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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Long-Term Outcomes of Heart Failure With Preserved or Mid-Range Ejection Fraction in the United States

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ABSTRACT

BACKGROUND Approximately one-half of all heart failure (HF) consists of heart failure with preserved ejection fraction (HFpEF) or heart failure with mid-range ejection fraction (HFmrEF). Although several recent trials have investigated treatments for HFpEF/HFmrEF, there is limited insight on the long-term clinical trajectory of this population.

OBJECTIVES The purpose of this study was to model clinical outcomes in patients with symptomatic (NYHA functional class II-IV) HFpEF/HFmrEF over 10 years.

METHODS We developed a Markov model with stable HF, HF hospitalization, and death states to follow a cohort of patients with HFpEF/HFmrEF treated with standard of care (SoC) recommended by the American Heart Association/American College of Cardiology/Heart Failure Society of America. Population characteristics and clinical event probabilities were derived from recent phase 3 HFpEF/HFmrEF trials. We used weighted averages for control and sodium-glucose cotransporter-2 inhibitor outcomes. SoC was informed by baseline treatments reported in clinical trials.

RESULTS In a cohort of U.S. patients with HFpEF/HFmrEF treated with SoC, our model estimated 0.53 cumulative HF hospitalizations per patient over 10 years. Overall, 37% had at least 1 HF hospitalization, and 26% experienced cardiovascular death. The model estimated 6.1 years of life expectancy from age 72 and total cost of care over this time of $123,900.

CONCLUSIONS HFpEF/HFmrEF is associated with high rates of HF hospitalization and cardiovascular mortality based on contemporary clinical trials in this population. Furthermore, clinical trial results are likely to be more optimistic than real-world outcomes. Continuing to optimize care and treatment may reduce clinical burden and improve population health. (JACC Adv 2024;3:101027) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF = heart failure with mid-range ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

SGLT2 = sodium-glucose cotransporter-2

SoC = standard of care

Heart failure (HF) is a highly prevalent, chronic, and progressive condition that affects approximately 64 million people worldwide and 6 million people in the United States.[1,2] Prevalence of HF is also projected to increase over time and is anticipated to affect over 8 million adults in the United States by 2030.[2]

Approximately one-half of those with HF have left ventricular ejection fraction (LVEF) that is normal or nearly normal, also referred to as heart failure with preserved ejection fraction (HFpEF) or heart failure with mid-range ejection fraction (HFmrEF).[3] Designation of HF subgroups by LVEF function is relatively recent in epidemiological studies but is clinically useful and indicative of both underlying pathology and sensitivity to therapy.[1,3] The universal classification proposed by Bozkurt et al defines HFmrEF as HF with LVEF 41% to 49% and HFpEF as HF with LVEF ≥50%.[4] Similarly, this study defines HFpEF/HFmrEF as all HF with LVEF ≥40%. Increasingly, research has focused on the pathology and sensitivity to therapy of HFpEF/HFmrEF as it differs from heart failure with reduced ejection fraction (HFrEF). Compared to HFrEF, those with HFpEF/HFmrEF are older, more commonly female, and more likely to have comorbid chronic renal failure and pulmonary hypertension, which are both strong predictors of in-hospital mortality.[5] HFrEF and HFpEF/HFmrEF are associated with similarly high burdens of hospitalization and quality-of-life impacts.

Most prior clinical trials in HF have focused on HFrEF, though there has been a recent increase in randomized trial evidence generated in HFpEF/HFmrEF. Since 2019, 3 large phase 3 clinical trials in contemporary HFpEF/HFmrEF populations have published positive results: the PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF), EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction), and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) studies.[6-8] Trials have shown a reduction in composite primary endpoints, defined by a combination of HF hospitalizations and cardiovascular deaths, in HFpEF/HFmrEF patients treated with sacubitril-valsartan, empagliflozin, and dapagliflozin against comparators.

Four large phase 3 clinical studies have also previously investigated inhibitors of the renin-angiotensin-aldosterone system in HFpEF/HFmrEF. No definitive benefit was observed in clinical trials investigating the safety and efficacy of candesartan, perindopril, or irbesartan (CHARM-Preserved [Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity], PEP-CHF [Perindopril in Elderly People with Chronic Heart Failure], and I-PRESERVE [Irbesartan in Heart Failure With Preserved Systolic Function] studies, respectively).[9-11] The TOPCAT (Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist) trial saw a reduction in its composite primary endpoint associated with spironolactone treatment in the subpopulation enrolled in the Americas only.[12]

To date, only sacubitril/valsartan (Entresto), empagliflozin (Jardiance), and dapagliflozin (Farxiga) have been approved by the Food and Drug Administration specifically for treating HFpEF/HFmrEF.[13,14] Given these recent approvals, the long-term clinical trajectory of patients with HFpEF/HFmrEF can be modeled using recent clinical trial data. The objective of this study was to simulate major clinical outcomes and medical costs in patients with symptomatic HFpEF/HFmrEF treated with usual care over a 10-year time horizon.

