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ORIGINAL RESEARCH PAPER

Cost-Effectiveness of Comprehensive Quadruple Therapy for Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Heart failure with reduced ejection fraction (HFrEF) is one of the most costly and deadly chronic disease states. The cost effectiveness of a comprehensive quadruple therapy regimen for HFrEF has not been studied.

OBJECTIVES The authors sought to determine the cost-effectiveness of quadruple therapy comprised of beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and sodium glucose cotransporter-2 inhibitors vs regimens composed of only beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists (triple therapy), and angiotensin-converting enzyme inhibitors and beta-blockers (double therapy).

METHODS Using a 2-state Markov model, the authors performed a cost-effectiveness study using simulated populations of 1,000 patients with HFrEF based on the participants in the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial and compared them by treatment strategy (quadruple therapy vs triple and double therapy) from a United States health care system perspective. The authors also performed 10,000 probabilistic simulations.

RESULTS Treatment with quadruple therapy resulted in an increase of 1.73 and 2.87 life-years compared with triple therapy and double therapy, respectively, and an increase in quality-adjusted life-years of 1.12 and 1.85 years, respectively. The incremental cost-effectiveness ratios of quadruple therapy vs triple therapy and double therapy were $81,000 and $51,081, respectively. In 91.7% and 99.9% of probabilistic simulations quadruple therapy had an incremental cost-effectiveness ratio of <$150,000 compared with triple therapy and double therapy, respectively.

CONCLUSIONS At current pricing, the use of quadruple therapy in patients with HFrEF was cost effective compared with triple therapy and double therapy. These findings highlight the need for improved access and optimal implementation of comprehensive quadruple therapy in eligible patients with HFrEF. (J Am Coll Cardiol HF 2023;■:■–■)

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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

ACE = angiotensin-converting enzyme

ARN = angiotensin receptor-neprilysin

BB = beta-blocker

CV = cardiovascular

GDMT = guideline-directed medical therapy

HFH = heart failure hospitalization

HFrEF = heart failure with reduced ejection fraction

ICER = incremental cost-effectiveness ratio

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire–Overall Summary

MRA = mineralocorticoid receptor antagonist

QALY = quality-adjusted life-year

SGLT2 = sodium glucose cotransporter-2

Heart failure with reduced ejection fraction (HFrEF) is one of the most costly and deadly chronic disease states.[1,2] In the last decade, advancements in guideline-directed medical therapy (GDMT) have substantially improved outcomes for patients living with HFrEF, but pervasive underuse of GDMT results in only a small fraction of patients receiving maximum possible reduction in morbidity and mortality.[3] The new standard of HFrEF management, based on randomized controlled trial evidence and guidelines, has become quadruple therapy and involves initiation and titration of the 4 crucial pillars of GDMT: beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin (ARN) inhibitors, and sodium glucose cotransporter-2 (SGLT2) inhibitors.[4,5] Each of these medications have been shown to incrementally improve morbidity and mortality benefit in HFrEF regardless of background regimen and generally without heterogeneity among clinically relevant subgroups studied. One key, commonly stated, reason for the substandard adoption of quadruple therapy, especially in the United States, is the higher cost ARN inhibitor and SGLT2 inhibitor therapy compared with traditional HFrEF medical therapy.[6] Yet, in multiple separate individual therapy cost-effectiveness analyses both medications have been found to be cost effective.[7-11] However, the cost-effectiveness of these medications in a comprehensive quadruple therapy regimen for HFrEF has not been studied using a singular model. In this analysis, we sought to determine the cost effectiveness of quadruple therapy vs prior standard of care regimens composed only of angiotensin-converting enzyme (ACE) inhibitors, BBs, and MRAs (triple therapy) and ACE inhibitors and BBs (double therapy).

METHODS

MODEL OVERVIEW. A 2-state Markov model (Supplemental Figure 1) was developed to compare a population of patients with HFrEF treated with the current standard of GDMT[5] composed of ARN inhibitor, SGLT2 inhibitor, BB, and MRA (quadruple therapy) against historical regimens of BB, ACE inhibitor, and MRA (triple therapy) and BB and ACE inhibitor (double therapy). The population of patients in the model was predominantly New York Heart Association functional class II and III based on the patients enrolled in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, similar to other pivotal chronic outpatient trials in HFrEF.[12] In the PARADIGM-HF trial, almost all patients in the control arm were on BBs and ACE inhibitors and roughly one-half of the patients were on MRAs. Estimates for event rates were based on the patients in the control arm of this trial and benefits of more optimal GDMT were modeled on top of them using HRs from an analysis performed by Vaduganathan et al.[13] In their analysis, the authors modeled the mortality and morbidity incremental benefits of quadruple therapy (compared with triple therapy and double therapy) using trial-level estimates of key subgroups from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure),[14] PARADIGM-HF,[12] and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)[15] studies. Costs assumptions were estimated based on publicly available data. Lifetime costs and quality-adjusted life-years (QALYs) were calculated for each cohort using a 30-year time horizon and discounted by 3% annually. Incremental cost-effectiveness ratios (ICERs) of quadruple therapy against triple therapy and double therapy were then calculated to estimate cost effectiveness.

