PharmacoEconomics (2018) 36:1463–1473
https://doi.org/10.1007/s40273-018-0709-3

ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Patiromer and Spironolactone Therapy in Heart Failure Patients with Hyperkalemia

Mark Bounthavong[1] · Javed Butler[2] · Chantal M. Dolan[3] · Jeffrey D. Dunn[4] · Kathryn A. Fisher[3] · Nina Oestreicher[5,6] · Bertram Pitt[7] · Paul J. Hauptman[8] · David L. Veenstra[1]

Published online: 8 September 2018

Abstract

Background and Objective Certain patients with heart failure (HF) are unable to tolerate spironolactone therapy due to hyperkalemia. Patiromer is a novel agent used to treat hyperkalemia and has been shown to be efficacious, safe, and well-tolerated. The potential clinical outcomes and economic value of using patiromer and spironolactone in patients with HF unable to otherwise tolerate spironolactone due to hyperkalemia are unclear. The objective of this analysis was to model the potential pharmacoeconomic value of using patiromer and spironolactone in patients with a history of hyperkalemia that prevents them from utilizing spironolactone.

Methods We performed a cost-effectiveness analysis of treatment with patiromer, spironolactone, and an angiotensin-converting enzyme inhibitor (ACEI) in patients with New York Heart Association (NYHA) class III–IV HF compared with ACEI alone. A Markov model was constructed to simulate a cohort of 65-year-old patients diagnosed with HF from the payer perspective across the lifetime horizon. Clinical inputs were derived from the RALES and OPAL-HK randomized trials of spironolactone and patiromer, respectively. Utility estimates and costs were derived from the literature and list prices. Outcomes assessed included hospitalization, life expectancy, and quality-adjusted life-years (QALYs), costs, and the incremental cost-effectiveness ratio (ICER). One-way and probability sensitivity analyses were performed to test the robustness of the model findings.

Results Treatment with patiromer–spironolactone–ACEI was projected to increase longevity compared with ACEI alone (5.29 vs. 4.62 life-years gained, respectively), greater QALYs (2.79 vs. 2.60), and costs (US$28,200 vs. US$18,200), giving an ICER of US$52,700 per QALY gained. The ICERs ranged from US$40,000 to US$85,800 per QALY gained in 1-way sensitivity analyses.

Conclusion Our results suggest that the use of spironolactone–patiromer–ACEI may provide clinical benefit and good economic value in patients with NYHA class III–IV HF unable to tolerate spironolactone due to hyperkalemia.

Key Points for Decision Makers

Use of patiromer and spironolactone may be a cost-effective strategy in patients with advanced heart failure unable to tolerate spironolactone due to hyperkalemia.

Although drug costs were higher with this regimen, hospital costs were slightly lower.

The benefits of improved survival and quality of life with the addition of patiromer outweigh the incremental total costs.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40273-018-0709-3) contains supplementary material, which is available to authorized users.

✉ David L. Veenstra
veenstra@uw.edu

Extended author information available on the last page of the article

1 Introduction

Spironolactone, a mineralocorticoid receptor antagonist, was shown in RALES (Randomized Aldactone Evaluation Study) to lead to a 30% absolute reduction in the risk of death in patients with New York Heart Association (NYHA) class III–IV heart failure (HF) with reduced ejection fraction compared with placebo control [1]. However, spironolactone, as well as other renin–angiotensin–aldosterone system (RAAS) inhibitors, have been associated with increased risk of hyperkalemia, limiting their dosing and use [2–6]. Reports of increased hyperkalemia events associated with spironolactone and a RAAS inhibitor combination for HF treatment has increased the gap between real-world practice and clinical guideline recommendations for the use of RAAS inhibitors in patients with HF [2, 3, 5, 7, 8].

Providers and patients must weigh the benefits and risk of using spironolactone and RAAS inhibitors. Due to concerns about hyperkalemia, providers may discontinue or hesitate to initiate spironolactone. However, the introduction of patiromer, a potassium binder with a novel mechanism of action approved for the non-emergent treatment of hyperkalemia, in the USA (2015) [9] and Europe (2017) [10] may help address these limitations by allowing clinicians to better manage potassium levels and continue HF treatment. This could be important for patients who are on spironolactone and develop hyperkalemia or who experience hyperkalemia prior to the initiation of spironolactone.

However, the clinical and economic value of patiromer in combination with spironolactone treatment in patients with HF is unclear. As a result, we performed a cost-effectiveness analysis from the payer perspective to estimate the potential impact of using patiromer and spironolactone in patients with NYHA functional class III–IV HF receiving an angiotensin-converting enzyme inhibitor (ACEI) who are unable to tolerate spironolactone due to hyperkalemia.

2 Methods

We used a decision-analytic approach to model the disease course for HF. A Markov model was constructed to evaluate the cost-effectiveness of a treatment strategy including patiromer, spironolactone, and an ACEI (patiromer–spironolactone–ACEI) versus ACEI only in patients with NYHA III–IV HF and hyperkalemia from the US payer perspective (Fig. 1). The Markov model was composed of three health states: stable HF, hospitalization due to worsening HF (hospitalization), and death. For the simulation, all patients in the cohort began with stable HF and could transition to hospitalization, remain in stable HF, or experience mortality. Patients who experienced hospitalization would transition back to stable HF or death, but could not remain in the hospitalization state. Death was the absorbing state. All model inputs are listed in Table 1.

