Cost-Effectiveness Analysis of Sacubitril/Valsartan for Reducing the Use of Implantable Cardioverter-Defibrillator (ICD) and the Risk of Death in ICD-Eligible Heart Failure Patients with Reduced Ejection Fraction

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Abstract: Although previous cost–effectiveness evaluations of sacubitril/valsartan have demonstrated cardiovascular and economic benefits in heart failure patients with reduced ejection fraction (HFrEF), whether sacubitril/valsartan is cost-effective for reducing the need for implantable cardioverter-defibrillator (ICD) implantation and the risk of death in ICD–eligible patients has not been investigated in patients with HFrEF. Herein, we evaluated the cost-effectiveness of sacubitril/valsartan versus standard of care in reducing the need for ICD implantation and the death rate in HFrEF. A Markov model was developed from the Qatari hospital perspective, comprised of 'survival' and 'death' health states, and was based on 1-monthly Markovian cycles, a 20-years follow-up

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horizon, and a 3% discount rate. The model inputs were obtained from the literature and local sources. Sacubitril/valsartan resulted in a relative increase of 0.04 quality-adjusted life year (QALY) and 0.67 years of life lived (YLL)/person, with an incremental cost increase of QAR13,952 (USD3,832). Sacubitril/valsartan was associated with incremental cost effectiveness ratio of QAR341,113 (USD93,687)/QALYs gained and QAR24,431 (USD6,710)/YLL. Sensitivity analyses confirmed robustness, with the cost-effectiveness maintained in ≥96.5% of simulated cases. To conclude, sacubitril/valsartan is a cost-effective alternative to standard care against QALY gained and YLL in reducing the need for an ICD therapy and the rate of death among ICD-eligible HFrEF patients. (Curr Probl Cardiol 2022;47:101385.)

Introduction

The prevalence of heart failure is rapidly on the rise,[1] especially in the aging population. Approximately half of the heart failure patients have reduced ejection fraction (HFrEF).[2] The natural trajectory of the disease can be modified by the well-established pharmacological treatment, device therapy, and related care strategies.[1] The classic pillars of HFrEF treatment that have been shown to improve symptoms, lower heart failure hospitalization, and reduce mortality include angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA). Recently, sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has also been endorsed, as class I recommendation, by the international guidelines for the treatment of HFrEF [1,2] based on the results of the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. Sacubitril/valsartan significantly reduced the risk of cardiovascular mortality and hospitalization for heart failure when compared with enalapril.[3]

In addition to medical therapy, the role of implantable cardiac devices has been established for the treatment of patients with HFrEF.[2,4] Sudden cardiac death (SCD) is a leading cause of mortality among patients with heart failure,[5] mostly due to arrhythmias such as asystole, bradycardia, or ventricular tachycardia.[2] Implantable cardioverter defibrillators (ICD)

implantation is recommended for the primary prevention of SCD in HFrEF patients with an ejection fraction of 35% or less after at least three months of guideline-directed medical therapy.[2,4] ICD therapy is generally believed to reduce overall mortality.[5–8] A report by the National Institute for Health and Care Excellence on the effects and costs of prophylactic ICD therapy, however, concluded that the extent of its benefit is insufficient to make the device cost-effective.[9] Here, an analysis[10] of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril-Valsartan Therapy for Heart Failure (PROVE-HF)[11] trial examined the ICD eligibility after the initiation of sacubitril-valsartan for those without ICD. Irrespective of the good background medical therapy, there were improvements in the ejection fraction and beneficial ventricular remodeling that disqualified the patients from the prophylactic ICD eligibility.[10] Similarly, in the recent SAVE-ICD trial, Sacubitril/valsartan improved ejection fraction due to the reverse left ventricular remodeling after six months of therapy. Consequently, ICD implantation was prevented in approximately one out of four patients.[12] Although early initiation of ARNI therapy is currently encouraged, the uptake of therapy is modest due to cost.[13] The evaluation of health economic aspects of a drug is important,[14] to allow decision-making by stakeholders and policymakers given the increasingly limited budgets in healthcare.[15] Although previous studies of the cost-effectiveness of sacubitril/valsartan have revealed cardiovascular and economic benefits in patients with HFrEF,[15–21] whether sacubitril/valsartan reduces death and the need for ICD implantation with reasonable value in ICD patients has never been thoroughly evaluated in patients with HFrEF. Therefore, the aim of this study was to assess the cost-effectiveness of sacubitril/valsartan in reducing death and the need for ICD implantation in patients with HFrEF (i.e., ejection fraction $\leq$40%) due to the improvement in ejection fraction compared with standard care, i.e. enalapril. To the best of our knowledge, this study is the first in the literature that provides new insights into the economic worthiness of sacubitril/valsartan in reducing the need for ICD and the overall risk of death events among patients with HFrEF via improving the ejection fraction.

