	not serious	none	434/2886 (15.0%)	460/2295 (20.0%)	OR 0.69 (0.58 to 0.82)	53 fewer per 1,000 (from 73 fewer to 30 fewer)		High	IMPORTANT
Safety Outcomes - Syncope													
4	randomised trials	not serious	not serious	not serious	not serious	none	158/2875 (5.5%)	157/2766 (5.7%)	OR 1.00 (0.79 to 1.26)	0 fewer per 1,000 (from 11 fewer to 14 more)		High	IMPORTANT

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta-blockers	placebo	Relative (95% CI)	Absolute (95% CI)		
Safety Outcomes - VT or VF												
4	randomised trials	not serious	not serious	not serious	not serious	none	35/3035 (1.2%)	85/2908 (2.9%)	OR 0.40 (0.27 to 0.60)	17 fewer per 1,000 (from 21 fewer to 11 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Safety Outcomes - Dyspnea												
4	randomised trials	not serious	not serious	not serious	not serious	none	227/2217 (10.2%)	175/1810 (9.7%)	OR 0.79 (0.63 to 0.98)	19 fewer per 1,000 (from 34 fewer to 2 fewer)	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio; EXPLANATIONS: a. I^2 for heterogeneity = 79, p-value of 0.0002; b. I^2 for heterogeneity = 68%, p-value = 0.001; c. I^2 for heterogeneity = 74%, p-value = 0.001

APPENDIX 5. FOREST PLOTS OF DE NOVO META-ANALYSIS and the QUALITY OF LIFE STUDY

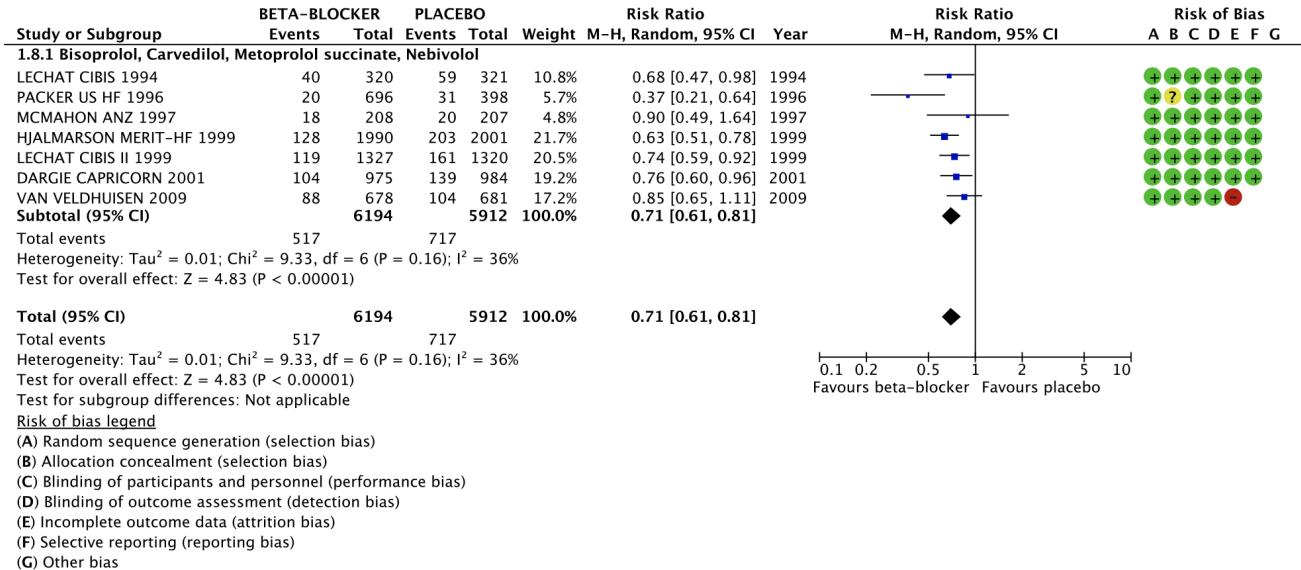


Figure 1. Forest plot on cardiovascular mortality

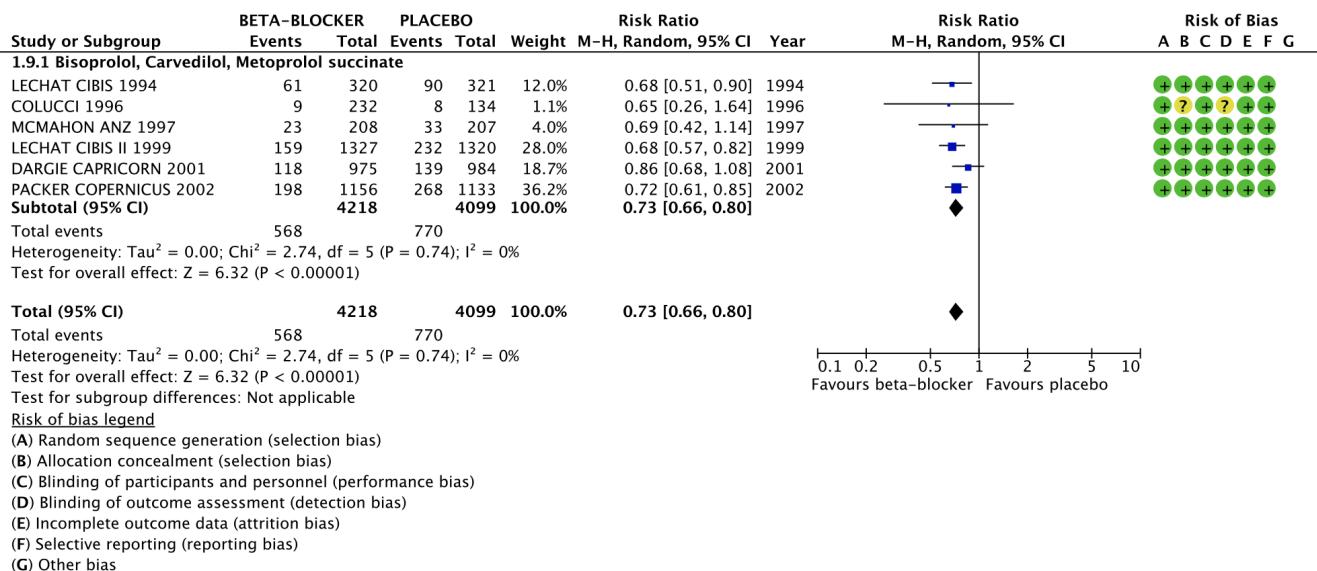
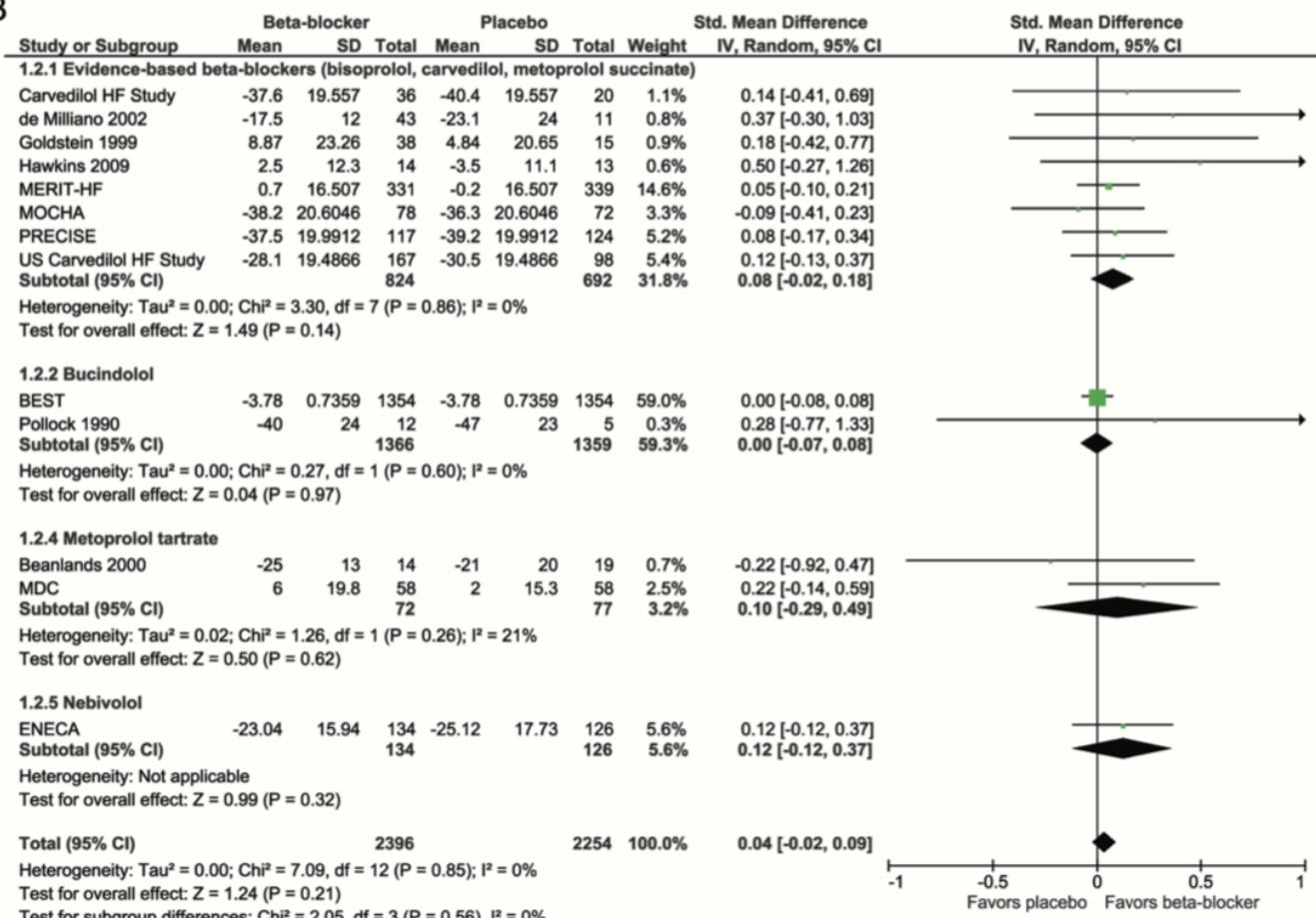


Figure 2. Forest plot for heart failure hospitalization

B

Figure 3. Forest plot for quality of life^[Turgeon]

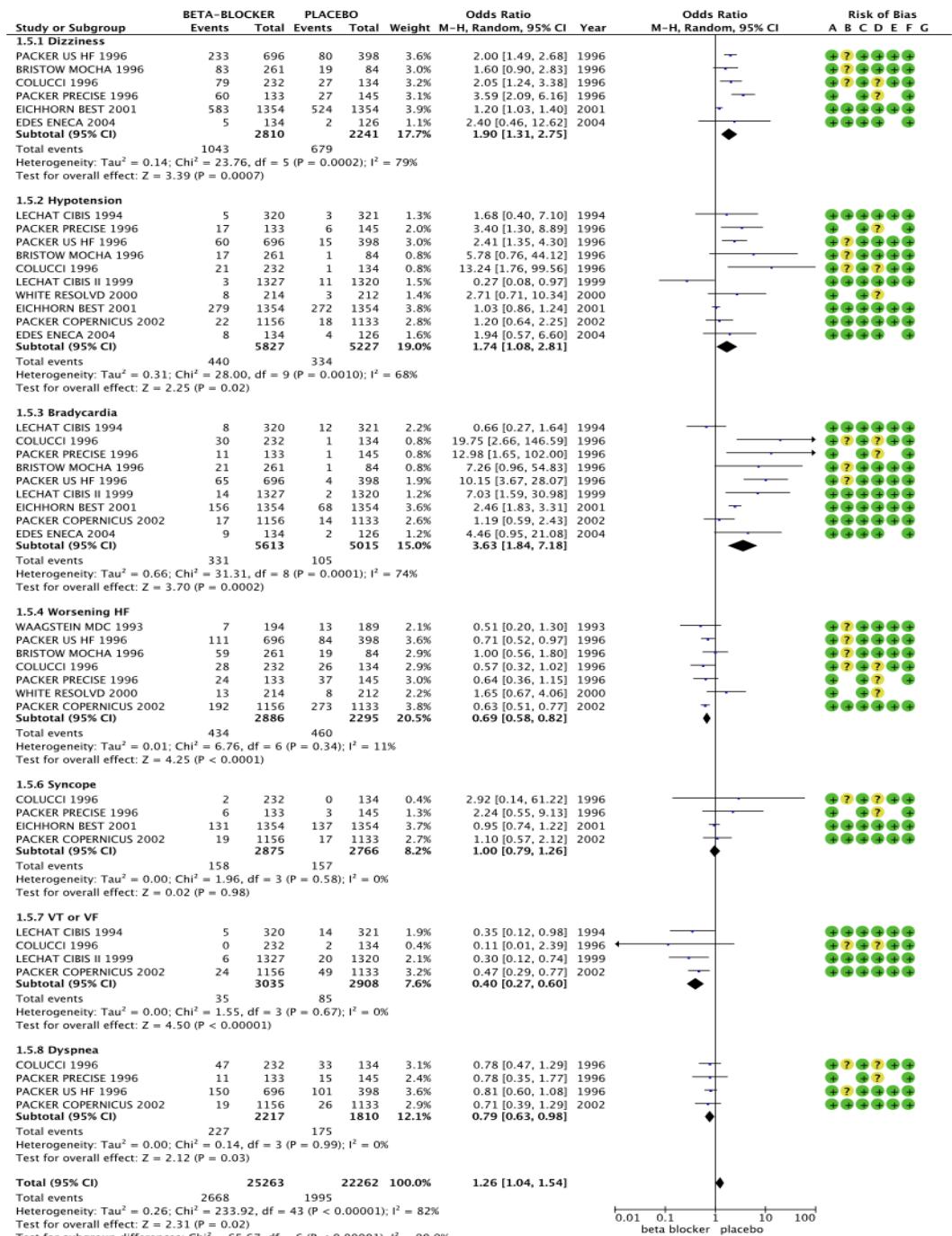


Figure 4. Forest plot on safety endpoints

APPENDIX 6. DETAILED TABLE ON RECOMMENDATION FROM INTERNATIONAL GROUPS

Group	Recommendation	Strength of recommendation Quality / Certainty of evidence
CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. Canadian Journal of Cardiology 37 (2021) 531e546. https://doi.org/10.1016/j.cjca.2021.01.017	<p>We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories:</p> <ul style="list-style-type: none"> a. ARNI (or ACEI/ARB); b. Beta-blocker; c. MRA; and d. SGLT2 inhibitor. 	GRADE Strong Recommendation; Moderate-Quality Evidence
Operational definition of HFrEF: Ejection fraction $\leq 40\%$	<p>We recommend that beta-blockers be initiated as soon as possible after the diagnosis of HF, including during the index hospitalization, provided that the patient is hemodynamically stable. Clinicians should not wait until hospital discharge to start b-blocker treatment in stabilized patients</p>	Strong Recommendation; High-Quality Evidence
	<p>We recommend patients with NYHA class IV symptoms be stabilized before initiation of b-blocker treatment</p>	Strong Recommendation; High-Quality Evidence
	<p>We recommend that b-blockers be initiated in all patients with an LVEF $< 40\%$ with previous MI</p>	Strong Recommendation; Moderate-Quality Evidence
	<p>Recommended dose: Carvedilol Starting: 3.125mg BID Target: 25mg BID (50mg if $>85\text{kg}$) Bisoprolol Starting: 1.25mg od Target: 10mg od</p>	

	<p>Metoprolol CR / XL Starting: 12.2mg to 25mg od Target: 200mg od</p>	
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 Heart, Lung and Circulation (2018) 27, 1123–1208 1443-9506/04/\$36.00 https://doi.org/10.1016/j.hlc.2018.06.1042 Operational definition of HFrEF: Ejection fraction less than 50%	<p>Beta blockers should be considered in patients with LV systolic dysfunction to decrease the risk of developing heart failure</p> <p>A beta blocker is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated, and once stabilised with no or minimal clinical congestion on physical examination, to decrease mortality and decrease hospitalisation.</p> <p>Specifically, bisoprolol, carvedilol, metoprolol (controlled release or extended release), or nebivolol</p>	<p>Strong FOR; low quality of evidence</p> <p>Strong recommendation FOR; high quality of evidence</p>
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 Operational definition of HFrEF: Ejection fraction \leq 40%	<p>In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.</p> <p><u>Dose recommendation</u></p> <p>Bisoprolol Starting: 1.25mg od Target: 10mg od Mean dose achieved: 8.6 total daily</p> <p>Carvedilol Starting: 3.125mg bid Target: 25-50mg bid Mean dose achieved: 37mg total daily</p> <p>Carvedilol CR</p>	<p>CoR I, LOE A</p>

