First-line Treatment with Empagliflozin and Metformin Combination Versus Standard Care for Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease in Qatar. A Cost-Effectiveness Analysis

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Abstract: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown to reduce cardiovascular events and mortality in patients with type 2 diabetes mellitus (T2DM), but they are currently not used as first-line therapy in clinical practice. This study sought to evaluate the cost-effectiveness of first-line empagliflozin plus standard care for patients with newly diagnosed T2DM and existing cardiovascular disease (CVD). A decision-analytic Markov model with one-year cycles and a lifetime time horizon was developed from the perspective of the Qatari healthcare system to compare first-line empagliflozin combined with metformin versus metformin monotherapy for patients aged 50 to 79 years with T2DM and existing CVD. Two health states were considered: Alive with CVD and T2DM

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and Dead. Patients could experience non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, and cardiovascular or non-cardiovascular death. Model inputs were ascertained from published and publicly available sources in Qatar. Costs and outcomes were discounted at 3% per annum. Sensitivity analyses were conducted to evaluate parameter uncertainty. The model predicted that adding empagliflozin to current standard care led to additional 1.9 years of life saved (YoLS) and 1.5 quality-adjusted life year (QALYs) per person, and an incremental cost of QAR 56,869 (USD 15,619), which equated to an incremental cost-effectiveness ratio of QAR 30,675 (USD 8,425) per YoLS and QAR 39,245 (USD 10,779) per QALY. Sensitivity analyses showed the findings to be robust. First-line empagliflozin combined with metformin appears to be a cost-effective therapeutic option for patients with T2DM and CVD. (Curr Probl Cardiol 2022;47:100852.)

Introduction

Diabetes mellitus (DM) is a major cause of disability and reduced quality of life. The International Diabetes Federation (IDF) Atlas predicts that DM will affect 642 million adults by 2040 and be the seventh leading cause of death in 2030 globally.[1,2] Patients with DM are 2 to 3 times more likely to develop cardiovascular disease (CVD) than those without DM.[3] The Middle East and North Africa region is expected to have one of the highest proportional increases in the number of patients with DM.[4] Type 2 diabetes mellitus (T2DM) and CVD have been recognized as Qatar's most significant burdens and are the leading cause of mortality.[5] In Qatar, 17% of the adult population has DM, which is higher than the global average.[6] It is also expected that the number of patients with DM will increase 2.5 times by 2045.[7] Recent studies showed that the prevalence of T2DM in Qatar is projected to increase from 16.7% in 2012 to at least 24% by 2050, with a total direct medical cost of around United States Dollar (USD) 3315 per patient in 2014.[4,8] Therefore, DM was recognized by the 2018 to 2022 Qatar National Health Strategy as a high-priority disease, with an aim to reduce the preventable mortality and hospital admissions by 5% and 15%, respectively.[9]

At present, a stepwise strategy has been used to manage T2DM, starting with non-pharmacological interventions. Currently, metformin monotherapy is the first-line therapy for newly diagnosed T2DM, followed by the addition of second-line therapies such as sulfonylurea, insulin, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, or glucagon-like peptide 1 agonists when optimal glycemic control is not achieved. SGLT2 inhibitors are added to metformin among patients with or at risk of CVD when initial therapy with metformin monotherapy fails to achieve glycemic control.[10,11] The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) demonstrated that empagliflozin added to metformin reduced CVD death and all-cause death by 38% and 32%, respectively, when compared to metformin monotherapy.[12] Given the unique mechanism of action of SGLT2 inhibitors and recent findings around their benefits for long-term outcomes, these agents are rapidly establishing their role in the management of T2DM beyond the glucose-lowering effect, and are an attractive option for initial combination with metformin.[13,14]

Here, and in line with the Qatar National Diabetes Control Strategy 2016 to 2022 vision "Preventing Diabetes Together", innovative population-based prevention strategies are highly needed to prevent T2DM complications and to improve the quality of life.[15] Therefore, the present study aimed to assess the cost-effectiveness of empagliflozin added to metformin versus metformin monotherapy as a first-line option for patients with newly diagnosed T2DM and existing CVD from the Qatari healthcare perspective.

Materials and Methods

Model Structure

A decision analytic Markov model (Fig 1) was structured to evaluate the incremental effects and costs of empagliflozin (10 or 25 mg once daily), combined with metformin (500 mg once daily) as first-line therapy, compared to metformin monotherapy (500 mg once daily). The model was constructed to estimate the number of CVD events arising from the Qatari population aged 50 to 79 years with newly diagnosed T2DM and existing CVD. The model comprised two health states: 'Alive with CVD and T2DM' and 'Dead'. The cycle length was one year. Patients who were in the 'Alive with CVD and T2DM' health state were at risk for experiencing a combination of CVD events (including non-

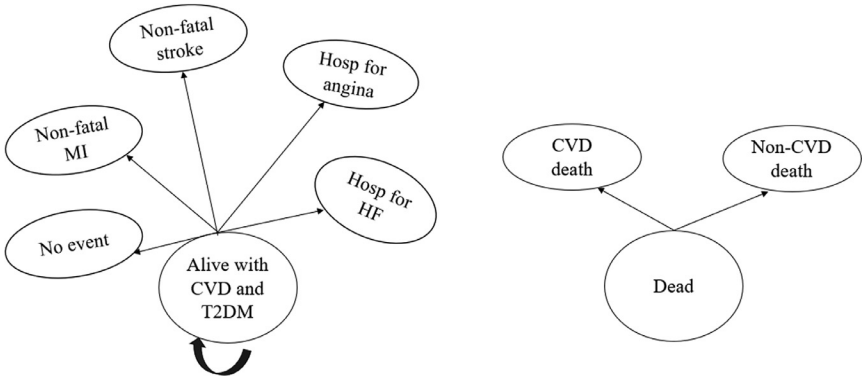

FIG 1. Diagram of the Markov state transition model and health states of first-line use of empagliflozin combined with metformin versus metformin monotherapy. *MI, myocardial infarction; Hosp, hospitalization; HF, heart failure; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

fatal myocardial infarction (MI), non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina), and death from cardiovascular or non-cardiovascular causes.