METHODS

MODEL STRUCTURE. A 3-state Markov model with a 1-month cycle length was developed (**Figure 1**). Data from clinical trials and other published sources were used to inform health state transitions. In the base case, patients enter the model in the stable HF health state. Stable HF was defined as having no acute HF events (defined as HF hospitalization, 30-day rehospitalization for HF, or death). Patients who experienced an HF hospitalization transitioned to stable HF after 1 cycle, unless they experienced death or readmission for HF within 30 days. While alive, all patients were at risk of treatment discontinuation, hyperkalemia, composite renal endpoint events, or death due to either a cardiovascular or noncardiovascular cause. Life years and costs were discounted at 3% per year with a half-cycle correction and reported for both 5- and 10-year time horizons. No ethical approval was required for this study.

POPULATION. The model simulated a cohort of patients with symptomatic (NYHA functional class II-IV) HF and LVEF ≥40% treated with the standard of care (SoC). Baseline population characteristics, event rates, and initial treatment distribution were based on 3 recent clinical trials, which are briefly described in **Table 1**.[6-8] The weighted average age across all 3

studies is 72.0 years at baseline and 53.6% of the population is male.

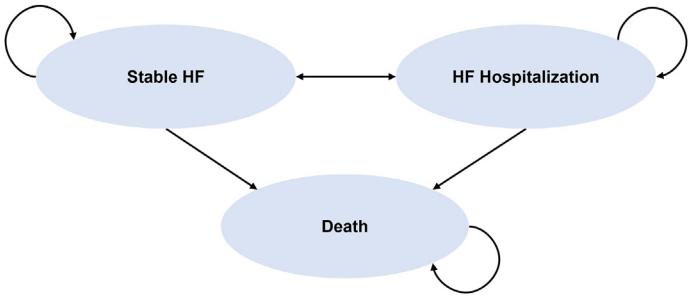
TREATMENT. SoC was defined based on the distribution of cardiovascular medications reported at baseline for the clinical trial populations (Table 2). In addition, we assumed that 20% of patients were treated with a sodium-glucose cotransporter-2 (SGLT2) inhibitor, which is considered to be part of standard of care in the United States.[15] Based on the results of the EMPEROR-Preserved trial, SGLT2 inhibitors received a Class 2a (moderate) recommendation for use in symptomatic HF with LVEF ≥50% from the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America Joint Committee Guideline for the Management of Heart Failure.[15] However, there is no published evidence to date on the uptake of SGLT2 inhibitors in HFpEF/HFmrEF populations. In this study, SGLT2 inhibitor uptake is based on utilization in HFrEF. A recent study of the Get with the Guidelines-Heart Failure Registry found that approximately 20% of patients hospitalized for HFrEF were discharged with an SGLT2 inhibitor.[16]

CLINICAL OUTCOMES. The model estimated the total number of HF hospitalizations, hyperkalemia episodes, composite renal endpoint events, and deaths due to cardiovascular or noncardiovascular causes. Transition probabilities were derived from incidence rates reported in the trial populations. Long-term event rates were extrapolated from phase 3 trials, which provide the best available contemporary outcomes among patients with HFpEF/HFmrEF treated with SGLT2 inhibitors. The median duration of follow-up in the PARAGON-HF, EMPEROR-Preserved, and DELIVER studies was 2.9, 2.2, and 2.3 years, respectively.[9-11] The per-month event probabilities were estimated as a weighted average of comparator arm and SGLT2 inhibitor arm outcomes (Table 3).

The per-month probability of transitioning from stable HF to HF hospitalization was calculated as a weighted average of incidence rates reported in the comparator and treatment arms of the trials. The base case analysis assumed that the risk of transitioning from stable HF to HF hospitalization was the same for the first and subsequent modeled HF hospitalizations.

The probability of remaining in HF hospitalization from 1 cycle to the next was based on the risk of 30-day readmissions for HF hospitalizations. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure study, a propensity score-matched cohort study, found that 9.0% of patients with HFpEF (LVEF of ≥50%) had an HF readmission within 30 days.[17,18]

FIGURE 1 Model Structure



A Markov model was developed with 3 health states and 1-month cycle lengths. Stable HF was defined as having no acute HF events. Patients who experienced an HF hospitalization transitioned to stable HF after 1 cycle unless they experienced death or readmission for HF within 30 days. While alive, all patients were at risk of discontinuing treatment, hyperkalemia adverse events, composite renal endpoint events, or death due to either a cardiovascular or noncardiovascular cause. HF = heart failure.

