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The economics of heart failure care

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ABSTRACT

Heart failure (HF) poses a significant economic burden in the US, with costs projected to reach $70 billion by 2030. Cost-effectiveness analyses play a pivotal role in assessing the economic value of HF therapies. In this review, we overview the cost-effectiveness of HF therapies and discuss ways to improve patient access. Based on current costs, guideline directed medical therapies for HF with reduced ejection fraction provide high economic value except for sodium-glucose cotransporter-2 inhibitors, which provide intermediate economic value. Combining therapy with the four pillars of medical therapy also has intermediate economic value, with incremental cost-effectiveness ratios ranging from $73,000 to $98,500/ quality adjusted life-years. High economic value procedures include cardiac resynchronization devices, implantable cardioverter-defibrillators, and coronary artery bypass surgery. In contrast, advanced HF therapies have previously demonstrated intermediate to

Abbreviations: ACEi, Angiotensin-Converting Enzyme Inhibitors; ACC/AHA, American College of Cardiology/American Heart Association; ADVANCE BTT, Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device Bridge to Transplant; ADVANCE BTT + CAP, Ventricular Assist Device for the Treatment of Advanced Heart Failure Bridge to Transplant + Continued Access Program; A-HeFT, African-American Heart Failure Trial; ARB, Angiotensin (II) Receptor Blockers; ARNI, Angiotensin Receptor-Neprilysin Inhibitors; ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; ATTR-CM, Transthyretin Amyloidosis Cardiomyopathy; BB, Beta Blockers; BTT, Bridge to Transplant; CABG, Coronary Artery Bypass Graft; CASTLE-AF, Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients; COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CVD, Cardiovascular Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EF, Ejection Fraction; EPHESUS, Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENDURANCE, Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure; FDA, Food and Drug Administration; GDMT, Guideline-Directed Medical Therapy; GUIDE-HF, The Hemodynamic-Guided Management of Heart Failure Trial; HF, Heart Failure; HFH, Heart Failure Hospitalizations; HFSA, Heart Failure Society of America; HFpEF, Heart Failure with Preserved Ejection Fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; HT, Heart Transplantation; ICER, Incremental Cost-Effectiveness Ratio; ICD, Implantable Cardiac Defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; ISHLT, International Society for Heart and Lung Transplantation; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LATERAL, Evaluation of a lateral thoracotomy implant approach for a centrifugal-flow left ventricular assist device: The LATERAL clinical trial; LVAD, Left Ventricular Assist Device; MEDAMACS, Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MI, Myocardial Infarction; MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; MONITOR-HF, Remote Hemodynamic Monitoring of Pulmonary Artery Pressures in Patients with Chronic Heart Failure; MR, Mitral Regurgitation; MRA, Mineralocorticoid Receptor Antagonists; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PAP, Pulmonary Artery Pressure Monitor; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PA, Pulmonary Artery; PIONEER-HF, Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode; QALY, Quality-Adjusted Life-Years; QoL, Quality of Life; RALES, Randomized Aldactone Evaluation Study; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; SAVE, Survival and Ventricular Enlargement; SHIFT, Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitors; SOLVD, Studies of Left Ventricular Dysfunction; STICH, Surgical Treatment for Ischemic Heart Failure Trial; TMVR, Transcutaneous Mitral Valve Repair; US, United States; USD, US Dollar; Val-HEFT, Valsartan Heart Failure Trial; VICTORIA, Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction.

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low economic value, but newer data appear more favorable. Given the affordability challenges of HF therapies, additional efforts are needed to ensure optimal care for patients. The recent Inflation Reduction Act contains provisions to reform policy pertaining to drug price negotiation and out-of-pocket spending, as well as measures to increase access to existing programs, including the Medicare low-income subsidy. On a patient level, it is also important to encourage patient and physician awareness and discussions surrounding medical costs. Overall, a broad approach to improving available therapies and access to care is needed to reduce the growing clinical and economic morbidity of HF.

Heart failure (HF) is a major global health concern, with an estimated prevalence of 26 million adults worldwide and 5.7 million in the US.[1,2] By 2030, it is projected that over 8 million patients in the US will have HF, and the annual cost of HF is expected to reach $70 billion.[1] Effective medical therapies have the potential to reduce HF morbidity but uptake of such therapies has been sub-optimal. Given the rising clinical and economic burden of HF, this review sought to summarize the current data on the costs and cost-effectiveness of contemporary HF care and outline ongoing challenges to patient affordability and access.

Economic burden of HF

The economic burden of heart failure is substantial, with an estimated annual cost of about $30,000 per patient in the US.[3–6] The total cost of HF in the US was estimated to be $31 billion in 2012 and is projected to increase by over two-fold to $70 billion in 2030.[1] Two-thirds of this amount are made up by direct costs of HF care. The remaining indirect costs include those attributable to lost employment.[1]

Inpatient hospitalizations make up nearly 50% of the direct costs of HF care.[7] Hospitalizations for HF have increased over time, growing by 26% to 1.2 million hospitalizations from 2013 to 2017.[8] HF is the 2nd most commonly billed Medicare inpatient diagnosis.[7] Despite a decrease in the average length of stay of HF hospitalizations (HFH) by nearly 2 days from 2002 to 2016 (from 8.6 to 6.5), the cost per hospitalization increased by 1.4% each year to $19,000 in 2016 dollars.[4] This rise in inpatient cost has been attributed to higher procedural utilization and the rising incidence of cardiogenic shock and renal failure requiring dialysis.[4]

Cost-effectiveness in HF

Cost-effectiveness analyses evaluate the economic value of healthcare strategies including diagnostic approaches, treatments, and disease monitoring. These analyses compare the difference in costs of care and clinical outcomes across two or more strategies. These analyses evaluate clinical outcomes as the difference in expected quality adjusted life-years (QALYs) – which incorporates both impact on survival and quality of life (QoL) - or the difference in life-years alone. The costs in a cost-effectiveness analysis vary based on the perspective of the analysis. Most cost-effectiveness analyses in cardiovascular medicine use a health system perspective, in which all direct costs of healthcare are included regardless of who pays those costs (insurance or payment). Broader economic analyses that use the societal perspective also include costs of care outside the healthcare system, such as the cost of caregivers, lost wages, or travel to a healthcare facility. The 2nd Panel on Cost-Effectiveness has recommended cost-effectiveness analyses have a time horizon that incorporates all relevant costs and clinical outcomes.[9] For the treatment of cardiovascular disease, that is typically a lifetime horizon.

Cost-effectiveness analyses summarize the economic value of different therapies based on the incremental cost-effectiveness ratio (ICER). The ICER is typically the difference in QALYs divided by the difference in costs. If a given strategy is both more effective and lower cost, that would be considered a dominant strategy and would be high value. Otherwise, the ICER is typically compared to thresholds to compare the cost-effectiveness across other interventions. The ACC/AHA have suggested a cost-effectiveness threshold of $<1\times$ GDP per capita (~$70,000/QALY in 2021) as high value and over $3\times$ GDP per capita (~$210,000/QALY in 2021) as low value with between those benchmarks as intermediate value.[10] Traditionally, analyses have used cost-effectiveness thresholds of under $50,000/QALY or $100,000/QALY as cost-effective. For this review, we used the GDP-based criteria in alignment with American College of Cardiology (ACC)/American Heart Association (AHA) guidance, incorporating year-over-year changes in dollar value.

There are two broad categories of economic models: trial-based analyses and model-based analyses. Trial-based analyses typically use patient-level clinical and economic data from the clinical trial and then model post-trial outcomes. Model-based analyses simulate clinical outcomes and economic costs based on published estimates of efficacy and cost. For both approaches, the uncertainty of the estimate is as important as the point estimate. Cost-effectiveness analyses include numerous assumptions that substantially impact the ICER estimate. These assumptions are varied in sensitivity analyses that estimate the uncertainty of the economic assessment.

There are several additional important considerations when interpreting cost-effectiveness analyses. First, cost-effectiveness analyses are inherently incremental and dependent on the comparative strategy. Therefore, appropriate comparators are necessary for accurate economic evaluation. Second, the primary driver of cost-effectiveness is effectiveness. Uncertainty in the efficacy data related to generalizability or potential bias increases the uncertainty of cost-effectiveness estimates. Finally, cost-effectiveness should not be used to determine which treatments an individual patient receives. Cost-effectiveness analyses can inform larger policy and system-level decisions regarding investment of limited resources. Even for such policy decisions, cost-effectiveness by itself should only be one of many inputs along with consideration of equity, budget impact, and the strength of underlying clinical data. Additional factors that may not be captured in the clinical data but are worthwhile to consider include long-term consequences for major life goals, such as education, work or family life, and effects on caregivers' quality of life.[11]

As a reflection of the growing economic burden of HF in the US, the 2022 AHA/ACC/ Heart Failure Society of America (HFSA) HF guidelines include value statements to evaluate the economic value of select where high-quality cost-effectiveness data are available.[12] These are summarized in Table 1. In the following sections, we provide an overview of the cost-effectiveness of HF therapies (Fig. 1). For comparability, we converted incremental costs and ICER estimates to 2022 US dollars (USD).[13]

Cost-effectiveness of 4 pillars of guideline-directed medical therapy (GDMT)

Four medication classes–beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEi), angiotensin (II) receptor blockers (ARB) or angiotensin receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i)—have been termed the 4 pillars of guideline-directed medical therapy for HF with reduced ejection fraction (EF;HFrEF) based on their substantial reduction in cardiovascular disease (CVD) death. SGLT2i carry an ACC/AHA/HFSA Class 2 A recommendation in HF with preserved EF (HFpEF) while ARNIs, MRAs, and ARBs carry a Class 2B

Table 1
Summary of value statements from 2022 AHA/ACC/HFSA heart failure guidelines[2].

