JAMA Cardiology | Original Investigation

Cost-effectiveness of Dapagliflozin for Treatment of Patients With Heart Failure With Reduced Ejection Fraction

Justin T. Parizo, MD; Jeremy D. Goldhaber-Fiebert, PhD; Joshua A. Salomon, PhD; Kiran K. Khush, MD, MAS; John A. Spertus, MD, MPH; Paul A. Heidenreich, MD, MS; Alexander T. Sandhu, MD, MS

IMPORTANCE In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin was shown to reduce cardiovascular mortality and hospitalizations due to heart failure while improving patient-reported health status. However, the cost-effectiveness of adding dapagliflozin therapy to standard of care (SOC) is unknown.

OBJECTIVE To estimate the cost-effectiveness of dapagliflozin therapy among patients with chronic heart failure with reduced ejection fraction (HFrEF).

DESIGN, SETTING, AND PARTICIPANTS This Markov cohort cost-effectiveness model used estimates of therapy effectiveness, transition probabilities, and utilities from the DAPA-HF trial and other published literature. Costs were derived from published sources. Patients with HFrEF included subgroups based on diabetes status and health status impairment due to heart failure. We compiled parameters from the literature including DAPA-HF, on which our model is based, and many other sources from December 2019 to February 27, 2021. We performed our analysis in February 2021.

EXPOSURES Dapagliflozin or SOC.

MAIN OUTCOMES AND MEASURES Hospitalizations for heart failure, life-years, quality-adjusted life-years (QALYs), costs, and the cost per QALY gained (incremental cost-effectiveness ratio).

RESULTS In the model, dapagliflozin therapy yielded a mean of 0.78 additional life-years and 0.46 additional QALYs compared with SOC at an incremental cost of $38 212, resulting in a cost per QALY gained of $83 650. The cost per QALY was similar for patients with or without diabetes and for patients with mild or moderate impairment of health status due to heart failure. The cost-effectiveness was most sensitive to estimates of the effect on mortality and duration of therapy effectiveness. If the cost of dapagliflozin decreased from $474 to $270 (43% decline), the cost per QALY gained would drop below $50 000.

CONCLUSIONS AND RELEVANCE These findings suggest that dapagliflozin provides intermediate value compared with SOC, based on American College of Cardiology/American Heart Association benchmarks. Additional data regarding the magnitude of mortality reduction would improve the precision of cost-effectiveness estimates.

JAMA Cardiol. 2021;6(8):926-935. doi:10.1001/jamacardio.2021.1437
Published online May 26, 2021.

Editorial page 875

Supplemental content

Author Affiliations: Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California (Parizo, Khush, Heidenreich, Sandhu); Stanford Health Policy, Centers for Health Policy and Primary Care and Outcomes Research, The Freeman Spogli Institute, Department of Medicine, Stanford University, Stanford, California (Goldhaber-Fiebert, Salomon); St Luke's Mid America Heart Institute, University of Missouri–Kansas City (Spertus); Division of Cardiology, Veterans Affairs Palo Alto Health Care System, Palo Alto, California (Heidenreich).

Corresponding Author: Justin T. Parizo, MD, Division of Cardiovascular Medicine, Stanford University School of Medicine, 870 Quarry Rd, Falk Building, Cardiovascular Medicine, Stanford, CA 94305 (jparizo@stanford.edu).

Heart failure is projected to affect 9.6 million persons in the US with a cost of $69.7 billion annually by 2030.[1] It contributes to 1 of 8 deaths in the US.[2,3] In recent years, several promising new HF treatment options have been approved. However, given concerns regarding health care costs, a cost-effectiveness evaluation of these therapies is imperative.

Dapagliflozin, a sodium-glucose cotransport 2 (SGLT2) inhibitor, is the newest medication approved by the US Food and Drug Administration for heart failure with reduced ejection fraction (HFrEF). In multiple diabetes treatment trials, SGLT2 inhibitors reduced the incidence of heart failure and hospitalizations for heart failure.[4-7] As a result, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial[8] evaluated dapagliflozin in patients with symptomatic HFrEF, with and without diabetes, compared with standard of care (SOC)—that is, standard heart failure device and drug therapy, which included appropriate treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or sacubitril-valsartan plus a β-blocker. In that study,[8] 4744 patients (2761 [58.2%] without type 2 diabetes) were randomized to dapagliflozin or placebo and were followed up for a median of 18.2 (range, 0-27.8) months. Dapagliflozin significantly reduced the primary composite end point of cardiovascular death, hospitalization for heart failure, or urgent visits for heart failure; reduced the secondary outcome of cardio-

vascular death; and improved patient-reported health status. Dapagliflozin had similar effectiveness for patients with and without diabetes.

At present, dapagliflozin's price is approximately $470 per month.[9] It remains unclear whether it is cost-effective at this price point. We performed an independent cost-effectiveness analysis of dapagliflozin in patients with HFrEF, with subgroup analyses by diabetes status and health status impairment due to heart failure.

Key Points

Question Is dapagliflozin cost-effective when added to standard of care for patients who have heart failure with reduced ejection fraction (HFrEF) with and without diabetes?

Findings This economic evaluation used a Markov model based on the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure population and found dapagliflozin had an incremental cost-effectiveness ratio of $83 650 per quality-adjusted life-year gained, indicating intermediate value according to American College of Cardiology/American Heart Association benchmarks. The cost-effectiveness of dapagliflozin was similar for subgroups with and without diabetes and among those with more or less impaired health status due to heart failure.

Meaning These findings suggest that dapagliflozin is cost-effective for patients with HFrEF; therefore, given evidence of clinical benefit and economic value, focus should be on increasing therapy rates among patients who have HFrEF with and without diabetes.

Methods

Decision Model

We developed a state-transition Markov cohort model that compares dapagliflozin and SOC without dapagliflozin across the DAPA-HF population (eFigure 1 in the Supplement).[8] The DAPA-HF trial included patients older than 18 years with left ventricular ejection fraction of 40% or less, New York Heart Association (NYHA) class II to IV heart failure, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels of at least 600 pg/mL (see DAPA-HF methods for complete inclusion criteria).[8] Patients with type 1 diabetes, hypotension (systolic blood pressure <95 mm Hg), or estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 were excluded. This economic simulation analysis was exempt from institutional review board approval and informed consent. DAPA-HF collected data on average for 18 months after enrollment/randomization, which occurred from February 15, 2017, to August 17, 2018. We developed our model and performed our analysis from December 2019 to February 27, 2021.