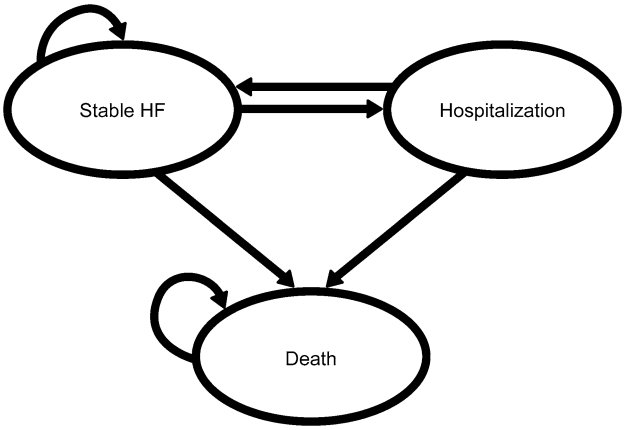

Fig. 1 Markov model for heart failure (HF). The circles represent health states, and each arrow represents a possible transition from one state to another. All simulated patients start in the stable HF state before progressing into (*1*) hospitalization, (*2*) death, or (*3*) remaining in the stable HF state. Patients remain in the hospitalization health state for only 1 month and return to stable HF or progress to death

Simulation was initiated around a hypothetical cohort of 65-year-old patients with HF. The Markov model had a cycle length of 1 month and a lifetime horizon. We assumed that treatment duration would be for 36 months based on the follow-up duration in RALES [1]. Treatment benefit was restricted to treatment duration, after which the cohort had the same risk of death and hospitalization as modeled in the ACEI-only control arm. In addition, we assumed that the ACEI used by the cohort would have a class-wide effect on mortality. This has been reported in several studies [11, 12]. All model assumptions are provided in the Electronic Supplementary Material Appendix.

When possible, we used evidence specific to patients with HF in the USA for model inputs. If there were no available results from prior studies for patients in the USA with HF, we used the best available contemporary source. Clinical parameters were primarily derived from the RALES trial [1], the OPAL-HK (Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors) study (42% of whom had HF) [13], and the Swedish Heart Failure Registry, one of the largest HF registries worldwide [14]. We conducted a literature review of randomized controlled trials (RCTs) of spironolactone in HF. Although we did identify more recent RCTs of spironolactone in HF, RALES is the most recent RCT conducted in chronic severe HF patients. For example, the TOPCAT (Treatment of Preserved Cardiac Function

Table 1 Parameters used in the cost-effectiveness analysis

Parameter	Value	Low range	High range	Distribution	Description	Source
Transition probabilities						
Stable HF to hospitalization for the placebo arm	0.030	0.024	0.036	Beta	Transition probability from stable HF to hospitalization in the placebo arm	Model calibration to RALES (Pitt et al., 1999 [1])
Adjustments						
Treatment effect on overall survival	0.70	0.60	0.82	Log-normal	Cox regression estimate	RALES (Pitt et al., 1999 [1])
Treatment effect on hospitalization due to worsening HF	0.65	0.54	0.77	Log-normal	Cox regression estimate	RALES (Pitt et al., 1999 [1])
Costs						
Cost of patiromer 8.4 g per dose	US$750	US$600	US$900	Normal	Monthly cost for patiromer 8.4 g daily	AnalySource [27]
Cost of spironolactone 50 mg per dose	US$24.47	US$19.57	US$29.36	Normal	The monthly cost for spironolactone 50 mg daily	AnalySource [27]
Hospitalization cost	US$11,322	US$9058	US$13,587	Normal	Adjusted for inflation using the Medical component of the CPI (ICD 9-CM: 428 [CHF NOS])	HCUP [29][a]
Utility						
Utility for stable HF	0.57	0.45	0.68	Beta	Weighted utility of stable HF (NYHA class II–IV)	Yao et al., 2007 [22] and RALES (Pitt et al., 1999 [1])
1-Month disutility associated with hospitalization	− 0.10	− 0.08	− 0.12	Normal	Disutility associated with hospitalization	Yao et al., 2008 [20]
Discount adjustment						
Discount rate for outcomes (QALYs)	0.03	0.00	0.05	Normal	Annual discount rate for QALYs	Neumann et al., 2017 [26]
Discount rate for costs	0.03	0.00	0.05	Normal	Annual discount rate for costs	Neumann et al., 2017 [26]
Discontinuation						
Discontinuation of drug combination	0.50	0.25	0.75	Beta	Proportion that discontinued treatment combination due to intolerance	OPAL-HK (Weir et al., 2015 [13]) + clinical experts
Survival function parameters: $S(t) = exp(\lambda t)^{\gamma}$						
Gamma	0.93				Ancillary parameter in the Weibull distribution	
Lambda	0.03				This is an endogenous variable and not changed	

CHF congestive heart failure, *CPI* Consumer Price Index, *HCUP* Healthcare Cost and Utilization Project, *HF* heart failure, *ICD-9-CM* International Classification of Disease, 9th Revision, Clinical Modification, *NOS* not otherwise specified, *NYHA* New York Heart Association class, *QALY* quality-adjusted life-year, *RALES* Randomized Aldactone Evaluation Study

[a]We used the ICD-9-CM: 428 for CHF (NOS) to estimate the cost associated with hospitalization

Heart Failure with an Aldosterone Antagonist) (2014) and Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) (2013) studies are both more recent than RALES; however, these studies were in patients with chronic HF who had preserved ejection fraction [15, 16]. In addition, the single-blind RCT study conducted by Vizzardi and colleagues (2014) [17] was limited to patients with NYHA class I and II with reduced ejection fraction. Thus, RALES provided the most recent RCT source for spironolactone in severe chronic HF.