The modeled population was at risk of experiencing additional clinical events until they transitioned to the death state. Based on recent clinical trials, the per-month risk of hyperkalemia and composite renal endpoint events was estimated to be 0.24% and 0.14%, respectively. The duration of each of these clinical events was modeled as 1 cycle. Hyperkalemia and sustained estimated glomerular filtration rate (eGFR) decline events were assumed to be managed either inpatient or outpatient based on the ratio of serious adverse events to all adverse events in clinical trials (41% outpatient vs 59% inpatient). In the PARAGON-HF trial, 29 patients in the comparator arm experienced renal failure, and 64 experienced any composite renal endpoint event.[7]

Based on recent clinical trials in HFpEF/HFmrEF, the per-month probability of experiencing cardiovascular death for patients with stable HF on SoC was calculated to be 0.30%. The per month risk of noncardiovascular death at baseline (age 72 years) in stable HF was calculated as 0.26% and assumed to increase with age proportionally to general mortality based on U.S. life tables.[19]

HF hospitalization and composite renal endpoint events were each associated with increased cardiovascular and noncardiovascular mortality. In a study of 4,128 patients with NYHA functional class II-IV HF and LVEF >45% enrolled in the I-PRESERVE trial (NCT00095238), the adjusted HR for mortality within 30 days was 9.39 following an HF hospitalization relative to those who were not

TABLE 1 Summary of Recent Phase 3 Trials in HFpEF/HFmrEF

Inclusion Criteria	EMPEROR-Preserved[6]	PARAGON-HF[7]	DELIVER[8]
Indication	LVEF >40% NYHA functional class II-IV	LVEF ≥45% NYHA functional class II-IV	LVEF >40% NYHA functional class II-IV
Intervention	Empagliflozin	Sacubitril-valsartan	Dapagliflozin
Comparator	Placebo	Valsartan	Placebo
Primary outcome	Cardiovascular death or HF hospitalization	Cardiovascular death or HF hospitalization	Cardiovascular death, unplanned HF hospitalization, or urgent visit for HF
Selected secondary outcomes	Rate of eGFR decline	Decline in renal function (eGFR decrease, development of ESRD, or death due to renal failure) Death from any cause	Cardiovascular death Death from any cause

DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; eGFR = estimated glomerular filtration rate; EMPEROR-Preserved = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; ESRD = end-stage renal failure; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; PARAGON-HF = Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF.

hospitalized for HF.[20] Separately, a study of the Swedish Heart Failure Registry merged with the Stockholm Creatinine Measurement Registry found that a decrease in eGFR of ≥50% within 1 year was associated with higher mortality in HF, regardless of LVEF.[21]

COSTS. Health state costs were derived from literature sources, many of which have previously been applied in an economic analysis of HFpEF/HFmrEF.[22] The cost of stable HF is estimated as the average outpatient cost of HF care based on 3 cohort studies of patients in the United States with long-term follow-up[22] (2.6-5 years).[22-25] The cost of HF hospitalization was also similarly based on the approach used in Zheng et al, accounting for the cost of hospital admission from an analysis of the Nationwide Inpatient Sample Healthcare Cost and Utilization Project and related physician fees.[22] Cardiovascular and noncardiovascular deaths were associated with a one-time cost based on the inpatient medical costs for patients with HF collected during the last year of life.[26] To avoid double-counting costs related to hospitalizations at end of life, the cost of HF hospitalizations over 1 year was subtracted. The cost of hyperkalemia is based on a claims study reporting inpatient and outpatient costs for managing acute hyperkalemia in patients with type 2 diabetes and chronic kidney disease.[27] The cost of the composite renal endpoint was based on a weighted average of the cost of a sustained eGFR decline of ≥40%, managed either outpatient or inpatient, and kidney failure. Inpatient costs of renal events were derived from a U.S. economic analysis of diabetic kidney disease, and the cost of outpatient management of sustained eGFR decline was estimated as the cost of 2 outpatient office visits and a basic metabolic panel with eGFR.[28-30]

Costs associated with stable HF and HF hospitalization were applied for each cycle that patients remained alive. Death-related costs were assigned as a one-time cost at transition to death. Both hyperkalemia and composite renal endpoint event costs were applied to 1 cycle duration.