Diagnostic/Therapy	2022 AHA/ACC/HFSA Value Designation[1]	Recommendation
ACEi/ARB	High Value (A)	ACEi/ARB treatment provides high value in patients with chronic HFrEF with current or previous symptoms, in whom ARNi is not feasible
ARNi	High Value (A)	ARNi treatment provides high value in patients with chronic symptomatic HFrEF
BB	High Value (A)	BB therapy provides high value in patients with HFrEF with current or previous symptoms
MRA	High Value (A)	MRA therapy provides high value in patients with HFrEF and NYHA class II to IV symptoms
ICD	High Value (A)	A transvenous ICD provides high value in primary prevention of sudden cardiac death when the risk of death from ventricular arrhythmia is deemed high and the risk of non-arrhythmic death is deemed low
Hydralazine and isosorbide dinitrate	High Value (B-NR)	Hydralazine and isosorbide dinitrate provides high value in patients self-identified as African-American with NYHA class III to IV HFrEF on optimal medical therapy with ACEi/ARB, BB, and MRA
CRT	High Value (B-NR)	CRT implantation provides high value in patients with LVEF ≤35%, sinus rhythm, LBBB with a QRS duration of ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT
SGLT2I	Intermediate Value (A)	SGLT2i therapy provides intermediate value in patients with symptomatic chronic HFrEF
Cardiac transplant	Intermediate Value (C-LD)	Cardiac transplantation provides intermediate economic value in patients with advanced HF despite GDMT
Tafamidis	Low Value (B-NR)	At 2020 list prices, tafamidis provides low value (>$180,000/QALY) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis
Mechanical circulatory support	Uncertain Value (B-NR)	Durable MCS devices provide low to intermediate value based on current costs and outcomes in patients with advanced HFrEF who have NYHA class I symptoms despite GDMT
PA pressure monitor	Uncertain Value (B-NR)	Wireless monitoring of PAP by implanted hemodynamic monitor provides uncertain value in patients with NYHA Class III HF with HF hospitalization within the last year

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin (II) receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta blockers; CRT, cardiac resynchronization device; ICD, implantable cardioverter-defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICER, incremental cost-effectiveness ratio; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonists; NYHA = New York Heart Association; QALY, quality-adjusted life-years; PAP, pulmonary artery pressure monitor; QALY, quality-adjusted life-years; SGLT2, sodium-glucose cotransporter-2 inhibitors.

[1] Value thresholds were set at the following: high value - ≤ $60,000/QALY; intermediate value - > $60,000/QALY and ≤ $180,000/QALY; low value - > $180,000/QALY based on 2019 USD.

[2] The level of evidence was based on the number and quality of economic analyses and the underlying clinical effectiveness data. Level of evidence A required at least 1 high-quality economic analysis without industry funding and a related clinical effectiveness statement with Level of Evidence A. Level of Evidence B required at least 1 high-quality economic analysis, a related clinical effectiveness statement with Level of Evidence A or B, and not meeting the requirements for Level of Evidence A. Level of Evidence C required at least 1 high-quality economic analysis and not meeting the requirements for Level of Evidence A or B.

recommendation. Multiple drug classes – BB, ACEI/ARB, and MRA – are available as low-cost generics. Two drug classes – SGLT2i and ARNI – are only currently available as higher cost branded drugs. Table 2 lists the average cost of each of these therapies across Medicare Part D plans. In the following sections, we describe the cost-effectiveness of GDMT.

BBs

Multiple cost-effectiveness analyses demonstrated the high value of BB therapy in HFrEF, even prior to generic BBs becoming available (Table 3). Metoprolol succinate was found to have an ICER of $3999 to $5964 per life-year (LY) in 2022 USD compared to no BB.[14,15] Carvedilol had an ICER ranging from $10,902 to $34,237.[14,16] The ICER for bisoprolol was $5396 per LY.[14] Follow-up studies after patent expiration demonstrated an ICER of $1547 per QALY for the addition of BB to ACEi therapy based on Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial data.[17]

MRA

MRAs carry a Class I recommendation in HFrEF and also provide high economic value.[12] Their cost-effectiveness has been demonstrated with efficacy data from 2 major trials. Using efficacy and inpatient resource utilization data from Randomized Aldactone Evaluation Study (RALES) and a time horizon of 35 months, spironolactone led to improved outcomes and lower costs compared with placebo.[18] Using efficacy and resource utilization data from Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 2 studies estimated an ICER for eplerenone between $26,202/QALY and $61,484/QALY over a lifetime horizon.[19,20] Since the publication of these prior analyses, generic availability of spironolactone and eplerenone have reduced their cost substantially (Table 2). A study using Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) efficacy data with generic costs showed that the addition of MRAs to BB and ACEi therapy resulted in an ICER of $586/QALY.[17]

ACEis/ARBs

Prior to the emergence of ARNIs, multiple studies demonstrated the cost-effectiveness of ACEis and ARBs in the treatment of HF. In a model using efficacy data from the Studies of Left Ventricular Dysfunction (SOLVD) trial, the ICER for enalapril versus placebo over a lifetime horizon was $215/QALY.[21] Using data for the Survival and Ventricular Enlargement (SAVE) trial, the ICER for captopril versus placebo was $10,464/QALY over a lifetime.[22] In the Valsartan Heart Failure Trial (Val-HEFT) trial, valsartan had better outcomes and was cost-saving relative to placebo in patients not taking ACE inhibitors.[23] Based on these evidence, patients with chronic HFrEF in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.

ARNI

The Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial demonstrated ARNI reduced CVD mortality and HFH compared with ACEi therapy.[24] Multiple cost-effective analyses have demonstrated ARNI therapy provides high economic value based on the PARADIGM-HF data. Three independent cost-effectiveness analyses each found an ICER between $51,000–$58,000/QALY.[25–27] Furthermore, Gaziano et al. demonstrated that inpatient initiation of ARNI therapy was cost-effective based on data from Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF).[28]

SGLT2i

Dapagliflozin and empagliflozin are both SGLT2i that have improved CVD outcomes among patients with HFrEF in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trials, respectively.[29,30] Based on this data, SGLT2i have been found to have intermediate economic value for patients with HFrEF. Parizo et al. used the published data from DAPA-HF and dapagliflozin cost estimates from Medicare Part D to estimate an ICER of $85,659/QALY in 2022 USD over a lifetime horizon.[31] They found dapagliflozin would have an ICER below $50,000/QALY at a cost of $3380 annually or lower. An analysis by Isaza et al. found a similar ICER of $69,941/QALY over a lifetime horizon.[32] They found the annual cost of dapagliflozin would need to be $2600 or lower to meet a $50,000/QALY threshold.

Quadruple therapy

Given the morbidity of HFrEF and the incremental benefit of therapies described above, the 2022 ACC/AHA/HFSA Heart Failure Guidelines recommend quadruple therapy with the drug classes described above. Understanding the cost-effectiveness of quadruple therapy is important given the incremental costs and benefits of combined therapy. Yan et al. investigated the cost-effectiveness of sequentially adding SGLT2i and/or ARNI therapy to prior standard of care BB/ACEi/MRA therapy.[33] Using published efficacy data from PARADIGM-HF, DAPA-HF, and EMPEROR-Reduced, they found SGLT2i addition had an ICER of $73,000 per QALY. Adding both SGLT2i and ARNI therapy had an ICER of $98,500 per QALY. Dixit et al. compared the economic value of treatment with BB/ACEi/MRA versus contemporary quadruple therapy with BB/ARNI/MRA/SGLT2i.[34] Using published trial data, they estimated quadruple therapy led to 1.12 increased QALYs and an ICER of $81,000/QALY over a 30-year time horizon. This data overall suggests the addition of both ARNI and SGLT2i therapy to optimal BB, ACEi, and MRA therapy provides likely intermediate economic value at current prices. The economic value of combined quadruple therapy would be expected to improve with forthcoming generic pricing of both therapies.

Cost-effectiveness of additional medical therapies for HF

Hydralazine and isosorbide dinitrate for HFrEF

Combined hydralazine and isosorbide dinitrate therapy has a Class I recommendation for improving symptoms and reducing mortality in Black patients with HFrEF and New York Heart Association (NYHA) class III-IV symptoms based on the African-American Heart Failure (A-HeFT) trial.[35] With A-HeFT trial data, Angus et al. showed that this combination yielded an ICER of $63,044 compared with placebo with the conservative assumption that there was efficacy only during the trial period of 12.8 months at the prior branded prices of hydralazine-nitrate therapy. Extension of efficacy by 1 year lowered the ICER to $46,715 per LY.[36] At current generic prices, the ICER of hydralazine-nitrate therapy would be expected to be substantially lower.

Ivabradine for HFrEF

Ivabradine carries a class 2 A recommendation for treatment of patients with NYHA II-III HFrEF on maximally tolerated doses of BB with a heart rate in sinus $\geq$70 bpm. Its efficacy was studied in the Ivabradine and Outcomes in Chronic Heart Failure (SHIFT) trial, which demonstrated a reduction in the composite endpoint of CVD death or HFH.[37] A single CEA evaluated ivabradine in the US health care system. This analysis estimated an ICER of $28,318/QALY for ivabradine therapy based on effectiveness estimates from SHIFT and costs from a large US claims database.[38] There are two important limitations for this analysis. First, the hospitalization cost estimates are higher than most published cost effective analyses. Second, the QoL benefit is based on the number of HFH rather than the observed difference in QoL in the SHIFT trial.