We selected the Swedish Heart Failure Registry because it was the most recent and largest of the registries identified in the literature ($n = 13,423$ HF patients with NYHA class II–IV) [14]. Another study by Ahmed [18] in patients from the USA and Canada evaluated the all-cause mortality in patients with chronic HF and found a 4-year

survival of 42% for 2441 chronic HF NYHA class III or IV patients, which was very similar to the Swedish Heart Failure Registry estimate used in our model (approximately 44% at 4 years and 40% at 5 years). We also note that the distribution of class III and IV HF patients in the RALES study was 72 and 27%, respectively, compared with 90 and 10% in the Swedish study.

We modeled life expectancy using RALES and estimated the Kaplan-Meier survival curve using a Weibull distribution to generate the best fit survival plots for the control arm. We used the overall mortality rate in the RALES study instead of the mortality rate of hospitalized patients to simulate the mortality of the population average. Several distributions were modeled including the exponential, log-normal, and log-logistic distributions, but the Weibull distribution was selected based on the Akaike Information Criteria (AIC). The survival curve for the patiromer–spironolactone–ACEI arm was derived by using the treatment effect on overall survival (Cox regression estimate) in the treatment arm of RALES [relative risk (RR) = 0.70]. The survival function for the placebo group was based on the Weibull distribution parameters (λ and γ):

$$S(t) = exp(\lambda t)^{\gamma}$$

where λ and γ denote the parameters from the Weibull distribution and t denotes the month when the Weibull distribution was fitted to the Kaplan–Meier curve.

Further adjustments were made to account for changes in treatment guidelines and advances made in HF treatment since the time the RALES trial was conducted by using mortality data from a recent investigation on NYHA functional class and HF survival [14]. In RALES, the baseline 3-year survival of the placebo arm was approximately 45%. To reflect current treatment practices and align with the more contemporary survival data in NYHA functional class III–IV patients from the Swedish Heart Failure Registry, the model baseline survival was adjusted to 40% survival at 5 years [14]. This adjustment was applied to the control arm, with no change in the treatment effect of spironolactone (which multiplies the hazard of death by 0.70). Indeed, using a lower mortality in the control arm leads to a lower absolute treatment effect for spironolactone.

Transition probabilities from the stable HF state to hospitalization were derived from RALES. The model was calibrated so that the number of hospitalizations within 36 months matched the RALES trial control arm. RR adjustment was made for the patiromer–spironolactone–ACEI arm in order to match the total hospitalizations reported in RALES [RR 0.65; 95% confidence interval (CI) 0.54–0.77]. Of note, there was a difference in the NYHA categories induced by treatment in RALES (33% improved in the placebo arm and 41% improved in the spironolactone arm), and we felt that excluding the treatment effect by NYHA category made for a more conservative analysis.

Not all patients were expected to successfully initiate patiromer and spironolactone for a variety of reasons, including tolerability and ongoing challenges with hyperkalemia; therefore, the estimate we used for treatment initiation success (proportion of patients who were able to remain on spironolactone with use of patiromer) was intended to capture discontinuation of the drug combination, not only patiromer. In the OPAL-HK study, 10% of subjects who received at least one dose of patiromer (24/243) in the initial treatment phase discontinued treatment within 4 weeks. Among subjects who continued onto the separate randomized phase and received patiromer, 18% (10/55) discontinued treatment within 8 weeks [13]. Based on these findings, we used a conservative probability of treatment continuation of 50% with a range of 25–75%. Treatment discontinuation was modeled to occur, on average, 2 months post-initiation. We opted not to use the results of the PEARL-HF (Evaluation of the Efficacy and Safety of RLY5016, a Polymeric Potassium Binder, in a Double-Blind, Placebo-Controlled Study in Patients with Chronic Heart Failure) trial because it did not meet the needs of the current study [19]. The PEARL-HF trial used a patiromer dose higher than the maximum US Food and Drug Administration (FDA)-approved dose, had a relatively small sample size, and the majority of patients did not have a history of drug discontinuation due to hyperkalemia.

We assigned a quality-of-life score (utility) to surviving patients to account for the impact of HF on patients' health-related quality of life. Similar to previous modeling studies, a specific utility score, based on NYHA functional classification, was assigned to both groups independent of treatment assignment [20, 21]. We used a weighted average of utility values derived from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial, a prospective study of cardiac resynchronization therapy in HF (Electronic Supplementary Material Table 1) [22]. The NYHA functional classification-specific utility scores were estimated using data from the EuroQol EQ-5D-3L, a commonly used measure of generic health status which was assessed at baseline and 90 days in the CARE-HF trial [23]. These utility values were selected as the severity of the patient population in the CARE-HF trial was similar to that of the RALES population.

We assumed that a hospitalization would result in a diminished health state. A disutility of − 0.1 was applied to each cycle in which a HF hospitalization occurred [20]. This disutility value, which is the estimated equivalent of moving down one severity level or health state in NYHA functional classification, has been frequently used in the HF economic literature [21, 24, 25]. Quality-adjusted life-years (QALYs) were estimated by calculating the area under the curve of the

treatment and control arms over the lifetime horizon. A 3% annual discount rate was applied to QALYs [26].

We used wholesale acquisition cost (WAC) for drug costs; the monthly cost of spironolactone 50 mg daily was US$24.47 and patiromer 8.4 g daily was US$750 [27]. The cost of spironolactone was determined by selecting the median price available from a number of generic equivalents. Additionally, we used the most recent cost available for patiromer at the time of this evaluation. To determine the impact of patiromer cost on the base-case results, we performed a scenario analysis where we applied a 28% discount to reflect the average industry discount to the WACs for patiromer, which was US$540 for a 30-day supply [28]. The hospitalization cost was derived from the Healthcare Cost and Utilization Project, based on a regularly occurring national survey [29]. We did not model drug costs for the control arm because the cost would be nullified by the same amount in the patiromer–spironolactone–ACEI arm. We also assumed that other costs, such as provider visits and laboratory testing, would be similar across treatment arms. All costs were adjusted for inflation using the medical component of the Consumer Price Index and expressed in 2016 US dollars [30]. A 3% annual discount rate was applied to costs [26].