The model outcomes included the number of non-fatal MI, non-fatal stroke, non-fatal heart failure, unstable angina, CVD and non-CVD deaths, total quality-adjusted life year (QALY) gained, total years of life saved (YoLS), total costs, and the incremental cost-effectiveness ratios (ICERs) for YoLS and QALY gained. A willingness-to-pay (WTP) threshold of USD 150,000 per additional YoLS and QALY gained was used as a reference threshold for cost-effectiveness.[16] Cost-effectiveness plane (CEPs) and Cost-Effectiveness Acceptability Curves (CEACs) were generated for the ICER outcomes. Long-term costs and effects were discounted at a rate of 3% annually, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.[17]

At its base-case, the Markov simulation model was based on a multivariate analysis that accounted for inherent uncertainties in transition probabilities, varying by their 95% confidence interval (CI) estimates, using Monte Carlo simulation via @Risk-7.6 (Palisade Corporation, NY, US). In total, 10,000 model simulations were conducted, using a triangular probability distributions to describe uncertainty (Table 1).

Model Population

The model was populated with 2019 Qatari data drawn from the Institute for Health Metrics and Evaluation (IHME), which is an independent population health research center that provides thorough information

TABLE 1. Model inputs for the base-case analysis, variation range and distribution

Parameter	Point estimate	Variation range		Point estimate	Variation range		Distribution	Reference
	Empagliflozin with metformin	Lower	Upper	Metformin monotherapy	Lower	Upper		
Transition probabilities for cycle 1 and beyond								
Non-fatal MI	0.0147	0.0128	0.0171	0.0171	0.0141	0.0204	Triangular	[12]
Non-fatal stroke	0.0104	0.0088	0.0124	0.0085	0.0065	0.0108	Triangular	[12]
Non-fatal HF	0.0088	0.0072	0.0104	0.0134	0.0108	0.0164	Triangular	[12]
Angina	0.0091	0.0078	0.0111	0.0091	0.0072	0.0118	Triangular	[12]
CVD death	0.0121	0.0104	0.0141	0.0194	0.0164	0.0228	Triangular	[12]
Other death	0.0065	0.0055	0.0081	0.0077	0.0062	0.0104	Triangular	[12]
Utility								
T2DM and CVD	0.78	0.73	0.83				Beta	[29]
Costs (QAR, USD)								
Empagliflozin	(1,496, 411)	(1,346, 370)	(1,646, 452)				Gamma	[HMC]
Metformin	(75, 21)	(68,24)	(83, 23)				Gamma	[HMC]
Non-fatal MI	(34,175, 9,386)	(30,758, 8,447)	(37,593, 10,324)				Gamma	[HMC]
Non-fatal stroke	(37,516, 10,303)	(33,764, 9,273)	(41,268, 11,333)				Gamma	[HMC]
Non-fatal HF	(41,461, 11,386)	(37,315, 10,248)	(45,607, 12,525)				Gamma	[HMC]
Unstable angina	(27,983, 7,685)	(25,185, 6,917)	(30,781, 8,453)				Gamma	[HMC]
CVD death	(22,754, 6,249)	(20,479, 5,624)	(25,029, 6,874)				Gamma	[HMC]
Annual costs of T2DM and CVD	(8,498, 2,334)	(5,949, 1634)	(11,047, 3,034)				Gamma	[24]

*CVD, cardiovascular disease; HF, heart failure; HMC, Hamad Medical Corporation; MI, myocardial infarction; QAR, Qatari Riyal; USD, United States Dollar. Variation of ± 95% confidence interval was used for the transition probabilities, ± 95% confidence interval for the utility, ± 10% for costs obtained from Hamad Medical Corporation, Qatar, and ± 30% for costs obtained from literature. All values were rounded.

TABLE 2. Qatari population with type 2 diabetes mellitus, cardiovascular disease, and on metformin monotherapy

Age group	Midpoint	Number of patients	Number of subjects with T2DM	Number of subjects with T2DM and CVD	Number of subjects with T2DM, CVD, and on metformin monotherapy
50-54	52	141,380	46,160.57	14,864	4,380
55-59	57	86,780	31,119.31	10,020	2,953
60-64	62	52,430	18,984.90	6,113	1,801
65-69	67	23,620	8,314.24	2,677	789
70-74	72	10,160	3,446.27	1,110	327
75-79	77	4,940	1,578.33	508	150
Total		319,310	109,603.62	35,292	10,399

*CVD, cardiovascular disease ; T2DM, type 2 diabetes mellitus.

concerning the world's most important health problems.[18] The population was all of Qataris aged 50 to 79 years with newly diagnosed T2DM, existing CVD and on metformin monotherapy. A total of 10,399 male and female Qatari patients was used and was stratified by a 5-year age group into six cohorts from 50-54, 55-59, 60-64, 65-69, 70-74, and 75-79 years, where the starting age in each modeled cohort group was the midpoint of each age group (e.g., 52 years for the age group 50-54 years).