It is worth noting that only 25% of patients in the SHIFT trial were on optimal BB dose. Ivabradine's mechanism of action is via heart rate reduction. Higher doses of BB therapy would not only reduce heart rate, but BBs also provide substantial mortality benefits at high economic value. Therefore, the clinical and economic benefit of ivabradine should be considered in the context of first optimizing BB therapy.

Vericiguat for HFrEF

Vericiguat is an oral soluble guanylyl cyclase stimulator that has a Class 2 A recommendation for reducing the composite of CVD death and HFH among high-risk patients with HF based on the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial.[39] Two economic analyses evaluated the cost-effectiveness of vericiguat. Chew and colleagues performed a trial-based economic analysis of the VICTORIA trial. They used trial estimates of clinical outcomes and costs over the 15-month mean trial follow-up and subsequently modeled post-trial costs and outcomes.[40] They estimated vericiguat led to a 0.43 increase in QALYs at an ICER of $66,509/QALY despite CVD mortality being similar between vericiguat and placebo (HR 0.93 [95% CI: 0.81–1.06]) and no observed improvement in QoL. Their analysis incorporated an interaction between baseline NT-BNP and the vericiguat treatment effect. In the VICTORIA trial, patients in the highest quartile of baseline NT-BNP level (>5314 ng/mL) had a non-significant increase in the primary outcome of CVD or HFH (HR 1.16 [95% CI: 0.99–1.35]) while those in lower NT-BNP quartiles had large reductions in the primary outcome. Those with a higher NT-BNP quartile also had the lowest survival. Therefore, modeling this treatment interaction increased gains in survival when modeling post-trial outcomes. Without including the NT-BNP-treatment interaction, the increase in QALYs was 0.17 and the ICER was $124,512/QALY. These findings emphasize the impact of patient selection, with regards to baseline NT-BNP for the economic value of vericiguat. A second cost-effectiveness analysis found a similar ICER of $84,428/QALY (in 2022 USD) via an analogous approach.[41]

SGLT2i for HFpEF

Multiple clinical trials have demonstrated SGLT2is improve clinical outcomes for patients with HFmrEF and HFpEF. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) found a significant 21% reduction (HR 0.69–0.90) in the composite primary outcome of CVD or HFH with empagliflozin therapy.[42] The trial did not demonstrate a significant reduction in CVD death (HR 0.91; 95% CI: 0.76–1.09). Zheng et al. performed an economic analysis based on published data from EMPEROR-Preserved.[43] They found the cost-effectiveness of empagliflozin was highly dependent on assumptions regarding the effect on CVD death. Without a reduction in CVD death, empagliflozin led to an increase of 0.1 QALYs per patient and an ICER of $437,442/QALY. Assuming empagliflozin reduced CVD deaths by 9% improved the ICER to $174,053/QALY. Incorporating a larger effect on QoL, as seen in three smaller trials of SGLT2i with more symptomatic patients, also improved the ICER substantially.[44–46]

A second economic analysis by Cohen and colleagues meta-analyzed data from both the EMPEROR-Preserved and DELIVER trials.[47] Consistent with analyses of SGLT2i across the EF spectrum that support an effect on CVD mortality, they assumed SGLT2i would lead to long-term reduction in CVD death. Their analysis found SGLT2i would have an ICER of $141,200/QALY. Without an effect on CVD death, they estimated an ICER of $337,400/QALY.

These models illustrate SGLT2i are intermediate in cost-effectiveness with an assumed reduction of CVD death and low value without such an

assumption. The cost-effectiveness is lower than SGLT2i for HFrEF despite relatively similar relative risk reduction. This is largely driven by a lower baseline CVD death rate and higher competing risk of non-CVD death for the HFpEF population in existing clinical trials. As a counterpoint, non-trial populations of HFpEF patients often have higher rates of CVD outcomes than those in clinical trials.[48]

A novel online drug distribution company, Cost Plus Drugs, has made bexagliflozin available at far lower prices than other branded SGLT2i.[49] However, there is no evidence of the benefit of bexagliflozin for HF patients. If one were to assume similar efficacy, bexagliflozin would provide high economic value for HFrEF and HFpEF patients at its current cost based on the analyses from prior studies.[31,32,43,47] While there is uncertainty about the class effect of SGLT2i, this may represent a viable alternative for patients in whom branded therapy is unaffordable.

Tafamidis for transthyretin amyloidosis (ATTR-CM)

Cardiac amyloidosis results from build-up of extracellular protein in the myocardium and is associated with significant morbidity and mortality.[50] In patients with ATTR-CM, caused by deposition of either pathogenic transthyretin or wild-type transthyretin, transthyretin tetramer stabilizer therapy with tafamidis has been shown to reduce CVD morbidity and mortality.[51]

While treatment with tafamidis carries a Class I recommendation, it provides low economic value at current prices. An analysis by Kazi and colleagues of the cost-effectiveness of tafamidis versus standard therapy used published efficacy data from the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT).[52] They estimated tafamidis cost $225,000 annually. While they estimated tafamidis led to an incremental gain of 1.29 QALYs per patient, this came at an incremental cost of $1,196,000, equating to an ICER of $901,000/QALY. A 92.6% price reduction from $225,000 to $16,563 would be needed to reduce the ICER to under $100,000/QALY. Of note, 2021 tafamidis price estimates in Medicare Part D are $19,560 for a 30-day fill prior to rebates, which are estimated at ~20–30% for branded drugs.[53]

Table 2
Average cost of selected HF drugs for 30-day supplies.

Drug	Generic/brand name	Average medicare cost[†]	Average out of pocket cost
Carvedilol	Generic	$5	$1
Lisinopril	Generic	$3	$1
Losartan	Generic	$6	$2
Spironolactone	Generic	$6	$2
Empagliflozin	Brand	$544	$37
Dapagliflozin	Brand	$538	$35
Sacubitril-Valsartan	Brand	$566	$46
Hydralazine	Generic	$9	$3
Isosorbide dinitrate	Generic	$49	$7
Vericiguat	Brand	$589	$34
Tafamidis	Brand	$19,560	$530

[†] Data sourced from 2021 Medicare Part D spending: https://data.cms.gov/provider-summary-by-type-of-service/medicare-part-d-prescribers/medicare-part-d-prescribers-by-geography-and-drug. Prices were rounded to the nearest dollar. These estimates do not include proprietary rebates offered by pharmaceutical companies for patented drugs, which average ~ 30% of their cost for branded drugs. Actual out-of-pocket costs will vary based on an individual's insurance plan.

Other treatments for cardiac amyloidosis are on the horizon although their pricing remains uncertain. ATTRibute-CM was a double-blinded, placebo-controlled trial that found transthyretin stabilizer acoramidis in ATTR-CM reduced CVD hospitalizations and improved QoL metrics.[54] As treatments for ATTR-CM continue to expand, it will be important to advocate for patient access and affordability.

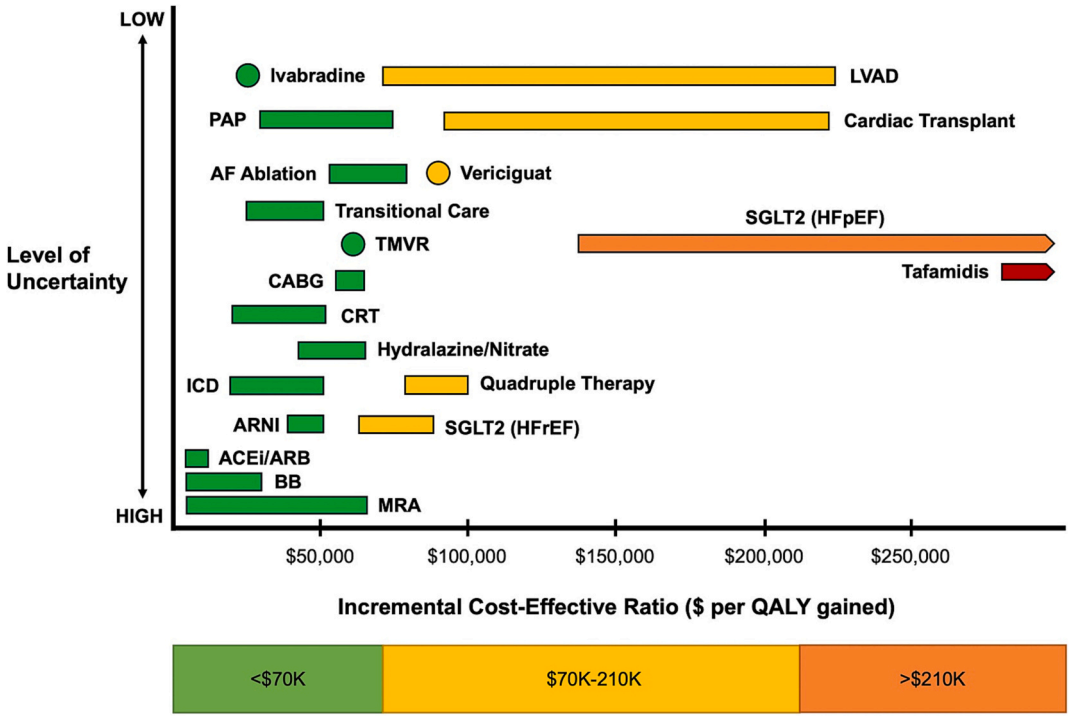

Fig. 1. Graphical representation of cost-effectiveness of selected diagnostics and therapies.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin (II) receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta blockers; CABG, coronary artery bypass surgery; CRT, cardiac resynchronization device; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonists; PAP, pulmonary artery pressure monitor; QALY, quality-adjusted life-years; SGLT2, sodium-glucose cotransporter-2 inhibitors; TMVR, transcutaneous mitral valve repair.