We performed 2 secondary subgroup analyses in which we separately evaluated (1) groups with and without diabetes within each arm and (2) 2 different levels of health status impairment due to heart failure within each arm. Both diabetes and heart failure health status affect the baseline morbidity rates.[8,10-13] Although relative treatment effects appeared similar across diabetes status, the DAPA-HF trial suggested possible effectiveness differences between patients with more and less severe heart failure. The effect of dapagliflozin was significantly larger among patients with NYHA class II vs III or IV disease. In addition, although not significant, the effectiveness estimates were greater for those with better health status (based on the Kansas City Cardiomyopathy Questionnaire Total Symptoms Score [KCCQ-TSS]; cardiovascular mortality: KCCQ-TSS ≤65.6 [hazard ratio (HR), 0.84], KCCQ-TSS 65.7-87.5 [HR, 0.78], and KCCQ-TSS >87.5 [HR, 0.72]; P = .82) and lower NT-proBNP levels.[10] However, the data are not entirely clear. Effectiveness point estimates were nonsignificantly smaller for patients with higher left ventricular ejection fraction and those without past hospitalization for heart failure. We stratified patients into mild and moderate impairment of health status due to heart failure using the KCCQ-TSS.

We used the KCCQ-TSS–based stratification owing to its superior reproducibility and prognostic significance compared with NYHA class as well as its patient-centered approach.[14-16] In DAPA-HF, baseline KCCQ-TSS tertiles correlated with probabilities of cardiovascular death (16.8% in the low [most severe impairment] tertile, 10.2% in the middle tertile, and 7.7% in the high tertile of KCCQ-TSS scores).[10] We created 2 strata: moderate (KCCQ-TSS <65.7) and mild (KCCQ-TSS ≥65.7) health status impairment due to heart failure.[10]

Transition probabilities were based on DAPA-HF trial outcomes and the natural history of HFrEF.[8] Patients had a monthly risk of hospitalization for heart failure, hospitalization for other causes, left ventricular assist device implantation, heart transplantation, cardiovascular or noncardiovascular death, and treatment intolerance (**Table 1**).

We developed our model from a health care payor perspective with a lifetime horizon (eMethods 1 in the Supplement).[23] Future costs and utilities were discounted to present value at 3% annually. The primary outcome was the incremental cost-effectiveness ratio (ICER), which we calculated as incremental cost divided by incremental quality-adjusted life-years (QALYs). We used the American College of Cardiology/American Heart Association value threshold for high value (ICER <$50 000), intermediate value (ICER $50 000-$150 000), and low value (ICER >$150 000).[24] Below we provide an overview of model parameters (Table 1, with additional details in eMethods 2 to 13 and eTables 1 to 9 in the Supplement).

Transition Probabilities

The monthly risk of hospitalization for heart failure, cardiovascular mortality, and noncardiovascular mortality for SOC were estimated from the DAPA-HF control arm (eMethods 2 in the Supplement).[8] We assumed risk increased with age based on prior literature (eTables 2 and 3 in the Supplement).[25-27] For patients treated with dapagliflozin, the probability of hospitalization for heart failure and cardiovascular mortality were calculated based on the SOC rates multiplied by the DAPA-HF HR (eMethods 3 in the Supplement). The SOC arm's noncardiovascular mortality rate was assumed for the dapagliflozin arm. We modeled an adverse event rate based on DAPA-HF; we assumed patients discontinued dapagliflozin therapy after an adverse event, incurred no further drug costs, and re-

Table 1. Select Model Inputs

Transition monthly probabilities and rate ratios	Value at baseline, %	Interval for sensitivity analysis or range of time-varying variable[a]	Source
Standard of care			
HFH	0.70	0.51 to 0.93	McMurray et al,[8] 2019
CVD	0.61	0.44 to 0.81	McMurray et al,[8] 2019
NCVD	0.12	0.09 to 0.16	McMurray et al,[8] 2019
Dapagliflozin			
Intolerance to dapagliflozin	0.26	0.19 to 0.35	McMurray et al,[8] 2019
Rate ratios			
HFH with diabetes	1.53	1.18 to 1.98	Petrie et al,[12] 2020
CVD with diabetes	1.49	1.15 to 1.93	Petrie et al,[12] 2020
NCVD with diabetes	1.54	1.31 to 1.77	Petrie et al,[12] 2020
HFH with moderate impairment of health status due to heart failure (relative to mild)[b]	1.60	1.27 to 2.00	McMurray et al,[8] 2019; Kosiborod et al,[10] 2020
CVD with moderate impairment of health status due to heart failure (relative to mild)	1.94	1.52 to 2.48	McMurray et al,[8] 2019; Kosiborod et al,[10] 2020
NCVD with moderate impairment of health status due to heart failure (relative to mild)	1.25	1.07 to 1.44	Ahmed,[13] 2007
HFH with dapagliflozin	0.71	0.60 to 0.84	McMurray et al,[8] 2019
CVD with dapagliflozin	0.83	0.69 to 0.98	McMurray et al,[8] 2019
Utilities			
Baseline			
Overall cohort	0.78	0.66 to 0.89	Thomas et al,[17] 2021; McMurray et al,[18] 2019
Heart failure without diabetes	0.80	0.67 to 0.90	Thomas et al,[17] 2021; Vaduganathan et al,[19] 2019; McMurray et al,[18] 2019
Heart failure with diabetes	0.76	0.64 to 0.87	Thomas et al,[17] 2021; Vaduganathan et al,[19] 2019; McMurray et al,[18] 2019
Mild impairment of health status due to heart failure	0.81	0.67 to 0.91	McMurray et al,[8] 2019; Kosiborod et al,[10] 2020; Thomas et al,[17] 2021
Moderate impairment of health status due to heart failure	0.73	0.61 to 0.83	McMurray et al,[8] 2019; Kosiborod et al,[10] 2020; Thomas et al,[17] 2021
Dapagliflozin	0.0083	0.0042 to 0.013	McMurray et al,[8] 2019; Thomas et al,[17] 2021
HFH, % baseline utility	−29	−14.6 to −43.7	Ambrosy et al,[20] 2016
Costs (monthly), 2020 $			
Dapagliflozin	473.64	236.82 to 710.46	CMS,[9] 2020
Standard of care	0	0	NA
HFH	12 253	6127 to 18 380	Ziaeian et al,[21] 2015
CVD	70 453	35 226 to 105 679	Reed et al,[22] 2012
NCVD	88 812	44 406 to 133 217	Reed et al,[22] 2012

Abbreviations: CMS, Centers for Medicare & Medicaid Services; CVD, cardiovascular death; HFH, heart failure hospitalization; NA, not applicable; NCVD, non-CVD.