In the base case, total discounted direct costs and QALYs were estimated for a lifetime horizon. Total direct costs were further categorized as drug- and hospitalization-related costs. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in the total costs by the difference in QALYs gained between the treatment and control arms. A treatment strategy was considered cost-effective if the ICER was less than the willingness-to-pay threshold, defined as US$100,000 per additional QALY gained [26]. According to recent, widely cited technology assessment guidelines, US$100,000–150,000 per QALY gained is considered a reasonable value-based benchmark [31].

One-way sensitivity analyses were conducted to assess the influence of parameter uncertainty on the ICER. A tornado diagram was generated to rank the impact for each parameter from descending order of impact on the ICER.

In a probabilistic sensitivity analysis, we modeled costs and RR using normal and log-normal distributions, respectively (Table 1). Probability and utility parameters were modeled using a beta distribution. Disutility and discount rate were modeled using a normal distribution. Monte-Carlo simulation was performed for 5000 iterations to generate a cost-effectiveness plane scatter diagram, which illustrated the uncertainty around the base-case estimate. Results were presented as point estimates with corresponding 95% credible intervals [32]. In addition, a cost-effectiveness acceptability curve was constructed to denote the probability of the treatment arm being cost-effective relative to the control arm across a range of willingness-to-pay thresholds.

We compared our model results to RALES prior to further adjustments of the baseline risk for the control arm. The parametric model (Weibull) survival curves were compared with the Kaplan-Meier curves reported by RALES using the AIC. In addition, mortality was similar between our model and the RALES data at 24 months for the control group (364 vs. 386 deaths, respectively). The number of hospitalizations in our model at 36 months was similar to that reported in the control arm of RALES (661 and 663, respectively).

We further validated our model by comparing the QALYs and costs with a previous economic model that used the RALES data [33]. At 35 months, Glick and colleagues [33] reported that the difference in QALYs and costs between the spironolactone and control arms were 0.13 QALYs and –US$713. In our simulations based on parameters and assumptions used by Glick and colleagues [33], the differences in QALYs and costs were 0.12 QALYs and –US$726.

We adjusted 5-year survival in the modeled ACEI-only arm to approximate the probability of survival in this more contemporary cohort compared to the RALES study (e.g., the 3-year survival in the RALES control arm was 45% compared with approximately 55% in the Swedish Heart Study, in which the vast majority of patients received a β-blocker). The 5-year survival for NYHA functional class III–IV patients in the Swedish Heart Study ranged from 30 to 49%, depending on clinical characteristics. We empirically adjusted the 5-year survival for the ACEI-only arm in the model to 38% to account for the higher proportion of NYHA functional class IV patients in the RALES population than in the Swedish Heart Study (31% vs. 10%); this estimate was varied in sensitivity analyses.

3 Results

Results of the cost-effectiveness analysis, which includes costs, QALYs, life-years gained, and the ICER over a lifetime horizon, are presented in Table 2. The patiromer–spironolactone–ACEI arm was associated with 0.67 additional life-years gained compared with the ACEI-only arm over a lifetime horizon (5.29 and 4.62 life-years gained, respectively). In addition, the patiromer–spironolactone–ACEI arm was associated with 0.33 greater total expected QALYs gained than the ACEI-only arm (2.93 vs. 2.60 QALYs, respectively).

In the base case, the treatment combination of patiromer–spironolactone–ACEI had greater total expected lifetime costs than the ACEI-only arm (US$28,200 vs. US$18,200, respectively). The majority of the cost difference was due to higher drug costs associated with the patiromer–spironolactone–ACEI arm, (+US$11,300). Over the lifetime horizon, the patiromer–spironolactone–ACEI arm

Table 2 Deterministic results comparing the patiromer–spironolactone–angiotensin-converting enzyme inhibitor arm versus the control arm

Treatment	Total costs (US$)	Life-years gained	QALYs	Drug costs (US$)	Hospitalization costs (US$)
Patiromer–spironolactone–ACEI	28,200	5.29	2.79	11,300	16,900
ACEI-only	18,200	4.62	2.60	0	18,200
Difference	10,000	0.67	0.19	11,300	− 1300
Incremental cost-effectiveness ratio	US$52,700 per QALY gained				

ACEI angiotensin-converting enzyme inhibitor, *QALY* quality-adjusted life-year

was associated with lower total expected hospitalization costs than the ACEI-only arm (US$16,900 vs. US$18,200, respectively), a cost savings of approximately US$1300 per patient. Additionally, at 36 months the number of hospitalizations per patient was 0.56 for the patiromer–spironolactone–ACEI arm and 0.79 for the ACEI-only arm, which were similar to those reported in RALES over 36 months.

Based on these findings, the ICER was estimated to be US$52,700 per QALY, suggesting that the patiromer–spironolactone–ACEI arm was cost-effective compared with the ACEI-only arm using a willingness-to-pay threshold of US$100,000 per QALY.

Since the patiromer cost was based on the WAC list price, we performed a scenario analysis using the average industry standard discount of 28%. Using this industry standard discount, we reported that the total costs for patiromer–spironolactone–ACEI arm and the ACEI-only arm were US$25,100 and US$18,200, respectively. In this scenario analysis, the ICER was estimated to be US$36,300 per QALY gained, further supporting our conclusion that the patiromer–spironolactone–ACEI arm was cost-effective compared with the ACEI-only arm.