Table 3
Cost-effectiveness studies for selected HF drugs.

Therapy	First author (year)	Incremental cost (time horizon)	QALY gain (years)	ICER ($/QALY)	Efficacy source	Comments/limitations
Sacubitril-valsartan for HFrEF	Gaziano (2016)	$40,354 vs enalapril (30 years)	0.78	$51,155	PARADIGM-HF	No outpatient costs
	King (2016)	$43,888 vs enalapril (lifetime)	0.75	$57,907	PARADIGM-HF	No outpatient costs; quality of life effect limited to hospitalizations
	Sandhu (2016)	$33,185 vs enalapril (lifetime)	0.62	$57,741	PARADIGM-HF	Similar economic value between NYHA Class II and Class III
SGLT2i for HFrEF	Parizo (2021)	$39,130 vs SOC (lifetime)	0.46	$85,659	DAPA-HF	Incremental utility based on patient-reported health status mapping Similar value with/without DM ICER better with mild health status impairment
	Isaza (2021)	$43,828 vs SOC (lifetime)	0.63	$69,941	DAPA-HF	Incremental utility based on patient-reported health status mapping Similar value with/without DM
SGLT2i for HFpEF	Zheng (2023)	$26,257 vs SOC (lifetime)	0.06	$437,442	EMPEROR-Preserved	Assumed no CV death benefit ICER $137,091/QALY with CV death
	Cohen (2023)	$26,300 vs SOC (lifetime)	0.19	$141,200	EMPEROR-Preserved, DELIVER	Assumed CV death reduction ICER $373,400/QALY without CV death Similar value with/without DM
Quadruple Therapy for HFrEF	Yan (2023)	$66,700 vs SGLT2/ACEi/MRA/BB (lifetime)	0.68	$98,500	PARADIGM-HF, DAPA-HF, EMPEROR-Reduced	Assumed treatment effects are independent
	Dixit (2023)	$90,132 vs ACEi/BB/ MRA; $94,549 vs ACEi/BB (lifetime)	1.12; 1.85	$81,000; $51,081	PARADIGM-HF, DAPA-HF, EMPEROR-Reduced, EMPHASIS-HF	Assumed treatment effects are independent
Tafamidis	Kazi (2020)	$1,195,977 vs SOC (lifetime)	1.29	$901,138	ATTR-ACT	Requires 92.6% price reduction for ICER≤ $150,000/QALY
Ivabradine	Kansal (2016)	-$9766 vs SOC; $5469 vs SOC for Medicare Advantage (10 years)	0.24	Dominant[¥]; $28,318	SHIFT	Incremental utilities based on number of hospitalizations; higher hospitalization costs
Vericiguat	Alsumali (2021)	$23,882 vs SOC (lifetime)	0.28	$68,107	VICTORIA	Models heterogeneity in treatment effect based on NT-BNP; without heterogeneity, ICER $127,503/QALY

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin (II) receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta blockers; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICER, incremental cost-effectiveness ratio; MRA, mineralocorticoid receptor antagonists; NYHA = New York Heart Association; QALY, quality-adjusted life-years; SGLT2, sodium-glucose cotransporter-2 inhibitors; SOC, standard of care.
Trial Abbreviations: ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; SHIFT, Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial; VICTORIA, Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction.
All costs were adjusted for inflation to 2022 using the Personal Consumption Expenditure price indexes for healthcare.
[¥] Denotes preferred strategy given superior clinical outcomes and lower costs.

Cost-effectiveness of additional HF treatments

Atrial fibrillation (AF) ablation

Multiple trials have demonstrated the benefit of AF ablation among patients with HFrEF. Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) randomized 363 patients with HFrEF to catheter ablation versus medical therapy.[55] The trial found a significant reduction in the composite of all-cause death or HFH (HR 0.62; 95% CI: 0.43–0.87) in addition to a reduction in mortality (HR 0.53; 95% CI: 0.32–0.86). Chew and colleagues evaluated the cost-effectiveness of AF ablation using a model-based analysis of CASTLE-AF data.[56] They estimated an ICER of $40,564/QALY with AF ablation compared with medical therapy. With a more conservative estimate of the mortality benefit (HR 0.86), the ICER remained $78,400/QALY. The primary limitation remains the overall generalizability of existing relatively small AF ablation trials with select populations across the broad HFrEF population.

Coronary artery bypass graft (CABG) surgery

The Surgical Treatment for Ischemic Heart Failure trial (STICH) found CABG surgery reduced all-cause mortality compared with medical therapy among patients with ischemic cardiomyopathy and reduced EF.[57] Chew and colleagues evaluated the economic value of CABG surgery via STICH trial data with post-trial extrapolation.[58] They estimated CABG surgery led to 1.01 additional QALYs over a lifetime horizon with an ICER of $63,989/QALY. The primary analysis conservatively assumed QoL gains with CABG surgery did not persist beyond the trial; if the QoL benefit persisted beyond the trial, the ICER was lower at $55,703/QALY.

Medical therapy for HFrEF has improved substantially since the STITCH trial. A recent trial of percutaneous coronary intervention for ischemic cardiomyopathy did not find any improvement in medical outcomes.[59] The improvement in outcomes with medical therapy alone may attenuate the magnitude of clinical benefit and economic value of CABG surgery. However, the morbidity of CABG surgery has also improved substantially over time.[60] Overall, the existing evidence suggests CABG surgery is likely intermediate value.

Implantable cardiac defibrillators (ICD) and cardiac resynchronization therapy (CRT)

ICD and CRT are critical HF therapies for select patients. There is a Class I recommendation for ICD implantation for HF patients with LVEF ≤35% despite GDMT with an expected survival beyond 1 year. The economic data for ICDs for primary prevention was evaluated in 3 RCTs, 1 observational study, and 3 simulation models.[61–66] Across these studies, the ICERs were consistently <$60,000/LY. The economic value was consistently high when the expected increase in life expectancy was projected to increase by >1 year. The economic value of ICD therapy is increased by higher risk of arrhythmic death and lower when the risk of non-arrhythmic death (cardiac or non-cardiac) is higher.

CRT has a Class I indication for patients with HF with LVEF ≤35%, sinus rhythm, a left bundle branch block, NYHA Class II-IV, and a QRS duration of >150 ms. There is also a Class IIA recommendation for broader cohorts with HFrEF. The cost-effectiveness of CRT was evaluated in 3 RCTs (COMPANION, MADIT-CRT, and REVERSE), 1 observational study, and 2 simulation models.[67–72] In the population with a Class I guideline recommendation for CRT – left bundle branch block with QRS duration >150 ms - the ICER was consistently <$60,000/QALY.[12] For other subgroups with a potentially smaller magnitude of CRT benefit, the economic value of CRT therapy is less certain.

Transcutaneous mitral valve repair (TMVR)

TMVR reduced HFH and all-cause mortality among patients with HFrEF with moderate-to-severe or severe secondary mitral regurgitation (MR) in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial.[73] Based on COAPT trial data with post-trial extrapolation, Baron et al. found TMVR and GDMT led to 0.82 additional QALYs compared with GDMT alone.[74] They found TMVR had an ICER of $60,068/QALY. This analysis illustrated TMVR is likely high to intermediate value for patients with HFrEF.

An alternate trial of TMVR, the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial, did not demonstrate a reduction in HFH or CVD death.[75] Experts have hypothesized the difference in trial results may be related to the ratio of MR relative to the degree of cardiomyopathy (proportionate vs. disproportionate MR) or procedural experience.[76] However, these conflicting results increase the uncertainty of the clinical, and subsequently, economic value of TMVR.

Pulmonary artery pressure (PAP) monitoring

PAP monitoring has been evaluated across 3 trials and has a 2B recommendation for patients with NYHA Class III HF and a recent HFH. In the CHAMPION trial, the CardioMEMS implantable PA sensor significantly reduced HFH compared with control (HR 0.63; 95% CI: 0.52–0.77).[77] Multiple model-based analyses evaluated the cost-effectiveness of the device based on the CHAMPION trial with an estimated ICER between $33,141/QALY and $87,567/QALY.[78–80] The estimates were highly sensitive to assumptions regarding the mortality benefit of prevented HFH and the duration of benefit. If HF hospitalization reduction did not translate to reduction in mortality, the ICER increased from $81,206/QALY to $181,798/QALY without a mortality reduction in the analysis by Sandhu et al.

Two additional clinical trials have been completed since these economic analyses. The Hemodynamic-GUIDEed Management of Heart Failure trial (GUIDE-HF) failed to demonstrate a significant reduction in HFH with PA pressure monitoring among patients with NYHA Class II or III HF.[81] In the Remote Hemodynamic Monitoring of Pulmonary Artery Pressures in Patients with Chronic Heart Failure trial (MONITOR-HF), PAP monitoring led to a large improvement in the KCCQ-OSS among patients in the CardioMEMS group compared with usual care.[82] A subsequent meta-analysis found a significant 30% (95% CI: 0.58–0.86) reduction in HFH across the three studies.[83] Additional economic analyses incorporating the composite of evidence are needed.