	<p>Starting: 10mg od Target: 80mg od Mean dose achieved: --</p> <p>Metoprolol succinate (CR/XL) Starting: 12.5-25mg od Target: 200mg od Mean dose achieved: 159 mg total daily</p>	
JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure https://doi.org/10.1016/j.cardfail.2021.04.023	Use in symptomatic patients to improve prognosis	Class I, LOE A, Grade MINDS ⁺ A, LOA MINDS ⁺⁺ I
Operational definition of HFrEF: Ejection fraction < 40%	Use in asymptomatic patients with left ventricular systolic dysfunction	Class IIa, LOE B, Grade MINDS ⁺ A, LOA MINDS ⁺⁺ II
	For atrial fibrillation among patients with HF, to control heart rate	Class I, LOE A, Grade MINDS ⁺ A, LOA MINDS ⁺⁺ I
	For patients with HFrEF with Hypertension	Class I, LOE A, Grade MINDS ⁺ A, LOA MINDS ⁺⁺ I
	For patients with Chronic Kidney Disease and HF	
	CKD Stage 3	Class I, LOE A, Grade MINDS ⁺ A, LOA MINDS ⁺⁺ I
	CKD Stage 4 to 5	Class IIa, LOE B, Grade MINDS ⁺ B, LOA MINDS ⁺⁺ II
	For patients with COPD or BA and HF	Class I, LOE A, Grade MINDS ⁺ A, LOA MINDS ⁺⁺ I
	Carvedilol Start at 2.5 mg/day,** and maintain at 5 to 20mg/day twice daily Bisoprolol Start at 0.625mg/day,** and maintain at 1.25 to 5mg/day once daily	
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure	A beta-blocker is recommended for patients with stable HFrEF to	Class I, LOE A

<p>European Heart Journal (2021) 42, 3599-3726 doi:10.1093/eurheartj/ehab368</p>	<p>reduce the risk of hospitalization and death.</p>	
<p>Operational definition of HFrEF: Ejection fraction \leq 40%</p>	<p>Beta-blockers should be considered for short- and long-term rate control in patients with HF and AF</p>	<p>Class IIa</p>
	<p>Recommended dosages: Bisoprolol: starting 1.25mg od target 10mg od</p> <p>Carvedilol: starting 3.125mg bid target 25mg bid (maximum dose of 50mg bid to patients weighing more than 85kg)</p> <p>Metoprolol succinate: starting: 12.5 to 25mg od, target 200mg od</p> <p>Nebivolol: starting 1.25mg od, target 10mg od (NB: not shown to reduce CV or all-cause mortality in patients with HF or non-inferior to a treatment that does)</p>	
<p>Chronic heart failure in adults: diagnosis and management NICE guideline Published: 12 September 2018 www.nice.org.uk/guidance/ng106</p> <p>Update information Minor changes since publication November 2021: We added a link to the NICE guideline on heart valve disease in recommendations 1.2.8, 1.2.15 and 1.4.2.</p> <p>For this specific guideline, it was beta-blockers in people with heart failure in atrial fibrillation</p>	<p>Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. [2010]</p> <p>Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. [2010, amended 2018]</p> <p>Switch people whose condition is stable and who are already</p>	

	taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. [2010]	
Clinical Practice Guidelines Management of Heart Failure 2019 4th edition ISBN 978-967-11794-4-4 National Heart Association of Malaysia © 2019 Electronic version available on the following website: http://www.moh.gov.my http://www.acadamed.org.my	Indicated in all patients: BB, Improves survival and delays progression in all classes of HF Recommended doses: Bisoprolol starting: 1.25 od target 10mg od Carvedilol 3.125mg bid target 25mg bd, 50mg bid if >85kg Metoprolol succinate CR or XL: starting 12.5 to 25mg od target 200mg od Nebivolol starting: 1.25mg od target 10mg od (one study showed reduction in composite death or CV hospitalization, no reduction in mortality [226])	Grade of Recommendation I, LOE A

+Medical Information Network Distribution Service Grades of Recommendations

Grade A Strongly recommended and supported by strong evidence; Grade B Recommended with moderately strong supporting evidence; Grade C1 Recommended despite no strong supporting evidence; Grade C2 Not recommended because of the absence of strong supporting evidence; Grade D Not recommended as evidence indicates that the treatment is ineffective or even harmful

++Medical Information Network Distribution Service Levels of Evidence (Levels of Evidence in the Literature on Treatment)

I Systematic review/meta-analysis of randomized controlled trials ; II One or more randomized controlled trials; III Nonrandomized controlled trials; IVa Analytical epidemiologic studies (cohort studies); IVb Analytical epidemiologic studies (case-control studies and cross-sectional studies); V Descriptive studies (case reports and case series); VI Not based on patient data, or based on opinions from a specialist committee or individual specialists

- The Evidence to Decision survey prior to voting showed that the majority of the CP considered the question a priority problem. There were moderate desirable and undesirable effects of beta blockers, with moderate certainty of evidence, favoring intervention. There were no included studies on certainty of evidence for required costs, with moderate costs and favors intervention for cost effectiveness. Majority of the CP voted for possibly important uncertainty/variability. There was a split vote between probably increased and increased for equity. Majority of the CP voted that it is feasible and acceptable. All members of the CP (100%) voted for treatment with 100% vote of strong recommendation.

Annex 12. RAS-blockers and ARNIs for the treatment of confirmed heart failure

APPENDICES

Appendix Table 1. Characteristic of Included Studies

Type of Study	Number of RCTs	Number of Patients	Follow-up Days	Drug of Interest	Control
Network Meta Analysis ³	28 RCTs	47,407	Median 500 days	Sacubutril/Valsartan ARB: candesartan, valsartan, losartan, telmisartan ACE-Is: fosinopril, trandolapril, spirapril/enalapril, benazepril, captopril	ARB: valsartan ACE-I: enalapril, captopril Placebo

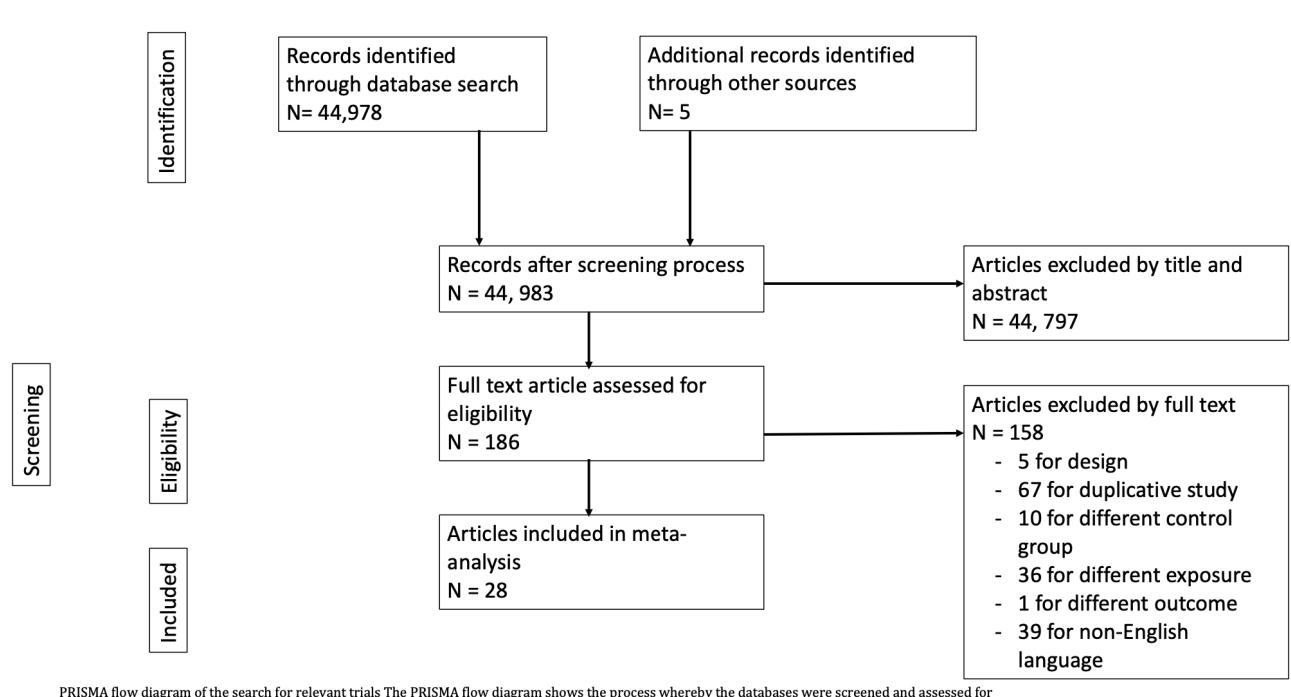
Appendix Table 2. Summary of Clinical Trials

Trial*	Author	Year	Follow-Up (Days)	LVEF (%)	Case			Control		
					n	Class	Generic	n	Class	Generic
LIFE	Mann et al	2021	168	≤35	167	ARNI	Sacubutril/valsartan	168	ARB	valsartan
Outstep-HF	Piepoli et al	2021	84	≤40	309	ARNI	Sacubutril/valsartan	310	ACE-I	enalapril
PARALLEL-HF	Tsutsui et al	2021	183	≤35	111	ARNI	Sacubutril/valsartan	112	ACE-I	enalapril
Evaluate-HF	Dessai et al	2019	84	≤40	231	ARNI	Sacubutril/valsartan	233	ACE-I	enalapril
Prime	Kang et al	2019	365	25–50	60	ARNI	Sacubutril/valsartan	58	ARB	valsartan
Pioneer-HF	Velazquez et al	2018	56	≤40	440	ARNI	Sacubutril/valsartan	441	ACE-I	enalapril
PARADIGM-HF	McMurray et al	2014	810	≤35	4,187	ARNI	Sacubutril/valsartan	4,212	ACE-I	enalapril
ARCH-J	Matsumori et al	2003	168	≤45	148	ARB	candesartan	144	placebo	placebo
CHARM-alternative	Granger et al	2003	1,011	≤40	1,013	ARB	candesartan	1,015	placebo	placebo
Valiant	Pfeffer et al	2003	741	≤45	4,909	ARB	valsartan	4,909	ACE-I	captopril
Heaven	Willemheimer et al	2002	84	≤45	70	ARB	valsartan	71	ACE-I	enalapril
OPTIMAAL	Dickstein et al	2002	986	≤35	2,744	ARB	losartan	2,733	ACE-I	captopril
Replace	Dunselman et al	2001	84	≤40	301	ARB	telmisartan	77	ACE-I	enalapril
Val-HeFT	Cohn et al	2001	690	≤40	2,511	ARB	valsartan	2,499	placebo	placebo
Elite II	Pitt et al	2000	555	≤40	1578	ARB	losartan	1574	ACE-I	captopril
Spice	Granger et al	2000	84	≤35	179	ARB	candesartan	91	placebo	placebo
RESOLVD	McKelvie et al	1999	301	≤40	327	ARB	candesartan	109	ACE-I	enalapril
Stretch	Riegger et al	1999	84	35–45	633	ARB	candesartan	211	placebo	placebo
Elite	Pitt et al	1997	336	≤40	352	ARB	losartan	370	ACE-I	captopril
LPES	Lang et al	1997	84	≤45	78	ARB	losartan	38	ACE-I	enalapril
Dickstein et al (1995)	Dickstein et al	1995	56	≤35	108	ARB	losartan	58	ACE-I	enalapril
Fest	Erhardt et al	1995	84	≤35	155	ACE-I	fosinopril	153	placebo	placebo
FHFSG	Brown et al	1995	168	≤35	116	ACE-I	fosinopril	125	placebo	placebo
Trace	Koher et al	1995	720–1,500	≤35	876	ACE-I	trandolapril	873	placebo	placebo
Cassis	Widimsky et al	1995	84	≤40	200	ACE-I	spirapril, enalapril	48	placebo	placebo
Colfer et al (1992)	Colfer et al	1992	84	≤35	114	ACE-I	bemazepril	58	placebo	placebo
Save	Pfeffer et al	1992	1260	≤40	1,115	ACE-I	captopril	1,116	placebo	placebo
SOLVD	SOLVD Investigators	1991	1242	≤35	1285	ACE-I	enalapril	1284	placebo	placebo

* References of all the trials are shown in Supplementary Table 2.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; LVEF = left ventricular ejection fraction.

Figure 1. PRISMA Diagram



Appendix Table 3. GRADE Pro Table for ARNI vs Placebo

Author(s):

Question: ARNI compared to placebo for adult Filipino patients with HFrEF

Setting: Outpatient setting

Bibliography:

Certainty assessment							Nº of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI	placebo	Relative (95% CI)	Absolute (95% CI)		
All cause mortality												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI	placebo	Relative (95% CI)	Absolute (95% CI)		
27	observational studies	not serious	not serious	serious ^a	not serious	strong association all plausible residual confounding would reduce the demonstrated effect			RR 0.75 (0.63 to 0.89)	1 fewer per 1,000 (from 1 fewer to 1 fewer)		CRITICAL
Cardiovascular death												
16	RCT	not serious	not serious	serious ^a	not serious	strong association all plausible residual confounding would reduce the demonstrated effect			RR 0.71 (0.57 to 0.89)	1 fewer per 1,000 (from 1 fewer to 1 fewer)		CRITICAL
Hospitalization for worsening heart failure												
18	RCT	not serious	not serious	serious ^a	not serious	strong association all plausible residual confounding would reduce the demonstrated effect			RR 0.60 (0.48 to 0.75)	1 fewer per 1,000 (from 1 fewer to 0 fewer)		CRITICAL
Hypotension												
19	RCT	not serious	not serious	serious ^a	not serious	strong association all plausible residual confounding would reduce the demonstrated effect			RR 2.98 (1.91 to 4.67)	3 fewer per 1,000 (from 5 fewer to 2 fewer)		IMPORTANT
Hyperkalemia												
14	RCT	not serious	not serious	serious ^a	not serious	strong association			RR 2.55 (1.32 to 4.90)	3 fewer per 1,000 (from 5 fewer to 1 fewer)		IMPORTANT
Renal Failure												
16	RCT	not serious	not serious	serious ^a	not serious	strong association			RR 1.23 (0.82 to 1.84)	1 fewer per 1,000 (from 2 fewer to 1 fewer)		IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Indirect evidence from a network meta analysis

Appendix Table 4. GRADE Pro Table for ARNI vs ARB

Author(s): Gonzales-Santos, Louella, Oliva, Raymond

Question: ARNI compared to ARB for Adult Filipinos with HFrEF

Setting: Outpatient Clinic

Bibliography:

No of studies	Study design	Risk of bias	Certainty assessment				No of patients	Effect		Certainty	Importance	
			Inconsistency	Indirectness	Imprecision	Other considerations		ARNI	ARB			
All cause mortality (follow-up: range 168 days to 365 days)												
2	randomised trials	not serious	not serious	serious ^a	not serious	none			RR 0.81 (0.68 to 0.96)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Cardiovascular Mortality (follow-up: range 168 days to 365 days)												
2	random - ised trials	not serious	not serious	serious	not serious	none			RR 0.79 (0.64 to 0.99)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Hospitalization for worsening heart failure (follow-up: range 168 days to 365 days)												
2	random- ised trials	not serious	not serious	serious ^a	not serious	none			RR 0.85 (0.69 to 1.03)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Hypotension (follow-up: range 168 days to 365 days)												
2	random - ised trials	not serious	not serious	serious ^a	not serious	none			RR 1.46 (1.02 to 2.10)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
Hyperkalemia (follow-up: range 168 days to 365 days)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI	ARB	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious ^a	not serious	none			RR 1.20 (0.73 to 1.97)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
Renal Failure (follow-up: range 168 days to 365 days)												
2	randomised trials	not serious	not serious	serious ^a	not serious	none			RR 0.67 (0.47 to 0.96)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

a. LIFE trial included patients with NYHA IV and hospitalized patients with HFrEF

Appendix Table 5. GRADE Pro Table for ARNI vs ACE-I

Author(s):

Question: ARNI compared to ACE-Is for adult Filipino patients with HFrEF

Setting: Outpatient clinic

Bibliography:

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI	ACE-Is	Relative (95% CI)	Absolute (95% CI)		
All cause mortality (follow-up: range 56 days to 810 days)												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.87 (0.74 to 1.01)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕○ High	CRITICAL
Cardiovascular death (follow-up: range 56 days to 810 days)												

№ of studies	Study design	Certainty assessment						№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI	ACE-Is	Relative (95% CI)	Absolute (95% CI)			
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.86 (0.71 to 1.04)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL	
Hospitalization for worsening heart failure (follow-up: range 56 days to 810 days)													
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.86 (0.72 to 1.03)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL	
Hypotension (follow-up: range 56 days to 810 days)													
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.69 (1.27 to 2.24)	2 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	
Hyperkalemia (follow-up: range 56 days to 810 days)													
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.29 (0.94 to 1.76)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	
Renal failure (follow-up: range 56 days to 810 days)													
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.93 (0.72 to 1.21)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	