In the one-way sensitivity analyses, model results were most influenced by the treatment effect on overall survival in the treatment arm (ICER range: US$40,000–85,800 per QALY gained) (Fig. 2). Other influential parameters (range greater than US$10,000 per QALY gained) included the monthly cost of patiromer, the utility for the stable HF health state, utility for hospitalization, and the discount rate. Overall, the ICERs ranged from US$30,000 to US$85,800 per QALY gained in one-way sensitivity analyses. However, none of these sensitivity analyses influenced the interpretation that the patiromer–spironolactone–ACEI arm was cost-effective compared with the ACEI-only arm because the ICERs remained below the threshold of US$100,000 per additional QALY gained. All of the results from the one-way sensitivity analyses suggest that patiromer–spironolactone–ACEI is considered *high value* (ICER < US$50,000 per QALY gained) or *intermediate value* (ICER ≥ US$50,000 to < US$150,000 per QALY gained) according to the American College of Cardiology/American Heart Association (ACC/AHA) "Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures" [34].

The probabilistic sensitivity analysis yielded a 95% credible interval between US$27,000 and US$95,500 per QALY gained (Electronic Supplementary Material Fig. 1). At the willingness-to-pay threshold of US$100,000 per QALY gained, the patiromer–spironolactone–ACEI arm was cost-effective in 98.8% of the simulations (Fig. 3).

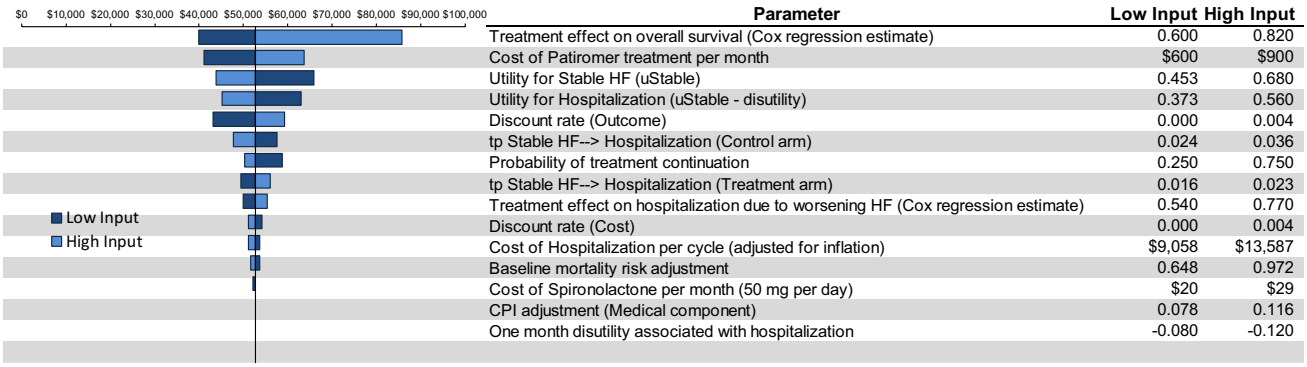

Fig. 2 Tornado diagram of the incremental cost-effectiveness ratios changes between the patiromer–spironolactone–ACEI strategy and ACEI-only strategy. *ACEI* angiotensin-converting enzyme inhibitor, *CPI* consumer price index, *HF* heart failure, *tp* transition probability

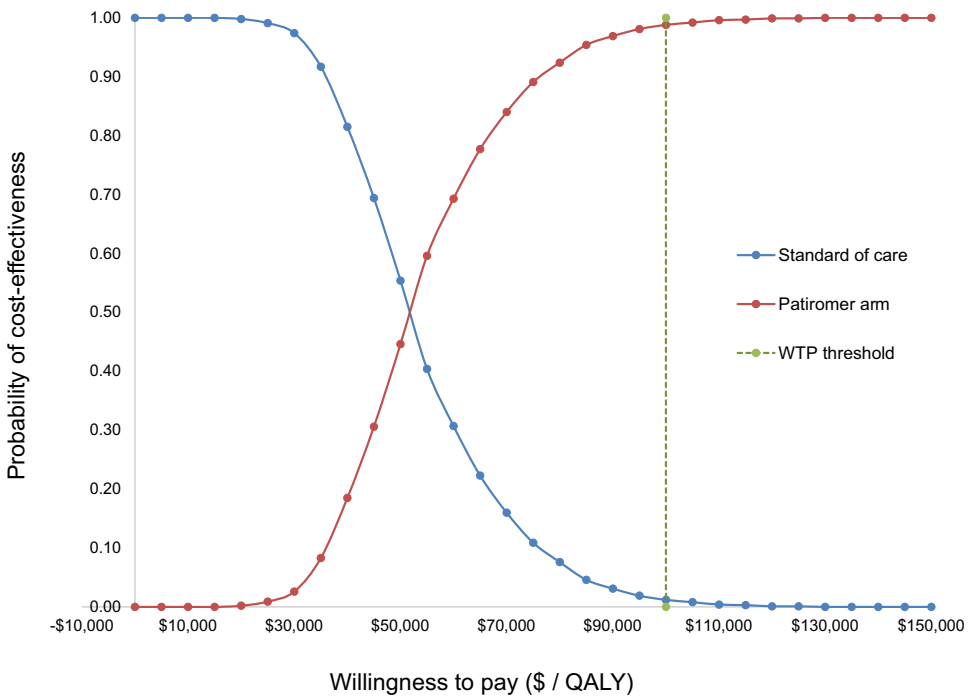

Fig. 3 Cost-effectiveness acceptability curve. The green line represents the willingness-to-pay threshold of US$100,000 per QALY gained. The indifference point between the patiromer–spironolactone–ACEI arm and the ACEI-only arm is the reported incremental cost-effectiveness ratio. *ACEI* angiotensin-converting enzyme inhibitor, *QALY* quality-adjusted life-year, *WTP* willingness to pay