Age-specific prevalence of T2DM among the Qatari population in 2019 was obtained from a recent Qatari study by Awad et al.[8] The prevalence of T2DM was as follows: 32.7% (50-54 years), 35.9% (55-59 years), 36.2% (60-64 years), 35.2% (65-69 years), 33.9% (70-74 years), and 32% (75-79). The prevalence of CVD and the proportion of metformin as monotherapy among Qatari patients with T2DM are lacking and were therefore obtained from published literature as 32.2% and 29.5%, respectively.[12,19] Details with regards to the model population are provided in Table 2. Cardiovascular and all-cause age-specific death rates, obtained from the IHME and the Ministry of Development Planning and Statistics in Qatar for the year 2016, respectively,[18,20] were used to adjust for the increase in the transition probabilities for cardiovascular and non-cardiovascular deaths from Cycle 2 onwards, assuming that the age-related increase was equal between non-fatal and fatal CVD risks.[21] The age-related increase for the risk of non-CVD death rates was determined by subtracting CVD mortality rates from all-cause mortality rates. Appendix 1 presents the results of the extrapolation of mortality data for death from cardiovascular and all causes.

Clinical Outcomes

CVD event rates as a result of empagliflozin combined with metformin versus metformin monotherapy were extracted from the EMPA-REG OUTCOME trial, which evaluated the cardiovascular morbidity and mortality between both groups in patients with T2DM and existing CVD over 3.1 years of follow-up.[12] Transition probabilities were calculated from the event rates using the formula by Briggs et al:[22] $r = -(1/3.1)*\ln(1-R)$, where r is the one-year rate and R is the 3.1-year rate. The formula $tp = 1 - e{-}r$ was then used to calculate the one-year transition probabilities. Survival analysis was carried out among the study patients who entered the model at age 52 years and were followed until death. A lifetime horizon was considered for this analysis.

Setting and Perspective

The study was conducted from the perspective of Hamad Medical Corporation (HMC). HMC is currently the leading healthcare provider in Qatar, including 13 major specialized hospitals, and is publicly financed by the Qatari National government.[23] At present, empagliflozin and dapagliflozin are the only SGLT2 inhibitors listed in the HMC formulary but only as second- or third-line options after inadequate control with metformin monotherapy, in addition to other oral hypoglycemic agents.

Resource Utilization and Costs

The costs of empagliflozin and metformin were calculated according to the 10 and 25 mg and the 500 mg daily doses, respectively. The annual costs of empagliflozin and metformin were derived from the pharmacy department at HMC and were calculated in Qatari Riyal (QAR) 1,496 (USD 411) and QAR 75 (USD 21) per year, respectively. Apart from medication costs, other direct health resource utilization costs, including the total management costs of acute events (non-fatal MI, non-fatal stroke, non-fatal heart failure, unstable angina, and CVD death) were obtained from the finance and costing department of HMC and were estimated to be QAR 34,175 (USD 9,386), QAR 37,516 (USD 10,303), QAR 41,461 (USD 11,386), QAR 27,983 (USD 7,685), and QAR 22,754 (USD 6,249), respectively. All acute event costs comprised hospitalization as well as follow-up costs. The cost of non-CVD death was not available; and hence it was assumed to be the same as the CVD death cost (with only half of population dying in hospital and half at home). The model also included the annual costs of T2DM with CVD, which included the

costs of hospitalization, emergency visits, office visits, pharmacy, and other ancillary care, and was obtained from the published literature, QAR 8,498 (USD 2,334).[24] All patients in this model were assumed to receive the same initial monitoring parameters, such as hemoglobin A1c reading, renal function, lipid profile, and blood pressure, and therefore monitoring costs were not included in the model. If a cost was not available at HMC, this was obtained from the literature and was adjusted, if not Qatari based, to its Qatari value using the health expenditure per capita and the Purchasing Power Parities (PPP) for GDP.[25-27] All cost were inflated to 2021 values using the Qatari Health Price Index,[28] and were presented in QAR and USD (Table 1).

Quality of Life

The primary health outcome of this cost-effective analysis is the QALY. We used utilities based on the Euro-QoL-5 Dimensions, 5 Levels (EQ-5D-5L) questionnaire from a multicenter, prospective observational study conducted in patients with T2DM.[29] The utility values used for patients who have diabetes with angina and diabetes with other coronary heart diseases were 0.81 (standard deviation (SD) $\pm$ 0.19) and 0.78 (SD $\pm$ 0.19), respectively. The weighted average of these utility values was used in the model, which was 0.78 (Table 1).

Subgroup Analysis

A subgroup analysis considered reporting results separately for males and females.

Sensitivity and Scenario Analyses

A series of deterministic sensitivity analyses (DSA) was performed to determine the model's sensitivity to potential input uncertainty. Uncertainty ranges of $\pm$ 95% CI were used as lower and upper bounds for utility data, while $\pm$ 10% of the base-case value was applied to cost data obtained from HMC and $\pm$ 30% to cost obtained from the literature.

Probabilistic sensitivity analysis (PSA) was undertaken to simulate real-life interactions between concurrent uncertainties of model inputs simultaneously. Included model inputs in the PSA are health utilities and costs conducted via the Monte Carlo simulation with 10,000 iterations. The beta distribution was used for utility values and Gamma distribution for costs (Table 1).

A number of scenario analyses was performed, including discount rate variability, removing the age-related trends for all the events, and limiting the time frame to 5-years, 10-years, 20-years, and 30-years, doubling the costs of acute events (non-fatal MI, non-fatal stroke, hospitalization for heart failure, hospitalization for angina, CVD death), and annual costs of T2DM and CVD management, and removing the costs of death.

Model Verification and Validation

To ensure face validity, experienced modellers assessed whether the model mets predictions based on simple calculations. The model inputs were then evaluated to check that expected effects were predicted, and the manual review of formulae and cross check of all inputs were completed. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was followed for the economic evaluation.[30] Finally, CVD and non-CVD death was validated in the Qatari population using outputs from our model.