SIMULATED POPULATION. We modeled 3 (double, triple, and quadruple therapy) hypothetical populations of 1,000 patients based on the control arm of the PARADIGM-HF trial (Supplemental Figure 2).[12] PARADIGM-HF was a double-blind, randomized, active clinical trial in which the efficacy of the ARN inhibitor, sacubitril-valsartan, was compared against the ACE inhibitor, enalapril (control), in patients with symptomatic HFrEF. Each simulated patient was a composite of the average PARADIGM-HF trial participant. In the trial, the mean age was approximately 64 years old, 77% patients were male, 66% were White, and 94% were New York Heart Association functional class II or III.[12] Additional baseline characteristics are reported in the trial manuscript. In our simulation, only de-identified patient data were used; therefore, local institutional review board approval was not required.

MODEL ASSUMPTIONS. The model perspective was U.S. health care based with a 30-year time horizon and assumed a single-payer health care system responsible for all health care costs. Each cycle of the Markov model represented 1 month. Patients existed in 1 of 2 states: alive or dead. Transitional probabilities were based on a per cycle death rate

TABLE 1 Input Parameters

	Costs		
	Distribution for PSA	**Base-Case Value in USD (95% CI in PSA)**	**First Author, Year**
HFH	γ	13,356 (8,411-19,532)	Parizo et al, 2021[10]
Urgent visit	γ	879 (554-1,290)	Isaza et al, 2021[8]
Non-HFH	γ	8,588 (5,331-12,501)	Parizo et al, 2021[10]
Annual costs			
Ambulatory care	γ	6,893 (2,673-13,072)	Bhatnagar, et al[17]
Double therapy	γ	35 (27-44)	VA Federal Supply Schedule Service[18]
Triple therapy	γ	53 (41-68)	
Quadruple therapy	γ	9,869 (7,584-12,516)	
	Event Rates		
	Distribution for PSA	**Monthly Event Rate**	**First Author, Year**
HFH			
Ref. cohort	NA	0.010	Mogensen et al, 2018[19]
Double therapy	β	0.013 (0.010-0.015)	Mogensen et al, 2018[19]
Triple therapy	β	0.008 (0.007-0.010)	Mogensen et al, 2018[19]
Quadruple therapy	β	0.005 (0.004-0.006)	Vaduganathan et al, 2020[13]
Urgent visit			
Ref. cohort	NA	0.0039	
Double therapy	β	0.0050 (0.0044-0.0056)	Okumura et al, 2016[20]
Triple therapy	β	0.0032 (0.0026-0.0039)	Okumura et al, 2016[20]
Quadruple therapy	β	0.0019 (0.0014-0.0026)	Okumura et al, 2016[20]
Non-HFH			
Ref. cohort	NA	0.027	Packer et al, 2015[45]
Double therapy	β	0.027 (0.022-0.032)	Packer et al, 2015[45]
Triple therapy	β	0.027 (0.022-0.032)	Packer et al, 2015[45]
Quadruple therapy	β	0.021 (0.017-0.026)	Packer et al, 2015;[45] Packer et al, 2020[21]
All-cause mortality		Rates of all-cause mortality were calculated based on prior actuarial analysis of HFrEF patients, U.S. general population, and HRs below (see Methods)	
	HRs		
	Distribution for PSA	**HR (Ref. Cohort, HR = 1)**	
Cardiovascular death			
Ref. cohort	NA	1.00	PARADIGM-HF 2014[12]
Double therapy	Log normal	1.15 (1.00-1.32)	Zannad et al, 2011[14]
Triple therapy	Log normal	0.90 (0.72-1.13)	Zannad et al, 2011[14]
Quadruple therapy	Log normal	0.62 (0.47-0.83)	Vaduganathan et al, 2020[13]
Noncardiovascular death		Assumed to be unaffected by GDMT	
Average Health Utility[a]			
Double therapy	NA	0.801	PARADIGM-HF 2014[12]
Triple therapy	NA	0.811	PARADIGM-HF 2014[12]
Quadruple therapy	NA	0.830	Lewis et al, 2017,[46] Kosiborod et al, 2020[47]

[a]Average health utility not simulated probabilistically because of minimal impact on outputs.

GDMT = guideline-directed medical therapy; HFH = heart failure hospitalization; NA = not applicable; PSA = probabilistic sensitivity analysis; Ref. = reference; USD = United States dollar.

detailed later. Alive patients accrued fixed costs from routine ambulatory care and drug acquisition and variable costs from hospitalizations or urgent visits. All costs were assumed to be in 2022 United States dollars with future costs and QALYs discounted 3% annually. Input parameters are listed in Table 1.