Materials and Methods

Model structure

A decision-analytic Markov model (Supplementary Material Figure S1) was constructed to compare the incremental effects and costs of

sacubitril/valsartan versus enalapril in improving ejection fraction (i.e., from ≤35% to >35%) and, hence, reducing death and the need for an ICD in a hypothetical cohort population of 1,000 people with HFrEF (i.e., ejection fraction ≤40%). The model comprised two health states: 'survival' and 'death'. The cycle length was 1-month, and a 20-year (i.e. lifetime horizon) follow-up was considered for this analysis.

The main model outcomes included the deaths and survival, total quality-adjusted life year (QALY) gained, total years of life lived (YLL), total costs, and the incremental cost-effectiveness ratios (ICERs) for QALY gained and YLL. A willingness-to-pay (WTP) threshold of 150,000 United States Dollars (USD) (547,500 QAR, Qatari Riyal) per additional QALY gained and YLL was used as a reference threshold for cost-effectiveness.[22–26] All future effects and costs were discounted at an annual rate of 3%, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.[27]

Setting and perspective

The present study was conducted from the perspective of Hamad Medical Corporation (HMC), the leading secondary and tertiary healthcare provider in Qatar, which is publicly financed by the Qatari national government.[28] Inputs of the study model are literature and publicly available, and no ethical approvals were required for the study.

Model population

The model simulated a hypothetical population of 1,000 individuals based on the characteristics of those in the PARADIGM-HF [3] and PROVE-HF[11] trials, where patients with a mean age of 65 years, New York Heart Association (NYHA) functional classes II, III, or IV, and an ejection fraction of ≤40% at 12-month follow-up, were included.

All-cause age-specific death rates for the Qatari population were used to adjust for the increase in the transition probabilities for deaths from Cycle 2 onwards.[29] The results of the extrapolation of all-cause data are presented in Supplementary Material Figure S2.

Clinical model inputs

Survival and death event probabilities were obtained from the PARADIGM-HF [3] trial, which is a double-blind trial that evaluated the cardiovascular morbidity and mortality between sacubitril/valsartan and

enalapril in a total of 8,442 patients with HFrEF, and from an evaluation of the PROVE-HF trial, by Felker et al,[10] which is an open-label, single-arm study that included 794 patients with HFrEF ≤40% who received sacubitril/valsartan over 12 months period.

The all-cause death rate with enalapril was obtained from the PARADIGM trial. For the all-cause death rate with sacubitril/valsartan, where, unlike with enalapril, the ejection fraction is anticipated to increase with sacubitril/valsartan, the all-cause death rate with sacubitril/valsartan was calculated based on that reported in the PARADIGM trial (17%), reduced as per the relative decrease in all-cause death reported with the increase in the ejection fraction from ≤35% to >35% with the sacubitril/valsartan in the Felker et al. study, i.e 47%.[10] The number of patients with ≤35% versus >35% ejection fractions, reported in the PARADIGM-HF trial, was revised based on the increase in ejection fraction from ≤35% to >35% in 62% of patients as a consequence of sacubitril/valsartan after 12 months, as reported by Felker et al.[10] Based on this revised number of patients with ≤35% versus >35% ejection fractions, the probability of death with each of ≤35% and >35% ejection fractions, also as reported by Felker et al. was used to calculate the overall all-cause death rate with sacubitril/valsartan. The Briggs et al. formula method [r = -(1/12)*ln (1-R)], [30] where r is the 1-month rate and R is the 12-month rate, followed by the ($tp = 1 - e^{-r}$) equation, was used to calculate the 1-month transition probabilities.

For the QALY gained calculation (life years x health state utility), utilities were based on the Euro-QoL-5 Dimensions, 5 Levels (EQ-5D-5L) scores, obtained from the Gaziano et al.[16] literature study. The utilities for patients with HFrEF on sacubitril/valsartan and enalapril were 0.84 and 0.83, respectively.