The model was entirely executed in Microsoft Excel.

Results

Base-Case Analysis

In patients with T2DM and existing CVD, use of empagliflozin plus metformin over metformin monotherapy resulted in additional 1.9 YoLS and 1.5 QALYs gained per person, at an incremental cost of QAR 56,869 (USD 15,619), which led to an ICER of QAR 30,675 (USD 8,425) (95% CI, QAR 22,698−60,596, USD 6,234−16,642) per YoLS and QAR 39,245 (USD 10,779) (95% CI, QAR 28,925−78,005, USD 7,944−21,424) per QALY (Table 3). The CEPs for QALY and YoLS showed that 100% of simulated results were within the ICER threshold of QAR 546,150 (USD 150,000) per QALY gained and YoLS (Fig 2). With regards to the overall survival analysis, most deaths occurred by (35-50) year time horizon (Appendix 2).

Subgroup Analysis

In males, empagliflozin plus metformin combination resulted in additional 1.9 YoLS and 1.5 QALYs gained per person, at an additional cost of QAR 56,512 (USD 15,521). These equated to ICERs of QAR 29,225 (USD 8,027) per YoLS and QAR 37,391 (USD 10,269) per QALY gained. In females, empagliflozin plus metformin combination resulted in

TABLE 3. The study clinical outcomes and costs in a cohort of 10,399 individuals treated with empagliflozin added to metformin compared to metformin monotherapy

	Events					
	Non-fatal MI	**Non-fatal stroke**	**Hospitalization for HF**	**Hospitalization for angina**	**CVD Death**	**Other Death**
Empagliflozin added to metformin	8,565	6,058	5,131	5,302	7,056	2,324
Metformin monotherapy	6,288	3,125	4,867	3,346	7,133	2,037
Difference	2,277	2,933	263	1,956	-78	287
Per person	0.219	0.282	0.025	0.188	-0.007	0.028
Discounted values						
	YoLS	QALYs	Acute event costs (QAR, USD)	Annual disease costs (QAR, USD)	Medication costs (QAR, USD)	Total healthcare costs (QAR, USD)
Empagliflozin added to metformin	122,497	95,746	(652,954,233, 179,333,750)	(766,570,492, 210,538,432)	(192,427,316,	(1,611,952,041, 52,850,123)
Metformin monotherapy	103,218	80,676	(528,369,229, 145,116,503)	(484,474,471, 133,060,817)	(7,706,310, 2,116,537)	(1,020,550,010, 280,293,856)
Difference	19,280	15,069	(124,585,004, 34,217,246)	(282,096,021, 77,477,616	(184,721,006, 50,733,587)	(591,402,031, 162,428,450)
Per person	1.9	1.5	(11,980, 3,290)	(27,126, 7,450)	(17,763, 4,879)	(56,869, 15,619)
ICER	(30,675, 8,425) (95% CI, QAR 22,698−60,596, USD 6,234−16,642)	(39,245, 10,779) (95% CI, QAR 28, 925−78,005, USD 7,944−21,424)				

*CVD, cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life years; QAR, Qatari Riyal; USD, United States Dollar; YoLS, years of life saved.
All values were rounded.