SURVIVAL MODEL. Overall survival was calculated by first creating a reference cohort based on the enalapril arm of the PARADIGM-HF trial.[12] In this cohort, 93% and 57% of patients were on BB and MRA therapy, respectively. Monthly death rates for the reference cohort from age 64 to 80 were calculated

from an actuarial analysis of the trial performed by Claggett et al.[16] In the supplemental material of their analysis,[16] the authors included 1-year all-cause mortality rates for the enalapril arm of the PARADIGM-HF trial (our reference cohort) from age 64 to 80. From age 81 to 94 monthly all-cause mortality rates increased proportionally to the rate of increase in the general U.S. population (Supplemental Figure 3). Supplemental Table 1 shows a comparison of the survival rates produced by the model in comparison with the survival rates reported by Claggett et al.[16]

COSTS. Ambulatory costs for routine office visits, laboratory tests, and other outpatient services were estimated based on the medical expenditure panel survey from 2009 to 2018 among U.S. adults with heart failure and adjusted for inflation to 2022 dollars.[17] Ambulatory costs were assumed to be the same for each cohort in the simulation. Drug prices were assumed to be the federal acquisition cost per the 2022 Federal Supply Schedule.[18] The cost of a heart failure hospitalization (HFH) and non-HFH were the values (after adjustment for inflation) used in a 2021 cost-effectiveness analysis of dapagliflozin in which the authors sourced from data from the Nationwide Inpatient Sample Healthcare Cost and Utilization Project.[10] Urgent visits were defined as an outpatient HF event that requires immediate medical attention that did not result in hospitalization. Average cost of an urgent outpatient visit was based on the inflation-adjusted value used in a 2020 cost-effectiveness analysis of dapagliflozin by Isaza et al.[8]

BENEFIT ASSUMPTIONS. All-cause mortality was assumed to be a function of cardiovascular (CV) death and non-CV death. CV death as a proportion of all-cause death was modeled to be begin at 84% in year 1, consistent with mortality data from the PARADIGM-HF[12] and DAPA-HF[15] trials, and decreased linearly to 50% in year 30, similarly to previous cost-effectiveness analyses.[9,10] Additionally, we assumed that GDMT would only modify the rate of CV death, because no GDMT agent has been shown to decrease non-CV death rates. Monthly death rates for each cohort were estimated by modifying the death rates calculated in the survival model of the reference cohort by the HRs for each therapeutic strategy. The HR for CV death for double therapy was calculated by removing the benefit of MRA therapy, which in EMPHASIS-HF was a 23% relative risk reduction in CV mortality.[14] In the reference cohort, 57% of patients were on MRA therapy. Removing this benefit yielded a HR of 1.15 for the double therapy cohort. The HR for triple therapy was calculated by adding the benefit of MRA therapy to the remaining 43% of patients in the reference cohort, yielding an HR of 0.90. The HR for quadruple therapy assumed a 31% relative risk reduction compared with triple therapy based on analysis by Vaduganathan et al,[13] yielding a HR of 0.62.

The rate of HFH for the reference cohort were based on the monthly rates in the PARADIGM-HF trial.[19] In similar methods to those used to calculate CV death rates, the rates of HFH were calculated for the remaining cohorts. Rates of urgent visits in the reference cohort were taken from a post hoc analysis of the PARADIGM-HF trial by Okumura et al.[20] The HRs for HFH were used to calculate the rates of urgent visits for the remaining cohorts. The HR for non-HFH in the quadruple therapy cohort was calculated by using the HR for sacubitril-valsartan (in PARADIGM-HF)[12] and empagliflozin (in EMPEROR-Reduced)[21] for non-HFH, yielding an HR of 0.8. The HR for empagliflozin was used in this case because DAPA-HF did not report non-HFHs. Because MRA therapy has not been shown to decrease non-HFH, the rates of non-HFH in the reference, double therapy, and triple therapy cohorts were all equal.

For each cohort, health utility was calculated and used to derive QALYs from life-years. Isaza et al[8] previously used an algorithm developed by Kazi et al,[22] which uses the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) scores reported in trials to calculate average health utility for simulated cohorts.[8] The KCCQ-OS from the PARADIGM-HF was used to calculate health utility.[12] Although KCCQ-OS scores were not reported in EMPHASIS-HF, improvements in health status have been noted with MRA therapy.[23] To account for this, 1 KCCQ-OS point was subtracted for the double therapy cohort and 1 point was added for the triple therapy cohort. The KCCQ-OS for the quadruple therapy cohort was calculated by adding the difference between sacubitril-valsartan arm (in PARADIGM-HF)[12] and dapagliflozin (in DAPA-HF)[15] and their respective controls, a total of 3.6 points.

STATISTICAL ANALYSES. The primary outcomes were costs, life-years, QALYs, and ICERs between the quadruple therapy cohort and the double and triple therapy cohorts, respectively. ICER was equal to the incremental lifetime discounted costs divided by the incremental QALYs (discounted). Additionally, 10,000 probabilistic simulations were performed by randomly varying the model inputs across defined distributions. For each model output, 95% CIs were ascertained based on the values from the 2.5 and 97.5 percentiles in the distribution of simulations.