Drug costs were calculated using pharmaceutical pricing data from the Federal Supply Schedule (FSS) and Veterans Affairs National Contracts, as well as the distribution of medications comprising SoC and the median maintenance dose of a representative drug from each therapeutic class.[31] The FSS allows for federal government agencies to purchase pharmaceuticals at prices negotiated between the Veterans Affairs and manufacturers.

All costs are reported in 2023 U.S. dollars and, where applicable, inflated using the consumer price index for medical care (**Table 4**).[32]

TABLE 2 Baseline Medications in Clinical Trial Populations

Therapeutic Class (Representative Drug)	EMPEROR-Preserved[a]	PARAGON-HF[b]	DELIVER[c]	Weighted Average
ACEIs (eg, lisinopril)	80.7%	66.1%	36.6%	36.9%
ARBs (eg, losartan)			36.3%	36.8%
Sacubitril/valsartan (Entresto)	2.2%	N/A	4.8%	3.6%
Beta-blockers (eg, carvedilol)	86.3%	61.0%	82.7%	77.8%
Diuretics (eg, furosemide)	NR	95.6%	76.8%	85.0%
Statins (eg, atorvastatin)	69.0%	NR	NR	69.0%
Aspirin (enteric-coated tablet)	42.0%	NR	NR	42.0%
SGLT2 inhibitors (eg, empagliflozin)[d]	N/A	NR	N/A	N/A

[a]Anker et al. *N Engl J Med*. 2021;385(16):1451-1461. [b]Solomon et al. *N Engl J Med*. 2019;381(17):1609-1620. [c]Solomon et al. *N Engl J Med*. 2022;387(12):1089-1098. [d]It is assumed that 20% of SoC-treated patients are treated with an SGLT2 inhibitor.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blocker; C = cardiovascular; N/A = not applicable; NR = not reported; SGLT2 = sodium-glucose cotransporter-2; SoC = standard of care; other abbreviations as in Table 1.

TABLE 3 Event Probabilities in EMPEROR-Preserved, PARAGON-HF, and DELIVER

	Incidence Rate (Per 100 Person-Years)				
	EMPEROR-Preserved[a]	PARAGON-HF[b]	DELIVER[c]	Weighted Average	Monthly Probability
Comparator arm					
Total HF hospitalizations	6.0	11.5	6.5	7.7	0.64%
Composite renal endpoint[d]	4.4	0.6	NR	2.7	0.23%
Hyperkalemia	2.2	0.9	NR	1.6	0.14%
Cardiovascular death	3.8	3.1	3.8	3.6	0.30%
All-cause mortality	6.7	5.0	7.6	6.6	0.55%
SGLT2 inhibitor-treated arm					
Total HF hospitalizations	4.3	N/A	5.0	4.7	0.39%
Composite renal endpoint[a]	3.6	N/A	NR	3.6	0.30%
Hyperkalemia	2.1	N/A	NR	2.1	0.18%
Cardiovascular death	3.4	N/A	3.3	3.3	0.28%
All-cause mortality	6.6	N/A	7.2	6.9	0.58%

[a]Anker et al. *N Engl J Med*. 2021;385(16):1451-1461. [b]Solomon et al. *N Engl J Med*. 2019;381(17):1609-1620. [c]Solomon et al. *N Engl J Med*. 2022;387(12):1089-1098. [d]Definition of composite renal endpoint differs slightly between trials: chronic dialysis, renal transplant, or sustained eGFR reduction ≥40% from baseline or <15 mL/min/1.73 m^2 (EMPEROR-Preserved); death from renal failure, ESRD, or eGFR decline ≥50% (PARAGON-HF).

SGLT2 = sodium-glucose cotransporter-2; other abbreviations as in Table 1.

TABLE 4 Base Case Model Inputs

	Value	Source
Transition probabilities, per month		
HF hospitalization	0.59%	EMPEROR-Preserved, PARAGON-HF, DELIVER[6-8]
Hyperkalemia	0.24%	
Composite renal endpoint	0.14%	
Cardiovascular death	0.30%	
Noncardiovascular death	0.26%	
Readmission for HF within 30 days	9.0%	Bozkurt et al, 2023, Tsimploulis et al, 2018[17,18]
Hyperkalemia management		
Managed outpatient	41%	EMPEROR-Preserved and PARAGON-HF[6,7]
Managed inpatient	59%	
Composite renal endpoint events		
Sustained eGFR decline, managed outpatient	23%	EMPEROR-Preserved and PARAGON-HF[6,7]
Sustained eGFR decline, managed inpatient	32%	
Kidney failure	45%	PARAGON-HF[7]
Mortality risk		
HF hospitalization (relative to stable HF)	9.39	Carson et al, 2015[20]
Composite renal endpoint	2.25	Löfman et al, 2019[21]
Costs, per month		
SoC[a]	147	Federal Supply Schedule[31]
Stable HF	687	Zheng et al, 2022[22]
HF hospitalization	15,404	
Cardiovascular death	91,026	
Noncardiovascular death	114,038	
Hyperkalemia	5,037	Betts et al, 2021[27]
Composite renal endpoint	7,078	Weighted average
Sustained eGFR decline, outpatient management[b]	198	CMS physician and laboratory fee schedules[28,29]
Sustained eGFR decline, inpatient management	7,731	Reifsnider et al, 2022[30]
Kidney failure	10,050	