[a] Indicates range for time-varying variable over the lifetime horizon of the model.

[b] Mild impairment of health status due to heart failure is defined as Kansas City Cardiomyopathy Questionnaire Total Symptoms Score of at least 65.7; moderate impairment, less than 65.7.

ceived no further risk reduction relative to the SOC arm (eMethods 4 in the Supplement).

The DAPA-HF trial did not report rates of left ventricular assist device implantation and heart transplantation. We estimated these rates from the literature, assuming no dapagliflozin effect on advanced therapy rates or outcomes (eMethods 5 in the Supplement).[1,28-31]

For subgroup analyses, we estimated subgroup-specific event rates using DAPA-HF data when available and otherwise from the literature (eMethods 6 in the Supplement). For the diabetes subgroup analysis, we assumed a similar dapagliflozin effect in both arms.[12] For the subgroups with health status impairment due to heart failure, we used different treatment effects based on baseline KCCQ-TSS. We calibrated each analysis to match the overall event rates and treatment effects observed in DAPA-HF (eMethods 7 and eTables 4 and 5 in the Supplement).

Costs

We estimated a 2020 monthly cost of dapagliflozin of $473.64 based on the Medicare Part D drug payments from calendar year 2018 (eMethods 8 and eTable 6 in the Supplement).[9] This cost comprised the total drug cost, including the dispensing fee, the drug plan payment, and the beneficiary copayment. Medicare Part D cost was chosen as opposed to wholesale acquisition cost because Medicare Part D data are consistently

and accurately reported and most patients with heart failure have Medicare coverage.[32] In a sensitivity analysis, we evaluated ±50% of this cost because the pricing may vary across payors or change over time. We also evaluated several cost scenarios, including entry of multiple generics, wholesale acquisition cost, retail pharmacy price, and uninsured cost.

We divided other health care costs into ambulatory and hospitalization costs (eMethods 9 and 10 and eTable 6 in the Supplement). We assumed outpatient heart failure care costs increased with age by 0.88% annually (eTable 7 in the Supplement).[33] Based on prior literature, we assumed similar outpatient costs among patients who had heart failure with and without diabetes (eMethods 9 in the Supplement).[33] Higher costs for moderate impairment of health status due to heart failure were based on estimates of cost differences between patients with NYHA class III or IV and class II.[34] The costs of hospitalization for heart failure and hospitalizations for other causes were derived from previous literature estimates.[21,35] Based on DAPA-HF proportions, we assumed the cost of a hospitalization for causes other than heart failure for severe adverse events (eg, diabetic ketoacidosis) and an outpatient clinic appointment for mild adverse events.[35,36] The cost of cardiovascular and noncardiovascular death were taken from literature estimates and applied as a one-time cost at the time of death (eMethods 10 in the Supplement).[22] Costs are inflation adjusted to 2020 using annual US Bureau of Economic Analysis Personal Consumption Expenditure–Health Index deflators.[37]

Health-Related Quality of Life

We estimated the mean baseline utility of the DAPA-HF population using the KCCQ-TSS (eMethods 11 and eTable 8 in the Supplement).[18] We used an algorithm that maps KCCQ-TSS scores to utility estimates.[17] The utility estimates are based on a US time trade-off valuation of EQ-5D-3L scores. We estimated a baseline utility of 0.78. To account for aging and disease progression, we modeled an annual utility decrease of 0.7%, which we varied in sensitivity analysis.[38] We estimated subgroup-specific differences for patients with and without diabetes.[19] For the heart failure health status subgroups, we estimated overall KCCQ scores based on subgroup KCCQ-TSS values and mapped these scores to estimated utilities.[10,17] We estimated the effect of dapagliflozin on utility based on the change in KCCQ observed in DAPA-HF (annual utility change of 0.008) (eMethods 12 in the Supplement).

We used literature estimates for disutilities associated with adverse events, as well as adjustment of long-term utility after advanced therapy (eMethods 13 and eTable 8 in the Supplement).[20,39-42] A disutility of 29% of baseline utility was used for the month of a hospitalization for heart failure.[20] The disutility for adverse events was again weighted to DAPA-HF proportions of mild (one-third of disutility of a hospitalization for causes other than heart failure) and severe (disutility of a hospitalization) adverse events.

As a sensitivity analysis, we tested an alternative model with generally higher utility estimates (eMethods 12 and eTable 9 in the Supplement). This model used prior literature estimates of utility based on populations similar to those in the DAPA-HF trial. We also removed the age-related decline in utility and estimated the dapagliflozin effect on utility based on the ratio of KCCQ-TSS change in DAPA-HF to PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) (annual utility change of 0.017).[43]

Sensitivity Analyses

We performed 1-way sensitivity analyses across all model parameters (Table 1 and eTables 1, 6, and 9 in the Supplement). Parameters were varied across 95% CIs where available. Conservatively wide distributions were estimated for other parameters. We performed threshold analyses of key parameters (eg, dapagliflozin mortality effect and cost) to determine values at which dapagliflozin became high-value (ICER <$50 000) or low-value (ICER >$150 000) treatment. Two-way sensitivity analyses were performed for parameter combinations hypothesized to have significant interactions.

We performed several clinically relevant scenario analyses (eMethods 14 in the Supplement). First, in 2 alternate analyses, we assumed dapagliflozin was only effective for 18 months (median DAPA-HF follow-up) or had decreasing effectiveness after 18 months. Second, we assumed the risk of advanced therapies increased after hospitalization for heart failure to incorporate a dapagliflozin effect on advanced therapy rates.[44,45] Third, we modeled a pill disutility of 0.5% of baseline utility among patients receiving dapagliflozin.[46,47] Fourth, we modeled an equivalent effect of dapagliflozin in the subgroups with mild and moderate impairment of health status due to heart failure to evaluate whether timing of initiation alone affects the value of dapagliflozin. Finally, based on evidence from DAPA-HF and other SGLT2 inhibitor trials, we modeled a dapagliflozin effect on noncardiovascular death using the rate ratio in DAPA-HF of 0.89.[4,5,8]

We performed a probabilistic sensitivity analysis to evaluate the overall uncertainty of our model's results (eMethods 15 in the Supplement). We simultaneously resampled all parameters across their uncertainty distributions for 10 000 simulations (distributions in eTables 1, 6, and 9 in the Supplement).