TABLE 2 Base Case Results

	Double Therapy (ACE Inhibitor, BB)	Triple Therapy (ACE Inhibitor, BB, MRA)	Quadruple Therapy (ARN Inhibitor, BB, MRA, SGLT2 Inhibitor)
Undiscounted cost per lifetime (USD)	95,383 (58,481-147,655)	102,328 (60,423-162,751)	217,612 (156,803-293,846)
Discounted cost per lifetime (USD)	79,948 (49,193-123,571)	84,185 (49,911-133,344)	174,497 (126,537-234,521)
QALYs (discounted)	5.45 (5.07-5.83)	6.18 (5.56-6.79)	7.30 (6.53-7.99)
Life-years (undiscounted)	8.12 (7.47-8.78)	9.26 (8.19-10.03)	10.99 (9.64-12.24)
ICER[a] of quadruple therapy (ARN inhibitor, BB, MRA, SGLT2 inhibitor)	$51,081 (26,695-92,002)	$81,000 (37,575-224,997)	–

Values are 95% CI in PSA. [a]ICER = Incremental discounted cost per lifetime ($)/incremental QALYs (discounted).

ACE = angiotensin-converting enzyme; ARN = angiotensin receptor-neprilysin; BB = beta-blocker; ICER = incremental cost-effectiveness ratio; MRA = mineralocorticoid receptor antagonist; QALY = quality-adjust life-year; SGLT2 = sodium glucose cotransporter-2; other abbreviations as in Table 1.

Sensitivity analyses were conducted for specific scenarios and a deterministic sensitivity analysis was performed to analyze the change in ICER at extremes of each input parameter. Additionally, analysis of the individual incremental value of sacubitril-valsartan and dapagliflozin was calculated to compare the present model against previously published cost-effectiveness analyses of the 2 drugs from a U.S. health care perspective. Microsoft Excel (Microsoft Corp.) and R Statistical Software (Foundation for Statistical Computing) were used for model creation and statistical analysis. Complete methodologies including consensus reporting checklists for cost-effectiveness analyses are available in the Supplemental Methods and Supplemental Tables 2-6.[24,25]

RESULTS

The mean survival in the model for patients in the double therapy cohort was 8.12 years. The use of triple therapy added an additional 1.14 years. Treatment with quadruple therapy resulted in 2.87 and 1.73 additional years of life compared with double therapy and triple therapy, respectively (**Table 2**). At 10 years, survival rates were 50.0%, 40.3%, and 33.3% for the quadruple therapy, triple therapy, and double therapy cohorts, respectively (**Figure 1**).

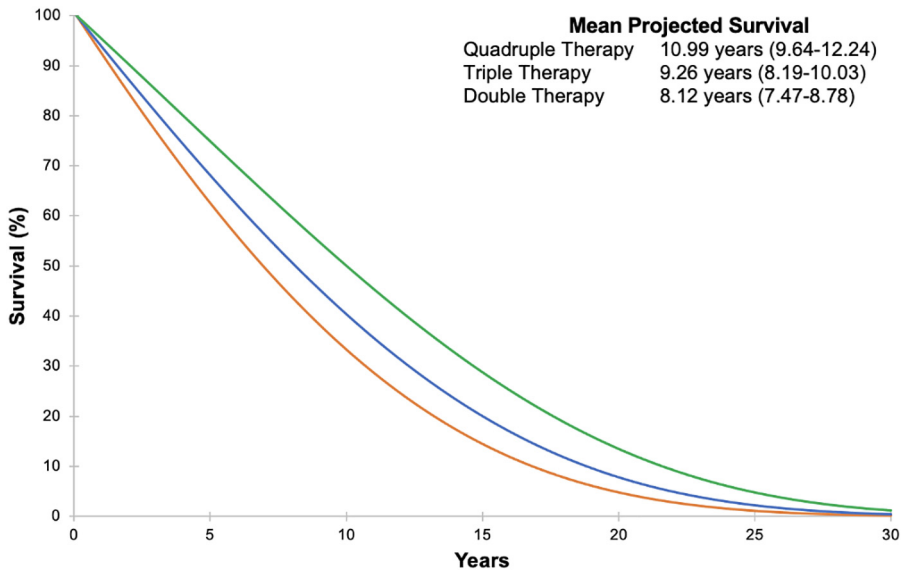
The ICERs of quadruple therapy vs triple therapy and double therapy were $81,000 and $51,081, respectively. Treatment with quadruple therapy increased both QALYs and lifetime cost compared with triple therapy and double therapy (**Table 2**). Costs were increased due to higher drug cost and increased lifespan (**Table 3**). The **Central Illustration** shows the incremental value of comprehensive quadruple therapy (vs triple therapy), compared against the incremental value of sacubitril-valsartan and dapagliflozin individually in the present model and in previously published cost-effectiveness analyses (Supplemental Tables 7 and 8).

PROBABILISTIC SIMULATIONS. In 10,000 probabilistic simulations quadruple therapy had mean ICERs of $81,337 (95% CI: $37,575-$224,997) and $51,131 (95% CI: $26,695-$92,002) compared with triple therapy and double therapy, respectively. In 91.7% and 99.9% of simulations quadruple therapy had an ICER of <$150,000 compared with triple therapy and double therapy, respectively (**Figure 2**). Simulations with ICERs of >$150,000 were associated with less treatment effect of quadruple therapy and thus had minimal incremental benefit in QALYs (Supplemental Figures 4 and 5).