4 Discussion

We modeled the potential clinical and economic impact of using patiromer with spironolactone among patients with NYHA class III–IV HF, a reduced left ventricular ejection fraction, and hyperkalemia estimating that patiromer–spironolactone–ACEI for the treatment of HF was cost-effective compared with ACEI monotherapy. The model yielded improvements in survival and health-related quality of life and reductions in hospitalization, which partially offset the cost of adding patiromer to HF therapy. Using a willingness-to pay-threshold of US$100,000 per additional QALY gained as our threshold, the patiromer–spironolactone–ACEI strategy was cost-effective across all of our sensitivity analyses and considered a *high value* strategy according to the ACC/AHA "Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures" [34]. This has important clinical and economic implications in HF treatment since hyperkalemia has been associated with under-dosing, and even non-prescribing, of RAAS inhibitors including mineralocorticoid receptor antagonists, and an increase in overall medical costs [2, 35, 36].

In RALES, the addition of spironolactone to standard therapy (ACEI, loop diuretic, or digoxin) was associated with a 35% relative reduction in hospitalization due to worsening HF [1]. In addition, patients on spironolactone had a higher probability of survival than those on placebo at 36 months (65% vs. 54%, respectively). In typical clinical practice, these benefits may not be achieved due to adverse effects associated with HF therapy, including hyperkalemia. Combinations using spironolactone and an ACEI have been reported to increase the risk of life-threatening hyperkalemia and renal failure [2–6]. This barrier to dosing has been reported to increase overall medical costs and healthcare resource utilization. A recent study reported that hyperkalemia in patients with HF increased the overall medical costs [36]. Moreover, hyperkalemia has been associated with discontinuation and suboptimal dosing of RAAS inhibitors in patients with HF [2]. Patiromer may provide clinicians with an additional tool to help overcome challenges associated with hyperkalemia management in patients who require RAAS inhibitor therapy, especially mineralocorticoid receptor antagonists.

The cost savings associated with reduced hospitalization was small over the lifetime horizon. The most likely reason for the similar number of hospitalizations between the two groups is due to the improvement in survival. As more patients are alive in the simulation, the opportunities for hospitalization increase, thereby resulting in an increase in hospitalization for both groups. Future studies will need to validate the mortality and hospitalization results found in this analysis.

Currently, no other known study has investigated the cost-effectiveness of the addition of a potassium binder to a spironolactone–ACEI treatment regimen. Glick and colleagues [33] reported that the reduction in hospitalization and improvement in survival contributed to the cost-effectiveness of the addition of spironolactone to standard therapy. Unlike our study, which used a lifetime horizon,

Glick and colleagues [33] limited their cost-effectiveness evaluation of spironolactone to 35 months. Spironolactone treatment was associated with an increase in 0.13 QALYs and a cost savings of US$713 compared with a treatment strategy without spironolactone. We compared our findings at 35 months with those of Glick and colleagues [33] as part of our model validation process, and observed similarities in the incremental costs and QALYs gained. This provided validation of our model's ability to simulate the disease, which was further adjusted to reflect current improvements in therapy and updates to treatment guidelines.

Our study had several limitations. First, our results were driven by data from RALES, which was conducted from 1995 to 1998 [1]. Treatment practices have changed since then, particularly in relation to increased use of β-blockers. To account for changes in survival for patients with HF since the RALES trial was conducted, we adjusted the mortality risk in the ACEI-only arm of the model using the Swedish Heart Failure Registry [14]. Despite these adjustments, the treatment effect of spironolactone in our model may still vary from that of contemporary clinical practice. However, when we varied the effectiveness of spironolactone over the 95% CI from RALES (0.60–0.82) in the one-way sensitivity analysis, the intervention remained cost-effective. For example, we tested extreme values for the RR of death associated with spironolactone and found that this would have to be as high as 0.86 for the intervention to exceed US$100,000 per QALY gained.

Second, while we do not have evidence on the long-term survival with the use of patiromer in combination with spironolactone in patients with NYHA class III–IV HF and reduced left ventricular ejection fraction (HFrEF), it is known that a relatively high percentage of patients initiating spironolactone for HF discontinue it within the first year, thereby removing its proven benefit on survival in this population [15]. Based on the results of this economic model, the combination of patiromer and spironolactone in these patients may allow a greater percentage of patients to maintain spironolactone over the long-term, with a potential reduction in cardiovascular mortality, hospitalizations for HF, and healthcare costs.

HF treatment is further complicated by chronic kidney disease (CKD), which can provoke hyperkalemia in patients taking a RAAS inhibitor, including mineralocorticoid receptor antagonists [35]. Our model did not explicitly take CKD into account, which limits the generalizability of our findings. Instead, the RALES population, upon which the primary measure of treatment benefit in the model was derived, were primarily patients with NYHA class III–IV with left ventricular ejection fraction no more than 35% and with serum creatinine less than 2.5 mg/dL. Future cost-effectiveness analyses will need to address the value of patiromer in the CKD population and its impact on overall clinical and economic consequences.

Not all patients will successfully continue treatment due to tolerability to patiromer, hyperkalemia challenges, and other factors. We used a conservative probability for treatment discontinuation (50%), which was higher than those reported in the OPAL-HK study (probabilities for discontinuation during the initial and randomized treatment phases of 10 and 18%, respectively) [13]. The ICER range for the one-way sensitivity analysis of treatment continuation was between US$40,600 and US$85,800 per QALY gained, which was still cost-effective using a threshold of US$100,000 per QALY gained. Despite using a broad range of estimates, the findings of the analysis were not fundamentally changed. Of note, sacubitril/valsartan was approved for treatment of HF [37]. Valuation of the clinical and economic effects of using patiromer in conjunction with sacubitril/valsartan is beyond the scope of this analysis and should be addressed in future studies.