Results

Model Calibration

We compared our model outcomes with DAPA-HF trial event rates during the median trial follow-up period of 18.2 (range, 0-27.8) months (eTables 4 and 5 in the Supplement).[8] Our model produced an SOC cardiovascular mortality rate of 7.9 events per 100 person-years compared with 7.9 events per 100 person-years in the DAPA-HF trial. The model's cardiovascular mortality rate ratio with dapagliflozin was 0.82 compared with 0.82 (95% CI, 0.69-0.98) in the DAPA-HF trial.

Base Case

In our model, patients in the SOC arm survived a mean of 8.5 life-years and had a mean of 2.0 hospitalizations for heart

Table 2. Outcomes of Dapagliflozin Treatment vs Standard of Care

Treatment group	Mean No. of HFH	Life-years[a]	Mean QALYs	Cost, $	Cost per life-year gained, $[b]	ICER, $/QALY
Full cohort						
Standard of care	2.0	8.5/7.0	5.2	145 371	NA	NA
Dapagliflozin	1.9	9.2/7.6	5.7	183 583	68 819	83 650
Diabetes status subgroups						
No diabetes						
Standard of care	2.3	9.9/8.0	6.0	152 637	NA	NA
Dapagliflozin	2.1	10.7/8.6	6.5	194 828	71 456	85 420
Diabetes						
Standard of care	1.8	7.2/6.1	4.4	138 264	NA	NA
Dapagliflozin	1.7	7.9/6.6	4.9	172 631	63 844	79 726
Heart failure health status subgroups[c]						
Mild impairment						
Standard of care	2.4	10.0/8.0	6.1	157 833	NA	NA
Dapagliflozin	2.3	11.0/8.7	6.7	202 646	64 986	78 483
Moderate impairment						
Standard of care	1.6	6.5/5.5	3.9	141 783	NA	NA
Dapagliflozin	1.4	7.0/5.9	4.2	172 045	77 892	97 608

Abbreviations: HFH, heart failure hospitalization; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life-years.

[a] Presented as undiscounted/discounted life-years.

[b] Costs per life-year gained uses discounted life-years because costs are discounted in the model.

[c] Mild impairment of health status due to heart failure is defined as Kansas City Cardiomyopathy Questionnaire Total Symptoms Score of at least 65.7; moderate impairment, less than 65.7.

failure. Patients in the dapagliflozin arm lived a mean of 0.78 more life-years with a mean of 0.13 fewer hospitalizations for heart failure. On a discounted basis, the SOC arm had a mean of 5.2 QALYs at a lifetime cost of $145 371, whereas the dapagliflozin arm experienced an additional 0.46 QALYs at an additional cost of $38 212, which included $35 708 in dapagliflozin costs. Dapagliflozin therapy had an intermediate value compared with SOC, with an ICER of $83 650 per QALY gained (**Table 2**).

Subgroup Analyses

We found that dapagliflozin had similar cost-effectiveness among patients with and without diabetes (Table 2). Among patients with diabetes, dapagliflozin led to fewer incremental QALYs (0.43) and costs ($34 367) compared with patients without diabetes (0.49 QALYs and $42 191, respectively). The ICERs were similar at $79 726 and $85 420 per QALY gained for patients with and without diabetes, respectively.

We found similar results among patients with mild and moderate impairment of health status due to heart failure. In the subgroup with mild impairment, patients in the SOC arm lived a mean of 10.0 years with 2.4 hospitalizations for heart failure. Patients in the dapagliflozin arm lived an additional 1.0 year with 0.08 fewer hospitalizations for heart failure at an incremental cost of $44 813, resulting in a cost per QALY gained of $78 483. In the moderate impairment subgroup, patients in the SOC arm lived a mean of 6.5 years with 1.6 hospitalizations for heart failure. Patients in the dapagliflozin arm lived an additional 0.5 years with 0.18 fewer hospitalizations for heart failure at an incremental cost of $30 262, resulting in a cost per QALY gained of $97 608.

Sensitivity Analysis

Treatment Efficacy

In 1-way sensitivity analyses (**Figure 1**), the decision was most sensitive to the HR for cardiovascular mortality with dapagliflozin, the duration of dapagliflozin effectiveness, and dapagliflozin cost. Across the 95% CI (0.69-0.98) for HR of cardiovascular mortality, the ICER spanned from $58 747 to $361 739 per QALY gained (Figure 1). For an ICER of $50 000 or less, the dapagliflozin HR for cardiovascular mortality would need to be less than 0.59; for an ICER $100 000 or less, less than 0.86; and for an ICER of $150 000 or less, less than 0.92. In the case where dapagliflozin is only effective for 18 months (trial duration), it costs $242 096 per QALY gained (Figure 1). To meet willingness-to-pay thresholds of $100 000 and $150 000 per QALY, dapagliflozin would need to be effective for at least 111 and 44 months, respectively. Dapagliflozin's effectiveness would need to decrease by 0.5% or less and by 3.0% or less monthly in the posttrial period to cost less than $100 000 and $150 000 per QALY gained, respectively. The results were notably insensitive to the risk of dapagliflozin intolerance or the effect on hospitalizations for heart failure (Figure 1).

Cost and Utilities

The cost of dapagliflozin may vary across payors and over time. In our main analysis, we used the Medicare Part D cost of $473.64. Varying this cost by ±50% led to a cost per QALY

Figure 1. Tornado Plot Demonstrating 1-Way Sensitivity Analysis for the Most Relevant Parameters

Parameter	Lower limit	Upper limit
HR of CVD	0.69	0.98
Duration of effectiveness	Lifelong	18 mo
Monthly cost of dapagliflozin	$237	$710
Baseline utility	0.89	0.66
Baseline monthly probability of CVD, %	0.81	0.44
RR for annual incremental risk of NCVD	1.00	1.16
RR for HFH with dapagliflozin	0.60	0.84
RR for annual incremental risk of HFH	1.00	1.31
Incremental utility of dapagliflozin	0.013	0.0042
Starting age, y	88	44
Cost of CVD	$105 679	$35 226
Cost of chronic heart failure management, % base case	50	150
Rate of baseline utility decline, %	0.35	1.10
Baseline monthly probability of NCVD, %	0.090	0.16
Cost of NCVD	$44 406	$133 217
Cost of HFH	$18 380	$6127
Cost of non-HFH	$3940	$11 819
Baseline monthly probability of HFH, %	0.93	0.51
RR for annual incremental risk of CVD	1.05	1.00

Parameters were tested across 95% CIs where available or across a reasonable distribution otherwise. CVD indicates cardiovascular death; HFH, heart failure hospitalization; HR, hazard ratio; NCVD, noncardiovascular death; QALY, quality-adjusted life year; and RR, rate ratio.