Transitional care services

Following discharge from a HFH, patients are at high risk of readmission or death. Transitional care interventions have been shown to improve outcomes following discharge; such interventions include disease management clinics, nurse case management, and nurse home visits.[84,85] A network meta-analysis of 53 trials found nurse home visits, disease management clinics, and nurse case management significantly reduced all-cause readmissions and the former two interventions reduced all-cause death.[84] Blum and colleagues evaluated the cost-effectiveness of these three interventions via a model-based analysis.[85] Each of the three interventions had an ICER under $50,000/QALY compared with standard care. Based on the meta-analysis, they estimated nurse home visits were associated with better clinical outcomes and lower costs than the other two interventions, with an ICER of $21,917/QALY compared with standard care. This work illustrates investment in transitional care services provides high economic value. The emergence of additional medical therapies that can improve HF outcomes only further underscores the economic value of transitional care for HF.

Advanced HF therapies

Advanced HF therapies – LV assist device (LVAD) and heart transplant (HT) – are critical for patients with progressive disease despite the therapies listed above. Table 4 summarizes the cost-effectiveness literature on LVAD and HT.

Earlier studies found unfavorable cost-effectiveness with more recent studies suggesting an improvement in the economic value of LVAD therapy. Rogers and colleagues used data from the REMATCH and HeartMate II Destination Therapy trials to estimate the clinical benefit of LVAD therapy compared with medical therapy.[86] They estimated a gain of 1.5 QALYs at an incremental cost of $317,958 for an ICER of $234,909/QALY. Long and colleagues compared LVAD vs. inotropic therapy among those eligible and ineligible for HT based on data from the ISHLT and INTERMACS registry and the REMATCH trial.[87] The ICERs for LVAD versus inotropic therapy ranged from $233,056/QALY to $221,264/QALY based on HT eligibility and waitlist duration. Shreibati and colleagues used data from MEDIMACS and INTERMACS to compare LVAD versus medical therapy among HT-ineligible patients.[88] Patients were stratified into “low-risk” and “high-risk” categories which resulted in ICERs of $234,515/QALY and $191,510/QALY, respectively.

In two more recent model-based studies, Mahr et al. and Silvestry et al. evaluated the cost-effectiveness of LVAD versus medical therapy using contemporary data. Mahr estimated an ICER of $68,104/QALY for LVAD via lateral thoracotomy versus medical therapy as bridge to HT based on data from the single-arm prospective LATERAL study.[89] Silvestry and colleagues used data from the ENDURANCE trial and the ADVANCE BTT observational study to evaluate the cost-effectiveness of intrapericardial centrifugal LVAD versus medical therapy. They estimated an ICER of $78,071/QALY in those eligible for transplant to $108,098/QALY in those ineligible for HT.[90] These studies may reflect the lower rates of post-implantation complications and readmissions with contemporary VAD therapy.[91] However, the studies are also notable for smaller disutility weights for LVAD and complications than alternate studies and efficacy estimates from non-randomized data. While there remains uncertainty, this data suggests improving economic value with contemporary LVAD therapy.

Long and colleagues evaluated the economic value of HT compared with medical therapy among patients with advanced HF requiring inotropic therapy. They found HT led to an increase of 4.12 QALYs at a lifetime incremental cost of $510,112 for an ICER of $112,019/QALY.

However, post-HT outcomes have improved substantially over time with a median survival exceeding 12 years in the last decade.[92]

Cost-effectiveness implications for implementation

Often additional efforts and resources are needed to ensure patients optimal care. Such implementation efforts are highly justified for treatments that are considered cost-effective by society. For example, if the society's willingness to pay is $100,000 per QALY gained, and a treatment costs only $80,000 per QALY gained, and the gain in QALY is 0.1 per person, then an additional $20,000 ($100,000–$80,000) can be spent for 10 patients to facilitate initiation and maintenance of treatment. The more cost-effective a care strategy is, the more funds can and should be spent on increasing its uptake.

Access, affordability and disparities in care

Individuals with CVD are at high risk of financial toxicity that can negativly impact QoL and adverse outcomes.[93] Lack of affordability is a substantial barrier to patient adoption of GDMT. Between 2014 and 2021, the average wholesale price for dapagliflozin increased by 78% and empagliflozin by 84%, as the number of conditions for which SGLT2is showed benefit expanded.[53] Similarly, the average wholesale price per unit of sacubitril/valsartan, the only ARNi on the market, also surged by 60% from 2015 to 2021 for a 30-day supply.[53]

To this end, patient out-of-pocket spending on GDMT is a substantial burden. A study of Medicare prescription drug plans found that median annual out-of-pocket costs of ARNi and SGLT2i therapy were $979 and $939, respectively versus $159 per year for ACEi generics.[94] Using patient cost-sharing as a gatekeeper to reduce spending on life-saving, high or intermediate value medications not only increases the morbidity of HF but also population disparities. Furthermore, 24% of insurance plans required prior authorization to prescribe sacubitril-valsartan, creating additional clinician-level barriers to implementing a guideline-recommended, high-value therapy. Multiple approaches are needed to counter the financial strain of high healthcare costs. In broad strokes, these can be categorized under system-wide policy reform, broader utilization of existing programs, and patient level initiatives.

Instituting policy reform

In recognition of the impact of high drug prices on healthcare costs, the government included provisions in the Inflation Reduction Act (IRA) of 2022 that will enable Medicare to negotiate lower prescription drug costs with pharmaceutical firms.[95] The initial ten drugs selected include empagliflozin and dapagliflozin as well as sacubitril-valsartan.[96] While

Table 4
Cost-effectiveness studies for selected HF devices.

Procedure (2022 cost)	First author (year)	Incremental cost (time horizon)	QALY gain (yrs)	ICER ($/QALY)	Efficacy source	Comments/limitations
LVAD ($197,991)[†]	Rogers (2012)	$317,958 continuous LVAD vs medical management (5 years)	1.5	$234,909	REMATCH, HeartMate II	Single-center costs No disutilities for complications Efficacy based on observational data
	Long (2014)	$534,896 centrifugal LVAD destination vs medical SOC; $355,942 LVAD BTT vs immediate heart transplant (lifetime)	2.21; 2.99	$233,056; $221,264	HeartMate II, REMATCH, INTERMACS	Efficacy data based on observational data
	Baras (2017)	$404,381 centrifugal LVAD vs medical SOC (lifetime)	1.74	$234,515	INTERMACS, MEDAMACS	Efficacy data based on observational data
	Mahr (2020)	$229,519 centrifugal LVAD BTT via thoracotomy vs medical SOC (lifetime)	3.37	$68,104	LATERAL	Smaller disutilities for LVAD and complications than prior studies Efficacy data based on observational data
	Silvestry (2021)	$127,503 intrapericardial centrifugal LVAD vs medical SOC (lifetime)	3.67	$78,071	ADVANCE BTT + CAP, ENDURANCE	Smaller disutilities for LVAD and complications than prior studies Efficacy data based on observational data
Heart Transplant	Long (2014)	$510,112 heart transplant vs medical SOC (lifetime)	4.12	$112,019	HeartMate II, REMATCH, INTERMACS	Efficacy data based on observational data
CardioMEMS ($27,305)[¥]	Sandhu (2016)	$22,817 CardioMEMS vs SOC (lifetime)	0.28	$87,567	CHAMPION	Higher value with HFpEF Mortality effect based on hospitalization rates Estimated utility based on patient-reported health status ICER $159,984 without mortality reduction
	Martinson (2016)	$5483 CardioMEMS vs SOC (5 years)	0.40	$13,934	CHAMPION	Time horizon limited to 5 years
	Schmier (2017)	$29,239 CardioMEMS vs SOC (5 years)	0.58	$50,209	CHAMPION	Time horizon limited to 5 years

Abbreviations: BTT, bridge to transplant; CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; LVAD, left ventricular assist device; NIS, Nationwide Inpatient Sample; PFS = Medicare Physician Fee Schedule, QALY, quality-adjusted life-years; SOC, standard of care.
Trial/Registry Abbreviations: ADVANCE BTT + CAP, Ventricular Assist Device for the Treatment of Advanced Heart Failure Bridge to Transplant + Continued Access Program; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA [New York Heart Association] Class III Heart Failure Patients; ENDURANCE, Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure; HeartMate II, Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LATERAL, Evaluation of a lateral thoracotomy implant approach for a centrifugal-flow left ventricular assist device: The LATERAL clinical trial; MEDAMACS, Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support; REMATCH, Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure.
[†] Cost derived from nationwide hospital-reported median Medicare rates, sourced from Turquoise Health database[81].
[¥] Cost derived from Outpatient Prospective Payment System Addendum B[111].

this represents one major step towards decreasing the financial burden of healthcare, implementation of negotiated prices is not expected until 2026. Additionally, pharmaceutical companies may enact strategies to mitigate the impact of negotiations and preserve pricing power.[97] Thus, the real-world effects of this provision remain to be seen.

Another provision of the bill, which calls for the restructuring of Medicare Part D, may have equivalent if not more far-reaching effects for patients with HF. This provision calls for a cap on cost-sharing on prescription drug costs, set at $3250 initially and then $2000 in 2025.[98] Given that over 1 million patients spend greater than $2000 annually on prescription drugs, this cap could bring about $1.7 billion in out-of-pocket savings annually.[99] The resultant benefit for patients would be substantial, as research has demonstrated a significant association between increased cost-sharing and decreased drug consumption. In one study, a 34% increase in out-of-pocket costs was associated with a 33% increase in monthly mortality and 23% decrease in drug consumption among Medicare beneficiaries.[100] Conversely, a randomized control trial which removed copayments for statins, BBs, ACEis, and ARBs after a MI boosted medication adherence by 4 to 6 percentage points and reduced rates of major adverse CVD events by 11%.[101] Taken together, these provisions have the potential to make the IRA a potent tool for improving access and affordability in HF.