While the Second Panel on Cost-Effectiveness in Health recommends including unrelated costs of the disease (e.g., HF), there are a plethora of communications either espousing or criticizing the inclusion of future unrelated healthcare costs and opportunity costs in cost-effectiveness analysis [38, 39]. We opted to not include unrelated healthcare costs because of the pragmatic problem of comparison to the vast majority of economic evaluations to date that do not include unrelated costs. However, if standard methods for estimated unrelated costs become available, we would revisit this analysis in the future.

While we have not specified whether the perspective of our analysis is a public or private US payer, we note that we have used the WAC to estimate the opportunity cost of patiromer. More recently, with availability of estimates of drug discount provided in the private and public sectors, analyses such as those conducted by ICER have used net prices. While we believe the use of net prices is appropriate, for consistency with previous analyses that commonly use WAC drug prices, and to be conservative, we used WAC for this analysis. However, we performed a scenario analysis using a 28% discounted price for patiromer to reflect the net price and reported that the ICER was US$36,300 per QALY gained, which was lower than the base-case ICER of US$52,700 per QALY gained. Lastly, we did not assess budget impact, which will depend on the number of patients with severe chronic HF and hyperkalemia within plans that might require patiromer and spironolactone use.

5 Conclusion

We performed a cost-effectiveness analysis to evaluate the potential outcomes of using patiromer and spironolactone in patients with HF unable to tolerate spironolactone due

to hyperkalemia. Findings from our economic model suggest that the addition of spironolactone and patiromer in NYHA class III–IV patients with HFrEF and hyperkalemia may be cost-effective from the US payer perspective when compared with ACEI-only treatment. Although drug costs were higher, hospital costs were lower and the benefits of improved survival and increased QALYs outweigh the incremental total costs. These findings were robust to sensitivity analyses and suggest that the use of patiromer in patients with advanced symptomatic HF unable to tolerate spironolactone due to hyperkalemia should be considered.

Acknowledgements Editorial support was provided by Impact Communication Partners, Inc.

Compliance with Ethical Standards

Conflict of Interest Mark Bounthavong and David L. Veenstra report consulting relationships with Relypsa, Inc., a Vifor Pharma Group Company. Javed Butler reports consultancy/advisory board fees from Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, Inc., a Vifor Pharma Group Company, Stealth Peptide, SC Pharma, Vifor, and ZS Pharma; other research support and research grants from European Union and the National Institutes of Health; and speaker/honoraria from Novartis and Janssen. Chantal M. Dolan and Kathryn A. Fisher are employees of CMD Consulting, and report consulting relationships with Genentech Inc., Gilead Sciences, Halozyme Therapeutics, Iconic Therapeutics, Semnur Pharmaceuticals and Relypsa, Inc., a Vifor Pharma Group Company. Jeffrey A. Dunn reports consultancy/advisory board fees from Relypsa, Inc., a Vifor Pharma Group Company. Nina Oestreicher reports previous employment by Relypsa, Inc., a Vifor Pharma Group Company at the time of the study. Bertram Pitt reports serving as a consultant to Sanofi, Relypsa, Merck, Bayer, AstraZeneca, scPharmaceuticals, Tricida, KBP Biosciences, Stealth Peptides, Sarfez, and AuraSense; stock options in scPharmaceuticals, Tricida, KBP Biosciences, Sarfez, and AuraSense; serving on data safety monitoring committees for and receiving personal fees from Johnson & Johnson; and, in addition, he has a pending patent EFS ID 14916043, application number licensed to the University of Michigan School of Medicine. Paul J. Hauptman reports consultant/advisory board fees, research grants, and speaker/honoraria from Relypsa, Inc., a Vifor Pharma Group Company.

Funding Funded by Relypsa, Inc., a Vifor Pharma Group Company.

Author Contributions The following describes the contributions each author made to this work: conception and design—all authors; data collection and analysis—MB and KAF; manuscript drafting—MB; revisions and approval of final manuscript—all authors.

Data Availability Statement All data analyzed or generated during this study are included in this published article (and its online supplementary information files). Any additional information about assumptions or analytic techniques in the current study are available from the corresponding author on reasonable request.

References

1. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709–17.
2. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2015;21:S212–20.
3. Schepkens H, Vanholder R, Billiouw J-M, Lameire N. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. Am J Med. 2001;110:438–41.
4. Abbas S, Ihle P, Harder S, Schubert I. Risk of hyperkalemia and combined use of spironolactone and long-term ACE inhibitor/angiotensin receptor blocker therapy in heart failure using real-life data: a population- and insurance-based cohort. Pharmacoepidemiol Drug Saf. 2015;24:406–13.
5. Saito M, Takada M, Hirooka K, Isobe F, Yasumura Y. Serum concentration of potassium in chronic heart failure patients administered spironolactone plus furosemide and either enalapril maleate, losartan potassium or candesartan cilexetil. J Clin Pharm Ther. 2005;30:603–10.
6. Saito M, Nakayama D, Takada M, Hirooka K, Yasumura Y. Carvedilol accelerate elevation of serum potassium in chronic heart failure patients administered spironolactone plus furosemide and either enalapril maleate or candesartan cilexetil. J Clin Pharm Ther. 2006;31:535–40.
7. Bozkurt B, Agoston I, Knowlton AA. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. J Am Coll Cardiol. 2003;41:211–4.
8. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351:543–51.
9. U.S. Food & Drug Administration. Veltassa (patiromer) powder for oral suspension. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205739Orig1s000TOC.cfm. Accessed 7 Aug 2018.
10. European Medicines Agency. Veltassa (patiromer). http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004180/human_med_002141.jsp&mid=WC0b01ac058001d124. Accessed 7 Aug 2018.
11. Cheng J, Zhang W, Zhang X, Han F, Li X, He X, Li Q, Chen J. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. JAMA Intern Med. 2014;174:773–85.
12. van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad J-J, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients. Eur Heart J. 2012;33:2088–97.
13. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372:211–21.