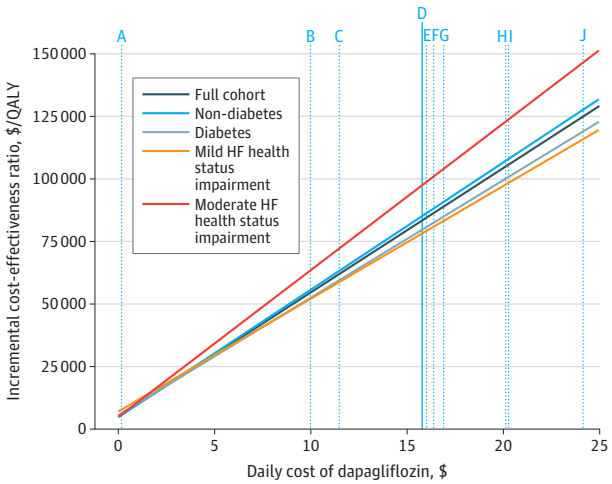
gained from $44 568 to $122 731 (Figure 1 and **Figure 2**). The dapagliflozin cost would need to decrease by 43% (from $474 to $270) to cost less than $50 000 per QALY gained. In Figure 2, we display dapagliflozin's ICER across different subgroups and estimated prices including uninsured patients, wholesale acquisition cost, Medicare Part D cost with estimated rebate, and a scenario with multiple available generic formulations (eTable 9 in the Supplement). The results were insensitive to changes in other cost parameters.

The baseline utility may vary substantially across different populations with heart failure. However, our results were relatively insensitive to baseline utility estimate, assumptions regarding utility decline, addition of a pill disutility, or other utility parameters (eTables 10 and 11 in the Supplement). In an alternate high-utility scenario, dapagliflozin's ICER remained similar ($73 581 per QALY gained) (eTable 12 in the Supplement).

Additional Sensitivity Analyses

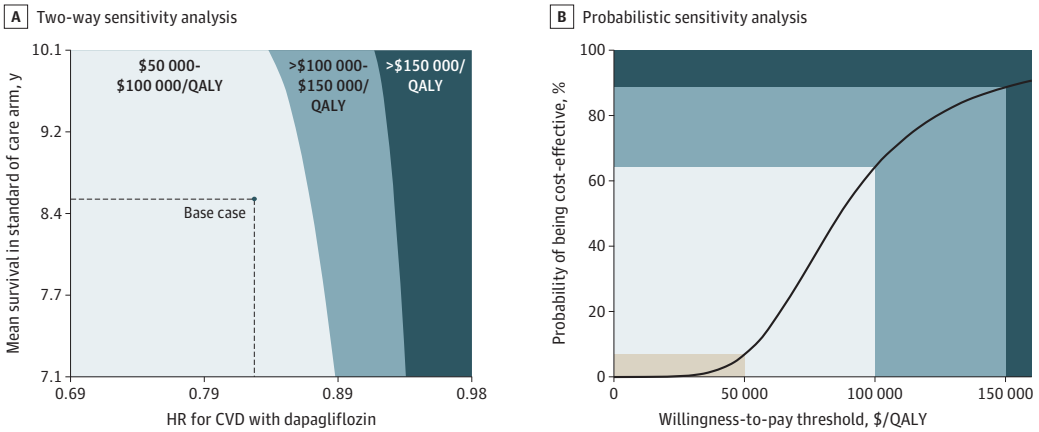
In our alternate model linking the HR of advanced therapies to recent hospitalizations for heart failure, dapagliflozin's ICER changed minimally owing to the relative rarity of advanced therapies (eTable 11 in the Supplement). When modeling an equal effect of dapagliflozin across heart failure health status subgroups, the incremental life-year increase from dapagliflozin was 0.07 years greater in the subgroups with mild vs moderate impairment of health status due to heart failure, and the ICER was similar ($103 778 vs $91 820 per QALY gained, respectively). Incorporating effects on noncardiovascular death decreased the ICER to $74 800 per QALY gained. Finally, **Figure 3**A shows a threshold analysis demonstrating the interaction of the probability of cardiovascular mortality in the SOC arm (displayed as mean survival) and the effect of dapagliflozin on cardiovascular mortality. Several other 2-way sensitivity analyses of parameters hypothesized to have interactions did not demonstrate notable interactions (eTable 13 in the Supplement),

Figure 2. Sensitivity Analysis of the Price of Dapagliflozin



The incremental cost-effectiveness ratio is plotted across a broad range of costs of dapagliflozin for the full cohort as well as each of our subgroups. The lower bound of costs of dapagliflozin is the lower limit of our 95% CI, but the upper bound was extended beyond the uninsured cost because our 95% CI did not include the uninsured cost. Vertical lines are plotted at different costs associated with dapagliflozin with the base case (Medicare Part D paid price to pharmacies). A indicates estimated generic cost ($0.17/d); B, Medicare Part D price after mean rebate (28.8%) ($9.99/d); C, Department of Veterans Affairs, Department of Defense, Public Health Service, and the Coast Guard (Big 4) ($11.50/d); D, base case ($15.79/d) and National Average Drug Acquisition Cost ($15.76/d); E, Federal Supply Schedule ($16.00/d); F, list price ($16.41/d); G, wholesale acquisition cost ($16.91/d); H, retail pharmacy price ($20.14/d); I, average wholesale price ($20.29/d); J, uninsured price ($24.18/d); HF, heart failure; and QALY, quality-adjusted life-year.