There are reasonable concerns that the reduction in per-unit drug pricing with the IRA will reduce pharmaceutical innovation. However, the cost-sharing cap will also increase the number of patients that receive therapy. The net balance across these two factors and the effect on overall revenue is unclear. It is clear that increasing the overall number of patients and the equity who can afford life-saving medical therapy is a notable achievement.

Improving access to existing programs

Multiple existing programs seek to alleviate the financial burden of healthcare for patients. One such program is the Medicare low-income subsidy program which caps generic copays at $4.30 and brand-name copays at $10.35 for Medicaid-eligible patients or patients with an income up to 135% of the federal poverty level.[102] Compared to a fully subsidized annual out-of-pocket cost of GDMT of <$50, those ineligible or unaware of this subsidy program would pay over $2300 plus nearly $500 in premiums.[103] However, nearly 27% of qualified patients are not enrolled in this program and 53% of near-poor patients who qualify for limited coverage are not enrolled.[104] Even for households that do not qualify, at an annual income of $47,000–the median income for senior households–out-of-pocket prescription drug costs would occupy nearly 5% of household income. The IRA increases eligibility to the full subsidy to households with an annual income at 150% of the poverty limit. However, the full impact of this program cannot be realized without awareness in the community and implementation of resources to enroll underserved patients.

Patient views of affordability and value

Patient perception of therapy value and affordability are as critical to access as cost-effectiveness. While the benefits of HF medical therapies are well-established, these data do not necessarily carry the same weight for patients faced with financial trade-offs between their medications and their food and housing. Concerns about out-of-pocket cost are associated with medication nonadherence, loss to follow-up, and disparities in outcomes.[105] In one study, 85% of patients were willing to take sacubitril-valsartan at an out-of-pocket cost of $10, but this dropped to 33% at a cost of $100.[106] This suggests a substantial disconnect between patients' perception of benefit and that of clinicians and cost-effectiveness analyses. This disconnect may be driven by both prevalent misconceptions regarding the risks of HF and the substantial medical and non-medical financial burdens faced by patients with HF. Discussing out-of-pocket costs along with the benefits of therapy may increase patient willingness to take medications, but cardiologists rarely discuss the affordability of medical therapy.[106,107]

A major barrier to such shared decision-making is the challenge of estimating the out-of-pocket expenses for individual patients. The push for price transparency aims to address this. The Price Transparency Rule of 2021 mandated hospitals disclose negotiated prices for treatments and then insurers to reveal out-of-pocket estimates for patients. However, compliance has been limited thus far and navigating the available data from both a patient and a physician perspective has been challenging enough that multiple companies have been started just on the value proposition of organizing these data.[108–110] It is not practical to expect the average patient or clinician to comb through an extensive list of prices for individual services and estimate the out-of-pocket cost. Increasing physician-patient cost-sensitive shared decision-making will require tools that directly feed patient-specific prices into a patient visit. Testing new strategies and tools to help clinicians be able to better discuss the cost and benefit of different treatments should be a priority for improving patient-centered HF care.

Conclusion

HF presents a global health challenge with a growing prevalence, morbidity, and economic impact. Numerous evidence-based therapies improve outcomes among patients with HF. Additionally, most HF therapies provide high or intermediate economic value at conventional cost-effectiveness thresholds. However, the affordability of therapies remains a major barrier to care and a driver of disparities. Efforts to enhance affordability, such as the Inflation Reduction Act of 2022, are crucial to reduce the economic strain on patients. Additionally, increasing the awareness and use of existing affordability programs such as the Medicare low-income subsidy program is important. Finally, there is a need to develop tools to facilitate shared decision-making around the cost and benefit of HF treatments to empower individuals to make informed healthcare choices. A broad approach to improving affordability and access is essential to ensure that evidence-based HF treatments are implemented broadly to reduce the growing clinical and economic morbidity of HF.

Authors contribution

Manuscript conceptualization: CW, PAH, and ATS. Data curation: CW, PAH, and ATS. Funding acquisition: ATS. Project administration, resources, and supervision: PAH and ATS. Writing - original draft: CW. Writing - review & editing: CW, PAH and ATS. All authors approved the final version of this manuscript.

Declaration of competing interest

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References

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States. *Circ Heart Fail*. 2013;6(3):606–619. https://doi.org/10.1161/HHF.0b013e318291329a.
2. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020 Mar 3;141(9):e139–e596. https://doi.org/10.1161/CIR.0000000000000757.
3. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol*. 2017;70(20):2476–2486. https://doi.org/10.1016/j.jacc.2017.08.074.
4. Khan SU, Khan MZ, Alkhouli M. Trends of clinical outcomes and health care resource use in heart failure in the United States. *J Am Heart Assoc*. 2020;9(14). https://doi.org/10.1161/JAHA.120.016782.