CI: confidence interval; RR: risk ratio

Appendix Table 6. GRADE Pro Table for ARB vs Placebo

Author(s):

Question: ARB compared to placebo for adult Filipinos with HFrEF

Setting: Outpatient setting

Bibliography:

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	placebo	Relative (95% CI)	Absolute (95% CI)		
All cause mortality												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.92 (0.84 to 1.01)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL
Cardiovascular mortality												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.90 (0.79 to 1.01)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL
Hospitalizations for worsening HF												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.71 (0.61 to 0.81)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL
Hypotension												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 2.04 (1.43 to 2.92)	2 fewer per 1,000 (from 3 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Hyperkalemia												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 2.13 (2.12 to 4.03)	2 fewer per 1,000 (from 4 fewer to 2 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Renal Failure												
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.84 (1.35 to 2.51)	2 fewer per 1,000 (from 3 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Angioedema												

Certainty assessment								No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	placebo	Relative (95% CI)	Absolute (95% CI)			
5	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.18 (0.36 to 3.89)	1 fewer per 1,000 (from 4 fewer to 0 fewer)	⊕⊕⊕⊕ High	IMPORTANT	

CI: confidence interval; RR: risk ratio

Appendix Table 7. GRADE Pro Table for ARB vs ACE-Is

Question: ARB compared to ACE-Is for adult Filipinos with HFrEF

Setting: Out patient setting

Bibliography:

Certainty assessment								No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	ACE-Is	Relative (95% CI)	Absolute (95% CI)			
All cause mortality													
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.07 (0.98 to 1.16)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕ ⊕ High	CRITICAL	
Cardiovascular mortality													
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.08 (0.97 to 1.20)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕ ⊕ High	CRITICAL	
Hospitalization for worsening HF													
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.02 (0.90 to 1.15)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕ ⊕ High	CRITICAL	
Hypotension													
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.15 (0.88 to 1.52)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕ ⊕ High	IMPORTANT	
Hyperkalemia													

Nº of studies	Study design	Risk of bias	Certainty assessment				Nº of patients		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	ARB	ACE-Is	Relative (95% CI)	Absolute (95% CI)		
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.07 (0.67 to 1.91)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕ ⊕ High	IMPORTANT
Renal failure												
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.40 (1.07 to 1.83)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕ ⊕ High	IMPORTANT
Angioedema												
9	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.59 (0.33 to 1.04)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕⊕ ⊕ High	IMPORTANT

CI: confidence interval; RR: risk ratio

Appendix Table 8. GRADE Pro Table for ACE-Is vs Placebo

Author(s):

Question: ACE compared to Placebo for adult Filipinos with HFrEF

Setting: Out patient setting

Bibliography:

Nº of studies	Study design	Risk of bias	Certainty assessment				Nº of patients		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	ACE	Placebo	Relative (95% CI)	Absolute (95% CI)		
All cause mortality												
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.86 (0.79 to 0.84)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕ High	CRITICAL
Cardiovascular Mortality												

Certainty assessment								Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE	Placebo	Relative (95% CI)	Absolute (95% CI)			
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.83 (0.74 to 0.93)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL	
Hospitalization for worsening Heart Failure													
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 0.69 (0.59 to 0.81)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ High	CRITICAL	
Hypotension													
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.77 (1.23 to 2.55)	2 fewer per 1,000 (from 3 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	
Hyperkalemia													
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.98 (1.09 to 3.60)	2 fewer per 1,000 (from 4 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	
Renal failure													
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 1.32 (0.96 to 2.06)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	
Angioedema													
7	randomised trials	not serious	not serious	not serious	not serious	none			RR 2.00 (0.53 to 7.51)	2 fewer per 1,000 (from 8 fewer to 1 fewer)	⊕⊕⊕⊕ High	IMPORTANT	

CI: confidence interval; RR: risk ratio

- The evidence to decision survey done prior to voting showed that the majority of the CP considered the question a priority problem. There were large desirable and small undesirable effects of RAAS blockers with moderate certainty of evidence, favoring intervention. There were no studies on certainty of evidence for required costs. There are moderate costs favoring intervention for cost-effectiveness. The majority voted for probably no important uncertainty/variability. The CP voted with probably increased equity that the use of RAAS blockers is feasible and acceptable. All members of the CP (100%)

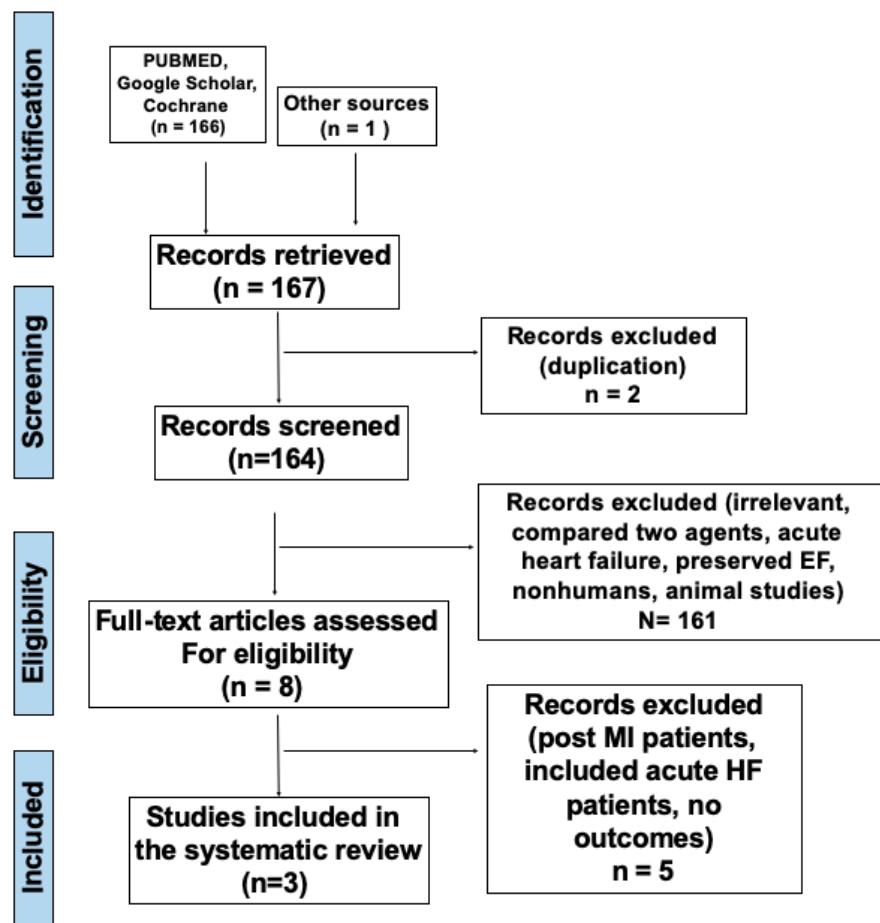
voted to recommend treatment. All members of the CP (100%) voted for strong recommendation of recommendation 10A while 77.8% voted for the strong recommendation of recommendation 10B.

Annex 13. MRAs for the treatment of confirmed heart failure

SEARCH STRATEGY

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	Search terms: spironolactone, eplerenone, heart failure *restricted articles to last 15 years and RCT	1/27/23 at 6:00 PM	154	2
CENTRAL	spironolactone, eplerenone, heart failure	1/27/23 at 6:00 PM	10	2
Google Scholar	spironolactone, eplerenone, heart failure	1/27/23 at 6:00 PM	60	2
ClinicalTrials.gov	spironolactone, eplerenone, heart failure	1/27/23 at 6:00 PM	109	1

PRISMA FLOW DIAGRAM



Study characteristics

Trial	Participants	Intervention	Control	Follow-up
Emphasis- HF (Zannad 2011)	HFrEF, EF ≤ 35%, NYHA II	Eplerenone (n = 1364) 25-50 mg OD	Standard of care + placebo (n = 1373) Angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both and a beta-blocker	21 months
Vizzardi 2014	NYHA I-II, EF < 40%	Spiro-lactone, 25 to 400 mg, N=65	Placebo + standard of care, n=65 Angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin	3.4 years

			receptor blocker [ARB] if not tolerated) and a beta-blocker,	
Akbulut	NYHA III, EF < 35%	Spirono-lactone 25 mg	ACE inhibitor (2.5 mg/day ramipril), loop diuretic (40 mg/day furosemide), and digitalis (0.25 mg/day digoxin)	12 weeks
Udelson	II-III, EF < 30%	Eplerenone 50 mg	ACEI and/or angiotensin receptor blocker and BB	9 months
Cicoira	left ventricular ejection fraction (\leq 45%)	Spirono-lactone 25 mg	ACE inhibitor +/- beta blocker	12 months
Berry	I-III, EF<40%	Spirono-lactone 25 mg, n=20	N=20 Beta-blocker and either an ACE inhibitor or an angiotensin receptor blocker for at least 30 days	12 weeks

RISK OF BIAS OF INCLUDED STUDIES

Study ID	Random sequence generation (selection bias)	allocation concealment (selection bias)	Blinding of participant and personnel (performance bias)	Blinding of outcome assessment (detection bias)	incomplete outcome data (attrition bias)	selective outcome reporting (reporting bias)	Overall	Comments
Zannad et al	L	L	L	L	L	L	L	
Vizzardi et al	U	U	U	U	L	U	H	Not powered for mortality outcome
Akbulut	U	U	U	U	L	U	H	
Cicoira	U	U	U	L	L	U	H	Unknown randomization process and allocation concealment
Berry	U	U	L	L	L	U	L	Low sample size
Udelson	L	L	L	L	L	U	L	

GRADE Evidence Profile

Certainty Assessment							Nº of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA	SOC in HFrEF	Relative (95% CI)	Absolute (95% CI)		
CV mortality												
2	randomised trials	serious ^a	not serious	not serious	not serious	none	150/1429 (10.5%)	193/1438 (13.4%)	RR 0.78 (0.64 to 0.96)	30 fewer per 1,000 (from 48 fewer to 5 fewer)	 Moderate	
All-cause mortality												
4	randomised trials	serious ^a	not serious	not serious	not serious	none	182/1581 (11.5%)	225/1583 (14.2%)	RR 0.81 (0.68 to 0.97)	27 fewer per 1,000 (from 45 fewer to 4 fewer)	 Moderate	
Hospitalizations from HF												
2	randomised trials	not serious	not serious	not serious	not serious	none	170/1471 (11.6%)	266/1482 (17.9%)	RR 0.64 (0.54 to 0.77)	65 fewer per 1,000 (from 83 fewer to 41 fewer)	 High	
Hyperkalemia												
4	randomised trials	serious ^a	not serious	not serious	serious ^b	none	132/1577 (8.4%)	57/1579 (3.6%)	RR 2.30 (1.70 to 3.11)	47 more per 1,000 (from 25 more to 76 more)	 Low	
Quality of life												
1	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	20	20	-	SMD 0.04 higher (0.58 lower to 0.66 higher)	 Low	

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

Explanations

a. Unclear method or randomization and allocation concealment

b. Wide CI

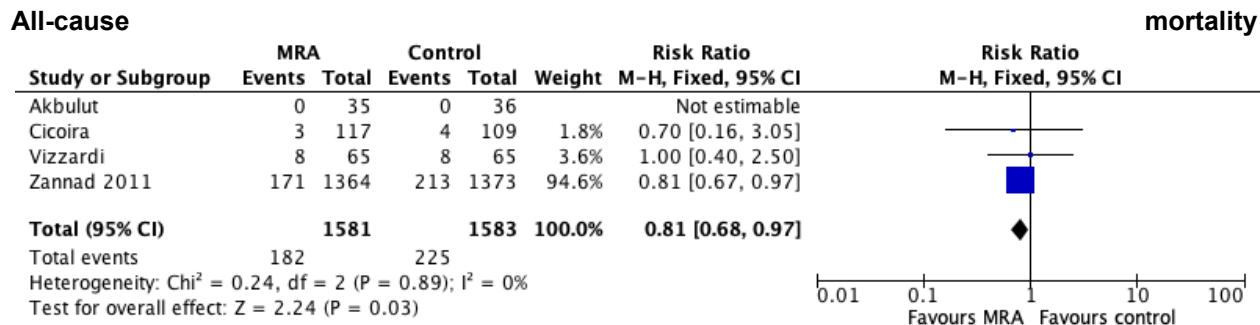
c. Crossed the line of no effect

Forrest plots

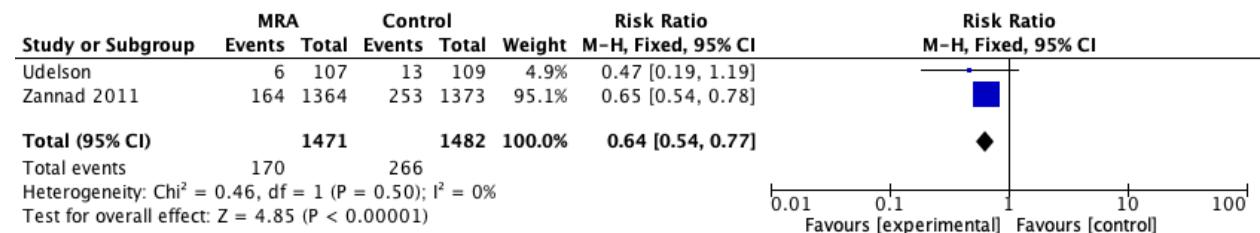
CV



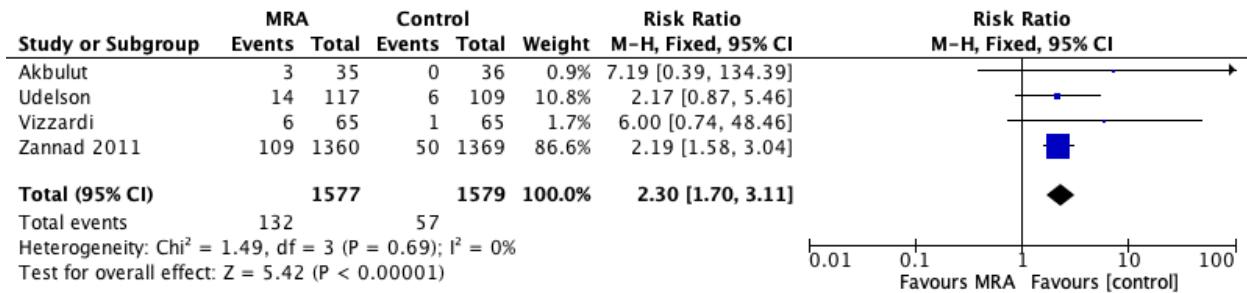
All-cause



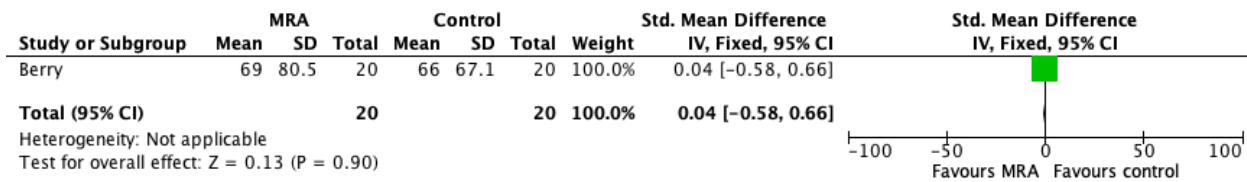
Hospitalizations from HF



Hyperkalemia



Quality of life



- The evidence to the decision survey prior to voting showed that 100% of the CP considered the question a priority problem. For the desirable effects, 63.6% voted for large desirable effects and 63.6% voted for small undesirable effects of MRA. There was also a low certainty of evidence (72.7%), favoring comparison for balance of effects. The 36.4% voted for probably no important uncertainty/variability and 36.4% voted for possibly important uncertainty variability in how much people value the main outcomes. As to balance of effects, 36.4% voted for favoring the comparison considering the balance of effects. 63.6% voted for moderate costs which probably favor intervention for cost-effectiveness at 45.5%. 36.4% voted for probably reduced equity and the intervention is acceptable (54.5%) and feasible to implement (72.7%). The majority also voted that MRA use is feasible and acceptable. Majority of the CP (90.9%) voted to recommend treatment with strong strength of recommendation at 90.9%.