Figure 3. Sensitivity Analyses



A, Two-way sensitivity analysis of monthly probability of cardiovascular death (CVD) and hazard ratio (HR) for CVD at different willingness-to-pay thresholds. The monthly probability of CVD and the HR for CVD with dapagliflozin treatment were simultaneously varied across their respective distributions. For each level of monthly probability of CVD, the mean survival in the standard of care arm in years was calculated and plotted as the y-axis. Combinations of monthly probability of CVD and HR for CVD with dapagliflozin treatment that result in incremental cost-effectiveness ratios (ICERs) of less than $50 000, $50 000 to $100 000, greater than $100 000 to $150 000, and greater than $150 000 per quality-adjusted life-year (QALY) gained. The black dot represents the ICER of $75 661 at the base case values of probability of CVD and HR for CVD with dapagliflozin treatment. B, Probabilistic sensitivity analysis of cost-effectiveness acceptability curve in the base case. All model parameters were independently varied across their distributions in a probabilistic sensitivity analysis for 10 000 iterations. We have plotted the percentage of iterations that were cost-effective across willingness-to-pay thresholds.

Probabilistic Sensitivity Analysis

In the probabilistic sensitivity analysis, dapagliflozin had an ICER below $50 000 per QALY gained in 8% of simulations, below $100 000 in 65%, and below $150 000 in 89%. Details are given in Figure 3B and eFigure 2 in the Supplement.

Discussion

We have demonstrated that dapagliflozin provides intermediate value, with a cost per QALY gained of $83 650 among patients with HFrEF based on the DAPA-HF trial. Dapagliflozin had similar value among patients with and without diabetes and patients with mild and moderate impairment of health status due to heart failure. The results were most sensitive to dapagliflozin's effect on cardiovascular mortality and its cost. In addition, dapagliflozin would need to remain effective for at least 44 months to have a cost per QALY gained of less than $150 000.

Although dapagliflozin decreases both hospitalization for heart failure and cardiovascular mortality, its intermediate value largely depends on the effect estimate on cardiovascular mortality. We found that dapagliflozin must reduce cardiovascular mortality by at least 8% and 14% for the cost per QALY gained to remain below $150 000 and $100 000, respectively. The DAPA-HF 95% CI ranged from a reduction of 2% to 31%. This finding emphasizes the importance of additional data to better estimate the extent to which dapagliflozin can reduce cardiovascular mortality. Pooling results with empagliflozin from the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial led to fairly similar estimates of cardiovascular mortality (HR, 0.86; 95% CI, 0.77-0.98).[48]

The DAPA-HF trial suggested potential heterogeneity of treatment effect across disease severity subgroups. The treatment effect point estimate for the primary composite outcome was greater for patients with milder disease severity based on NT-proBNP levels and KCCQ-TSS score and was significantly greater for NYHA class. We found that dapagliflozin provided similar value across heart failure health status strata, although in the subgroup with mild health status impairment due to heart failure, the cost per QALY gained was lower, and there was a larger absolute life-year and QALY benefit despite lower baseline event rates. This finding emphasizes the potential benefit of starting dapagliflozin therapy early.

Although SGLT2 inhibitors have demonstrated a broad range of benefits, we conservatively limited our analysis to the effect on heart failure outcomes. In DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events Trial) and CREDENCE (Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation Trial), dapagliflozin and canagliflozin, respectively, significantly reduced renal outcomes, including kidney failure and death.[6,7] In DAPA-HF, there were fewer noncardiovascular deaths among patients in the dapagliflozin arm. Including a reduction of noncardiovascular death reduced the ICER further. Other non–heart failure effects may further improve the value among patients who are at high risk for those outcomes.

The cost of dapagliflozin likely varies substantially across payors. In addition, publicly available drug cost estimates often fail to account for manufacturer rebates. We modeled the cost-effectiveness of multiple different prices; with our cost estimate incorporating manufacturer rebate, we found dapagliflozin has intermediate value, with an ICER of $61 139 per QALY gained (Figure 2 and eTable 9 in the Supplement). The

cost of dapagliflozin would need to exceed $875 (85% higher than the estimated Medicare Part D paid price to pharmacies) to be low value. Most notably, the US patent for dapagliflozin expired in October 2020, and multiple generic options would be expected to enter the market in the coming years, driving price competition that could significantly lower the cost of dapagliflozin. If the introduction of generic drugs drops the price below $270, dapagliflozin would have high value.

Our use of the KCCQ to stratify our cohort on heart failure health status has advantages over traditional NYHA stratification. Being patient-reported, the KCCQ estimates quality of life directly from patients, which is often inconsistent with clinician assessment.[49] The KCCQ is more prognostic and reproducible as a standardized measurement tool, whereas the NYHA class has significant interoperator variability.[50,51] Using the KCCQ will help clinicians compare their patients with a given published analysis. Therefore, we believe using patient-reported health status as an estimate of illness severity stratification is an appealing alternative to traditional approaches in clinical trials and economic analyses.

Previous cost-effectiveness analyses, including those by McEwan et al,[27] Savira et al,[52] and Yao et al,[53] have found that dapagliflozin is cost-effective among patients with HFrEF. These analyses focused on non-US settings, including the UK, with an ICER of £5822 (US$7681); Germany, with an ICER of €5379 (US$6044); Spain, with an ICER of €9406 (US$10 569); Australia, with an ICER of $12 482 (US$8759); and China, with an ICER of $3828. McEwan et al[27] used primary data from the DAPA-HF trial and estimated 0.48 QALYs gained with dapagliflozin at an incremental cost of £2780 in the UK compared with 0.46 QALYs gained and incremental cost of $38 212 in our analysis. Their markedly lower ICER largely stems from differences in the annual cost of dapagliflozin ($5684 in the US vs £477 in the UK [US$629]) as well as higher health care costs in the US. In both analyses, exploratory subgroup analyses by diabetes and heart failure health status showed similar ICERs.

It is important to note that fewer than 1% of the trial population had NYHA class IV. The effectiveness, and thereby cost-effectiveness, in this population remains unclear.[8] In addition, only 11% of patients were receiving sacubitril-valsartan. Although a post hoc analysis indicated the effects of dapagliflozin were independent of sacubitril-valsartan use, further evaluation of the interaction between dapagliflozin and sacubitril-valsartan will be important.

Understanding therapy cost-effectiveness is critical for decision-making for health care systems and payors. However, affordability to patients remains an equally if not more important issue with regard to therapy access and adoption. The out-of-pocket costs will likely play a major role in driving suboptimal use of dapagliflozin. For therapies of high or intermediate value, payors and health care systems must reduce financial barriers that contribute to decreased use of health care services and worse outcomes.