[a]Calculated based on FSS cost for generic formulation, if available, and median maintenance dose for HF indication of medications (Table 2), with assumption that 20% of population would also be treated with an SGLT2 inhibitor. [b]Based on 2 outpatient physician visits and 1 basic metabolic panel with eGFR.

CMS = Centers for Medicare and Medicaid Services; eGFR = estimated glomerular filtration rate; FSS = Federal Supply Schedule; other abbreviations as in Table 2.

TABLE 5 Input Values for 1-Way Sensitivity Analysis

	Base Case	Low Value	High Value	Value Range
SGLT2 inhibitor utilization, %	20%	10%	50%	200%
Stable HF-to-HF hospitalization, per-month probability	0.59%	0.53%	0.65%	20%
Readmission for HF within 30 days, probability	9.0%	7.67%	10.31%	29%
Hyperkalemia, per-month probability	0.24%	0.22%	0.27%	20%
Composite renal endpoint, per-month probability	0.14%	0.13%	0.16%	20%
Cardiovascular death, per-month probability	0.30%	0.27%	0.32%	20%
Noncardiovascular death, per-month probability	0.26%	0.23%	0.28%	20%
HF hospitalization, HR	9.39	5.72	15.42	103%
Sustained eGFR decline, HR	2.25	1.52	2.97	64%
Kidney failure, HR	5.9	5.4	6.5	19%
Kidney failure events, % of composite renal endpoint	45.3%	0%	100%	221%
SoC drug costs, monthly	$147	$133	$162	20%
Stable HF cost per month	$687	$618	$755	20%
HF hospitalization cost per month	$15,404	$13,863	$16,944	20%
Cardiovascular death cost	$91,026	$81,923	$100,128	20%
Noncardiovascular death cost	$114,038	$102,634	$125,442	20%
Hyperkalemia cost per month	$5,037	$4,533	$5,541	20%

Abbreviations as in Table 2.

SENSITIVITY ANALYSIS. One-way sensitivity analyses were conducted to identify the impact of impact of clinical parameter uncertainty clinical parameter uncertainty and key drivers of model outcomes. Inputs for 1-way sensitivity analysis are shown in Table 5. The high and low values for each parameter tested were based on 95% CIs, where available. For the proportion of patients treated with SGLT2 inhibitors, a broader range of 10% to 50% was considered given significant uncertainty around the uptake of this class of medications in the HFpEF/HFmrEF population. A higher end of up to 50% is considered given that generic SGLT2 inhibitors may soon become available in the United States. Due to a lack of data on the composition of renal outcomes, a range of 0% to 100% was tested for the proportion of composite renal endpoint events consisting of kidney failure. All remaining variables were varied by a range of ±10% from the base case value.

TABLE 6 Aggregate Model Results

	Time Horizon	
	5 Years	10 Years
Clinical outcomes		
Cumulative HF hospitalizations	0.32	0.53
Cardiovascular deaths	0.16	0.26
Noncardiovascular deaths	0.17	0.34
Cardiovascular events[a]	0.48	0.79
Hyperkalemia	012	0.20
Composite renal endpoint events	0.07	0.12
Costs (discounted)[b]		
Drug costs	7,000	10,800
Stable HF	32,400	49,900
HF hospitalizations	4,700	7,200
Cardiovascular death	13,400	20,800
Noncardiovascular death	17,700	33,600
Hyperkalemia	600	900
Composite renal endpoint	500	700
Total[c]	76,100	123,900

[a]Includes the sum of any HF hospitalizations and cardiovascular deaths. [b]Costs shown are rounded to the nearest $100. [c]Total shown may differ from the calculated sum due to rounding.