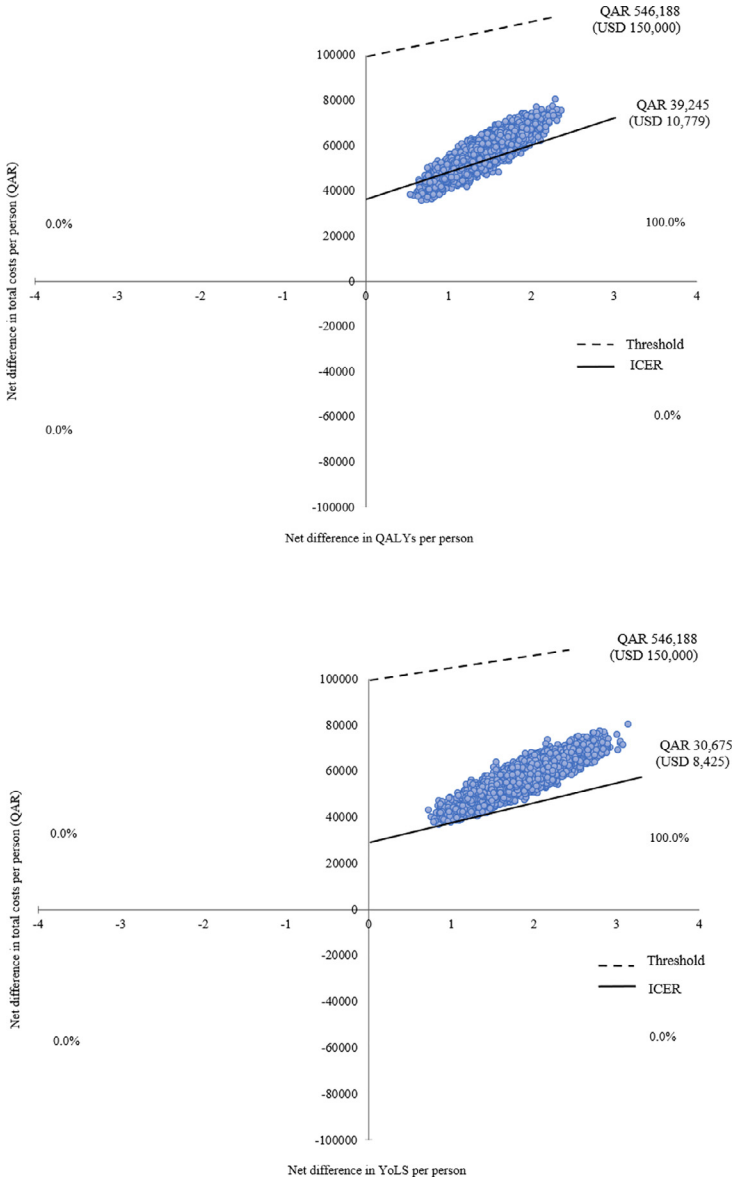

FIG 2. Scatter plot of incremental QALYs and YoLS against incremental costs. These scatterplots of the base-case multivariate uncertainty analysis present the results of 10,000 simulations during which model input variables were allowed to vary simultaneously. The x-axis represents the incremental difference in QALY/YoLS, while the y-axis represents the incremental costs. The clustering of simulation results in the upper right quadrant shows that 100% of iterations were within thresholds of cost per QALY and YoLS. *QALY, quality-adjusted life year; YoLS, years of life saved, QAR, Qatari Riyal; USD, United States Dollar.

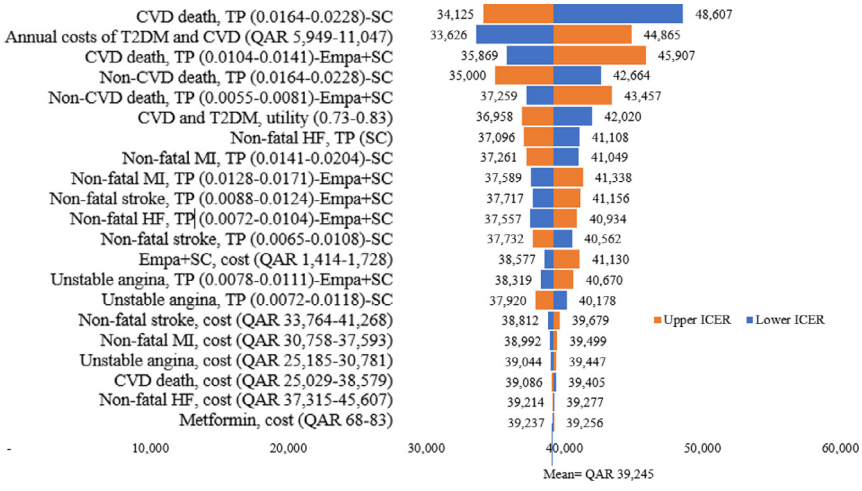

FIG 3. Tornado diagram of variables as per their influence on the outcome. *CVD, cardiovascular disease; SC, standard care; T2DM, type 2 diabetes mellitus; TP, transition probability; HF, heart failure; Empa, empagliflozin; MI, myocardial infarction; ICER, incremental cost-effectiveness ratio.

an additional 1.7 YoLS and 1.3 QALYs gained per person, at an additional cost of QAR 55,831 (USD 15,334), which translated to ICERs of QAR 32,377 (USD 8,892) per YoLS and QAR 41,423 (USD 11,377) per QALY gained.

Sensitivity Analyses

DSA. Results from the DSA are displayed in the Fig 3 as a 'tornado diagram'. Transition probabilities for CVD death in the metformin monotherapy group and the annual costs of managing T2DM with CVD were the main driving factors that influenced outcomes. In contrast, costs of non-fatal heart failure and metformin monotherapy were the factors that affected the outcomes the least (Fig 3).

PSA. The CEP revealed minor changes over the base-case analysis. Empagliflozin plus metformin was cost-effective in 86.9% and 86.7% of simulated cases per QALY gained and YoLS, respectively, and cost saving in 0.1% of simulated cases (Fig 4). In line with the CEPs, the CEACs revealed that there is a greater than 80% probability that empagliflozin plus metformin is cost-effective per QALY/YoLS (Appendix 3).