5. Yoon J, Fonarow GC, Groeneveld PW, et al. Patient and facility variation in costs of VA heart failure patients. *JACC Heart Fail*. 2016;4(7):551–558. https://doi.org/10.1016/j.jchf.2016.01.003.
6. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004-2016. *BMC Cardiovasc Disord*. 2018;18(1). https://doi.org/10.1186/s12872-018-0815-3.
7. Heidenreich PA, Fonarow GC, Opsha Y, Sandhu AT, Sweitzer NK, Warraich HJ. Economic issues in heart failure in the United States. *J Card Fail*. 2022;28(3):453–466. https://doi.org/10.1016/j.cardfail.2021.12.017.
8. Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;6(8):952–956. https://doi.org/10.1001/jamacardio.2020.7472.
9. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093–1103. https://doi.org/10.1001/jama.2016.12195.
10. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association task force on performance measures and task force on practice guidelines. *J Am Coll Cardiol*. 2014;63(21):2304–2322. https://doi.org/10.1016/j.jacc.2014.03.016.
11.. *Understanding "Contextual Considerations and Potential Other Benefits or Disadvantages"*. ICER; 2023. Accessed September 30, 2023 https://icer.org/understanding-contextual-considerations-and-potential-other-benefits-or-disadvantages/.
12.. 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*. 2023. https://doi.org/10.1161/CIR.0000000000001063. Accessed August 30, 2023.
13.. U.S. Bureau of Economic Analysis. *Personal Consumption Expenditures: Health Care: Outpatient Services: Physician Services (Chain-Type Price Index)*. FRED, Federal Reserve Bank of St. Louis; January 1, 1929. Published. Accessed February 6, 2021 https://fred.stlouisfed.org/series/DPHYRG3A086NBEA.
14. Gregory D, Udelson JE, Konstam MA. Economic impact of beta blockade in heart failure. *Am J Med*. 2001;110(Suppl 7A):74S–80S. https://doi.org/10.1016/s0002-9343(98)00387-8.
15. Caro JJ, Migliaccio-Walle K, O'Brien JA, et al. Economic implications of extended-release metoprolol succinate for heart failure in the MERIT-HF trial: a US perspective of the MERIT-HF trial. *J Card Fail*. 2005;11(9):647–656. https://doi.org/10.1016/j.cardfail.2005.06.433.
16. Delea TE, Vera-Llonch M, Richner RE, Fowler MB, Oster G. Cost effectiveness of carvedilol for heart failure. *Am J Cardiol*. 1999;83(6):890–896. https://doi.org/10.1016/s0002-9149(98)01066-2.
17. Banka G, Heidenreich PA, Fonarow GC. Incremental cost-effectiveness of guideline-directed medical therapies for heart failure. *J Am Coll Cardiol*. 2013;61(13):1440–1446. https://doi.org/10.1016/j.jacc.2012.12.022.
18. Glick HA, Orzol SM, Tooley JF, Remme WJ, Sasayama S, Pitt B. Economic evaluation of the randomized aldactone evaluation study (RALES): treatment of patients with severe heart failure. *Cardiovasc Drugs Ther*. 2002;16(1):53–59. https://doi.org/10.1023/a:1015371616135.
19. Zhang Z, Mahoney EM, Kolm P, et al. Cost effectiveness of eplerenone in patients with heart failure after acute myocardial infarction who were taking both ACE inhibitors and beta-blockers: subanalysis of the EPHESUS. *Am J Cardiovasc Drugs*. 2010;10(1):55–63. https://doi.org/10.2165/11319940-000000000-00000.
20. Weintraub WS, Zhang Z, Mahoney EM, et al. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. *Circulation*. 2005;111(9):1106–1113. https://doi.org/10.1161/01.CIR.0000157146.86758.BC.
21. Glick H, Cook J, Kinosian B, et al. Costs and effects of enalapril therapy in patients with symptomatic heart failure: an economic analysis of the studies of left ventricular dysfunction (SOLVD) treatment trial. *J Card Fail*. 1995;1(5):371–380. https://doi.org/10.1016/s1071-9164(05)80006-5.
22. Tsevat J, Duke D, Goldman L, et al. Cost-effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol*. 1995;26(4):914–919. https://doi.org/10.1016/0735-1097(95)00284-1.
23. Reed SD, Friedman JY, Velazquez EJ, Gnanasakthy A, Califf RM, Schulman KA. Multinational economic evaluation of valsartan in patients with chronic heart failure: results from the valsartan heart failure trial (Val-HeFT). *Am Heart J*. 2004;148(1):122–128. https://doi.org/10.1016/j.ahj.2003.12.040.
24. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med*. 2014;371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077.
25. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. *JAMA Cardiol*. 2016;1(6):666–672. https://doi.org/10.1001/jamacardio.2016.1747.
26. King JB, Shah RU, Bress AP, Nelson RE, Bellows BK. Cost-effectiveness of sacubitril-valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. *JACC Heart Fail*. 2016;4(5):392–402. https://doi.org/10.1016/j.jchf.2016.02.007.
27. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-effectiveness of sacubitril-valsartan in patients with heart failure with reduced ejection fraction. *Ann Intern Med*. 2016;165(10):681–689. https://doi.org/10.7326/M16-0057.
28. Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction. *JAMA Cardiol*. 2020;5(11):1236–1244. https://doi.org/10.1001/jamacardio.2020.2822.
29. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413–1424. https://doi.org/10.1056/NEJMoa2022190.
30. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303.
31. Parizo JT, Goldhaber-Fiebert JD, Salomon JA, et al. Cost-effectiveness of dapagliflozin for treatment of patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;6(8):926–935. https://doi.org/10.1001/jamacardio.2021.1437.
32. Isaza N, Calvachi P, Raber I, et al. Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. *JAMA Netw Open*. 2021;4(7), e2114501. https://doi.org/10.1001/jamanetworkopen.2021.14501.
33. Yan BW, Spahillari A, Pandya A. Cost-effectiveness of quadruple therapy in management of heart failure with reduced ejection fraction in the United States. *Circ Cardiovasc Qual Outcomes*. 2023;16(6), e009793. https://doi.org/10.1161/CIRCOUTCOMES.122.009793.
34. Dixit NM, Parikh NU, Ziaeian B, Jackson N, Fonarow GC. Cost-effectiveness of comprehensive quadruple therapy for heart failure with reduced ejection fraction. *JACC Heart Fail*. 2023;11(5):541–551. https://doi.org/10.1016/j.jchf.2023.01.004.
35. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351(20):2049–2057. https://doi.org/10.1056/NEJMoa042934.
36. Angus DC, Linde-Zwirble WT, Tam SW, et al. Cost-effectiveness of fixed-dose combination of isosorbide dinitrate and hydralazine therapy for blacks with heart failure. *Circulation*. 2005;112(24):3745–3753. https://doi.org/10.1161/CIRCULATIONAHA.105.563882.
37. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875–885. https://doi.org/10.1016/S0140-6736(10)61198-1.
38. Kansal AR, Cowie MR, Kielhorn A, et al. Cost-effectiveness of ivabradine for heart failure in the United States. *J Am Heart Assoc*. 2016;5(5), e003221. https://doi.org/10.1161/JAHA.116.003221.
39. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883–1893. https://doi.org/10.1056/NEJMoa1915928.
40. Chew DS, Li Y, Bigelow R, et al. Cost-effectiveness of vericiguat in patients with heart failure with reduced ejection fraction: the VICTORIA randomized clinical trial. *Circulation*. 2023;0(0). https://doi.org/10.1161/CIRCULATIONAHA.122.063602.
41. Alsumali A, Djatche LM, Briggs A, et al. Cost effectiveness of vericiguat for the treatment of chronic heart failure with reduced ejection fraction following a worsening heart failure event from a US medicare perspective. *Pharmacoeconomics*. 2021;39(11):1343–1354. https://doi.org/10.1007/s40273-021-01091-w.
42. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451–1461. https://doi.org/10.1056/NEJMoa2107038.
43. Zheng J, Parizo JT, Spertus JA, Heidenreich PA, Sandhu AT. Cost-effectiveness of empagliflozin in patients with heart failure with preserved ejection fraction. *JAMA Intern Med*. 2022;182(12):1278–1288. https://doi.org/10.1001/jamainternmed.2022.5010.
44. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med*. 2021;27(11):1954–1960. https://doi.org/10.1038/s41591-021-01536-x.
45.. AstraZeneca. International, Multicentre, Parallel-Group, Randomised, Double-Blind, Placebo-Controlled, Phase III Study Evaluating the Effect of Dapagliflozin on Exercise Capacity in Heart Failure Patients With Preserved Ejection Fraction. clinicaltrials.gov. Accessed December 31, 2022 https://clinicaltrials.gov/study/NCT03877224; 2021.
46. Spertus JA, Birmingham MC, Nassif M, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. *Nat Med*. 2022;28(4):809–813. https://doi.org/10.1038/s41591-022-01703-8.
47. Cohen LP, Isaza N, Hernandez I, et al. Cost-effectiveness of sodium-glucose cotransporter-2 inhibitors for the treatment of heart failure with preserved ejection fraction. *JAMA Cardiol*. 2023;8(5):419–428. https://doi.org/10.1001/jamacardio.2023.0077.
48. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol*. 2017;70(20):2476–2486. https://doi.org/10.1016/j.jacc.2017.08.074.
49. New Diabetes Med. *Brenzavvy, Available Through Mark Cuban's Online Pharmacy*. Formulary Watch; July 13, 2023. Published. Accessed September 30, 2023 https://www.formularywatch.com/view/new-diabetes-med-brenzavvy-available-through-mark-cuban-s-online-pharmacy.
50. Antonopoulos AS, Panagiotopoulos I, Kouroutzoglou A, et al. Prevalence and clinical outcomes of transthyretin amyloidosis: a systematic review and meta-analysis. *Eur J Heart Fail*. 2022;24(9):1677–1696. https://doi.org/10.1002/ejhf.2589.
51. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007–1016. https://doi.org/10.1056/NEJMoa1805689.
52. Kazi DS, Bellows BK, Baron SJ, et al. Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation*. 2020;141(15):1214–1224. https://doi.org/10.1161/CIRCULATIONAHA.119.045093.

53.. Medicare Part D Prescribers - by Geography and Drug - Centers for Medicare & Medicaid Services Data. Accessed September 30, 2023 https://data.cms.gov/provider-summary-by-type-of-service/medicare-part-d-prescribers/medicare-part-d-prescribers-by-geography-and-drug; 2023.

54.. *Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy*. American College of Cardiology; 2023. Accessed September 1, 2023 https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2023/08/24/02/29/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fClinical-Trials%2f2023%2f08%2f24%2f02%2f29%2fattribute-cm.

55. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378(5):417–427. https://doi.org/10.1056/NEJMoa1707855.

56. Chew DS, Loring Z, Anand J, et al. Economic evaluation of catheter ablation of atrial fibrillation in patients with heart failure with reduced ejection fraction. *Circ Cardiovasc Qual Outcomes*. 2020;13(12), e007094. https://doi.org/10.1161/CIRCOUTCOMES.120.007094.

57. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364(17):1607–1616. https://doi.org/10.1056/NEJMoa1100356.

58. Chew DS, Cowper PA, Al-Khalidi H, et al. Cost-effectiveness of coronary artery bypass surgery versus medicine in ischemic cardiomyopathy: the STICH randomized clinical trial. *Circulation*. 2022;145(11):819–828. https://doi.org/10.1161/CIRCULATIONAHA.121.056276.

59. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med*. 2022;387(15):1351–1360. https://doi.org/10.1056/NEJMoa2206606.

60. Alkhouli M, Alqahtani F, Kalra A, et al. Trends in characteristics and outcomes of hospital inpatients undergoing coronary revascularization in the United States, 2003-2016. *JAMA Netw Open*. 2020;3(2), e1921326. https://doi.org/10.1001/jamanetworkopen.2019.21326.

61. Zwanziger J, Hall WJ, Dick AW, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the multicenter automatic defibrillator implantation trial (MADIT)-II. *J Am Coll Cardiol*. 2006;47(11):2310–2318. https://doi.org/10.1016/j.jacc.2006.03.032.

62. Mushlin AI, Hall WJ, Zwanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. Multicenter automatic defibrillator implantation trial. *Circulation*. 1998;97(21):2129–2135. https://doi.org/10.1161/01.cir.97.21.2129.

63. Mark DB, Nelson CL, Anstrom KJ, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the sudden cardiac death in heart failure trial (SCD-HeFT). *Circulation*. 2006;114(2):135–142. https://doi.org/10.1161/CIRCULATIONAHA.105.581884.

64. Cowie MR, Marshall D, Drummond M, et al. Lifetime cost-effectiveness of prophylactic implantation of a cardioverter defibrillator in patients with reduced left ventricular systolic function: results of Markov modelling in a European population. *Europace*. 2009;11(6):716–726. https://doi.org/10.1093/europace/eup068.

65. Al-Khatib SM, Anstrom KJ, Eisenstein EL, et al. Clinical and economic implications of the multicenter automatic defibrillator implantation trial-II. *Ann Intern Med*. 2005;142(8):593–600. https://doi.org/10.7326/0003-4819-142-8-200504190-00007.

66. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med*. 2005;353(14):1471–1480. https://doi.org/10.1056/NEJMsa051989.

67. Noyes K, Veazie P, Hall WJ, et al. Cost-effectiveness of cardiac resynchronization therapy in the MADIT-CRT trial. *J Cardiovasc Electrophysiol*. 2013;24(1):66–74. https://doi.org/10.1111/j.1540-8167.2012.02413.x.

68. Heerey A, Lauer M, Alsolaiman F, Czerr J, James K. Cost effectiveness of biventricular pacemakers in heart failure patients. *Am J Cardiovasc Drugs*. 2006;6(2):129–137. https://doi.org/10.2165/00129784-200606020-00007.

69. Gold MR, Padhiar A, Mealing S, Sidhu MK, Tsintzos SI, Abraham WT. Economic value and cost-effectiveness of cardiac resynchronization therapy among patients with mild heart failure: projections from the REVERSE long-term follow-up. *JACC Heart Fail*. 2017;5(3):204–212. https://doi.org/10.1016/j.jchf.2016.10.014.