Limitations

This study has some limitations. Our effects and transition probabilities were largely based on a single trial; however, this was a large trial that is consistent with the literature with regard to the use of dapagliflozin in patients who have diabetes.[6,54] Also, limited evidence is available on the duration of dapagliflozin's effectiveness. Given the sensitivity of the model to this parameter, this is an important question for postmarket monitoring. In addition, although we believe the KCCQ is an appealing tool for reproducible and prognostic stratification of patients with heart failure, it does not provide an exact estimate of utilities. In addition, although several SGLT2 inhibitors are being studied for HFrEF, this analysis does not indicate broad cost-effectiveness across this class. Finally, we did not model long-term transitions in heart failure severity owing to limited data and focus on the DAPA-HF trial.

Conclusions

This economic evaluation study demonstrates that dapagliflozin provides intermediate value among patients with HFrEF regardless of diabetes or heart failure–related health status. This effect is largely driven by a decrease in cardiovascular mortality. These results were insensitive to variation of model parameters except for the HR of cardiovascular mortality with dapagliflozin treatment, the cost of dapagliflozin, and the duration of effectiveness. Additional data regarding the mortality effect and long-term effectiveness of dapagliflozin are critical to a better understanding of its cost-effectiveness.

ARTICLE INFORMATION

Accepted for Publication: March 5, 2021.

Published Online: May 26, 2021. doi:10.1001/jamacardio.2021.1437

Author Contributions: Dr Sandhu was the principal investigator. Drs Parizo and Sandhu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Parizo, Goldhaber-Fiebert, Salomon, Khush, Spertus, Sandhu.
Acquisition, analysis, or interpretation of data: Parizo, Heidenreich, Sandhu.
Drafting of the manuscript: Parizo.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Parizo, Salomon, Sandhu.
Obtained funding: Parizo.
Administrative, technical, or material support: Parizo, Sandhu.
Supervision: Goldhaber-Fiebert, Salomon, Khush, Sandhu.

Conflict of Interest Disclosures: Dr Khush reported receiving personal fees from CareDx, Inc, outside the submitted work. Dr Spertus reported consulting for Janssen Pharmaceutica NV, Novartis International AG, Amgen Inc, Bayer AG, Myokardia, and Merck & Co, Inc, on patient-reported outcomes; serving as study principal investigator for Janssen; receiving grants from Abbott Vascular for collection of patient-reported outcome data; serving on the scientific advisory board of United Healthcare; serving as board member for Blue Cross Blue Shield of Kansas City outside the submitted work; and holding a patent for copyright to the Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire with royalties paid. No other disclosures were reported.

Funding/Support: The research reported in this publication was supported by awards 1F32HL149253-01 (Dr Parizo) and 1K23HL151672-01 (Dr Sandhu) from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or

approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Heidenreich PA, Albert NM, Allen LA, et al; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606-619. doi:10.1161/HHF.0b013e318291329a

2. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292(3):344-350. doi:10.1001/jama.292.3.344

3. Benjamin EJ, Blaha MJ, Chiuve SE, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485

4. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720

5. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

6. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389

7. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744

8. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303

9. Centers for Medicare & Medicaid Services. Part D Prescriber Data CY 2018. Modified December 3, 2020. Accessed February 9, 2021. https://www.cms.gov/research-statistics-data-systems/medicare-provider-utilization-and-payment-data/medicare-provider-utilization-and-payment-data-part-d-prescriber/part-d-prescriber-data-cy-2018

10. Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. *Circulation*. 2020;141(2):90-99. doi:10.1161/CIRCULATIONAHA.119.044138

11. MacDonald MR, Petrie MC, Varyani F, et al; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme. *Eur Heart J*. 2008;29(11):1377-1385. doi:10.1093/eurheartj/ehn153

12. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. 2020;323(14):1353-1368. doi:10.1001/jama.2020.1906

13. Ahmed A. A propensity matched study of New York Heart Association class and natural history end points in heart failure. *Am J Cardiol*. 2007;99(4):549-553. doi:10.1016/j.amjcard.2006.08.065

14. Kelkar AA, Spertus J, Pang P, et al. Utility of patient-reported outcome instruments in heart failure. *JACC Heart Fail*. 2016;4(3):165-175. doi:10.1016/j.jchf.2015.10.015

15. Kosiborod M, Soto GE, Jones PG, et al. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation*. 2007;115(15):1975-1981. doi:10.1161/CIRCULATIONAHA.106.670901

16. Heidenreich PA. Patient-reported outcomes: the future of heart failure care. *JACC Heart Fail*. 2019;7(10):875-877. doi:10.1016/j.jchf.2019.06.006

17. Thomas M, Jones PG, Cohen DJ, et al. Predicting the EQ-5D from the Kansas City Cardiomyopathy Questionnaire (KCCQ) in patients with heart failure. *Eur Heart J Qual Care Clin Outcomes*. 2021;qcab014. Published online March 16, 2021. doi:10.1093/ehjqcco/qcab014

18. McMurray JJV, DeMets DL, Inzucchi SE, et al; DAPA-HF Committees and Investigators. The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. *Eur J Heart Fail*. 2019;21(11):1402-1411. doi:10.1002/ejhf.1548

19. Vaduganathan M, Fonarow GC, Greene SJ, et al. Health-related quality of life in comorbid heart failure with reduced ejection fraction and diabetes mellitus. *J Am Coll Cardiol*. 2019;74(25):3176-3178. doi:10.1016/j.jacc.2019.10.020

20. Ambrosy AP, Hernandez AF, Armstrong PW, et al. The clinical course of health status and association with outcomes in patients hospitalized for heart failure: insights from ASCEND-HF. *Eur J Heart Fail*. 2016;18(3):306-313. doi:10.1002/ejhf.420

21. Ziaeian B, Sharma PP, Yu T-C, Johnson KW, Fonarow GC. Factors associated with variations in hospital expenditures for acute heart failure in the United States. *Am Heart J*. 2015;169(2):282-289.e15. doi:10.1016/j.ahj.2014.11.007

22. Reed SD, Li Y, Dunlap ME, et al. In-hospital resource use and medical costs in the last year of life by mode of death (from the HF-ACTION randomized controlled trial). *Am J Cardiol*. 2012;110(8):1150-1155. doi:10.1016/j.amjcard.2012.05.059

23. Neumann PJ, Ganiats TG, Russell LB, Sanders GD, Siegel JE. *Cost-effectiveness in Health and Medicine*. 2nd ed. Oxford University Press; 2016. Accessed October 11, 2020. https://oxford.universitypressscholarship.com/view/10.1093/acprof:oso/9780190492939.001.0001/acprof-9780190492939

24. Anderson JL, Heidenreich PA, Barnett PG, et al; ACC/AHA Task Force on Performance Measures; ACC/AHA Task Force on Practice Guidelines. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129(22):2329-2345. doi:10.1161/CIR.0000000000000042

25. Gustafsson F, Torp-Pedersen C, Seibaek M, Burchardt H, Køber L; DIAMOND study group. Effect of age on short and long-term mortality in patients admitted to hospital with congestive heart failure. *Eur Heart J*. 2004;25(19):1711-1717. doi:10.1016/j.ehj.2004.07.007

26. Arias E, Heron M, Tejada-Vera B. United States life tables eliminating certain causes of death, 1999-2001. *Natl Vital Stat Rep*. 2013;61(9):1-128.