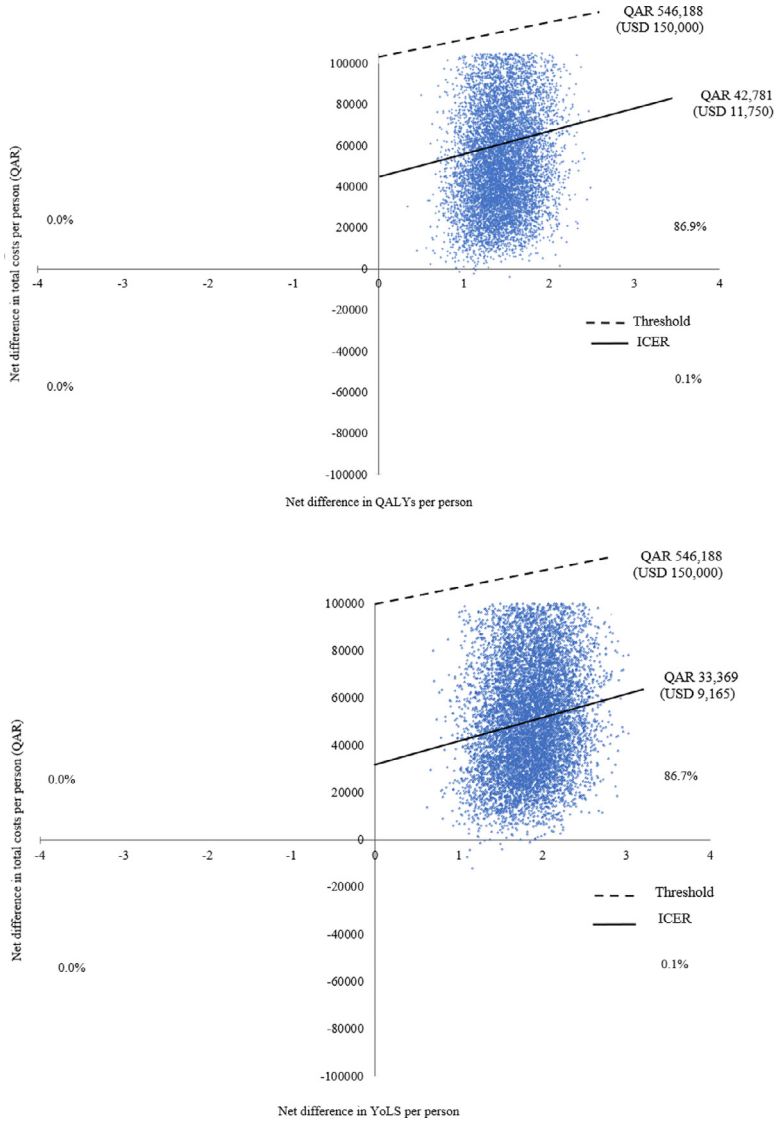

FIG 4. Scatter plot of incremental QALYs and YoLS against incremental costs. These scatterplots of the PSA varying all model inputs simultaneously present the results of 10,000 simulations during which model input variables were allowed to vary simultaneously. The x-axis represents the incremental difference in QALY/YoLS while the y-axis represents the incremental costs. The clustering of simulation results in the upper right quadrant shows that approximately 86.9% and 86.7% of iterations were within thresholds of cost per QALY and YoLS, respectively and 0.1% of simulated cases were cost saving per QALY and YoLS. *QALY, quality-adjusted life year; YoLS, years of life saved; QAR, Qatari Riyal; USD, United States Dollar; PSA, probabilistic sensitivity analysis.

TABLE 4. Results of scenario analyses

Variables	ICER (cost per QALY) (QAR, USD)	ICER (cost per YoLS) (QAR, USD)
Base-case	*(39,245, 10,779)*	*(30,675, 8,425)*
Discounting 1%	(38,040, 10,448)	(29,733, 8,166)
Discounting 4%	(39,941, 10,970)	(31,219, 8,574)
Discounting 5%	(40,696, 11,177)	(31,808, 8,736)
Discounting 6%	(41,506, 11,400)	(32,442, 8,910)
Time frame 5 years	(97,202, 26,697)	(75,974, 20,866)
Time frame 10 years	(56,587, 15,542)	(44,229, 12,148)
Time frame 20 years	(40,919, 11,238)	(31,983, 8,784)
Time frame 30 years	(39,360, 10,810)	(30,764, 8,449)
No age-related trends for any of the events	(30,792, 8,457)	(24,067, 6,610)
Doubling the costs of acute events (non-fatal MI, non-fatal stroke, hospitalization for heart failure, hospitalization for angina, CVD death), and cost of chronic diabetes and CVD management	(77,221, 21,209)	(60,357, 16,577)
Without death costs	(40,838, 11,216)	(31,920, 8,766)

*CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QAR, Qatari Riyal; QALY, quality adjusted life years; USD, United States Dollar.

Scenario Analyses

The results of the scenario analyses are shown in Table 4, which showed that in all cases, the ICERs remained within the threshold of USD 150,000 (QAR 546,150). Of note, when shorter time horizons were applied, the ICERs increased to QAR 97,202 (USD 26,697) per QALY gained at 5 years, QAR 56,587 (USD 15,542) at 10 years, QAR 40,919 (USD 11,238) per QALY gained at 20 years, and QAR 39,360 (USD 10,810) at 30 years.

Model Verification and validation

The validation revealed that our model was robust but overpredicted CVD death. The results of cheers assessment are reported in Appendix 4.

Discussion

Cardiovascular risk factors such as poor glycemic control and suboptimal lipid control place diabetic patients at increased risk for developing cardiovascular complications, including MI, stroke, angina, heart failure, and death. Therefore, it is of paramount importance to curb the progression of T2DM and its CVD complications by implementing new therapeutic strategies for the improvement of T2DM and CVD outcomes. This

study provides insights into the clinical and economic implications of empagliflozin plus metformin as first-line therapy if all eligible patients were to immediately begin therapy with empagliflozin. The EMPA-REG OUTCOME trial, which provides the highest level of evidence to date about the clinical efficacy of empagliflozin in patients with T2DM and existing CVD, found that there was a lower all-cause and CVD mortality in patients with a history of CVD, which implies that this subpopulation could even further benefit with immediate use of empagliflozin plus metformin.[12] Compared to other SGLT2 inhibitors, empagliflozin has also been found to be more effective with regards to all-cause and cardiovascular mortality reduction in patients with T2DM.[13]

The findings suggest that the benefits of adding empagliflozin to metformin as first-line therapy offset their high long-term costs in HMC in Qatar for patients with newly diagnosed T2DM and existing CVD. From a public healthcare perspective in Qatar, the base-case analysis revealed that adding empagliflozin to metformin as first-line therapy may be cost-effective and had a favorable ICER of QAR 30,675 (USD 8,425) per YoLS and QAR 39,245 (USD 10,779) per QALY over a lifetime horizon. The cost-effectiveness was maintained throughout various sensitivity analyses.

Cost-effectiveness evaluations play an essential role to support the decision-making that seeks to understand the value of competing health technologies and management strategies. Previous work showed that the implementation and uptake of SGLT2 inhibitors as second-line options in Qatar is generally high,[31] which enhances its potential first-line use among the Qatari population beyond its traditional glucose-lowering effect.