Annex 14. SGLT2i for the treatment of confirmed heart failure

APPENDIX A: 1) SEARCH STRATEGY and YIELD (24 January 2023, 9:00 pm) for PUBMED:

Search	Query	Results
#38	Search: #9 and #29 and #35 and #37	113
#37	Search: #30 or #31	43,050
#36	Search: #9 and #29 and #33 and #35	0
#35	Search: #20 or #34	6,100
#34	Search: sodium-glucose transport protein 2 (SGLT2) inhibitors	1,647
#33	Search: #30 and #31 and #32	41
#32	Search: outpatient clinic	106,512
#31	Search: adults with reduced ejection fraction	12,657
#30	Search: adults with chronic heart failure	32,441
#29	Search: #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28	4,185,397
#28	Search: side effects	2,878,244
#27	Search: safety profile	78,047
#26	Search: adverse events	323,243
#25	Search: quality of life	515,019
#24	Search: hospitalization for heart failure	133,550
#23	Search: death from any cause	676,576
#22	Search: all cause death	676,576
#21	Search: cardiovascular mortality	231,347
#20	Search: #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19	5,432
#19	Search: "1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglucitol" [Supplementary Concept] Sort by: Most Recent	84
#18	Search: luseogliflozin	150
#17	Search: "remogliflozin etabonate" [Supplementary Concept]Sort by: Most Recent	25

Search	Query	Results
#16	Search: remogliflozin	47
#15	Search: "Canagliflozin"[Mesh] Sort by: Most Recent	937
#14	Search: canagliflozin	1,689
#13	Search: "dapagliflozin" [Supplementary Concept] Sort by: Most Recent	1,311
#12	Search: Dapagliflozin	2,438
#11	Search: "empagliflozin" [Supplementary Concept] Sort by: Most Recent	1,324
#10	Search: empagliflozin	2,579
#9	Search: #1 or #2 or #3 or #4 or #7 or #8	2,244,634
#8	Search: "Guidelines as Topic"[Mesh] AND "Practice Guidelines as Topic"[Mesh] AND "Guideline" [Publication Type] AND "Clinical Protocols"[Mesh] AND "Practice Guideline" [Publication Type] AND "Evidence-Based Practice"[Mesh]Sort by: Most Recent	2
#7	Search: Clinical practise guidelines	769
#6	Search: "Systematic Review" [Publication Type] AND "Systematic Reviews as Topic"[Mesh] AND "Root Cause Analysis"[Mesh] Sort by: Most Recent	0
#5	Search: "Systematic Review" [Publication Type] AND "Systematic Reviews as Topic"[Mesh] AND "Root Cause Analysis"[Mesh] - Schema: all Sort by: Most Recent	0
#4	Search: Systematic review	289,407
#3	Search: "Meta-Analysis" [Publication Type] AND "Meta-Analysis as Topic"[Mesh] AND "Network Meta-Analysis"[Mesh] Sort by: Most Recent	3,035
#2	Search: meta-analysis	265,246
#1	Search: (randomized controlled trial [pt] OR controlled clinical trial[pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((sing* [tw] OR doubt* [tw] OR treble* [tw] OR trial* [tw]) AND (mask*[tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw] Not (animals [mh] NOT human [mh]))	482,175

2) SEARCH STRATEGY and YIELD (24 January 2023, 10:00 pm) for COCHRANE LIBRARY:

Enter a search term and select a PICO vocabulary term from the dropdown

<input type="button" value="-"/> Heart Failure With Reduced Ejection Fraction	<input type="button" value="Lookup ▾"/>	<input checked="" type="radio"/> Population
<input type="button" value="AND"/> Empagliflozin	<input type="button" value="Lookup ▾"/>	<input checked="" type="radio"/> Intervention
<input type="button" value="OR"/> Dapagliflozin	<input type="button" value="Lookup ▾"/>	<input type="radio"/> Comparison
<input type="button" value="OR"/> Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors	<input type="button" value="Lookup ▾"/>	<input checked="" type="radio"/> Intervention
<input type="button" value="AND"/> Cardiovascular Mortality	<input type="button" value="Lookup ▾"/>	<input type="radio"/> Comparison
<input type="button" value="AND"/> Quality of Life	<input type="button" value="Lookup ▾"/>	<input checked="" type="radio"/> Outcome
<input type="button" value="AND"/> Hospitalization	<input type="button" value="Lookup ▾"/>	<input type="radio"/> Intervention
<input type="button" value="AND"/> Adverse Event	<input type="button" value="Lookup ▾"/>	<input type="radio"/> Comparison
<input type="button" value="AND"/> All Cause Mortality	<input type="button" value="Lookup ▾"/>	<input checked="" type="radio"/> Population
<input type="button" value="AND"/> Deteriorating Renal Function	<input type="button" value="Lookup ▾"/>	<input type="radio"/> Intervention
<input type="button" value="+"/>	<input type="button" value="Clear All"/>	<input type="button" value="Run search"/>

No filters available

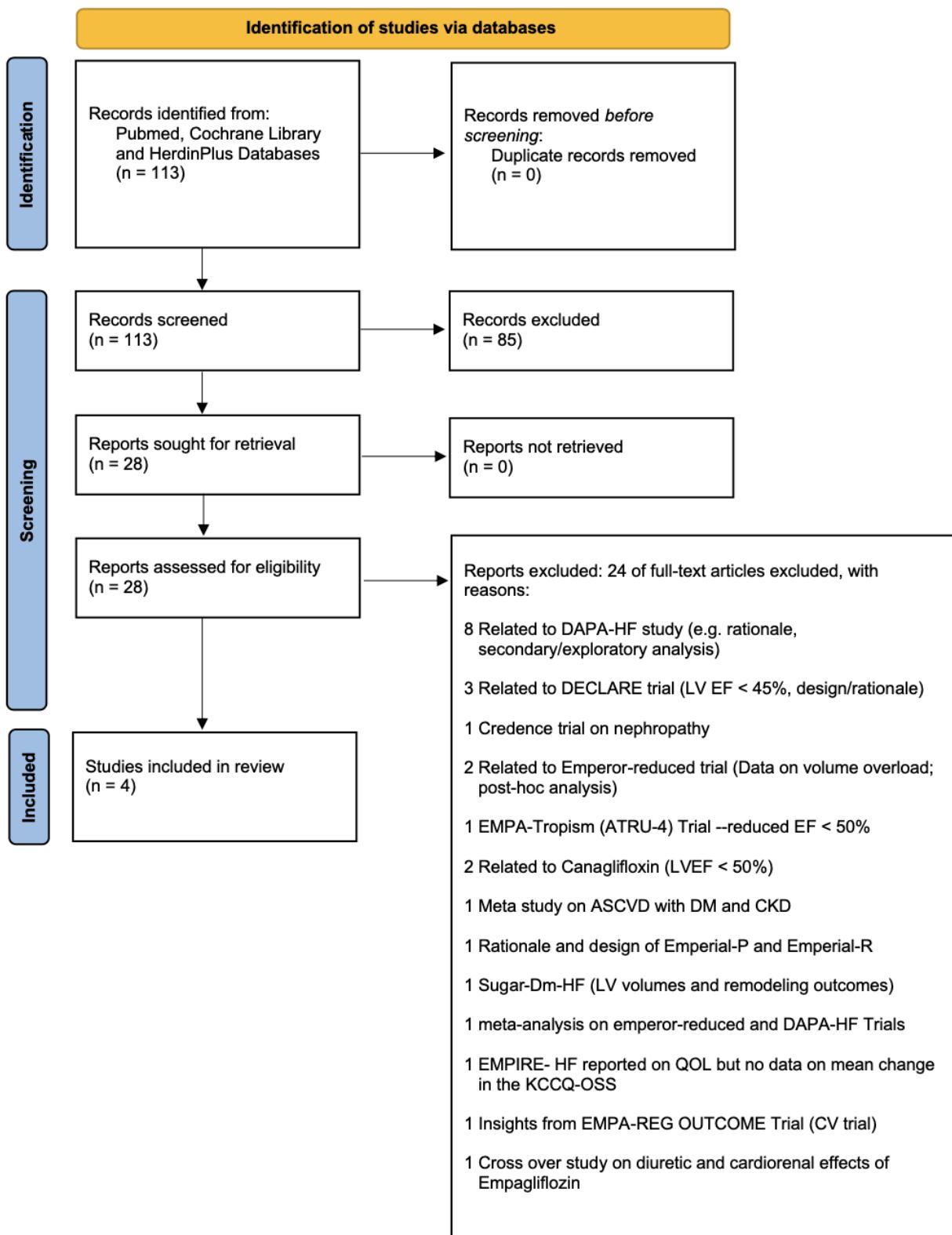
Cochrane Reviews
0

0 results matching '**Population** "Heart Failure With Reduced Ejection Fraction" AND "**Hospitalization**" AND "**Adverse Event**" AND **Intervention** "Empagliflozin" OR "Dapagliflozin" OR "Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors" AND "**Quality of Life**" AND **Outcome** "Cardiovascular Mortality" AND "All Cause Mortality" AND "Deteriorating Renal Function""
24, January 2023

3) SEARCH STRATEGY and YIELD (31 January 2023, 1:40pm) for HERDIN PLUS:

Query	Date
prevalence AND chronic heart failure	31 January 2023
SGLT2 inhibitors AND reduced ejection fraction	31 January 2023
Dapagliflozin AND reduced ejection fraction	31 January 2023
Empagliflozin AND reduced ejection fraction	31 January 2023
Chronic heart failure AND reduced ejection fraction	31 January 2023
randomized controlled trials AND SGLT2 inhibitors	31 January 2023

APPENDIX B: PRISMA Diagram



APPENDIX C: Characteristics of Included Studies

Studies	DAPA-HF (N = 4744) 2019	Emperor-reduced (N = 3730) 2019	Emperial-Reduced (N = 312); 2020	Define-HF (N = 263) 2021
Enrollment period	2017-2018	2017-1019	2018-2019	2016-2019
Sites	410 sites in 20 countries Asians: 23.5%	520 sites in 20 countries Asians 13.2%	109 centers in USA, Canada, Australia and Europe Asians = 1%	26 sites in the United States No Asians
Key inclusion criteria	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	HFrEF (NYHA class II–IV HF with LVEF ≤ 40%)	HFrEF (NYHA class II–III HF with LVEF ≤ 40%)
Key exclusion criteria	eGFR <30mL/min/1·73m ² ; SBP <95 mm Hg	eGFR <20mL/min/1·73m ² ; SBP <100 mm Hg	Acute decompensated heart failure within 4 weeks prior to screening and up to baseline. eGFR (CKD-EPIcr) < 20 mL/min/1.73 m ² or requiring dialysis. Type 1 diabetes.	Recent hospitalization (within 30 days) for decompensated HF, eGFR <30 mL/min/1.73m ² at the screening visit (using modified MDRD equation), and history of type 1 diabetes mellitus.
Interventions	Dapagli!ozin 10 mg (2373) or placebo (2371)	Empagali!ozin 10 mg (1863) or placebo (1867)	Empagali!ozin 10 mg (95) or placebo (95)	Dapagli!ozin 10 mg (131) or placebo (132)
Definition of “standard care”	“standard heart-failure device therapy and standard drug therapy”	“appropriate treatments for heart failure”	“guideline directed standard of care”	“guideline-recommended HF therapies”
Risk of Bias	Low	Low	Low	Low (allocation not clear but other parameters are low risk)

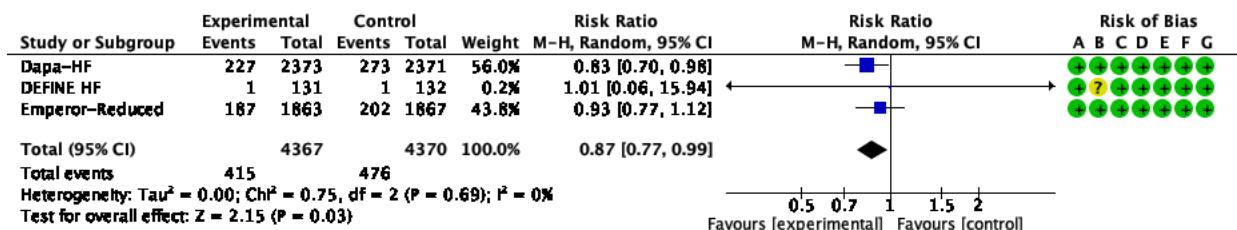
Median follow-up	18.2 months	16 months	12 weeks	12 weeks
Outcomes	<p>Primary: composite of worsening heart failure* or cardiovascular (CV) death</p> <p>Secondary: composite of hospitalization for HF or CV death; total number of hospitalizations for HF, CV deaths, change from baseline to 8 months in the KCCQ score**, death from any cause</p> <p>Prespecified outcome: safety analyses</p> <p>* heart failure hospitalization or urgent visit</p>	<p>Primary: composite of adjudicated CV death or hospitalization for heart failure</p> <p>Secondary: composite of hospitalization for HF or CV death; change from baseline to 52 weeks in the KCCQ clinical summary score; death from any cause</p> <p>Prespecified outcome: safety analyses</p>	<p>Primary endpoint was 6-minute walk test distance (6MWTD) change to Week 12.</p> <p>Secondary endpoints: Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) and Chronic Heart Failure Questionnaire Self-Administered Standardized format (CHQ-SAS) dyspnea score at week 12</p> <p>Others: safety analyses</p>	<p>Dual primary outcomes were (1) mean NT-proBNP (N-terminal pro b-type natriuretic peptide) and (2) proportion of patients with 5-point increase in HF disease-specific health status on the Kansas City Cardiomyopathy Questionnaire overall summary score, or a 20% decrease in NT-proBNP.</p> <p>No report on the mean difference between the two groups. KCCQ was reported as dichotomous variable (≥ 5 points increase or as total mean score)</p> <p>Others: all-cause mortality, cardiovascular mortality and safety outcomes</p>
Mean age, years	66.3 (10.9)	66.5 (11.2)	69 (10.2)	61.3 years
Sex				
Men	1109 (23.4)	893 (23/9%)		73%
Women	893 923.9%)	2837 (76.1%)	80 (25.6%)	27%
NYHA functional class II				
III-IV	3203 (67.5%) 1541 (32.5%)	2800 (75.1%) 930 (24.9)	202 (64.7%) 110 (35.3%)- III	66% 34% (class III)
Mean LVEF, %	31.1% (6.8)	27.2% (6.1)	30.3% (6.7)	26%

Median NT-proBNP, pg/ml	1437 (IQR 85, 2650)	1910 (IQR 1115, 3480)	1489 (IQR 821, 2919)	1136 pg/ml (IQR 615, 2267)
Mean eGFR, mL/min/1.73m ²	65.8 (19.4)	62.2 (21.5)	55.0 (43.0, 73.8)-Median	69
Diabetes	2139 (45.1%)	1856 (49.8%)	187 (59.9%)	166 (62%)
History of HF hospitalisation	2251 (47.4%)	1151 (30.9%)		85%
Heart Failure medical therapy Ace inhibitor ARB ARNI MRA B-blocker				
	2662 (56.1%)	1703 (45.7%)	173 (55.4%)-ACE/ARB	59% on Ace or ARB)
	1307 (27.6%)	908 (24.3%)	114 (36.5%)	33%
	508 (10.7%)	727 (19.5%)	182 (58.3%)	61%
	3370 (71.0%)	2661 (71.3%)	295 (94.6%)	97%
	4558 (96.1%)	3533 (94.7%)		

APPENDIX D: Forest plots of the outcomes

I. Efficacy Outcomes

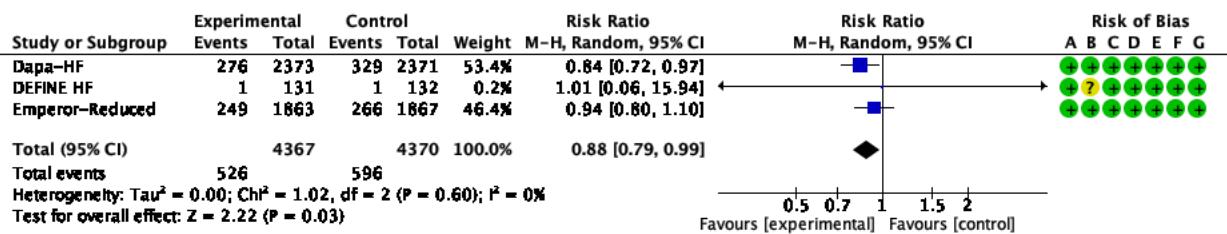
Figure 1: Cardiovascular Mortality



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

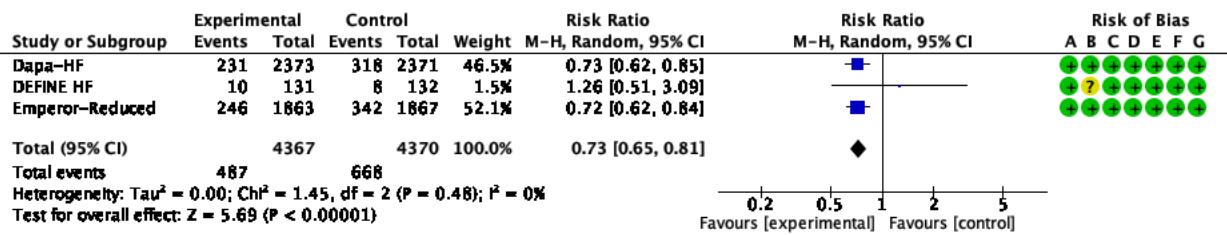
Figure 2: Death from any cause



Risk of bias legend

- (A) Random sequence generation (selection bias)
 - (B) Allocation concealment (selection bias)
 - (C) Blinding of participants and personnel (performance bias)
 - (D) Blinding of outcome assessment (detection bias)
 - (E) Incomplete outcome data (attrition bias)
 - (F) Selective reporting (reporting bias)
 - (G) Other bias