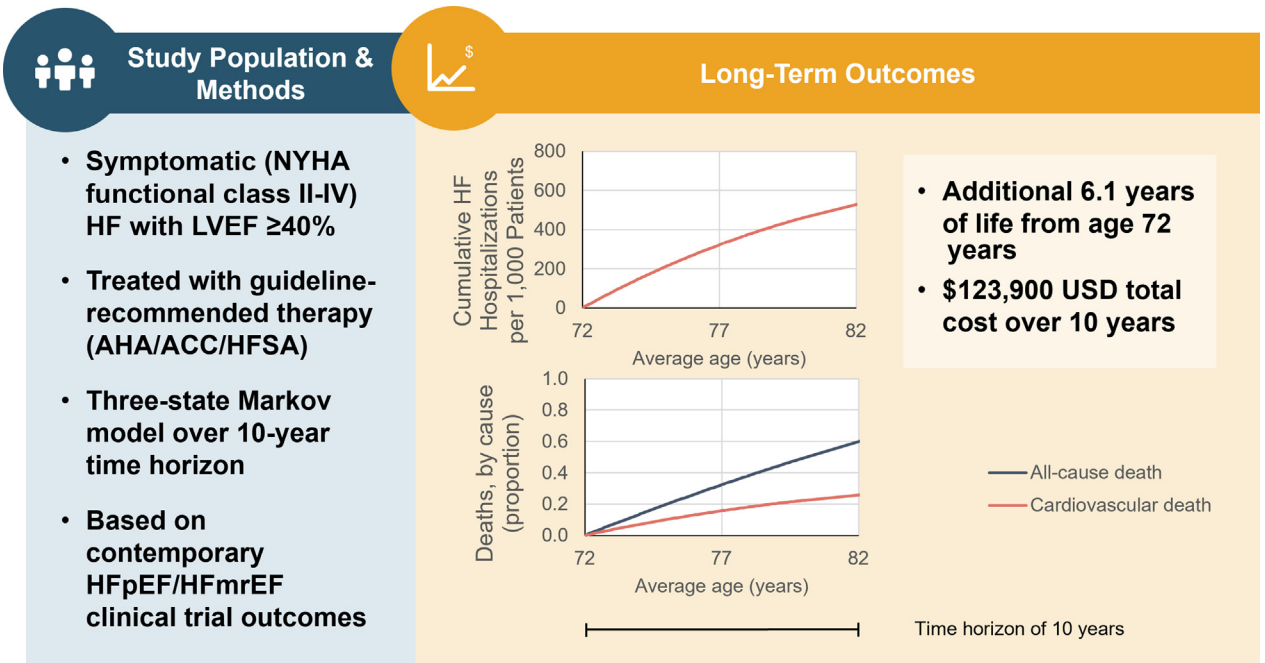
HF = heart failure.

RESULTS

Clinical events and costs of care were modeled over 5- and 10-year time horizons for cohorts of patients treated with SoC (Table 6). HF hospitalizations, cardiovascular deaths, and all-cause deaths over time starting at age 72 are shown in the Central Illustration.

We estimated that 37% of patients would experience at least 1 HF hospitalization, and 16% would experience multiple HF hospitalizations over 10 years. On average, patients with symptomatic HFpEF/HFmrEF on SoC experienced 0.53 cumulative HF hospitalizations, and 26% experienced cardiovascular death. The average frequency of hyperkalemia and composite renal endpoint events was 0.20 and 0.12, respectively, over the modeled timeframe. The total discounted cost of care over 10 years was $123,900. The largest contributors were stable HF health state costs ($49,900), followed by noncardiovascular and cardiovascular death costs ($33,600 and $20,800, respectively).

CENTRAL ILLUSTRATION **Long-Term Outcomes of Heart Failure With Preserved or Mid-Range Ejection Fraction: A Markov Model**



Sun LA, et al. JACC Adv. 2024;3(7):101027.

The simulation model included outcomes of recent phase 3 clinical trials, assuming treatment with contemporary standards of care in HFpEF/HFmrEF. The cumulative incidence of HF hospitalizations and proportion of patients experiencing cardiovascular or noncardiovascular death are shown over a 10-year time horizon starting at age 72 years. Over a 10-year time horizon, a cohort of 1,000 patients experienced 528 HF hospitalizations, lived an additional 6.1 years on average, and accumulated a total cost of $123,900 related to HF. ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFSA = Heart Failure Society of America; LVEF = left ventricular ejection fraction; SoC = standard of care; USD = United States dollars.

In comparison, 26% of the modeled cohort had at least 1 HF hospitalization over a 5-year time horizon, and 7% had multiple HF hospitalizations. The cumulative frequency of HF hospitalizations and cardiovascular deaths was 0.32 and 0.16, respectively. The average number of hyperkalemia and composite renal endpoint events in the modeled cohort was 0.12 and 0.07, respectively. The total discounted cost of care was $76,100.

Based on the results of 1-way sensitivity analyses, the 2 most impactful drivers of life expectancy for the modeled cohort were noncardiovascular mortality and cardiovascular mortality (Figure 2A). The mortality risk associated with HF hospitalization and proportion of patients treated with SGLT2 inhibitors were also among the top drivers of estimated life expectancy.