The health state transition probability and utility model inputs can be seen in Table 1.

Resource utilization and costs

Given the study perspective, only direct medical costs were included in the analysis. The costs of sacubitril/valsartan (49/51 mg twice daily) and enalapril (10 mg twice daily) were calculated as per extracted unit costs from the pharmacy department at HMC. The ICD cost, and the overall direct health resource utilization costs per heart failure event per patient, regardless of survival or death outcomes, and excluding the medication costs, were each based on the Finance and Costing Department of HMC. The cost of a non-ICD patient was the cost of overall direct health resource utilization per heart failure patient, added to the medication

Table 1. Model inputs for the base-case analysis

Parameter	Value at baseline	Reference
Transition probabilities		
Sacubitril-valsartan		
Death	0.0115	Felker et al.[10]
Survival	0.1558	Felker et al.[10]
SoC		
Death	0.0081	PARADIGM trial[3]
Survival	0.0579	PARADIGM trial[3]
Utility		
Patients with heart failure on sacubitril-valsartan	0.84	Gaziano et al.[20]
Patients with heart failure on enalapril	0.83	Gaziano et al.[20]
Costs, QAR (USD)		
Sacubitril-valsartan per patient per 1-month	700 (192)	HMC
Enalapril per patient per 1-month	119 (33)	HMC
Event (survival/death) per patient	26,137 (7,179)	HMC
ICD per patient	4,571 (1,256)	HMC
Total cost in an ICD patient	31,408 (8,626)	30,827 (8,467)
Total cost in an non-ICD patient	26,837 (7,371)	26,256 (7,211)
Total cost per patient, including the proportional use of ICD	27,518 (7,558)	26,928 (7,396)

HMC: Hamad Medical Corporation, ICD: implantable cardioverter-defibrillators, QAR: Qatari Riyal, SoC: standard of care, USD: United States Dollar.

cost. The cost of ICD patient was the cost of non-ICD patient, added to the ICD cost. Based on the proportional ICD use among patients, as per the PARADIGM trial, overall cost per patient, including ICD and non-ICD use, was calculated. The use of the ICD device in the enalapril group is based on that reported in the PARADIGM trial. The use of the ICD device in the sacubitril/valsartan group was based on that reported in the PARADIGM trial, reduced by 62%, which is the probability of patients whose ejection fraction increased to >35% with sacubitril/valsartan, in which the ICD use was prevented, as reported by Felker et al.[10] All costs were adjusted to 2022 values using the Qatari Health Price Index,[31] and were presented in Qatari Riyal (QAR) and USD.

Table 1 presents the model inputs for the base-case analysis, including the cost inputs. All patients in this model were assumed to receive the same additional therapies and monitoring parameters and, therefore, the cost of these was not included in the model.

Sensitivity analyses

Univariate, multivariate, and scenario sensitivity analyses were conducted to investigate the robustness of the model inputs' uncertainty

and to increase the generalizability of findings. A univariate sensitivity analysis was conducted to assess the impact of assigning an uncertainty range of ±15% to the cost of event (survival/death), cost of sacubitril/valsartan, and cost of ICD, and an uncertainty range of ±40% to the cost of enalapril, using a triangular type of sampling distribution. Multivariate analysis, which allowed all model inputs to be simultaneously varied, simulating real-life uncertainty, was performed with a trigen sampling distribution for the transition probabilities, using 95% confidence interval (CI) estimates. For the health utility values, a beta distribution was used, and for the cost values, a gamma type of distribution was used.

The univariate and multivariate analyses were based on 1,000 iterations via Monte Carlo simulation using @Risk-7.6® (Palisade Corporation, NY, US). The results of the univariate and multivariate analyses were presented graphically as cost-effectiveness planes (CEPs) and cost-effectiveness acceptability curves (CEACs).

Several scenario analyses were performed by (i) changing the discount rate, (ii) removing the age-related trends for all the events, (iii) reducing the model time frame to 5-years, 10-years, or 15-years, (iv) considering 3-month Markovian cycles, and (v) considering costs of cardiac resynchronization therapy in 28.5% of patients receiving sacubitril/valsartan as reported in the PROVE-HF trial.