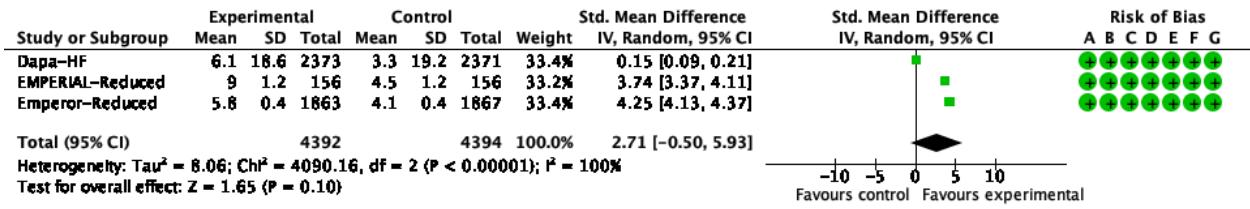
Figure 3: Hospitalization for heart failure



Risk of bias legend

- (A) Random sequence generation (selection bias)
 - (B) Allocation concealment (selection bias)
 - (C) Blinding of participants and personnel (performance bias)
 - (D) Blinding of outcome assessment (detection bias)
 - (E) Incomplete outcome data (attrition bias)
 - (F) Selective reporting (reporting bias)
 - (G) Other bias

Figure 4A : Change in quality of life score on KCCQ

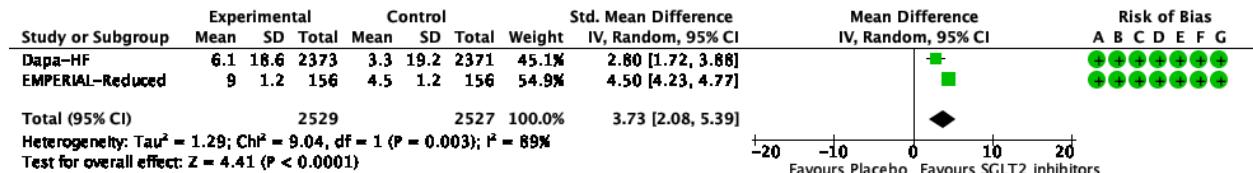


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Note: For Dapa-HF, the score was taken at 8th month; for Emperor-Reduced, the score was taken at 52 weeks or 13th month, and for Emperial-Reduced, final score was taken at 12 weeks

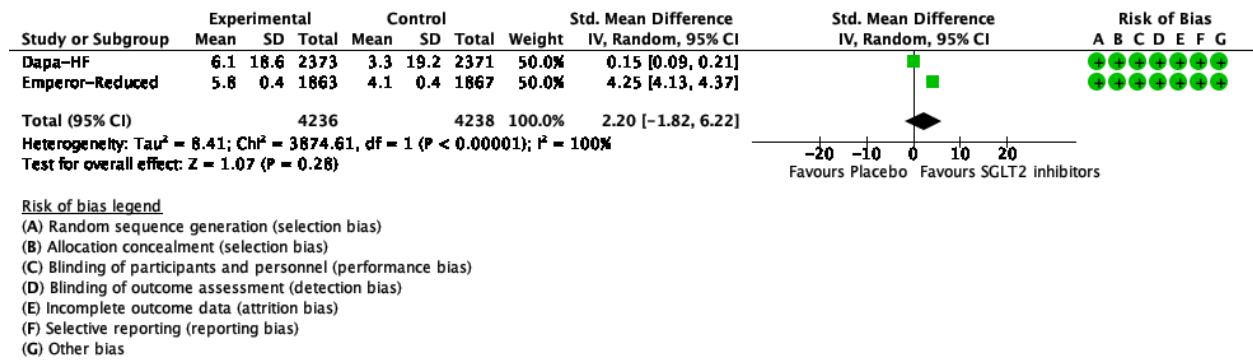
Figure 4B: Sensitivity analysis: Trials that used similar domain, KCCQ-TSS



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 4C: Sensitivity analysis: Trials with KCCS (either TSS or CSS) measured at longer period of observation



B. Safety Outcomes

Figure 5: Worsening renal function

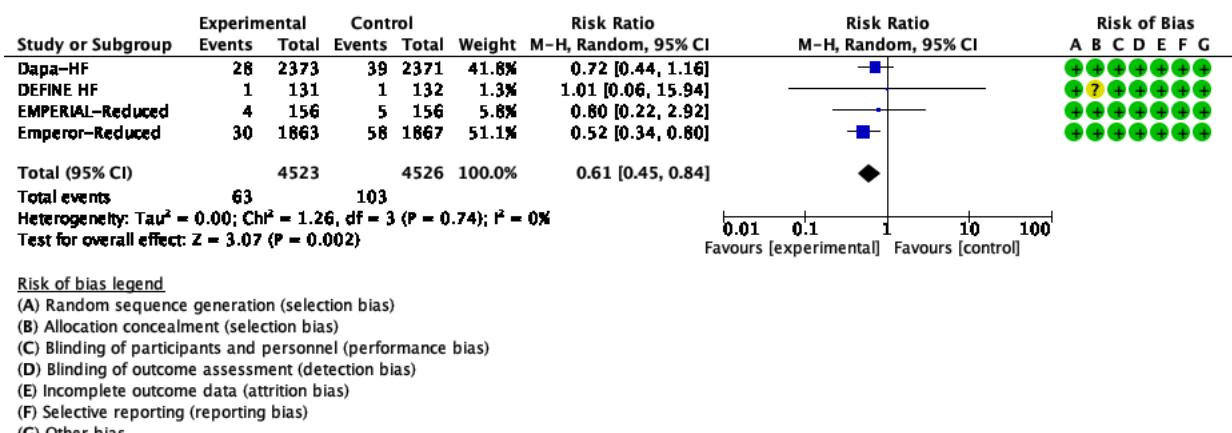
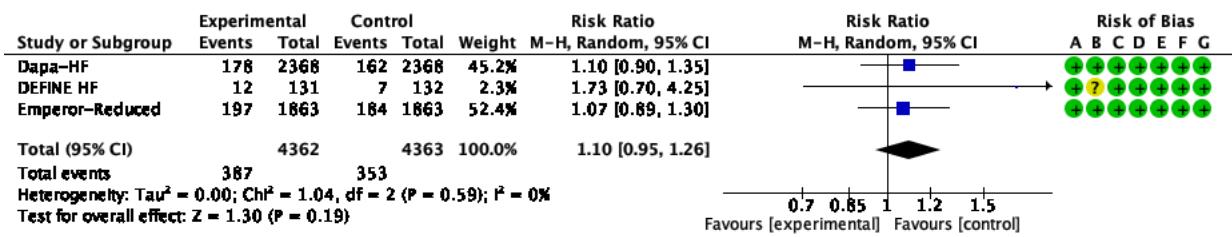


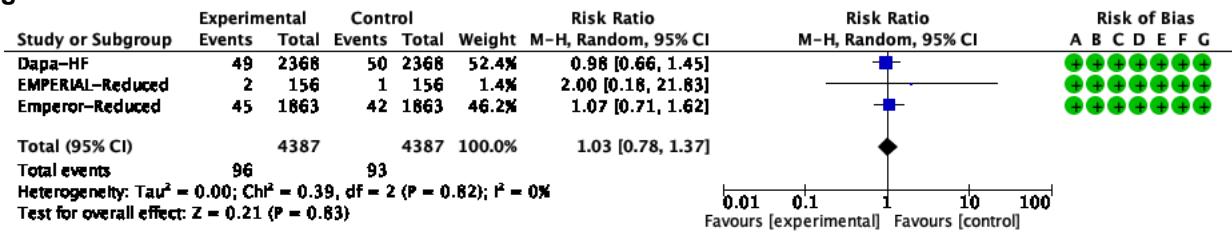
Figure 6: Volume Depletion



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

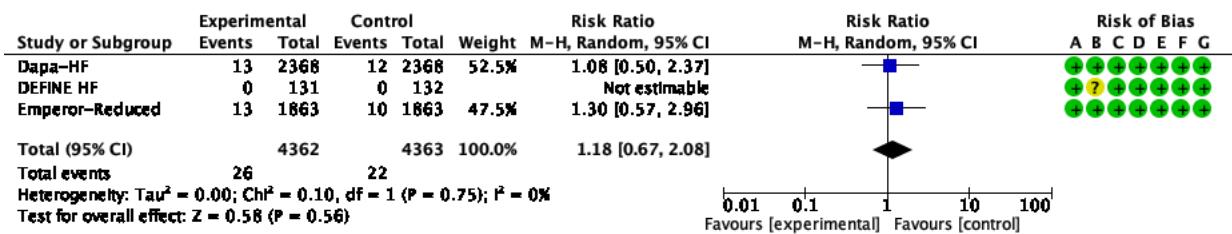
Figure 7: Fractures



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

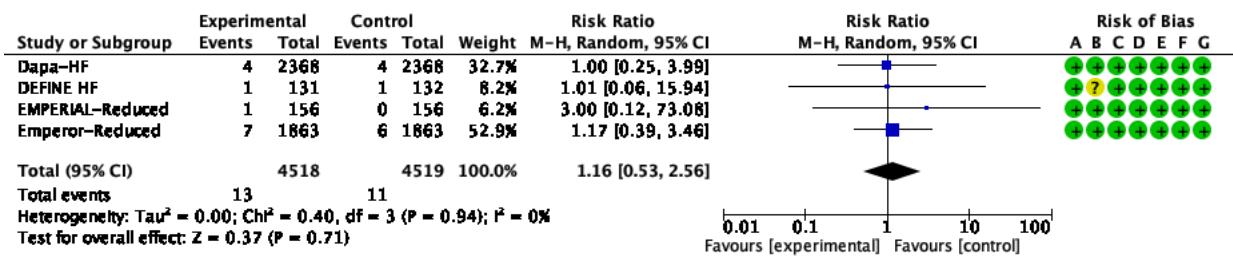
Figure 8: Amputation



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

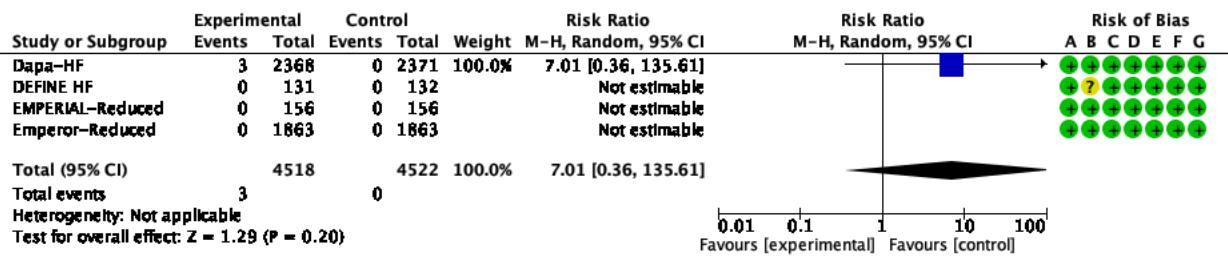
Figure 9: Major hypoglycemia among those with diabetes mellitus



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

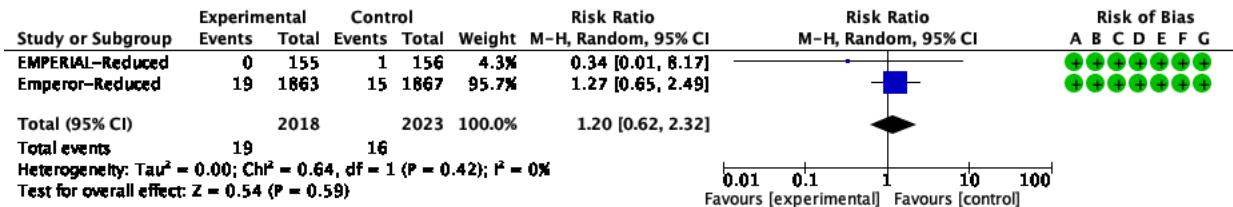
Figure 10: Diabetic ketoacidosis



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

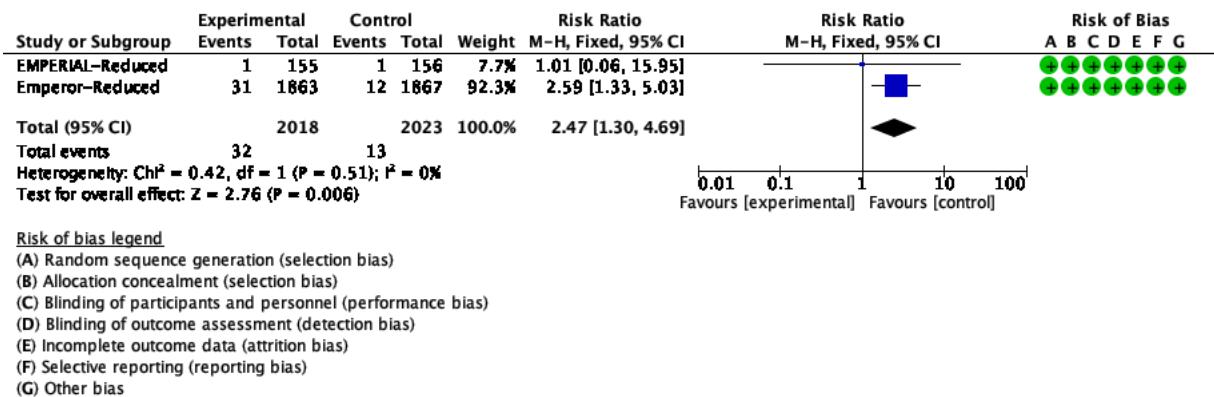
Figure 11: Complicated Urinary Tract Infection



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 12: Genital infections



APPENDIX E: GRADE Evidence Profile table

Author(s): Noemi Pestaño, MD

Question: SGLT2 Inhibitors compared to Placebo for patients with chronic heart failure and reduced ejection fraction (HReRF)

Setting: Out-patients

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A. Efficacy Outcomes

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	not serious	not serious	none	415/4367 (9.5%)	476/4370 (10.9%)	RR 0.87 (0.77 to 0.99)	14 fewer per 1,000 (from 25 fewer to 1 fewer)	⊕⊕⊕ HIGH	CRITICAL
Cardiovascular mortality												
3	randomised trials	not serious	not serious	not serious	not serious	none	526/4367 (12.0%)	596/4370 (13.6%)	RR 0.88 (0.79 to 0.99)	16 fewer per 1,000 (from 29 fewer to 1 fewer)	⊕⊕⊕ HIGH	CRITICAL
Death from any cause												
3	randomised trials	not serious	not serious	not serious	not serious	none	487/4367 (11.2%)	668/4370 (15.3%)	RR 0.73 (0.65 to 0.81)	41 fewer per 1,000 (from 54 fewer to 29 fewer)	⊕⊕⊕ HIGH	CRITICAL
Hospitalization for heart failure												
3	randomised trials	not serious	serious ^a	not serious	not serious	none	4392	4394	-	MD 3 higher (0.79 higher to 5.21 higher)	⊕⊕⊕○ MODERATE	CRITICAL

B. Safety Outcomes

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
Worsening renal function												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	not serious	none	63/4523 (1.4%)	103/4526 (2.3%)	RR 0.61 (0.45 to 0.84)	9 fewer per 1,000 (from 13 fewer to 4 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Volume depletion												
3	randomised trials	not serious	not serious	not serious	not serious	none	387/4362 (8.9%)	353/4363 (8.1%)	RR 1.10 (0.95 to 1.26)	8 more per 1,000 (from 4 fewer to 21 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Fracture												
3	randomised trials	not serious	not serious	not serious	not serious	none	96/4387 (2.2%)	93/4387 (2.1%)	RR 1.03 (0.78 to 1.37)	1 more per 1,000 (from 5 fewer to 8 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Amputation												
3	randomised trials	not serious	not serious	not serious	serious a,b,c,d	none	26/4362 (0.6%)	22/4363 (0.5%)	RR 1.18 (0.67 to 2.08)	1 more per 1,000 (from 2 fewer to 5 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Major hypoglycemia among those with DM												
4	randomised trials	not serious	not serious	not serious	serious a,b,c,d	none	13/4518 (0.3%)	11/4519 (0.2%)	RR 1.16 (0.53 to 2.56)	0 fewer per 1,000 (from 1 fewer to 4 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Diabetic ketoacidosis												

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2 inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
4	ran-domised trials	not serious	not serious	not serious	serious a,b,c,d	none	3/4518 (0.1%)	0/4522 (0.0%)	RR 7.01 (0.36 to 135.6 1)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
Complicated Urinary Tract Infection												
2	ran-domised trials	not serious	not serious	not serious	serious a,b,c,d	none	19/2018 (0.9%)	16/2023 (0.8%)	RR 1.20 (0.62 to 2.32)	2 more per 1,000 (from 3 fewer to 10 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Genital Infections												
2	ran-domised trials	not serious	not serious	not serious	serious a,b,c,d	none	32/2018 (1.6%)	13/2023 (0.6%)	RR 2.47 (1.30 to 4.69)	9 more per 1,000 (from 2 more to 24 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

- a. Not a primary outcome and not powered to detect differences
- b. Number of events was small
- c. Wide confidence interval
- d. Most of the safety outcomes were assessed using descriptive statistics (frequency) only

- The evidence to decision survey conducted prior to voting showed that the 81.8% of the CP considered it as a priority problem and measures to alleviate these epidemiological and economic burdens are imperative, especially those that will reduce cardiovascular outcomes. Majority (72.7%) voted for large desirable effects and small undesirable effects of SGLT2i. There was high certainty of evidence favoring comparison for balance of effects. There were no studies on the certainty of evidence of required costs. 54.5% of the CP voted for moderate costs probably favoring cost effectiveness of the intervention. 45.5% voted for possibly important uncertainty/variability with probably increased equity. The majority (81.8%) voted that SGLT2i is probably acceptable and 54.5% voted that it is feasible to implement. All members of the CP (100%) voted to recommend treatment; 90.9% of the CP voted to give the treatment a strong recommendation.