SENSITIVITY ANALYSIS. The cost effectiveness of quadruple therapy was most sensitive to a decrease in the relative risk for CV death. If the relative risk reduction of quadruple therapy compared with triple therapy was decreased from 38% to 17%, the ICERs increase to $203,541 (vs triple therapy) and $70,056 (vs double therapy). If the relative risk reduction of quadruple therapy is increased from 32% to 53%, the ICERs decrease to $59,476 (vs triple therapy) and $43,817 (vs double therapy). If the durability of effectiveness of quadruple therapy was limited to only 5 years after which it was only as effective as triple therapy, the ICERs increased to $169,904 (vs triple therapy) and $70,771 (vs double therapy).

If the cost of dapagliflozin and sacubitril-valsartan was simulated to become generic in 10 years, the ICERs decreased to $61,317 (vs triple therapy) and $39,224 (vs double therapy). The patent for dapagliflozin is set to expire in 2025, in this scenario the ICERs decreases to $54,535 (vs triple therapy) and $35,139 (vs double therapy). Faridi et al[26] reported that the average out-of-pocket cost for quadruple therapy for Medicare recipients; using this cost ($1,128 per year), the ICERs decrease to $11,651

FIGURE 1 Markov Model Survival Curves



Survival for double **(orange)**, triple **(blue)**, and quadruple **(green)** therapy cohorts. Greatest gains in survival are seen with quadruple therapy with 1-year, 5-year, and 10-year survival rates of 95.4%, 74.9%, and 50.0%, respectively.

(vs triple therapy) and $9,308 (vs double therapy). If both dapagliflozin and sacubitril-valsartan were available currently in generic forms and priced similarly to current generic GDMT agents, the ICERs become <$5,000 in both cases. **Figure 3** shows a deterministic analysis in the change in ICER at the 2.5th and 97.5th percentiles of the probabilistic simulations for the input parameters (Supplemental Table 9).

DISCUSSION

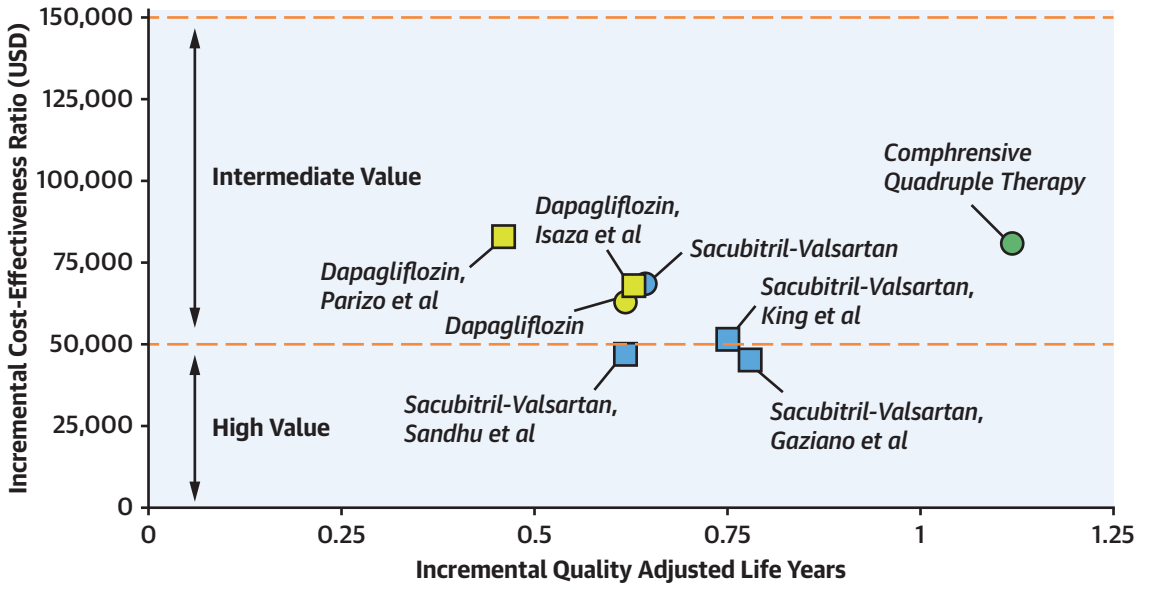
In this cost-effectiveness analysis, a model based on the clinical event reductions demonstrated in the pivotal randomized controlled trials for MRAs, ARN inhibitors, and SGLT2 inhibitors for HFrEF and extrapolated over a lifetime was used to investigate the economic value of quadruple therapy. This evaluation found for a U.S. HFrEF patient population with