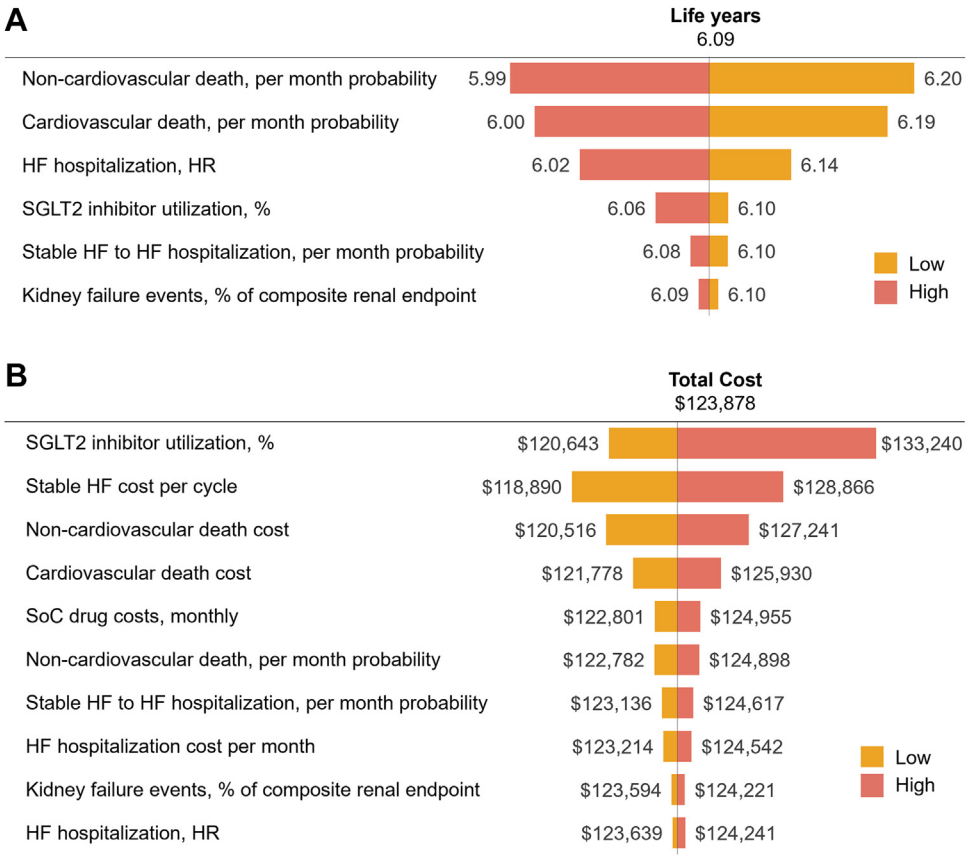
Analyses were also conducted to identify drivers of the total cost of care for the modeled cohort (Figure 2B). Total cost was most sensitive to the proportion of patients treated with SGLT2 inhibitors and monthly cost of stable HF, followed by the cost of noncardiovascular death and the cost of cardiovascular death.

DISCUSSION

Over a third of HF patients in the simulation would experience at least 1 more HF hospitalization, and over a quarter would die from a cardiovascular cause over a 10-year period. These results illustrate that adequate disease control has yet to be achieved with the available treatment options for HFpEF/HFmrEF. Methods of optimizing care will continue to evolve as research efforts better characterize this subpopulation of HF.

A strength of this research is that it anticipates and includes emerging use of SGLT2 inhibitors, which

FIGURE 2 Tornado Diagrams for 1-Way Sensitivity Analyses



One-way sensitivity analyses were conducted to identify the most impactful contributors to variation in (A) life expectancy and (B) total cost. The 2 factors that impacted life expectancy the most were noncardiovascular mortality and cardiovascular mortality, followed by mortality risk associated with HF hospitalization and treatment with SGLT2 inhibitors. Parameters that resulted in a life expectancy range of <0.01 years are not shown. Total cost was most sensitive to the proportion of patients treated with SGLT2 inhibitors, followed by the monthly cost of stable HF and costs of noncardiovascular death and cardiovascular death. eGFR = estimated glomerular filtration rate; HF = heart failure; SGLT2 = sodium-glucose cotransporter-2; SoC = standard of care.

have recently shown positive phase 3 outcomes in HFpEF/HFmrEF populations. There is also a small proportion of patients assumed to be on sacubitril-valsartan. To account for the clinical impact of SGLT2 inhibitor uptake in the HFpEF/HFmrEF population, we derived our event probabilities from a weighted average of both control and intervention arm data from the clinical trials.