27. McEwan P, Darlington O, McMurray JJV, et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *Eur J Heart Fail*. 2020;22(11):2147-2156. doi:10.1002/ejhf.1978

28. Benjamin EJ, Muntner P, Alonso A, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528. doi:10.1161/CIR.0000000000000659

29. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14(10):591-602. doi:10.1038/nrcardio.2017.65

30. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. *J Heart Lung Transplant*. 2017;36(10):1080-1086. doi:10.1016/j.healun.2017.07.005

31. Scientific Registry of Transplant Recipients. The SRTR/OPTN Annual Data Report. Published February 17, 2021. Accessed February 27, 2021. https://www.srtr.org/reports-tools/srtroptn-annual-data-report/

32. Levy J, Rosenberg M, Vanness D. A transparent and consistent approach to assess US outpatient drug costs for use in cost-effectiveness analyses. *Value Health*. 2018;21(6):677-684. doi:10.1016/j.jval.2017.06.013

33. Dunlay SM, Shah ND, Shi Q, et al. Lifetime costs of medical care after heart failure diagnosis. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):68-75. doi:10.1161/CIRCOUTCOMES.110.957225

34. Liao L, Anstrom KJ, Gottdiener JS, et al. Long-term costs and resource use in elderly participants with congestive heart failure in the Cardiovascular Health Study. *Am Heart J*. 2007;153(2):245-252. doi:10.1016/j.ahj.2006.11.010

35. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-effectiveness of sacubitril-valsartan in patients who have heart failure with reduced ejection fraction. *Ann Intern Med*. 2017;166(8):607-608. doi:10.7326/L17-0044

36. Centers for Medicare & Medicaid Services. Physician Fee Schedule. Updated April 1, 2021. Accessed June 18, 2020. https://www.cms.gov/medicare/medicare-fee-for-service-payment/physicianfeesched?redirect=/physicianfeesched

37. National Data (National Income and Product Accounts). Price Indexes for Personal Consumption Expenditures by Major Type of Product and by Major Function. Accessed September 17, 2020. https://apps.bea.gov/iTable/iTable.cfm?reqid=19&step=2#reqid=19&step=2&isuri=1&1921=underlying

38. Berg J, Lindgren P, Mejhert M, Edner M, Dahlström U, Kahan T. Determinants of utility based on the EuroQol Five-Dimensional Questionnaire in patients with chronic heart failure and their change over time: results from the Swedish Heart Failure Registry. *Value Health*. 2015;18(4):439-448. doi:10.1016/j.jval.2015.02.003

39. Jaagosild P, Dawson NV, Thomas C, et al; SUPPORT Investigators; Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments. Outcomes of acute exacerbation of severe congestive heart failure: quality of life, resource use, and survival. *Arch Intern Med*. 1998;158(10):1081-1089. doi:10.1001/archinte.158.10.1081

40. Kirklin JK, Naftel DC, Kormos RL, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients [published correction in J Heart Lung Transplant. 2015;34(10):1356]. *J Heart Lung Transplant*. 2013;32(2):141-156. doi:10.1016/j.healun.2012.12.004

41. Sharples LD, Dyer M, Cafferty F, et al. Cost-effectiveness of ventricular assist device use in the United Kingdom: results from the Evaluation of Ventricular Assist Device Programme in the UK (EVAD-UK). *J Heart Lung Transplant*. 2006;25(11):1336-1343. doi:10.1016/j.healun.2006.09.011

42. Sutcliffe P, Connock M, Pulikottil-Jacob R, et al. Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model. *Health Technol Assess*. 2013;17(53):1-499, v-vi. doi:10.3310/hta17530

43. McMurray JJV, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077

44. Tsiouris A, Paone G, Nemeh HW, et al. Short and long term outcomes of 200 patients supported by continuous-flow left ventricular assist devices. *World J Cardiol*. 2015;7(11):792-800. doi:10.4330/wjc.v7.i11.792

45. OPTN/SRTR 2018 annual data report: preface. *Am J Transplant*. 2020;20(s1)(suppl s1):1-10. doi:10.1111/ajt.15670

46. Hutchins R, Pignone MP, Sheridan SL, Viera AJ. Quantifying the utility of taking pills for preventing adverse health outcomes: a cross-sectional survey. *BMJ Open*. 2015;5(5):e006505. doi:10.1136/bmjopen-2014-006505

47. Fontana M, Asaria P, Moraldo M, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. *Circulation*. 2014;129(24):2539-2546. doi:10.1161/CIRCULATIONAHA.113.007595

48. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020;396(10254):819-829. doi:10.1016/S0140-6736(20)31824-9

49. Goode KM, Nabb S, Cleland JGF, Clark AL. A comparison of patient and physician-rated New York Heart Association class in a community-based heart failure clinic. *J Card Fail*. 2008;14(5):379-387. doi:10.1016/j.cardfail.2008.01.014

50. Chan PS, Soto G, Jones PG, et al. Patient health status and costs in heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation*. 2009;119(3):398-407. doi:10.1161/CIRCULATIONAHA.108.820472

51. Raphael C, Briscoe C, Davies J, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart*. 2007;93(4):476-482. doi:10.1136/hrt.2006.089656

52. Savira F, Wang BH, Kompa AR, et al. Cost-effectiveness of dapagliflozin in chronic heart failure: an analysis from the Australian healthcare perspective. *Eur J Prev Cardiol*. 2020;2047487320938272. Published online July 14, 2020 doi:10.1177/2047487320938272

53. Yao Y, Zhang R, An T, Zhao X, Zhang J. Cost-effectiveness of adding dapagliflozin to standard treatment for heart failure with reduced ejection fraction patients in China. *ESC Heart Fail*. 2020;7(6):3582-3592. doi:10.1002/ehf2.12844

54. Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190