TABLE 3 Additional Base Case Results

	Double Therapy (ACE Inhibitor, BB)	Triple Therapy (ACE Inhibitor, BB, MRA)	Quadruple Therapy (ARN Inhibitor, BB, MRA, SGLT2 Inhibitor)
CV deaths[a]	773	713	610
Non-CV deaths	226	283	378
Average age at death	72.1 (71.5-72.8)	73.3 (72.2-74.0)	75.0 (73.6-76.2)
HFH per lifetime	1.22 (0.97-1.49)	0.90 (0.70-1.13)	0.64 (0.45-0.87)
Urgent visits per lifetime	0.49 (0.42-0.56)	0.36 (0.28-0.45)	0.26 (0.18-0.35)
Non-HFH per lifetime	2.61 (2.09-3.20)	2.98 (2.33-3.71)	2.83 (2.22-3.50)
HFH per year	0.15 (0.12-0.18)	0.10 (0.08-0.12)	0.06 (0.04-0.08)
Urgent visits per year	0.06 (0.05-0.07)	0.04 (0.03-0.05)	0.02 (0.02-0.03)
Non-HFH per year	0.32 (0.26-0.39)	0.32 (0.26-0.39)	0.26 (0.21-0.31)
Total hospitalization and urgent visit cost per year	$4,825 ($3,428-$6,535)	$4,099 ($2,835-$5,678)	$3,010 ($2,046-$4,213)
Ambulatory and drug cost per year	$6,050 ($2,732-$13,114)	$6,069 ($2,871-$13,100)	$15,920 ($11,843-$23,283)

Values are n or median (IQR). [a]Proportion of CV:non-CV death not probabilistically simulated
CV = cardiovascular; other abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Comparative Cost-Effectiveness of Novel HFrEF Medical Therapy**



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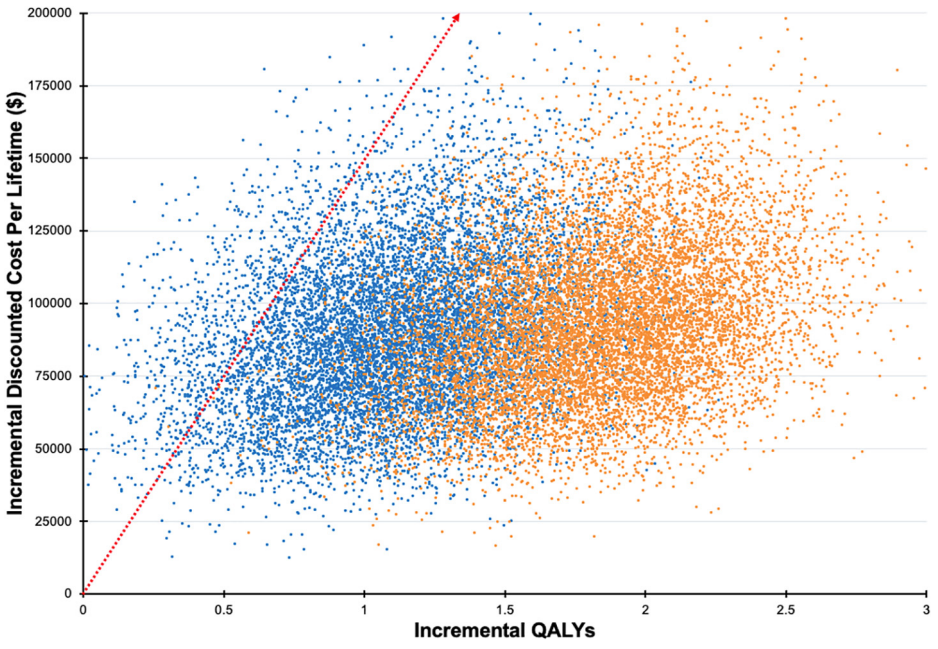
Comparison of incremental cost-effectiveness ratios and incremental quality adjusted life-years in the present analysis **(circles)** with previously published analyses **(squares)** of sacubitril-valsartan, dapagliflozin, and quadruple therapy. The present analysis is the first to compare the cost-effectiveness of a comprehensive quadruple therapy regimen vs triple therapy. The annual cost of drug in each analysis **(from left to right)**: dapagliflozin (Parizo), $5,684; sacubitril-valsartan (Sandhu), $4,563; dapagliflozin, $4,820; dapagliflozin (Isaza), $4,192; sacubitril-valsartan, $5,049; sacubitril-valsartan (King); $4,560; sacubitril-valsartan (Gaziano), $4,500. HFrEF = heart failure with reduced ejection fraction; USD = United States dollar.

similar clinical characteristics to those enrolled in the PARADIGM-HF trial, treatment with quadruple therapy yielded therapy yielded the greatest gains in QALYs and at current pricing, vs triple therapy or double therapy, resulted in ICERs of $81,000 and $51,081, respectively. These ICERs are well below the threshold established by the American College of Cardiology/American Heart Association (<$150,000) threshold for low value.[27] In a probabilistic sensitivity analysis, the likelihood of the ICERs being > the $150,000 threshold set for low value interventions was only 8.3% and 0.1% when compared against triple and double therapy, respectively.[28] This evaluation provides important insights as to the economic implications of quadruple therapy if applied broadly to eligible patients with HFrEF in U.S. clinical practice.