Annex 15. CV Specialist referral for the management of heart failure

APPENDIX 1

Table 1: Resource Stratified Framework for Cardiovascular Care Centers according to level of care (adapted from Department of Health DO 2021-0001)

Level of Care	Specialty			Intermediate
	National Specialty Center (NSC) Philippine Heart Center (PHC)	Center of Excellence	Maximal	Enhanced
		Level 3 Hospital (Advanced Comprehensive Cardiovascular Care)	Level 3 Hospital (Basic Comprehensive Cardiovascular Center)	Level 2 Hospital
Current Licensing Standard	Designated Hospitals	Level 2 plus teaching and training facility	Level 2 plus teaching and training facility	At least 1 Internal Medicine Department plus Departments of Pediatrics, Obstetrics, and Surgery with accredited programs AND an Intensive Care Unit (ICU)
General Description of Service Capability	<ul style="list-style-type: none"> > Capacity of managing ALL cardiovascular cases <ul style="list-style-type: none"> -End referral -Policy-making and protocol development > Highest level of clinical service, training and research > Clinical Practice Guidelines (CPG) development 	<ul style="list-style-type: none"> > Capacity of managing all simple and some complex cardiovascular cases > Second opinion center > May have the highest level of clinical service, training and research 	<ul style="list-style-type: none"> > Capacity of managing all simple and some complex cardiovascular cases with option for PHC assistance > Requires specialized multidisciplinary teams (such as HF MDTs) > Full clinical services 	<ul style="list-style-type: none"> > Management of higher/advanced stages of medical cardiovascular care > Management requiring intensive care

<p>Heart Care Services</p> <p>Procedures (Diagnosis and Treatment)</p>	<p>Heart Surgery (Open/Closed)</p> <ul style="list-style-type: none"> > Simple and advanced cardiovascular surgery including: <ul style="list-style-type: none"> > Coronary artery bypass graft surgery (CABG) and ischemic complications > Multivalvular Heart Surgery > Minimally invasive cardiac surgery (MICS) > Open, endovascular, vascular surgery for great vessels and peripheral vessels > Simple and complex Congenital Heart Disease (CHD) surgery > Neonatal Heart surgery > Grown up Congenital Heart (GUCH) surgery >Permanent Pacemaker ICD implantation 	<p>Heart Surgery (Open/Closed)</p> <ul style="list-style-type: none"> >Simple + some complex cardiovascular cases <ul style="list-style-type: none"> > CABG and ischemic complications > Multivalvular Heart Surgery > Simple MICS > Open, endovascular, vascular surgery for great vessels and peripheral vessels > Simple and some complex CHD surgery > GUCH surgery >Permanent Pacemaker ICD implantation 	<p>Heart Surgery (Open/Closed)</p> <ul style="list-style-type: none"> >Mainly simple cardiovascular + some complex urgent cases <ul style="list-style-type: none"> > CABG > Valve Surgery > Simple Minimally invasive cardiac surgery > Open, endovascular, vascular surgery for great vessels with PHC assist > Peripheral vascular surgery > Mainly simple CHD <ul style="list-style-type: none"> - VSD, ASD, PDA - Simple, Tetralogy of Fallot - Simple GUCH > Permanent Pacemaker implantation 	N/A
	<p>Catheterization Laboratory</p> <ul style="list-style-type: none"> > Coronary Angiogram and Percutaneous Coronary Intervention (PCI) > Transcatheter valve replacement > Percutaneous Mitral balloon valvuloplasty (PBMV) > Hemodynamic Studies > PPBV/PABV/PV stenting, CoA dilatation >Device closure PDA, VSD, ASD devices <p>EPS</p> <ul style="list-style-type: none"> > Radiofrequency ablation (RF) 3D mapping Pacemaker implantation, temporary, permanent 	<p>Catheterization Laboratory</p> <ul style="list-style-type: none"> > Coronary Angiogram, PCI > PBMV > TAVR with PHC > Hemodynamic Studies > Balloon Atrial Septostomy device closure > PDA, VSD, ASD devices <p>EPS</p> <ul style="list-style-type: none"> > Pacemaker implantation, temporary, permanent 	<p>Catheterization Laboratory</p> <ul style="list-style-type: none"> > Coronary Angiogram, PCI > PBMV > TAVR with PHC > Hemodynamic Studies > Balloon Atrial Septostomy device closure > PDA, VSD, ASD devices (if with 2d echo, TEE) <p>EPS</p> <ul style="list-style-type: none"> > Pacemaker implantation, temporary, permanent 	N/A

	<p>Advanced services</p> <ul style="list-style-type: none"> > Intensive/Critical Care for Post Heart Surgery > Critical Care for Post Catheter Care > Clinical Pathways for complex surgery > CPG on perioperative assessment 	<p>Advanced services as 2nd Opinion Center</p> <ul style="list-style-type: none"> > Intensive/Critical Care for Post Heart Surgery > Critical Care for Post Catheter Care > Clinical Pathways for complex surgery > CPG on perioperative assessment 	<ul style="list-style-type: none"> > Intensive/Critical Care for Post Heart Surgery > Critical Care for Post Catheter Care > Clinical Pathways -CABG -VSD -TOF 	<ul style="list-style-type: none"> > OPD and in-patient specialists and subspecialists > Internists competent in: <ul style="list-style-type: none"> -Hypertension complications -Heart failure medical control before surgery/cath -Rheumatic Heart Disease
Cardio-vascular Care Equipment and Services	<p>Multispecialty Cardiovascular Diagnostic and Treatment Laboratories</p> <p>2D/3D Transthoracic and transesophageal echocardiography (TTE/TEE)</p> <p>Stress test</p> <p>Vascular Laboratory</p> <p>Cardiovascular (CV) Radiology</p> <p>MRI/CT</p> <p>Interventional Electrophysiology (EPS) laboratory,</p> <p>RF with 3D mapping</p> <p>CV Nuclear Medicine</p>	<p>Heart Station</p> <p>Electrocardiogram (ECG)</p> <p>Holter monitoring</p> <p>2D TTE TEE</p> <p>Stress test / Echo</p> <p>Cath Lab, preferably 2</p> <p>Vascular Laboratory</p> <p>At least two (2) dedicated cardiac operating rooms (OR)</p> <p>Complete Open Heart equipment, instruments and supplies for Basic Adult and Pediatric cases</p>	<p>Heart Station</p> <p>Electrocardiogram (ECG)</p> <p>Holter monitoring</p> <p>24-hour Ambulatory BP</p> <p>2DED TTE TEE</p> <p>Vascular Laboratory</p> <p>Complete Open Heart equipment, instruments and supplies for Basic Adult and Pediatric cases</p>	<p>Equipment</p> <p>ECG</p> <p>24-hour Ambulatory BP</p> <p>Chest X-ray with portable X-ray for ICU</p> <p>Portable 2DED Complete laboratory</p>
Fixed Assets/ Equipment	<p>8-10 CV ORs</p> <p>Hybrid OR</p> <p>6 Catheterization Laboratories with Dedicated Pedia and EPS rooms</p> <p>Cardiovascular ICU</p> <p>Dedicated SICU (3 SICUs with 15-20 beds per ICU)</p> <p>Separate Medical ICU</p>	<p>At least 2 CV ORs</p> <p>2 Catheterization Laboratories with Dedicated Pedia time</p> <p>Cardiovascular ICU (5-10 beds)</p>	<p>1 CV OR</p> <p>1 Catheterization Laboratory</p> <p>Cardiovascular ICU (2-5 beds)</p>	<p>NA</p> <p>NA</p> <p>NA</p>

	and Pedia ICUs for Chronic Intensive Care			
	CV Radiology all DICOM CT angiography (CTA) MR Angiography (MRA) Special procedures	Radiology CTA MRA	Radiology CT scan	NA
Human Resource Assets	CV surgeons > 10 in all subspecialties as Department	At least 5 CV surgeons including 1 Pedia CV surgeon	At least 3 CV surgeons including 1 Pedia CV surgeon	At least 1 General surgeon
	CV anesthesiologists > 5 in all subspecialties	At least 2 with plantilla	At least 1 with plantilla with visiting CV anesthesiologists	At least 1 anesthesiologist
	Invasive and Non-invasive Cardiologists capable of intensive care At least 5 per Division with at least 2 Pedia interventionists	At least 2 per subspecialty	At least 1 per subspecialty	NA
	Adult Cardiologists At least 20 as Department with at least 5 per subspecialty	At least 5 Adult Cardiologists	At least 2 Adult Cardiologists	Preferably at least 1 visiting Adult Cardiologist
	Pedia Cardiologists At least 10 as Department with at least 1 per subspecialty	At least 3 with 1 Pediatric Interventionist	At least 2 with 1 Pediatric Interventionist	At least 1 Visiting Pediatric Cardiologist
	Certified CV Nurse Practitioners at least 50% of all OR and ICU nurses	At least 20% of all OR and ICU nurses	At least 20% of all OR and ICU nurses	At least 1 Certified CV Nurse practitioner
	CV OR Nurses, at least 2 per OR	At least 4 CV OR Nurses	At least 2 CV OR Nurses	General OR Nurses
	Perfusionists, at least 2 per OR Other allied CV specialists	At least 2	At least 2	NA
Other services	Promotive/Preventive CV research	Promotive/Preventive CV research	Research in collaboration with	NA

	At least 5 ongoing	At least 1 ongoing	national center at least 1	
	Multicenter CV research, at least 1	Multicenter CV research, encouraged	Research in collaboration with national center, encouraged	NA
	Capability to host international scientific meetings, at least 2 per year	Capability to host national or international scientific meetings, at least 1 per year	Capability to host regional scientific meetings	Local scientific meetings
	Accredited CV Fellowship and Residency Training programs Fellowship for ALL subspecialties	Preferably with Accredited CV training program at least Adult Cardiology	Preferably with at least Consortium training program with National Center with approval of specialty societies	Residency Level 3
Common services	Social Service, Nutrition, Psychosocial support, Psychiatric services, Wellness, Family Support, Accommodation, Practical support, Palliative Care, Cardiac Rehabilitation			

Appendix 2

Table 1: Summary of Search Strategy as of May 2023 (Timely referral)

Question 13. Among adult Filipinos diagnosed with chronic heart failure (HFrEF) at the outpatient clinic, what is the effect of timely referral to higher levels of care					
Database/ Sources	Time Period Searched	Inclusion Criteria	Exclusion Criteria, if any	Search terms	Full Search Strategy
ACC/AHA Guidelines ESC Guidelines NICE Guidelines Japanese Guidelines Malaysian Guidelines Australian Guidelines Databases Medline Pubmed SCOPUS Google Scholar Cochrane Reviews HERDIN plus Gray literature	Up to May 2023	Population: adult patients Disease: chronic HF, HFrEF Meta analysis, RCT or observational studies	Pediatric patients Acute HF Decompensated HF	Congestive heart Failure or "HFrEF" Higher Levels of Care Secondary Care Tertiary care	(timely referral to secondary, tertiary hospitals) AND (chronic heart failure)) AND (outcomes) Filters: Associated data, Books and Documents, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review " ("timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]) AND ("referral and consultation"[MeSH Terms] OR ("referral"[All Fields] AND "consultation"[All Fields])) OR "referral and consultation"[All Fields] OR "referral"[All Fields] OR "referrals"[All Fields] OR "referrer"[All Fields] OR "referrers"[All Fields]) AND "secondary"[MeSH Subheading] OR "secondary"[All Fields] AND ("tertiary care centers"[MeSH Terms] OR ("tertiary"[All Fields] AND "care"[All Fields] AND "centers"[All Fields]) OR "tertiary care centers"[All Fields] OR ("tertiary"[All Fields] AND "hospitals"[All Fields])) OR "tertiary hospitals"[All Fields] AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) AND ((booksdocs[Filter] OR clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (data[Filter]))

Table 2: Summary of Revised Search Strategy as of May 2023 (Poor Prognostic factors)

Question 13. Among adult Filipinos diagnosed with chronic heart failure (HFrEF) at the outpatient clinic, what is the effect of timely referral to higher levels of care					
Database/ Sources	Time Period Searched	Inclusion Criteria	Exclusion Criteria, if any	Search terms	Full Search Strategy
ACC/AHA Guidelines ESC Guidelines NICE Guidelines Japanese Guidelines Malaysian Guidelines Australian Guidelines Databases Medline Pubmed SCOPUS Google Scholar Cochrane Reviews HERDIN plus Gray literature	Up to May 2023	Population: adult patients Disease: chronic HF, HFrEF Meta analysis, RCT or observational studies	Pediatric patients Acute HF Decompensated HF	Congestive heart failure or "HFrEF" Prognostic factors, indicators Outpatient setting mortality	(chronic heart failure with reduced ejection fraction) AND (prognostic factors, indicators)) AND (mortality) Filters: Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review (("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("reduce"[All Fields] OR "reduced"[All Fields] OR "reduces"[All Fields] OR "reducing"[All Fields]) AND ("eject"[All Fields] OR "ejected"[All Fields] OR "ejecting"[All Fields] OR "ejection"[All Fields] OR "ejectional"[All Fields] OR "ejections"[All Fields] OR "ejects"[All Fields]) AND ("dose fractionation, radiation"[MeSH Terms] OR ("dose"[All Fields] AND "fractionation"[All Fields] AND "radiation"[All Fields]) OR "fractionation"[All Fields] OR "chemical fractionation"[MeSH Terms] OR ("chemical"[All Fields] AND "fractionation"[All Fields]) OR "chemical fractionation"[All Fields] OR "fraction"[All Fields] OR "fraction s"[All Fields] OR "fractionate"[All Fields] OR "fractionated"[All Fields] OR "fractionates"[All Fields] OR "fractionating"[All Fields] OR "fractionationed"[All Fields] OR "fractionations"[All Fields] OR "fractionator"[All Fields] OR "fractionators"[All Fields] OR "fractioned"[All Fields] OR "fractioning"[All Fields] OR "fractionized"[All Fields] OR "fractions"[All Fields]) AND ((("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR ("prognostic"[All Fields] AND "factors"[All Fields]) OR "prognostic factors"[All Fields]) AND ("indicate"[All Fields] OR "indicated"[All Fields] OR "indicates"[All Fields] OR "indicating"[All Fields] OR "indicative"[All Fields] OR "indicatives"[All Fields] OR "indicators and reagents"[Pharmacological Action] OR "indicators and reagents"[MeSH Terms] OR ("indicators"[All Fields] AND "reagents"[All Fields]) OR "indicators and reagents"[All Fields] OR "indicator"[All Fields]))

					Fields] OR "indicators"[All Fields] OR "indice"[All Fields] OR "indices"[All Fields])) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter])
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Table 3: Summary of Revised Search Strategy as of May 2023 (HF Multidisciplinary Teams)