Results

Base-Case Analysis

Among HFrEF patients receiving sacubitril/valsartan therapy, and as a consequence of increased ejection fraction from ≤35% to >35%, death rate was 13%, compared to 19.8% with enalapril. Sacubitril/valsartan was associated with an additional total healthcare cost of QAR 13,952 (USD 3,832) and an additional 0.04 QALYs gained per patient, compared to enalapril which resulted in an ICER of QAR 341,113 (USD 93,687)) per QALY gained per person, which is cost-effective based on the predefined WTP threshold. Sacubitril/valsartan also yielded an additional 0.67 YLL, relative to enalapril. Based on this and the incremental QAR 13,952 (USD 3,832) increase in cost per person, compared with enalapril, sacubitril/valsartan is associated with an ICER of QAR 24,431(USD 6,710) per YLL per person, which is below the WTP threshold. Table 2 presents a summary of the base-case outcomes.

Table 2. Base-case analysis outcomes

Outcomes	Sacubitril-valsartan	SoC
Average total healthcare cost per person, QAR (USD)	24,427 (6,709)	10,475 (2,877)
Difference in QALYs per patient	0.04	
Difference in YLL per patient	0.58	
ICER per QALYs per patient, QAR (USD)	341,113 (93,687)	
ICER per YLL per patient, QAR (USD)	23,992 (6,710)	

ICD: implantable cardioverter-defibrillators, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life years, QAR: Qatari Riyal, SoC: standard of care, USD: United States Dollar, YLL: years of life lived. All values were rounded to the nearest whole number.

Sensitivity Analyses

Univariate sensitivity analysis. The model was insensitive to the predefined uncertainty ranges assigned to the cost of event (survival/death), cost of sacubitril/valsartan, cost of enalapril, and cost of ICD, where sacubitril/valsartan remained cost-effective against QALYs gained in 100% of simulated cases (Supplementary Material Figure S3), and remained cost-effective against YLL in 100% of cases (Supplementary Material Figure S4). Mean outcomes of the univariate sensitivity analysis are presented in Table 3.

Table 3. One-way sensitivity analyses results

Uncertain parameter	ICER/QALYs, QAR (USD)	ICER/YLL, QAR (USD)
One-way sensitivity analysis		
Cost of heart failure event (survival/death) per patient	Mean: 341,114 (93,687), 95% CI 294,548 to 388,377 (80,898 to 106,668)	Mean: 23,993 (6,590), 95% CI 20,776 to 27,310 (5,706 to 7,501)
Cost of sacubitril-valsartan per patient per 1-month	Mean: 341,115 (93,687), 95% CI 338,902 to 343,369 (93,079 to 94,306)	Mean: 23,991 (6,589), 95% CI 23,836 to 24,151 (6,589 to 6,633)
Cost of enalapril per patient per 1-month	Mean: 341,109 (93,686), 95% CI 340,673 to 341,556 (93,566 to 93,808)	Mean: 23,991 (6,589), 95% CI 23,961 to 24,023 (6,581 to 6,598)
Cost of ICD per patient	Mean: 341,112 (93,686), 95% CI 338,973 to 343,300 (93,099 to 94,287)	Mean: 23,993 (6,590), 95% CI 23,841 to 24,144 (6,548 to 6,631)

ICD: implantable cardioverter-defibrillators, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life years, QAR: Qatari Riyal, SoC: standard of care, USD: United States Dollar, YLL: years of life lived. All values were rounded to the nearest whole number.

Multivariate sensitivity analysis. Against both the QALYs gained and the YLL, the probabilistic sensitivity analysis of adding the uncertainty in event rates, utility values, and cost values to the base-case model, resulted in mean ICERs with sacubitril/valsartan that are maintained below the WTP threshold, confirming cost effectiveness. Aganst QALY, sacubitril/valsartan was cost effective in onliand distributions in the multivariate sensitivity analysis and the outcomes are presented in Table 4.

The distribution among the different cost-effectiveness states can be seen, for both of the QALY and YLL outcomes, in the cost-effectiveness probability curve and cost-effectiveness plane, Supplementary Materials Figure S5 and Figure S6, respectively.

According to a regression tornado analysis of parameters and their influence on the outcome (Supplementary Material Figure S7), the main driver of the model outcome was the cost of patient event (survival/death), followed by the utility with sacubitril/valsartan, cost of ICD, while the probability of death with sacubitril/valsartan was the least influential model input.

Scenario analysis outcomes. The results of the scenario analysis are shown in Supplementary Material Table S1. The model outcome was insensitive to any of the tested input scenarios, where none reversed the overall base-case outcomes.