Despite significantly higher medication costs, the incremental decreases in HFHs and CV mortality drives the value of quadruple therapy. ICERs were most sensitive to changes in relative risk reduction of quadruple therapy for CV death and changes in drug pricing. However, only a substantial reduction in the CV relative risk reduction of quadruple therapy would result in ICERs of >$150,000. A scenario in which sacubitril-valsartan and dapagliflozin were available as generic medications today would result in near net cost savings, signifying the importance of making life-saving therapies affordable. However, despite the current high cost of ARN inhibitors and SGLT2 inhibitors relative to generic HFrEF therapy, access for patients is crucial given the immense life-prolonging benefits at ICERs of <$150,000. In the present model, treatment with quadruple therapy resulted in 1.73 and 2.87 additional years of life compared with triple therapy and double therapy, respectively. Given that there are an estimated 3 million patients with HFrEF in the United States, a switch from double therapy to quadruple therapy for just 10% of these patients could potentially add >1 million years of life.[29] Contemporary studies suggest <10% of HFrEF patients are maximally optimized on GDMT.[3]

In the present model, sacubitril-valsartan and dapagliflozin together in a quadruple therapy regimen remained cost-effective compared with

FIGURE 2 Probabilistic Sensitivity Analysis



Probabilistic simulations of incremental costs and benefit of quadruple therapy vs triple therapy **(blue)** and double therapy **(orange)**. **Dotted red line** represents an ICER of $150,000. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

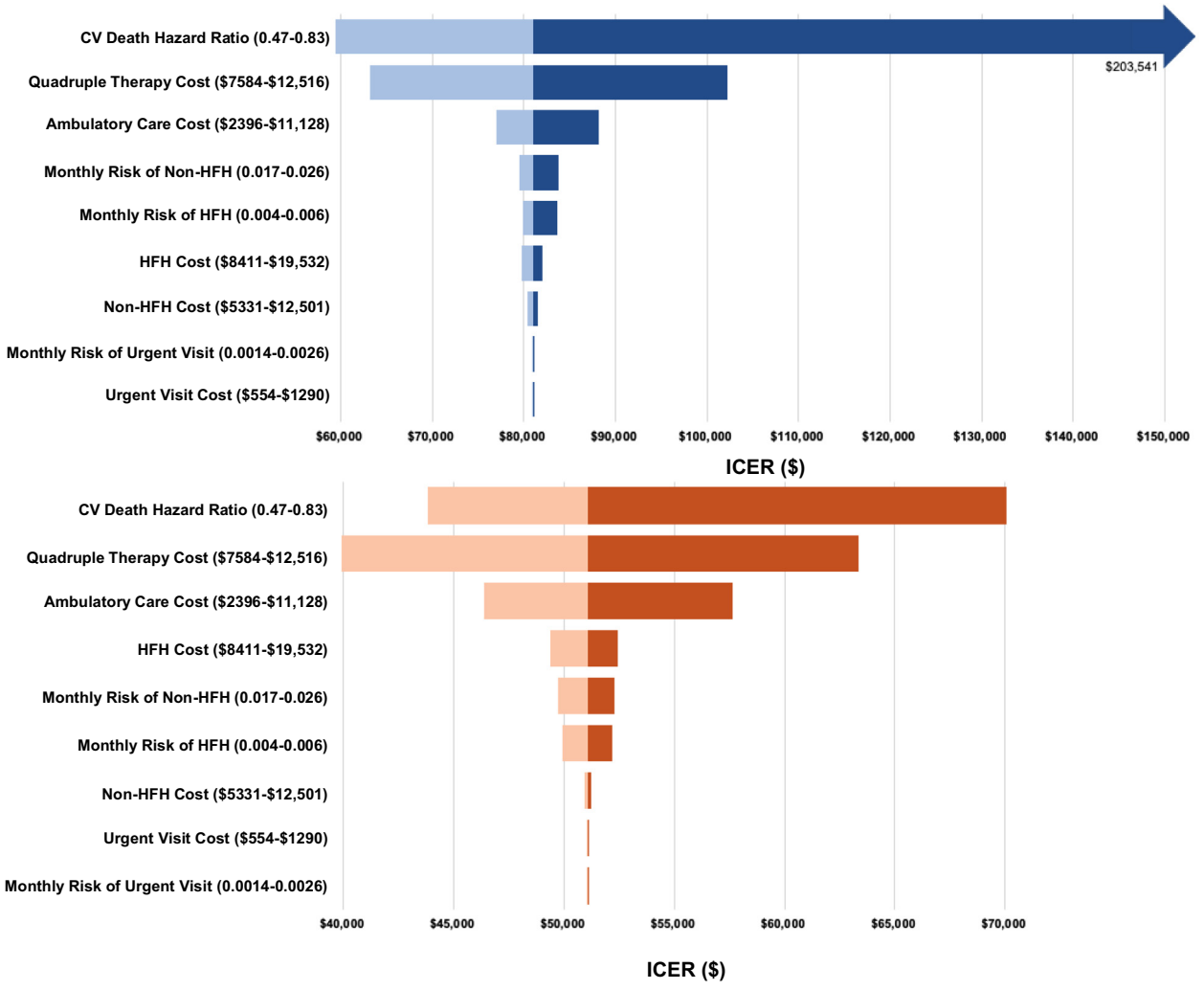
traditional regimens because of proportional increases between lifetime costs and QALYs. When viewed in comparison with other HFrEF treatments, quadruple therapy is comparatively cost effective and notably results in the most substantial gains in QALYs and life-years.[30-35] Additionally, the number of patients eligible for quadruple therapy far exceeds that for other HF therapies, such as ivabradine, cardiac resynchronization therapy, and mitral valve transcatheter edge-to-edge repair, providing an opportunity for substantial societal benefit with widespread adoption of optimal therapy.[5]