These findings provide a more up-to-date long-term clinical trajectory for symptomatic HFpEF/HFmrEF patients. Tromp et al had previously investigated the association between age and outcomes in patients with HFpEF/HFmrEF based on the CHARM-Preserved, I-PRESERVE, and TOPCAT studies, which predate approvals for sacubitril-valsartan and empagliflozin in HFpEF/HFmrEF.[33] All 3 trials were completed prior to 2014. Tromp et al report that 11% of patients age ≤55 years and 29% of patients age ≥85 years were hospitalized within 5 years. This is consistent with our results, which estimate that 26% of the modeled cohort, starting at age 72 years, would be hospitalized for HF at least once over 5 years. Similarly, cardiovascular mortality occurred in 17% of those aged 75 to 84 years in Tromp et al's study, compared to 16% in our modeled cohort. Cardiovascular outcomes were similar, despite the assumption that of a portion of patients would be treated with an SGLT2 inhibitor.

STUDY LIMITATIONS. We report a simulation modeling exercise informed by existing clinical trials and other

data. Long-term event rates used to simulate 5- and 10-year outcomes are extrapolated from the PARAGON-HF, EMPEROR-Preserved, and DELIVER studies, which have a shorter duration of follow-up ranging from 2.2 to 2.9 years (median). Clinical trial subjects are also likely to have higher adherence and to be more closely monitored than the general HFpEF/HFmrEF population seeking symptom control. Notably, the PARAGON-HF study control arm was given valsartan, whereas the EMPEROR-Preserved and DELIVER trial control arms received placebo. Additionally, the PARAGON-HF trial enrolled patients with LVEF ≥45%, whereas EMPEROR-Preserved and DELIVER had broader criteria of LVEF >40%.

There is limited evidence of outcomes specific to the HFpEF/HFmrEF population. While 1 study reports that 30-day readmissions due to HF occur among 9.0% of the study cohort, all-cause 30-day readmissions are as high as 24.2%.[17,18] It is possible that the true rate of 30-day readmissions due to HF has been underestimated. Although the model considers a composite renal endpoint, there is a lack of data on the risk of disaggregated outcomes (sustained eGFR decline and kidney failure) in HFpEF/HFmrEF populations. Comorbid diabetes was also not considered in this model.

To date, there is no published data on the uptake of SGLT2 inhibitors among patients with HFpEF/HFmrEF. The simulation model assumes a prevalence based on utilization among HFrEF patients and explores a broad range of sensitivity analyses.

This simulation model estimates the direct costs of a HFpEF/HFmrEF cohort treated with usual care, but does not estimate indirect costs, such as impact on productivity or quality of life. Further, the model accounts for drug costs using FSS pricing data, but the actual cost paid for drugs may vary across payers, given the lack of transparency on negotiated discounts and rebates.

CONCLUSIONS

Symptomatic HF with LVEF ≥40% is associated with high rates of HF hospitalization and risk of cardiovascular death. Even with newer treatments for HFpEF/HFmrEF, there is still significant unmet clinical need and economic burden in this population. Optimizing care and treatment may contribute to greater life expectancy and fewer adverse outcomes for patients with HFpEF/HFmrEF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Patients with HFpEF or HFmrEF are at high risk of hospitalization for HF and cardiovascular death despite treatment with current SoC and uptake of recently approved SGLT2 inhibitors, which were added to American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines based on the outcomes of recent clinical trials. A high proportion of patients are predicted to experience HF hospitalizations, and nearly half of deaths within a 10-year time horizon are due to a cardiovascular cause. Long-term outcomes may be improved with better use of medications that have been studied in HFpEF or HFmrEF populations specifically and have demonstrated both safety and efficacy.

TRANSLATIONAL OUTLOOK: Clinical trial experience in HFpEF/HFmrEF is limited compared to that of HFrEF, which has a longer history of being studied and characterized as a prevailing phenotype of HF. As a result, clinical guidance on treatment and care planning for HFpEF and HFmrEF is also relatively lacking. This study highlights the need to address barriers to optimizing care in this patient population by identifying optimal treatment regimens that may reduce HF hospitalizations and cardiovascular deaths. Given the high hospitalization burden of HFpEF/HFmrEF populations, transitions of care and education on guideline-directed medical therapy are key points of intervention that may improve patient outcomes and reduce health care costs. This will require efficient coordination between inpatient and outpatient health care settings, increased awareness and education on guideline-directed medical treatment of HFpEF/HFmrEF, and continued generation of clinical trial evidence in HFpEF and HFmrEF patient populations.

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