Discussion

Our model suggested that the use of sacubitril/valsartan in ICD patients reduced the overall risk of death events by 23.5% (i.e. death rate reduction from 17% to 13%) and resulted in 0.04 QALYs gained and 0.58 YLL per person, with an incremental cost difference of QAR 13,952 (USD 3,832) in favor of sacubitril/valsartan when considering YLL outcome.

To the best of our knowledge, this study is the first in the literature that provides new insights into the economic worthiness of sacubitril/valsartan in reducing the need for ICD and the overall risk of death events among patients with HFrEF via improving the ejection fraction. In Qatar, this is the first economic evaluation, of any kind, of sacubitril/valsartan and its resource use.

Our model suggested that the use of sacubitril/valsartan in the study's HFrEF patients was cost-effective compared to enalapril, i.e. an ICER of QAR 347,666 (USD 95,486) per QALYs gained per person, and at an ICER of QAR 24,431 (USD 6,710) YLL per person, compared with

Table 4. Probabilistic sensitivity analyses results

Uncertain variable	Point estimate	Distribution, uncertainty range	ICER/QALY, QAR (USD)	ICER/YLL, QAR (USD)
Death with sacubitril-valsartan, transition probability	0.01158	Trigen (0.0042- 0.0161)	Mean: 410,286 (112,685), 95% CI 287,323 to 767,995 (78,913 to 210,930)	Mean: 28,367 (7,791), 95% CI 23,808 to 42,394 (6,539 to 11,644)
Survival with sacubitril-valsartan, transition probability	0.1558	Trigen (0.1453- 0.1894)		
Death with enalapril, transition probability	0.0081	Trigen (0.0068- 0.0129)		
Survival with enalapril, transition probability	0.0579	Trigen (0.0491- 0.0632)		
Utility of patients with heart failure on sacubitril-valsartan	0.84	Beta (alpha: 48.16, beta: 9.17)		
Utility of patients with heart failure on enalapril	0.83	Beta (alpha: 51.01, beta: 9.52)		
Cost of sacubitril-valsartan over 1-month, QAR (USD)	700 (192)	Gamma		
Cost of enalapril over 1-month,, QAR (USD)	119 (33)	Gamma		
Cost of event (survival/death)per patient, QAR (USD)	26,137 (7,179)	Gamma		
Cost of ICD per patient, QAR (USD)	4,571 (1,256)	Gamma		

ICD: implantable cardioverter-defibrillators, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life years, QAR: Qatari Riyal, SoC: standard of care, USD: United States Dollar, YLL: years of life lived. All values were rounded to the nearest whole number.

enalapril. This is based on the Qatari governmental healthcare system perspective.

The robustness of our results was further confirmed in a series of uncertainty and scenario analyses, which demonstrated that the outcomes are maintained against the variability in different key model parameters. In our analysis, the main driver of the outcome was the cost of event (survival/death), followed by health utility with sacubitril/valsartan, and cost of ICD. This is expected for the two cost inputs, given the considerable high cost value of both variables in our model, QAR 4,571 (USD 1,256) and QAR 26,137 (USD 7,179), respectively.

Despite that our study has a different objective and our findings cannot be compared with other contemporary cost-effectiveness evaluations, current data on cost-effectiveness of sacubitril/valsartan in patients with HFrEF showed inconsistent findings given the considerable variation among countries with regards to the healthcare system, resource utilization, model inputs and assumptions, and country-specific WTP thresholds.[20] Unlike our study, all-cause death event probability of sacubitril/valsartan reported in previous models was modeled based on the PARADIGM-HF trial, whereas in our study, all-cause death rate of sacubitril/valsartan was calculated based on that reported in the PARADIGM trial (17%), reduced as per the relative decrease in all-cause death reported with the increase in the ejection fraction from $\leq$35% to $>$35% with the sacubitril/valsartan in the Felker et al. study.[10] The study by Gaziano et al. concluded that early initiation of sacubitril/valsartan during hospitalization is cost saving compared to enalapril over a lifetime horizon, from both US healthcare and societal perspectives, as compared with after-hospitalization initiation.[16] Similar to their model, in our study we did not consider changes in adverse events. Nevertheless, discontinuation of medications due to events such as hypotension and hyperkalemia was lower in those receiving sacubitril/valsartan than enalapril. Additionally, in line with our and Gaziano et al. studies, we did not consider emergency visits reductions due to lack of available data. Our results, however, are different with regards to the cost of event (survival/death), utility with scabutril/valsartan, and cost of ICD being the key drivers behind the outcome, compared to the cost of sacubitril/valsartan and cost of heart failure admission in their study. Furthermore, despite that the Gaziano et al. adopted a societal perspective, indirect costs were not considered in their model. Another study by King et al. based in the United States from a third-party perspective, suggested that the cost-effectiveness of sacubitril/valsartan versus enalapril is highly dependent on the duration of treatment, ranging from USD 249,411 per