The cost-effectiveness of quadruple therapy is of relative high value when compared against therapies for other highly prevalent diseases in the United States, such as atherosclerotic CV disease, type 2 diabetes, and cancer. For example, the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab was shown based on initial pricing to have a ICER of $268,637 in patients with atherosclerotic CV disease.[36] Oral semaglutide, which has shown mortality benefit for patients with type 2 diabetes, was estimated to have an ICER of between $100,000 and $150,000 compared with background type 2 diabetes therapy.[37] Additionally, many new cancer therapeutics have ICERs that exceed $200,000.[38]

Unfortunately, the high cost of drugs in the United States limits patient access to lifesaving therapies for HFrEF and many other chronic diseases.[39] Although this cost effectiveness analysis has demonstrated the economic value of quadruple therapy from a health care system and societal standpoint, individual patients may face restricted access, daunting prior authorization requirements, high out-of-pocket expenses, and financial toxicity. Further, these barriers may exacerbate inequity in HF care and outcomes. When cost-effective medications are available that extend lifespan and improve quality of life, clinicians, payers, and policymakers should make every effort to ensure that prior authorization requirements, limited formularies, and out-of-pocket cost are not barriers for patients to access these medications. In a disease as prevalent as HFrEF, a commitment to affordable drug pricing for life-prolonging therapies found with the quadruple therapy regimen would have enormous societal benefit.

STUDY LIMITATIONS. Our analysis has several limitations. First, the model perspective was United

FIGURE 3 Deterministic Analysis



Deterministic analysis at the 2.5th and 97.5th percentiles of input parameters. ICER of quadruple therapy vs triple therapy **(blue)** and double therapy **(orange)**. CV = cardiovascular; HFH = heart failure hospitalization; other abbreviation as in Figure 2.

States only and each health care system will have different drug pricing, patient populations, and cost-effectiveness thresholds. Second, although we attempted to account for a wide range of cost assumptions in probabilistic sensitivity analysis, cost will vary depending on source data. Third, our survival model was based on an actuarial analysis of the PARADIGM-HF trial[16] because long-term follow-up data are lacking due to the recency of the trial. Fourth, the relative risk reduction used to model the benefit of quadruple therapy were taken from an analysis by Vaduganathan et al,[13] which was based on 3 trials, EMPHASIS-HF, PARADIGM-HF, and DAPA-HF. However, real-world data of sacubitril-valsartan,[40] as well as randomized controlled trials of the SGLT2 inhibitor, empagliflozin,[21,41] support the effect sizes that we modeled. Fifth, our model does not account for the possible discontinuation of ARN inhibitors and SGLT2 inhibitors due to side effects, although in the PARADIGM-HF and DAPA-HF trials drug discontinuation was not more common in the intervention arms compared with the control.[12,15] Notably, to provide a conservative ICER, we also did not model the known decreased incidence of type 2

diabetes and chronic kidney disease seen with SGLT2 inhibitors (compared with placebo)[8], the decreased incidence of hyperkalemia and angioedema seen with ARN inhibitors (compared with ACE inhibitors),[42] the likely decreased use of device therapies because of improved ejection fraction and cardiac remodeling associated with ARN inhibitors and SGLT2 inhibitors,[43,44] the possible decrease in indirect health care costs, and gains in productivity due to increased quality and length of life.

CONCLUSIONS

At current pricing, the use of quadruple therapy with ARN inhibitors, BBs, MRAs, and SGLT2 inhibitors in patients with HFrEF was cost effective compared with triple therapy (ACE inhibitors, BBs, and MRAs) and double therapy (ACE inhibitors and BBs) with ICERs of $81,000 and $51,081, respectively. For patients with HFrEF, the optimization of a drug regimen to include all 4 pillars of GDMT results in substantially increased survival, fewer hospitalizations and urgent visits, and improved quality of life, with high to intermediate economic value. These findings highlight the need for improved access and optimal implementation of comprehensive quadruple therapy in eligible patients with HFrEF.

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Dr Fonarow has consulted for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Eli Lilly, Janssen, Medtronic, Merck, Novartis, and Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with HFrEF, quadruple therapy with ARN inhibitor, BB, MRA, and SGLT2 inhibitor has the potential to increase lifespan 2 to 3 years when used instead of historic double or triple drug regimens.

COMPETENCY IN SYSTEMS-BASED PRACTICE: The ICER of quadruple therapy is representative of high to intermediate economic value when viewed in the context of American College of Cardiology/American Heart Association guidelines for cost effectiveness.

TRANSLATIONAL OUTLOOK 1: Clinicians, payers, and policymakers need to be engaged to help remove barriers to optimal uptake of quadruple therapy.

TRANSLATIONAL OUTLOOK 2: The cost effectiveness of quadruple therapy needs to be established in patients with an ejection fraction of >40%.

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KEY WORDS cost-effectiveness analysis, heart failure with reduced ejection fraction, high-value care, incremental cost effectiveness ratio, guideline-directed medical therapy, Markov model

APPENDIX For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.