Question 13. Among adult Filipinos diagnosed with chronic heart failure (HFrEF) at the outpatient clinic, what is the effect of timely referral to higher levels of care					
Database/ Sources	Time Period Searched	Inclusion Criteria	Exclusion Criteria, if any	Search terms	Full Search Strategy
ACC/AHA Guidelines ESC Guidelines NICE Guidelines Japanese Guidelines Malaysian Guidelines Australian Guidelines Databases Medline Pubmed SCOPUS Google Scholar Cochrane Reviews HERDIN plus Gray literature	Up to May 2023	Population: adult patients Disease: chronic HF, HFrEF Meta analysis, RCT or observational studies	Pediatric patients Acute HF Decompensated HF Access to multidisciplinary teams Mortality Worsening heart failure Hospitalization Quality of life	Congestive heart failure or "HFrEF" Congestive heart failure or "HFrEF" OR ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND (("interdisciplinary studies"[MeSH Terms] OR ("interdisciplinary"[All Fields] AND "studies"[All Fields]) OR "interdisciplinary studies"[All Fields] OR "multidisciplinary"[All Fields]) AND ("therapy"[MeSH Subheading] OR "therapy"[All Fields] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields])) AND ("program"[All Fields] OR "program s"[All Fields] OR "programme"[All Fields] OR "programed"[All Fields] OR "programes"[All Fields] OR "programing"[All Fields] OR "programmability"[All Fields] OR "programmable"[All Fields] OR "programmably"[All Fields] OR "programme"[All Fields] OR "programme s"[All Fields] OR "programmed"[All Fields] OR "programmer"[All Fields] OR "programmer s"[All Fields] OR "programmers"[All Fields] OR "programmes"[All Fields] OR "programming"[All Fields] OR "programmings"[All Fields] OR	

					"programs"[All Fields])) AND ("primary health care"[MeSH Terms] OR ("primary"[All Fields] AND "health"[All Fields] AND "care"[All Fields]) OR "primary health care"[All Fields] OR ("primary"[All Fields] AND "care"[All Fields])) OR "primary care"[All Fields])) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (data[Filter]))
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Appendix 2: Study Characteristics

Table 4. Characteristics of included Studies

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Rao, 2007	Prospective RCT	UK	112	Heart failure with LV dysfunction present Follow up: 3-12 months Mean Age: 72+/- 10	Specialist care (Cardiology) N: 53 Mean age: 71.5	Non specialist care (General Practitioner Care) N: 59 Mean Age: 72.2	Composite endpoint of all-cause mortality and all-cause hospitalization
Peters-Klimm, et al. 2010	RCT	Germany	197	Population: HFrEF (EF <45%) Follow-up: 12 months Mean Age: 69.6	Support of doctor assistants in GP practices. Combination of home visits, telephone monitoring, recall-reminder systems, and GP feedback Care Team: GP, Trained Doctor Assistant, Nurse N:97 Mean Age: 70.4 (71.1)	General Practitioner with no case management was applied N:100 Mean Age: 68.9 (9.7)	Mortality HF hospitalizations Generic and Disease Specific QoL
Hancock, 2012	Pilot RCT using a PROBE design	UK	28	Population: HFrEF Follow-up: 6 months Mean Age: 83.7 (6.9)	HF service in long-term care facilities, consisting of initial	General Practitioner led care N: 12 Mean Age: 81.8	Mortality HF Hospitalization

					<p>visit by cardiologist who initiated plan of treatment and follow-up visits by HF nurse specialists</p> <p>Care Team: Cardiologist, HF nurse specialist, GP with special interest in HF, GP</p> <p>N: 16 Mean Age: 85.1</p>		
Kalter- Leibovici et al. 2017	Multicenter open label RCT	Israel	1360	<p>Population: Moderate to severe chronic heart failure with reduced EF</p> <p>Follow-up: 2.7 years (median)</p> <p>Mean Age: 70.8 (11.3)</p>	<p>Nurse case management with regular remote contact between visits to HF centres. Telemonitoring of patient biometric data. Six monthly visits at HF centre and cardiologist evaluation. Counselling by dietitians and social workers as needed.</p> <p>Care Team: Cardiologist, nurse, social worker/dietitian N: 682 Mean Age: 70.8 (11.6)</p>	<p>Referred to their Primary care after provision of a treatment plan by cardiologists at the heart failure center</p> <p>N: 678 Mean Age: 70.7 (11)</p>	Mortality HF Admission
Pant, 2022	RCT, single center study	India	80	<p>Population: Stable HFrEF</p> <p>Follow up: 1 year</p>	<p>Multidisciplinary Heart Failure Clinic</p> <p>Care Team: Cardiologist, trained nurses, dietician, social worker and other specialties on demand</p> <p>N: 40 Mean Age: 54.5 +/- 9.6</p>	<p>Cardiology Outpatient clinic</p> <p>N: 40 Mean Age: 55.6 +/- 9.9</p>	<p>Composite death from any cause and hospitalization for HF</p> <p>Secondary endpoints: Quality of life</p>

Appendix 3:

Table 5: Grade Evidence Profile Table

Nr of studies	Study design	Risk of bias	Certainty assessment				referral to multidisciplinary team (including cardiologists)	Nr of patients		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations		usual care	Relative (95% CI)	Absolute (95% CI)			
CV mortality (follow-up: mean 6 months)													
4	randomised trials	serious ^a	not serious	serious ^b	not serious	none	243/878 (27.7%)	229/871 (26.3%)	OR 1.08 (0.87 to 1.35)	15 more per 1,000 (from 26 fewer to 62 more)		Low	CRITICAL
HF hospitalization													
5	randomised trials	Serious ^a	not serious	Serious ^b	not serious	none	328/890 (36.9%)	358/887 (40.4%)	OR 0.85 (0.69 to 1.03)	38 fewer per 1,000 (from 85 fewer to 7 more)		Low	CRITICAL

CI: confidence interval; OR: odds ratio

Explanations

- a. There was no blinding, allocation concealment done as these were intervention studies of standard of care
- b. There studies that were reviewed did not answer the clinical question directly
- c. There was no blinding and allocation concealment done as these were intervention studies of standard of care

Appendix 4: Forest Plots

Figure 1: Mortality

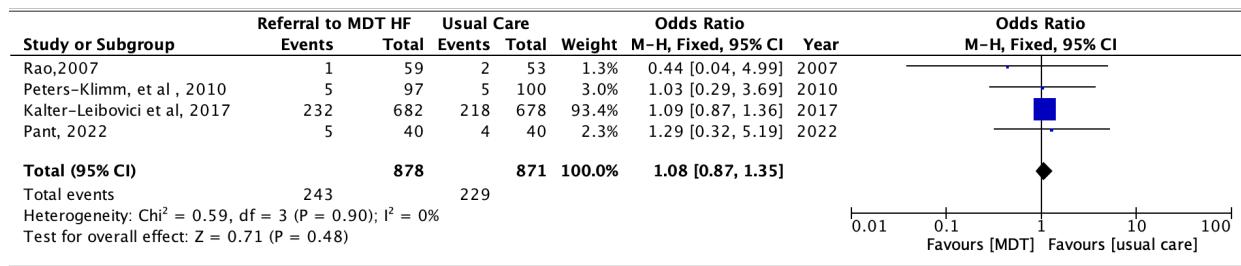
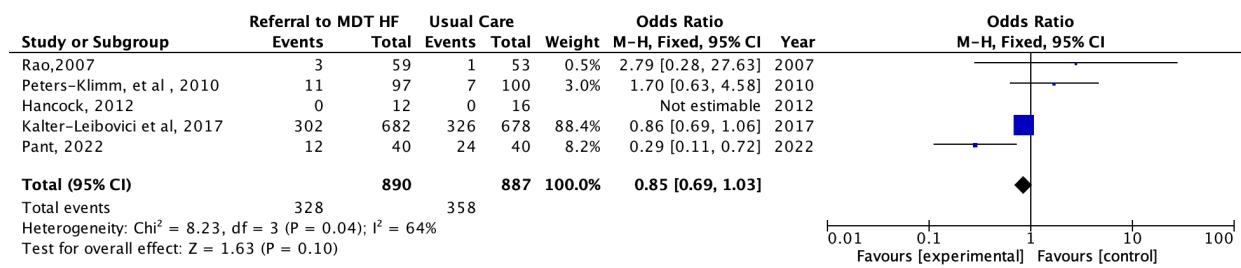


Figure 2: HF Hospitalization



- The evidence to decision survey prior to voting showed that the majority of the CP considered it as a priority problem. There was moderate desirability and a split vote on small vs trivial undesirable effect. There was moderate certainty of evidence, favoring intervention for balance of effects. The majority voted for large costs with no study on cost effectiveness. The majority voted for possibly important uncertainty/variability with probably increased equity. The vote was split between probably acceptable and acceptable. Referral was probably feasible. The entire CP (100%) voted to recommend referral while there was a 50-50 split between strong and weak during the vote regarding the strength of recommendation.

Annex 16: Palliative care for the management of heart failure.

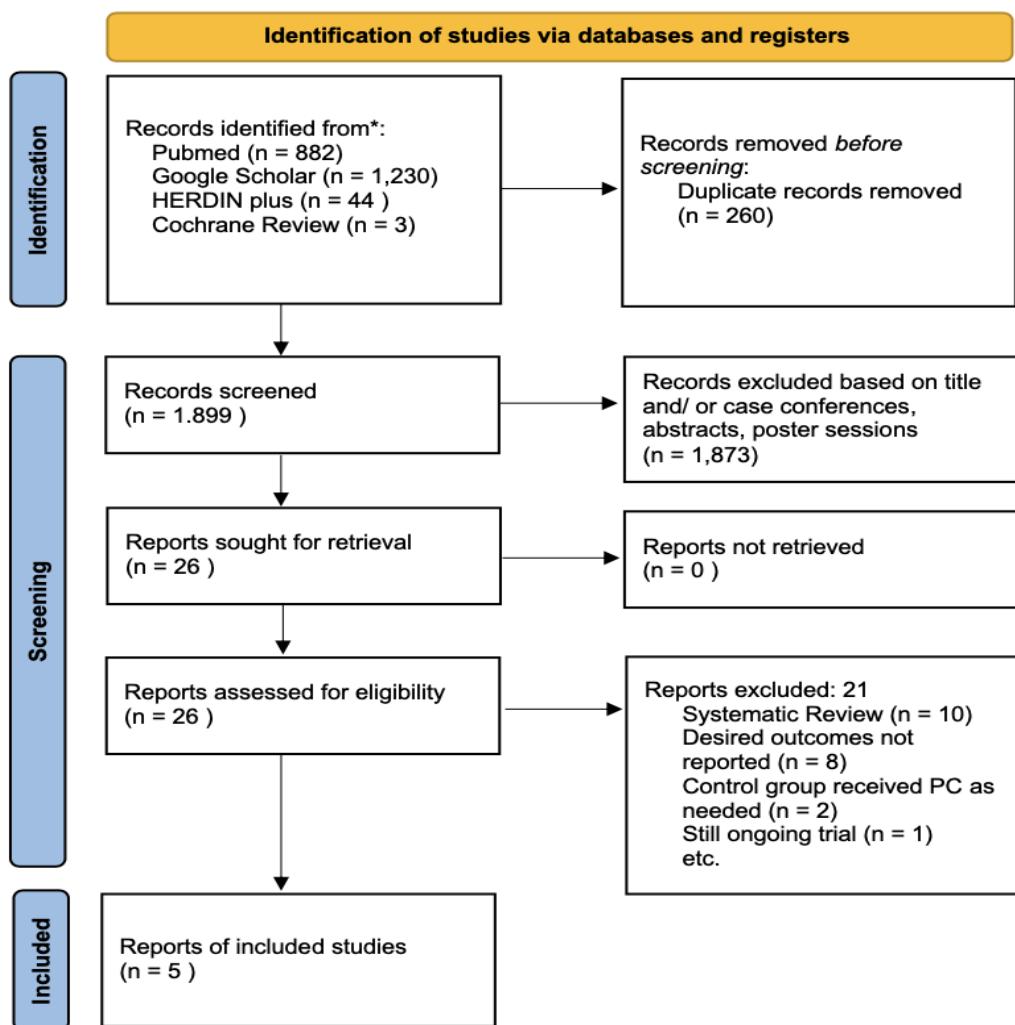
APPENDICES

Table 1. Search strategy

Question 14. Among adult Filipinos diagnosed with chronic heart failure (HFrEF) at the outpatient setting, what is the effect of palliative care on quality of care and incidence of worsening heart failure, heart failure hospitalizations, and cardiovascular mortality?					
Database/ Sources	Time Period Searched	Inclusion Criteria	Exclusion Criteria, if any	Search terms	Full Search Strategy
ACC/AHA Guidelines ESC Guidelines NICE Guidelines Canadian Guidelines Japanese Guidelines Malaysian Guidelines Australian Guidelines Databases Medline Pubmed Google Scholar Cochrane Reviews HERDIN plus	2012 to 2022	Population: adult patients Disease: chronic HF, HFrEF Meta analysis or RCT	Pediatric patients Acute HF Decompensated HF	Congestive heart failure Palliative care Mortality Hospitalization Quality of life Outpatient Meta analysis Randomized controlled trials Systematic review	(((((((("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields])) OR "heart failure"[All Fields])) AND ("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields])) OR "palliative care"[All Fields])))) AND ("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR "outpatient"[All Fields])) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) AND ("hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields])) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields])) AND ("randomized controlled trial"[All Fields] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields] OR "randomised controlled trials"[All Fields])) AND ("meta-analysis"[All Fields] OR

					"meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields])) AND ("systematic review"[All Fields] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields]) AND ("2013/01/09"[PDat] : "2023/01/06"[PDat])
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Summary of Search Strategy as of January 6, 2023



Search as of January 6, 2023

Figure 1. PRISMA flow chart

Table 2. Characteristics of included studies

Study ID & Design Country Setting	Population	Palliative Care (Intervention)	Usual Care (Control)	Outcomes
Brännström & Boman [6] 2014 PREFER study Sweden RCT	Population: Heart failure patients. Inclusion Criteria: NYHA III-IV patients with at least one of the following: hospitalization in the past 6 months due to heart failure; frequent or continuous IV support; poor quality of life; cardiac cachexia; life expectancy <1 yr. Follow-up: 1, 3, 6 months.	N= 36 Mean age = 81.9 years Services: Structured, person-centered care at home. Interdisciplinary, home-based collaborative care to provide heart failure disease management and palliative care services. Meeting with nurses who uses a model for person-centered palliative care called the 6 Ss: self-image, self-determination, social relationships, symptom control, synthesis and surrender. Domains: Physical, psychological, social, spiritual, structural, end of life (6) Care Team: Physician: Yes (palliative care & cardiologist) Nurse: Specialized nurses, palliative care nurses Other: Physiotherapist, occupational therapist	N= 36 Mean age = 76.6 years Services: Usual care provided mainly by general practitioners or doctors and/ or nurse-led heart failure clinic with home visits and phone calls that varied substantially from several times per day to every other week. Diuretic therapy was administered at home on demand for worsening symptoms.	QOL: KCCQ & EQ-5D Survival Hospitalization Worsening Heart Failure
Ng et al. [8] 2018 China RCT	Population: Advanced Heart failure Inclusion Criteria: At least 2 of the indicators from the National Gold Standards	N= 43 Mean age = 78.3 years Services: PC nurse managers with volunteers (nursing students) monthly home visits up to 12 weeks; telephone support. First month intervention was	N= 41 Mean age = 78.4 years Services: Usual care (for 12 weeks) described as an unstructured episodic home care service with two social calls.	QOL: McGill QoL

	<p>Framework, Prognostic Indicator Guidance 2008, (i) HF with New York Heart Association stage III or IV, (ii) patient thought to be in the last year of life, (iii) repeated hospital admissions with symptoms of HF, (iv) existence of physical or psychological symptoms despite optimal therapy.</p> <p>Follow-up: Hospital discharge, 12 weeks, and 24 weeks (only 12 week outcomes were included in this review due to crossover design).</p>	<p>more intensive followed by maintenance intervention. The interventions were governed by standard protocols which include the use of the Omaha system.</p> <p>Domains: Physical and psychological symptom assessment/ management social support; Spiritual/ existential care; Goals of care Treatment preferences; End-of-life issues; Care transition (6)</p> <p>Care Team:</p> <p>Physician: Yes</p> <p>Nurse: Yes</p>		
O'Donnell et. al., [4] 2018 SWAP-HF study Boston, Massachusetts, USA RCT	<p>Population: Heart failure patients</p> <p>Inclusion Criteria: Current or recently hospitalized heart failure patients with additional high risk prognostic features</p> <p>Follow-up: 6 months</p>	<p>N= 26</p> <p>Mean age= 74.7 years</p> <p>Services: Social worker led palliative care service which starts with a structured discussion regarding goals of care. This is followed by home visits and phone calls.</p> <p>Domains: Structural, physical, social, legal, psychological, end of life (6)</p> <p>Care Team</p> <p>Physician: Yes (palliative care & cardiologist)</p> <p>Nurse: Yes</p> <p>Other: Psychiatrist, social worker</p>	<p>N= 24</p> <p>Mean age= 69.2 years</p> <p>Service: Usual care, all patients will receive printed materials containing information about advance care planning. They will also receive the Brigham and Women's heart failure guide palliative care and advanced planning discussions will be initiated at the discretion of the team</p>	QOL: KCCQ Survival
Rogers et al. [5] 2017 PAL-HF study North Carolina, USA RCT	<p>Population: Heart failure patients.</p> <p>Inclusion Criteria: 18 years or age or older, advanced heart failure; hospitalized patients or discharged within past 2 weeks;</p>	<p>N = 75</p> <p>Mean age= 71.9 years</p> <p>Services: Goal is a structured and reproducible approach with an interdisciplinary team addressing physical symptoms, psychosocial,</p>	<p>N = 75</p> <p>Mean age = 69.8 years</p> <p>Services: Heart failure care by a cardiologist-directed team during transition care and general practitioners, cardiologist or nurse practitioner after discharge focusing on guideline directed medical therapy and serial</p>	QOL: Heart failure specific QOL: KCCQ General QOL: Functional Assessment of Chronic