70. Feldman AM, de Lissovoy G, Bristow MR, et al. Cost effectiveness of cardiac resynchronization therapy in the comparison of medical therapy, pacing, and defibrillation in heart failure (COMPANION) trial. *J Am Coll Cardiol*. 2005;46(12):2311–2321. https://doi.org/10.1016/j.jacc.2005.08.033.

71. Nichol G, Kaul P, Huszti E, Bridges JFP. Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure. *Ann Intern Med*. 2004;141(5):343–351. https://doi.org/10.7326/0003-4819-141-5-200409070-00102.

72. Woo CY, Strandberg EJ, Schmiegelow MD, et al. Cost-effectiveness of adding cardiac resynchronization therapy to an implantable cardioverter-defibrillator among patients with mild heart failure. *Ann Intern Med*. 2015;163(6):417–426. https://doi.org/10.7326/M14-1804.

73. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307–2318. https://doi.org/10.1056/NEJMoa1806640.

74. Baron SJ, Wang K, Arnold SV, et al. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation. *Circulation*. 2019;140(23):1881–1891. https://doi.org/10.1161/CIRCULATIONAHA.119.043275.

75. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297–2306. https://doi.org/10.1056/NEJMoa1805374.

76. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging*. 2019;12(2):353–362. https://doi.org/10.1016/j.jcmg.2018.11.006.

77. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;377(9766):658–666. https://doi.org/10.1016/S0140-6736(11)60101-3.

78. Sandhu AT, Goldhaber-Fiebert JD, Owens DK, Turakhia MP, Kaiser DW, Heidenreich PA. Cost-effectiveness of implantable pulmonary artery pressure monitoring in chronic heart failure. *JACC Heart Fail*. 2016;4(5):368–375. https://doi.org/10.1016/j.jchf.2015.12.015.

79. Schmier JK, Ong KL, Fonarow GC. Cost-effectiveness of remote cardiac monitoring with the CardioMEMS heart failure system. *Clin Cardiol*. 2017;40(7):430–436. https://doi.org/10.1002/clc.22696.

80. Martinson M, Bharmi R, Dalal N, Abraham WT, Adamson PB. Pulmonary artery pressure-guided heart failure management: US cost-effectiveness analyses using the results of the CHAMPION clinical trial. *Eur J Heart Fail*. 2017;19(5):652–660. https://doi.org/10.1002/ejhf.642.

81. Lindenfeld J, Zile MR, Desai AS, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet*. 2021;398(10304):991–1001. https://doi.org/10.1016/S0140-6736(21)01754-2.

82. Brugts JJ, Radhoe SP, Clephas PRD, et al. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial. *Lancet*. May 19, 2023. https://doi.org/10.1016/S0140-6736(23)00923-6. Published online. S0140-6736(23)00923-6.

83. Clephas PRD, Radhoe SP, Boersma E, et al. Efficacy of pulmonary artery pressure monitoring in patients with chronic heart failure: a meta-analysis of three randomized controlled trials. *Eur Heart J*. May 20, 2023. https://doi.org/10.1093/eurheartj/ehad346. Published online. ehad346.

84. Van Spall HGC, Rahman T, Mytton O, et al. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail*. 2017;19(11):1427–1443. https://doi.org/10.1002/ejhf.765.

85. Blum MR, Øien H, Carmichael HL, Heidenreich P, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of transitional care services after hospitalization with heart failure. *Ann Intern Med*. 2020;172(4):248–257. https://doi.org/10.7326/M19-1980.

86. Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. *Circ Heart Fail*. 2012;5(1):10–16. https://doi.org/10.1161/CIRCHEARTFAILURE.111.962951.

87. Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. *Circ Heart Fail*. 2014;7(3):470–478. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000807.

88. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, Owens DK, Hlatky MA. Cost-effectiveness of left ventricular assist devices in ambulatory patients with advanced heart failure. *JACC Heart Fail*. 2017;5(2):110–119. https://doi.org/10.1016/j.jchf.2016.09.008.

89. Mahr C, McGee E, Cheung A, et al. Cost-effectiveness of thoracotomy approach for the implantation of a centrifugal left ventricular assist device. *ASAIO J*. 2020;66(8):855–861. https://doi.org/10.1097/MAT.0000000000001209.

90. Silvestry SC, Mahr C, Slaughter MS, et al. Cost-effectiveness of a small intrapericardial centrifugal left ventricular assist device. *ASAIO J*. 2020;66(8):862–870. https://doi.org/10.1097/MAT.0000000000001211.

91. Yuzefpolskaya M, Schroeder SE, Houston BA, et al. The society of thoracic surgeons intermacs 2022 annual report: focus on the 2018 heart transplant allocation system. *Ann Thorac Surg*. 2023;115(2):311–327. https://doi.org/10.1016/j.athoracsur.2022.11.023.

92. Khush KK, Cherikh WS, Chambers DC, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38(10):1056–1066. https://doi.org/10.1016/j.healun.2019.08.004.

93. Slavin SD, Khera R, Zafar SY, Nasir K, Warraich HJ. Financial burden, distress, and toxicity in cardiovascular disease. *Am Heart J*. 2021;238:75–84. https://doi.org/10.1016/j.ahj.2021.04.011.

94. Faridi KF, Dayoub EJ, Ross JS, Dhruva SS, Ahmad T, Desai NR. Medicare coverage and out-of-pocket costs of quadruple drug therapy for heart failure. *J Am Coll Cardiol*. 2022;79(25):2516–2525. https://doi.org/10.1016/j.jacc.2022.04.031.

95.. Rep. Yarmuth JA. D K 3. H.R.5376 - 117th Congress (2021-2022): Inflation Reduction Act of 2022. Published. Accessed September 14, 2023 https://www.congress.gov/bill/117th-congress/house-bill/5376; August 16, 2022.

96. House TW. *Biden-Harris Administration Announces First Ten Drugs Selected for Medicare Price Negotiation*. The White House; August 29, 2023. Published. Accessed September 14, 2023 https://www.whitehouse.gov/briefing-room/statements-releases/2023/08/29/fact-sheet-biden-harris-administration-announces-first-ten-drugs-selected-for-medicare-price-negotiation/.

97.. Sachs R. *Understanding the Democrats' Drug Pricing Package*. Health Affairs Forefront; 2023. https://doi.org/10.1377/forefront.20220810.661571.

98. Zheng J, Sandhu AT. The inflation reduction act expands prescription drug affordability. *J Am Coll Cardiol*. 2023;81(21):2112–2114. https://doi.org/10.1016/j.jacc.2023.03.415.

99. Narasimmaraj PR, Oseran A, Tale A, et al. Out-of-pocket drug costs for medicare beneficiaries with cardiovascular risk factors under the inflation reduction act.

J Am Coll Cardiol. 2023;81(15):1491–1501. https://doi.org/10.1016/j.jacc.2023.02.002.
100. Chandra A, Flack E, Obermeyer Z. *The Health Costs of Cost-Sharing*. Published online. February 2021. https://doi.org/10.3386/w28439.
101. Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365(22):2088–2097. https://doi.org/10.1056/NEJMsa1107913.
102.. Centers for Medicare & Medicaid Services. Resource and Cost-Sharing Limits for Low-Income Subsidy (LIS). Accessed October 3, 2023. https://www.cms.gov/files/document/2021-lis-resource-limits-memo.pdf; 2021
103. Sandhu AT, Heidenreich PA. The affordability of guideline-directed medical therapy. *Circulation*. 2021;143(11):1073–1075. https://doi.org/10.1161/CIRCULATIONAHA.120.053291.
104. Roberts ET, Glynn A, Cornelio N, et al. Medicaid coverage "cliff" increases expenses and decreases care for near-poor medicare beneficiaries. *Health Aff (Millwood)*. 2021;40(4):552–561. https://doi.org/10.1377/hlthaff.2020.02272.
105. Van Alsten SC, Harris JK. Cost-related nonadherence and mortality in patients with chronic disease: a multiyear investigation, national health interview survey, 2000-2014. *Prev Chronic Dis*. 2020;17:E151. https://doi.org/10.5888/pcd17.200244.
106. Rao BR, Speight CD, Allen LA, et al. Impact of financial considerations on willingness to take sacubitril/valsartan for heart failure. *J Am Heart Assoc*. 2022;11(12), e023789. https://doi.org/10.1161/JAHA.121.023789.
107. Rao BR, Akrobetu DJ, Dickert NW, et al. Deciding whether to take sacubitril/valsartan: how cardiologists and patients discuss out-of-pocket costs. *J Am Heart Assoc*. 2023;12(7), e028278. https://doi.org/10.1161/JAHA.122.028278.
108. Wei C, Milligan M, Lam M, Heidenreich PA, Sandhu A. Variation in cost of echocardiography within and across US hospitals. *J Am Soc Echocardiogr*. January 10, 2023. https://doi.org/10.1016/j.echo.2023.01.002. Published online. S0894-7317(23)00006-8.
109.. Turquoise Health. Accessed July 19, 2022 https://turquoise.health/; 2022.
110.. Certainly Health. Book Doctors Without Surprise Bills. Accessed September 14, 2023 https://certainlyhealth.com/; 2023.
111.. Centers for Medicare & Medicaid Services. Addendum A and Addendum B Updates. Accessed September 19, 2023 https://www.cms.gov/medicare/payment/prospective-payment-systems/hospital-outpatient/addendum-a-b-updates; 2023.