14. Braunschweig F, Linde C, Benson L, Ståhlberg M, Dahlström U, Lund LH. New York Heart Association functional class, QRS duration, and survival in heart failure with reduced ejection fraction: implications for cardiac resynchronization therapy. Eur J Heart Fail. 2017;19:366–76.
15. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–92.
16. Edelmann F, Wahter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Aldo-DHF Investigators, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA. 2013;309:781–91.
17. Vizzardi E, Nodari S, Caretta G, D'Aloia A, Pezzali N, Faden G, et al. Effects of spironolactone on long-term mortality and morbidity in patients with heart failure and mild or no symptoms. Am J Med Sci. 2014;347:271–6.
18. Ahmed A. A propensity-matched study of New York Heart Association class and natural history end points in chronic heart failure. Am J Cardiol. 2007;99:549–53.
19. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang I-Z. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011;32:820–8.
20. Yao G, Freemantle N, Flather M, Tharmanathan P, Coats A, Poole-Wilson PA, SENIORS Investigators. Long-term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure: an individual patient-based simulation model. Pharmacoeconomics. 2008;26:879–89.
21. King JB, Shah RU, Bress AP, Nelson RE, Bellows BK. Cost-effectiveness of sacubitril-valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. JACC Heart Fail. 2016;4:392–402.
22. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert J-C, Cleland JGF. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter–defibrillator. Eur Heart J. 2007;28:42–51.
23. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37:53–72.
24. Pandor A, Thokala P, Gomersall T, Baalbaki H, Stevens JW, Wang J, et al. Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation. Health Technol Assess. 2013;17:1–207 **(v–vi)**.
25. Ford E, Adams J, Graves N. Development of an economic model to assess the cost-effectiveness of hawthorn extract as an adjunct treatment for heart failure in Australia. BMJ Open. 2012;2:e001094. https://doi.org/10.1136/bmjopen-2012-001094.
26. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-effectiveness in health and medicine. 2nd ed. New York: Oxford University Press; 2016.
27. AnalySource®. AnalySource®—suite of drug pricing services. https://www.analysource.com/. Accessed 9 Dec 2017.
28. Aitken M, Kleinrock M. Medicine use and spending in the U.S.: a review of 2017 and outlook to 2022. IQVIA Institute for Human Data Science (formerly the IMS Institute); 2018. https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022. Accessed 27 Aug 2018.
29. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). 2014. http://www.ahrq.gov/research/data/hcup/index.html. Accessed 11 Apr 2017.
30. United States Department of Labor. Consumer Price Index (CPI). Bureau of Labor Statistics. https://www.bls.gov/cpi/. Accessed 11 Dec 2016.
31. Institute for Clinical and Economic Review. Overview of the ICER value assessment framework and update for 2017–2019. 2017.
32. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. 1st ed. New York: Oxford University Press, USA; 2006.
33. Glick HA, Orzol SM, Tooley JF, Remme WJ, Sasayama S, Pitt B. Economic evaluation of the randomized aldactone evaluation study (RALES): treatment of patients with severe heart failure. Cardiovasc Drugs Ther. 2002;16:53–9.
34. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2304–22.
35. Shirazian S, Grant CD, Mujeeb S, Sharif S, Kumari P, Bhagat M, et al. Underprescription of renin-angiotensin system blockers in moderate to severe chronic kidney disease. Am J Med Sci. 2015;349:510–5.
36. Polson M, Lord TC, Kangethe A, Speicher L, Farnum C, Brenner M, et al. Clinical and economic impact of hyperkalemia in patients with chronic kidney disease and heart failure. J Manag Care Spec Pharm. 2017;23:S2–9.
37. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, PARADIGM-HF Investigators and Committees, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
38. van Baal P, Morton A, Brouwer W, Meltzer D, Davis S. Should cost effectiveness analyses for NICE always consider future unrelated medical costs? BMJ. 2017;359:j5096.
39. Nyman J. Cost recommendations in the second edition of cost-effectiveness in health and medicine: a review. MDM P&P. 2018;3:1–6.

Affiliations

Mark Bounthavong[1] · Javed Butler[2] · Chantal M. Dolan[3] · Jeffrey D. Dunn[4] · Kathryn A. Fisher[3] · Nina Oestreicher[5,6] · Bertram Pitt[7] · Paul J. Hauptman[8] · David L. Veenstra[1]

1 Department of Pharmacy, University of Washington, 1959 NE Pacific St, HSB H375-P, Box 357630, Seattle, WA 98195-7630, USA

2 Division of Cardiology, Stony Brook University, Stony Brook, NY, USA

3 CMD Consulting, Sandy, UT, USA

4 Magellan Rx, Salt Lake City, UT, USA

5 Epidemiology, HEOR and Observational Research, Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA, USA

6 Department of Clinical Pharmacy, University of California, San Francisco, CA, USA

7 University of Michigan School of Medicine, Ann Arbor, MI, USA

8 Division of Cardiology, Department of Medicine, Saint Louis University School of Medicine, Saint Louis, MI, USA