	<p>previous heart failure hospitalization within a year; high 6-month mortality risk; dyspnea at rest or minimal exertion.</p> <p>Follow-up: 2, 6, 12, and 24 weeks</p>	<p>spiritual, and advanced care planning.</p> <p>Domains: Physical, psychological, social, spiritual, structural, legal, end of life (7)</p> <p>Care Team:</p> <p>Physician: Yes (cardiologist, hospice and palliative care, psychiatrist)</p> <p>Nurse: Yes (palliative care nurse practitioner)</p>	<p>monitoring of end organ function.</p>	Illness Therapy-Palliative Care (FACIT-PAL). Hospitalization Survival
Wong et al. [9] 2016 Hong Kong, China RCT	<p>Population: Heart failure patients in the end of life.</p> <p>Inclusion Criteria: 2 of the following: (i) NYHA III or IV, (ii) patient thought to be in last year of life, (iii) 3 hospitalizations in last year (iv) physical or psychosocial symptoms despite optimal therapies</p> <p>Follow-up: 12 weeks.</p>	<p>N= 43</p> <p>Mean age= 78.3 years</p> <p>Services: 12 weeks of palliative care management, consisting of weekly home visits/ telephone calls for first four weeks; followed by monthly home visits and tele-monitoring.</p> <p>Domains: Structural, psychological, social, physical, legal, end of life (7)</p> <p>Care Team</p> <p>Physician: Yes (palliative care specialist)</p> <p>Nurse: Nurse case managers</p> <p>Other: Trained volunteers.</p>	<p>N= 41</p> <p>Mean age= 78.4 years</p> <p>Services: Usual care: could have involved palliative care medical clinic consultation, discharge advice and referrals (if appropriate). Two social calls from an assistant unrelated to palliative care were also provided.</p>	QOL: McGill QOL questionnaire, and chronic heart failure questionnaire (CHQ) – Chinese Survival

Author(s): Elmer Jasper B. Llanes, M.D.

Table 3. GRADE Evidence Profile table

Question: Palliative care compared to Usual care for adult Filipinos with chronic heart failure
Setting: Outpatient
Bibliography:

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative care	Usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality												

4	randomised trials	serious ^a	not serious	not serious	serious ^b	none	44/180 (24.4%)	44/176 (25.0%)	OR 0.97 (0.60 to 1.57)	6 fewer per 1,000 (from 83 fewer to 94 more)	 Low	CRITICAL
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Rehospitalization

3	randomised trials	serious ^a	not serious	not serious	not serious	none	70/154 (45.5%)	96/152 (63.2%)	OR 0.48 (0.30 to 0.77)	180 fewer per 1,000 (from 292 fewer to 63 fewer)	 Moderate	CRITICAL
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Quality of Life (follow-up: mean 1-6 months; assessed with: Mc Gill QoL and KCCQ)

5	randomised trials	serious ^a	not serious	not serious	not serious	none	189	182	-	SMD 0.37 SD higher (0.16 higher to 0.57 higher)	 Moderate	IMPORTANT
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Worsening heart failure

1	randomised trials	serious ^a	not serious	not serious	serious ^b	none	2/28 (7.1%)	5/32 (15.6%)	OR 0.42 (0.07 to 2.33)	84 fewer per 1,000 (from 143 fewer to 145 more)	 Low	IMPORTANT
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CI: confidence interval; OR: odds ratio; SMD: standardised mean difference

Explanations

a. There was performance bias due to inability to blind patients. Some detection biases were also unclear in most of the studies.
 b. Confidence interval was too wide to know the benefit or harm.

Figure 2. Rehospitalization

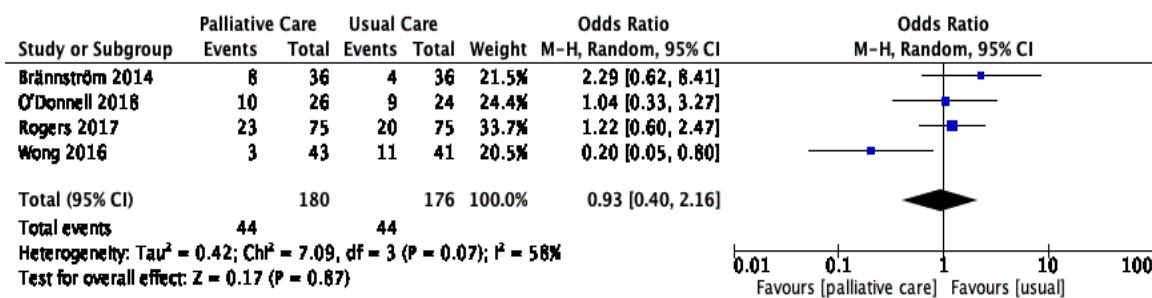


Figure 3. Quality of Life

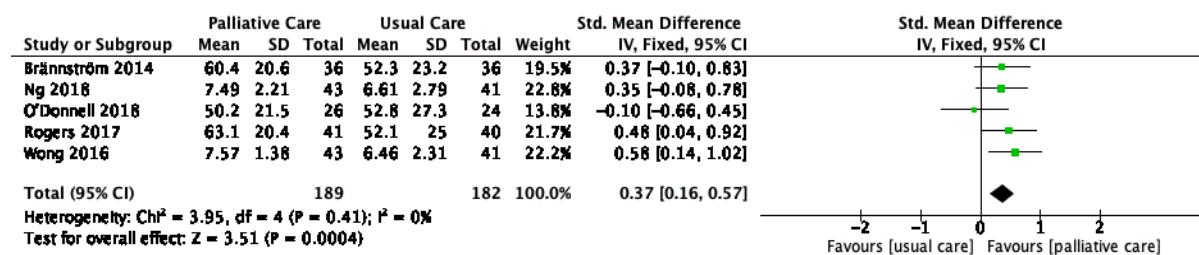


Figure 4. Mortality

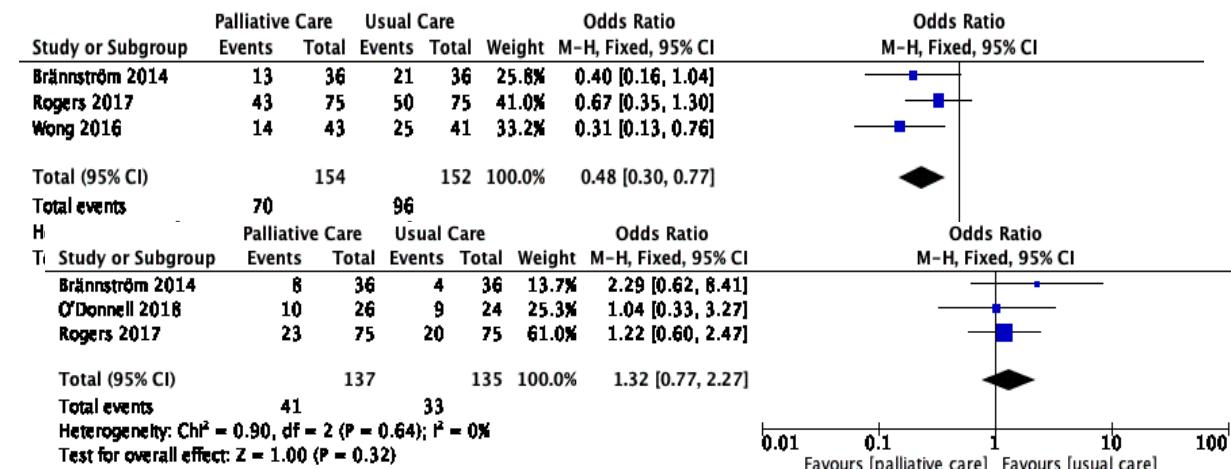


Figure 5. Mortality without the Wong study

The evidence to decision survey prior to voting showed that the majority of the CP considered it as a priority problem. There were a moderate desirable effect and a small

undesirable effect. There was a moderate certainty of evidence, probably favoring intervention for balance of effects. The majority voted for no studies on the certainty of evidence of required costs with a split vote between moderate costs and moderate savings. There was a split vote between probably favoring intervention and no study on cost-effectiveness. The majority voted for a possibly important uncertainty/variability value with probably increased equity. The majority voted that it is probably acceptable, with a split vote between probably feasible and feasible. Ninety percent (90%) of the CP voted to recommend referral to palliative care, while with 70% voted for a strong recommendation.

Annex 17: AGREE Reporting Checklist (Self Evaluation)



AGREE Reporting Checklist 2016

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.	<input checked="" type="checkbox"/> Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) <input checked="" type="checkbox"/> Expected benefit(s) or outcome(s) <input checked="" type="checkbox"/> Target(s) (e.g., patient population, society)	16
2. QUESTIONS Report the health question(s) covered by the guideline, particularly for the key recommendations.	<input checked="" type="checkbox"/> Target population <input checked="" type="checkbox"/> Intervention(s) or exposure(s) <input checked="" type="checkbox"/> Comparisons (if appropriate) <input checked="" type="checkbox"/> Outcome(s) <input checked="" type="checkbox"/> Health care setting or context	17-22
3. POPULATION Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.	<input checked="" type="checkbox"/> Target population, sex and age <input checked="" type="checkbox"/> Clinical condition (if relevant) <input checked="" type="checkbox"/> Severity/stage of disease (if relevant) <input type="checkbox"/> Comorbidities (if relevant) <input type="checkbox"/> Excluded populations (if relevant)	16
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.	<input checked="" type="checkbox"/> Name of participant <input checked="" type="checkbox"/> Discipline/content expertise (e.g., neurosurgeon, methodologist) <input checked="" type="checkbox"/> Institution (e.g., St. Peter's hospital) <input type="checkbox"/> Geographical location (e.g., Seattle, WA) <input checked="" type="checkbox"/> A description of the member's role in the guideline development group	iii, 25-26, 229-238

<p>5. TARGET POPULATION PREFERENCES AND VIEWS</p> <p>Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) <input checked="" type="checkbox"/> Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) <input checked="" type="checkbox"/> Outcomes/information gathered on patient/public information <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations 	16, 28-31
<p>6. TARGET USERS</p> <p>Report the target (or intended) users of the guideline.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) <input checked="" type="checkbox"/> How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care) 	17
DOMAIN 3: RIGOUR OF DEVELOPMENT		
<p>7. SEARCH METHODS</p> <p>Report details of the strategy used to search for evidence.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) <input checked="" type="checkbox"/> Time periods searched (e.g., January 1, 2004 to March 31, 2008) <input checked="" type="checkbox"/> Search terms used (e.g., text words, indexing terms, subheadings) <input checked="" type="checkbox"/> Full search strategy included (e.g., possibly located in appendix) 	26-29, 45-46, 55-56, 71-72, 84, 93-94, 103-104 115, 126, 138-139, 155, 167, 176-177, 197, 212
<p>8. EVIDENCE SELECTION CRITERIA</p> <p>Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Target population (patient, public, etc.) characteristics <input checked="" type="checkbox"/> Study design <input checked="" type="checkbox"/> Comparisons (if relevant) <input checked="" type="checkbox"/> Outcomes <input type="checkbox"/> Language (if relevant) <input type="checkbox"/> Context (if relevant) 	17, 26-29

<p>9. STRENGTHS & LIMITATIONS OF THE EVIDENCE</p> <p>Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Study design(s) included in body of evidence <input checked="" type="checkbox"/> Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) <input checked="" type="checkbox"/> Appropriateness/relevance of primary and secondary outcomes considered <input checked="" type="checkbox"/> Consistency of results across studies <input checked="" type="checkbox"/> Direction of results across studies <input checked="" type="checkbox"/> Magnitude of benefit versus magnitude of harm <input checked="" type="checkbox"/> Applicability to practice context 	27-29
<p>10. FORMULATION OF RECOMMENDATIONS</p> <p>Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) <input checked="" type="checkbox"/> Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) <input checked="" type="checkbox"/> How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote) 	30
<p>11. CONSIDERATION OF BENEFITS AND HARMS</p> <p>Report the health benefits, side effects, and risks that were considered when formulating the recommendations.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Supporting data and report of benefits <input checked="" type="checkbox"/> Supporting data and report of harms/side effects/risks <input checked="" type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks <input checked="" type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks 	86, 107-110, 116-119 127-128 139-146, 156- 160, 167- 170, 177-179 197-198 200-205
<p>12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE</p> <p>Describe the explicit link between the recommendations and the evidence on which they are based.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations <input checked="" type="checkbox"/> Link between each recommendation and key evidence (text description and/or reference list) <input checked="" type="checkbox"/> Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline 	43- 44, 53 - 54, 69-71, 82-84, 91-94, 100-104, 113-115, 124-126, 136-139, 152-157,

		166-168, 175-180, 193-196, 211- 214
13. EXTERNAL REVIEW Report the methodology used to conduct the external review.	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) <input checked="" type="checkbox"/> Methods taken to undertake the external review (e.g., rating scale, open-ended questions) <input checked="" type="checkbox"/> Description of the external reviewers (e.g., number, type of reviewers, affiliations) <input checked="" type="checkbox"/> Outcomes/information gathered from the external review (e.g., summary of key findings) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations) 	33- 36
14. UPDATING PROCEDURE Describe the procedure for updating the guideline.	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> A statement that the guideline will be updated <input checked="" type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur <input type="checkbox"/> Methodology for the updating procedure 	36-37
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> A statement of the recommended action <input checked="" type="checkbox"/> Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) <input checked="" type="checkbox"/> Relevant population (e.g., patients, public) <input checked="" type="checkbox"/> Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) <input checked="" type="checkbox"/> If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline 	30
16. MANAGEMENT OPTIONS Describe the different options for managing the condition or health issue.	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Description of management options <input checked="" type="checkbox"/> Population or clinical situation most appropriate to each option 	12-14

<p>17. IDENTIFIABLE KEY RECOMMENDATIONS</p> <p>Present the key recommendations so that they are easy to identify.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms <input checked="" type="checkbox"/> Specific recommendations grouped together in one section 	8-11, 43, 53, 69, 83, 92, 102, 114, 125, 137, 153, 167, 176, 194, 211
DOMAIN 5: APPLICABILITY		
<p>18. FACILITATORS AND BARRIERS TO APPLICATION</p> <p>Describe the facilitators and barriers to the guideline's application.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Types of facilitators and barriers that were considered <input checked="" type="checkbox"/> Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) <input checked="" type="checkbox"/> Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) <input checked="" type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations 	26, 30, 224
<p>19. IMPLEMENTATION ADVICE/TOOLS</p> <p>Provide advice and/or tools on how the recommendations can be applied in practice.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Additional materials to support the implementation of the guideline in practice. For example: <ul style="list-style-type: none"> ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned 	6-7, 12-14, 31

<p>20. RESOURCE IMPLICATIONS Describe any potential resource implications of applying the recommendations.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) <input checked="" type="checkbox"/> Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) <input checked="" type="checkbox"/> Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations 	49, 61, 76, 88, 98, 109, 120, 131, 145, 162, 170, 187, 205, 218
<p>21. MONITORING/ AUDITING CRITERIA Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations <input checked="" type="checkbox"/> Criteria for assessing impact of implementing the recommendations <input checked="" type="checkbox"/> Advice on the frequency and interval of measurement <input type="checkbox"/> Operational definitions of how the criteria should be measured 	225
DOMAIN 6: EDITORIAL INDEPENDENCE		
<p>22. FUNDING BODY Report the funding body's influence on the content of the guideline.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> The name of the funding body or source of funding (or explicit statement of no funding) <input checked="" type="checkbox"/> A statement that the funding body did not influence the content of the guideline 	ii
<p>23. COMPETING INTERESTS Provide an explicit statement that all group members have declared whether they have any competing interests.</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Types of competing interests considered <input checked="" type="checkbox"/> Methods by which potential competing interests were sought <input checked="" type="checkbox"/> A description of the competing interests <input checked="" type="checkbox"/> How the competing interests influenced the guideline process and development of recommendations 	38-39, 232-238

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For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at <http://www.agreetrust.org>.