QALYs gained at 3 years to USD 50,959 per QALYs gained over a lifetime horizon. However, similar to our findings, death rates associated with the sacubitril/valsartan and enalapril had the largest impact on the model.[17] In line with our and the King et al. studies, Sandhu et al. also reported that the cost-effectiveness of sacubitril/valsartan versus enalapril is dependent on the duration of treatment, ranging from USD 47,053 per QALYs gained at 27 months to USD 120,623 per QALYs gained over a lifetime horizon from a societal perspective.[18] Similar to Gaziano et al. study, Sandhu et al. did not include indirect costs in their model. van der Pol et al. nevertheless, revealed that sacubitril/valsartan might be cost-effective only when the maximum daily costs of sacubitril/valsartan is €5.50 per day at a WTP threshold of €20,000 per QALYs gained or €14.14 per day at a WTP threshold of €50,000 per QALYs gained, and it is not likely for sacubitril/valsartan to be cost-saving considering its daily price at their study setting. It is worth mentioning that compared to our model, their model was only limited to 42 months and sacubitril/valsartan and enalapril maintained the same probabilities of death after this period.[19] Similarly, based on the Singapore healthcare setting, Liang et al. followed the patients over a time horizon of 10 years and suggested that at the current daily price, sacubitril/valsartan is unlikely to be cost-effective compared with enalapril in patients with HFrEF from a healthcare perspective. A price reduction of 32−70% was needed for sacubitril/valsartan to be considered cost-effective.[20]

Based on the multiple scenarios sensitivity analyses performed, it was observed that the ICER was reduced when we considered shorter durations of the time horizon and increased when we excluded age-death trends. Therefore, duration of treatment and adjustment of transition probabilities according to age-related death trends are important factors for consideration by decision makers when assessing the economic benefit of using sacubitril/valsartan for ICD eligible patients.

There is no official approved WTP in Qatar. Guiding decision in such cases, the World Health Organization (WHO) suggested that the value of the threshold in a country can be within 1-3 times the gross domestic product (GDP) per capita in the country. Qatar's GDP per capita has been one of the world's highest, and will calculate a WTP threshold range that is too large to be directly implemented. This study adopted a threshold value of USD 150,000,[22−24] an increasingly accepted higher threshold value in the literature and, importantly, is also within the range suggested by the WHO for Qatar.

This study has limitations to be acknowledged. The input parameters of our model, except for the cost information, were derived from the PARADIGM-HF and PROVE-HF trials, which did not enroll patients from Qatar or the Middle East region. In addition, our analysis did not consider the medication-related adverse events of both sacubitril/valsartan and enalapril, e.g. hypotension, cough, hyperkalemia, or increased serum creatinine. These, however, may not have affected the analysis given that the adverse events in the PARADIGM-HF trial[3] were mild and did not require additional therapy. Furthermore, an inherent limitation of the Markov is that we extrapolated the results beyond the median follow-up time of the PARADIGM-HF and PROVE-HF trials to a lifetime horizon, which may lead to uncertainty. Another limitation is that the NYHA functional classes of heart failure were not considered in our model. Since this study was conducted from the perspective of the governmental healthcare system, non-direct costs were not included in the analysis.[19]

Conclusions

Based on the study perspective and assumptions made, and compared to enalapril, the increased ejection fraction, and reduced death and need for ICD therapy, with sacubitril/valsartan was cost-effective among ICD-eligible HFrEF patients in Qatar.

Author contribution

Al-Badriyeh D conceived the study design. Al-Badriyeh D and Abushanab D performed data collection, data analysis, and interpreted results. Kaddoura R provided data sources. Kaddoura R and Abushanab D wrote the first manuscript draft. Arabi AR and Alyafei S contributed to result interpretation. All authors reviewed the manuscript drafts critically, and read and approved the final manuscript.

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Supplementary materials

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