Only a limited number of cost-effectiveness analyses have been published on empagliflozin to date, and most were conducted in Western settings and for second-line use. Our results provide new insight and perspective in this regard. A study conducted in the UK by Kansal et al that compared second-line empagliflozin plus standard of care versus standard of care concluded that empagliflozin was cost-effective, and associated with an ICER of £4,083 per QALY gained over a lifetime horizon.[32] A Greece-based healthcare perspective analysis of second-line empagliflozin plus standard of care found the medication to also be cost-effective. It increased the mean survival (14.01 versus 11.87 life years per person over a lifetime horizon) and increased QALYs (7.75 versus 6.83), calculating an ICER of €4,633 per QALY, compared to standard of care.[33] The immediate use versus delayed use of dapagliflozin plus metformin in patients with T2DM, but without existing CVD, was

evaluated by Chin et al from the Australian healthcare perspective, and suggested that the immediate addition of dapagliflozin was cost-effective.[34]

There is no approved WTP cost-effectiveness threshold in Qatar. While the World Health Organization suggests using 1 to 3 times the GDP per capita as the value of the threshold in a country, it is acknowledged that this is arbitrary and not based on any methodological justification.[35] In addition, the average 2019 GDP per capita (PPP) in Qatar was approximately USD 94,028;[36] one of the world's highest. Thus, adopting the WHO recommendation for calculating the WTP will result in a range of values that is too wide to be directly useful, i.e. USD 64,781 to 194,343. In this study, we adopt a threshold value of USD 150,000, which is increasingly accepted as a higher threshold value in the literature, which is also within the range suggested by WHO for Qatar.[16]

While the utility values vary across different settings, it is highly associated with the socioeconomic status of the country.[37] Within this context, locally-specific health utility values for T2DM patients with existing CVD are not available in Qatar and, hence, the utility data in this study was obtained from an international and multicenter study.[29] which have a comparable quality of life to that in the Qatari setting; being one of the wealthiest countries in the world with one of highest gross domestic incomes per capita.[38]

One of the strengths in the current study is that the population of the study represents the Qatari setting, which makes the population reliable and relevant. Also, the base-case analysis was based on multivariate uncertainty analysis, which accounted for inherent simultaneous uncertainty associated with the main clinical rates of empagliflozin as adapted from the EMPA-REG OUTCOME trial.

The current analysis is not without limitations. First, the real-world adherence to empagliflozin plus metformin therapy may differ from in the EMPA-REG OUTCOME trial, the estimates of costs, effectiveness, and safety profiles might be altered. Secondly, this analysis is only applicable to T2DM with existing CVD and not to primary prevention patient settings or other populations at lower risk of CVD. Thirdly, other complications such as retinopathy, nephropathy, neuropathy, and peripheral arterial disease were not included in the model. Including them will only add to the benefit of empagliflozin. Fourthly, the side effects of empagliflozin, such as genital infections, were excluded from the model because these are considered transient events and may not always be included in the overall hospitalization costs. Lastly, the results of this analysis are specific to the Qatari setting and the results of this study should not be

extrapolated to patients in different settings, especially due to variations in the resource utilization, inflation rates, disease prevalence, and death rates.

Conclusion

In summary, from the perspective of the Qatari HMC healthcare system, our results suggest that the benefits of first-line therapy of empagliflozin added to metformin monotherapy, are achieved at an acceptable cost in patients with newly diagnosed T2DM and existing CVD.

Author contributions

DA developed the model, performed the analyses, and wrote the first draft of the manuscript. DB contributed to the analyses, interpretation of data, and revised the manuscript. ZA and DL conceived the study, contributed to the analyses, interpretation of data, and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval

The study did not require ethics approval.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2021.100852.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. Eighth edition 2017. Available at: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html. Accessed 14 March 2020.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
3. BIG HEARTS BRILIANT MINDS. Impact report 2018. Available at: https://baker.edu.au/-/media/documents/who-we-are/corporate-reports/baker-institute-impact-report-2018.pdf. Accessed 20 June 2020.

4. Bener A, Al-Hamaq AOAA. Predictions burden of diabetes and economics cost: contributing risk factors of changing disease prevalence and its pandemic impact to qatar. *Exp Clin Endocrinol Diabetes* 2016;124:504–11.
5. Innovative Approaches to Prevention Tackling the Global Burden of Cardiovascular Disease. Report of the WISH Cardiovascular Disease Forum 2016. Available at: https://www.wish.org.qa/wp-content/uploads/2018/01/IMPJ4495_WISH_CArdio_Disease_181116_WEB.pdf. Accessed 20 June 2020.
6. Qatar's Forth National Human Development Report. Realising Qatar National Vision 2030 the right to development. 2015. Available at: http://hdr.undp.org/sites/default/files/qatar_nhdr4_english_15june2015.pdf. Accessed 10 September 2020.
7. Diabetes. Ministry of Public Health. Available at: https://phs.moph.gov.qa/data/diabetes/. Accessed 30 November 2020.
8. Awad SF, O'Flaherty M, El-Nahas KG, et al. Preventing type 2 diabetes mellitus in Qatar by reducing obesity, smoking, and physical inactivity: mathematical modeling analyses. *Popul Health Metr* 2019;30(17):20.
9. National Health Strategy 2018-2022. Available at: https://lc.ucalgary.edu.qa/ld.php?content_id=41255610. Accessed 23 November 2020.
10. The Royal Australian College of General Practitioners. General practice management of type 2 diabetes 2016−18. Available at: https://www.racgp.org.au/FSDEDEV/media/documents/Clinical%20Resources/Guidelines/Diabetes/General-practice-management-of-type-2-diabetes_1.pdf. Accessed 27 March 2020.
11. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43:S98–S110.
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 Diabetes. *N Engl J Med* 2015;373:2117–28.
13. Täger T, Atar D, Agewall S, et al. comparative efficacy of sodium-glucose cotransporter-2 Inhibitors (SGLT2i) for cardiovascular outcomes in Type 2 Diabetes: a systematic review and network meta-analysis of randomised controlled trials. Heart Fail Rev. 2020.
14. Kaur KK, Allahbadia G, Singh M. Role of Combination Therapy with SGLT2 Inhibitor with Metformin as Initial Treatment for Type2 DiabetesAdvantages of Oral Fixed Drug Pill Like Empagliflozin/Metformin in Patients with Cardiovascular and Renal Risk-A Short Communication. *Archives of Diabetes and Endocrine System* 2019;2:15–9.
15. Qatar National Diabetes Strategy. Preventing Diabetes Together 2016-2022. Available at: https://www.moph.gov.qa/Style%20Library/MOPH/Files/strategies/Qatar%20National%20Diabetes%20Strategy/12477%20PA%20National%20Diabetes%20Eng%20.compressed.pdf. Accessed 30 November 2020.
16. Thresholds for the cost−effectiveness of interventions: alternative approaches. Available at: https://www.who.int/bulletin/volumes/93/2/14-138206/en/#:~:text=Benchmark%20interventions,-Originally%20proposed%20by&text=In%20the%20USA%2C%20for%20example,dialysis%20for%20chronic%20renal%20disease.&text=This%20threshold%20has%20recently%20been,150%20000%20per%20QALY%20gained. Accessed 10 September 2020.

17. Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. *Health Policy Plan* 2020;35:107–14.
18. Institute for Health Metrics and Evaluation. Available at: http://www.healthdata.org/about. Accessed 30 September 2020.
19. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol* 2018;17:83.
20. Ministry of Development Planning and Statistics. Births & Deaths In the State of Qatar, 2016. Available at: https://www.psa.gov.qa/en/statistics/Statistical%20Releases/Population/BirthsDeaths/2016/Birth_death_2016_EN.pdf. Accessed 10 September 2020.
21. Briffa TG, Hobbs MS, Tonkin A, et al. Population trends of recurrent coronary heart disease event rates remain high. *Circ Cardiovasc Qual Outcomes* 2011;4:107–13.
22. Briggs A, Claxton K, Sculpher M. Decision Modeling for Health Economics Evaluation. In: Briggs A, Claxton K, Sculpher M, eds. *Oxford*, Oxford University. Press; 2006.
23. Hamad Medical Corporation. Available at: https://www.hamad.qa/EN/Pages/default.aspx. Accessed 10 November 2020.
24. Candrilli SD, Meyers JL, Boye K, et al. Health care resource utilization and costs during episodes of care for type 2 diabetes mellitus-related comorbidities. *J Diabetes Complications* 2015;29:529–33.
25. Health spending. Available at: https://data.oecd.org/healthres/health-spending.htm. Accessed 15 October 2020
26. Qatar - Gross domestic product per capita based on purchasing-power-parity in current prices. Available at: https://knoema.com/atlas/Qatar/GDP-per-capita-based-on-PPP#:~:text=Qatar%20%2D%20Gross%20domestic%20product%20per,power-%2Dparity%20in%20current%20prices&text=GDP%20per%20capita%20based%20on%20PPP%20of%20Qatar%20increased%20from,average%20annual%20rate%20of%202.47%25. Accessed 15 October 2020
27. Ademi Z, Yukic T, Jorisa VS, et al. Adaptation of cost-effectiveness analyses to a single country: the case of bariatric surgery for obesity and overweight. *Swiss Med Wkly* 2018;148:w14626.
28. Qatar: Inflation rate from 1984 to 2021. Available at: https://www.statista.com/statistics/379995/inflation-rate-in-qatar/. Accessed 15 October 2020.
29. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health utility scores for people with type 2 diabetes in U.S. managed care health plans: results from Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care* 2012;35:2250–6.
30. Husereau D, Drummond M, Petrou S, et al. Economic evaluation publication guidelines-CHEERS good reporting practices task force. consolidated health economic evaluation reporting standards (CHEERS) explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health* 2013;16:231e50.

31. Al AdAwi R, Jassim Z, Elgaily D, Abdelaziz H, Sree B, Ibrahim M. Assessment of dapagliflozin effectiveness as Add-on Therapy for the Treatment of Type 2 Diabetes mellitus in a qatari population. *Sci Rep* 2019;3(9):6864.
32. Kansal A, Reifsnider OS, Proskorovsky I, et al. Cost-effectiveness analysis of empagliflozin treatment in people with Type 2 diabetes and established cardiovascular disease in the EMPA-REG OUTCOME trial. *Diabet Med* 2019;36:1494–502.
33. Gourzoulidis G, Tzanetakos C, Ioannidis I, et al. Cost-effectiveness of empagliflozin for the treatment of patients with Type 2 Diabetes mellitus at increased cardiovascular risk in Greece. *Clin Drug Investig* 2018;38:417–26.
34. Chin KL, Ofori-Asenso R, Si S, et al. Cost-effectiveness of first-line versus delayed use of combination dapagliflozin and metformin in patients with Type 2. *Diabetes. Sci Rep.* 2019;9:3256.
35. Cameron D, Ubels J, Norstrom F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action* 2018;11:1447828.
36. GDP per capita. PPP (current international $). The World Bank; 2020. Available at: https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD. Accessed December 12.
37. Mielck A, Vogelmann M, Leidl R. Health-related quality of life and socioeconomic status: inequalities among adults with a chronic disease. *Health Qual Life Outcomes* 2014;12:58.
38. Qatar GDP. Available at: https://tradingeconomics.com/qatar/gdp. Accessed 10 November 2020.