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RESEARCH ARTICLE

Cost-effectiveness of immediate initiation of dapagliflozin in patients with a history of heart failure

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Aims To compare the cost-effectiveness of immediate and 12-month delayed initiation of dapagliflozin treatment in patients with a history of hospitalization for heart failure (HHF) from the UK, Canadian, German, and Spanish healthcare perspectives.

Methods and results A cost-utility analysis was conducted using a decision-analytic Markov model with health states defined by Kansas City Cardiomyopathy Questionnaire scores, type 2 diabetes mellitus status and incidence of heart failure (HF) events. Patient-level data for patients with prior HHF from the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial were used to inform the model inputs on clinical events and utility values. Healthcare costs were sourced from the relevant national reference databases and the published literature. Compared to standard therapy, immediate initiation of dapagliflozin decreased HHF (187 events), urgent HF visits (32 events) and cardiovascular mortality (18 events). Standard therapy was associated with lifetime costs of £13 224 and 4.02 quality-adjusted life years (QALYs). Twelve-month delayed initiation of dapagliflozin was associated with total discounted lifetime costs and QALYs of £16 660 and 4.61, respectively, compared to £16 912 and 4.66, respectively, for immediate initiation. Compared to standard therapy, immediate and 12-month delayed initiation of dapagliflozin yielded an incremental cost-effectiveness ratio (ICER) of £5779 and £5821, respectively. Compared to 12-month delayed initiation, immediate initiation of dapagliflozin had an ICER of £5263. Results were similar from the Canadian, German, and Spanish healthcare perspectives.

Conclusion Both immediate and 12-month delayed initiation of dapagliflozin are cost-effective. However, immediate initiation provides greater clinical benefits, with almost 10% additional QALYs gain, compared to 12-month delayed initiation of dapagliflozin and should be considered standard of care.

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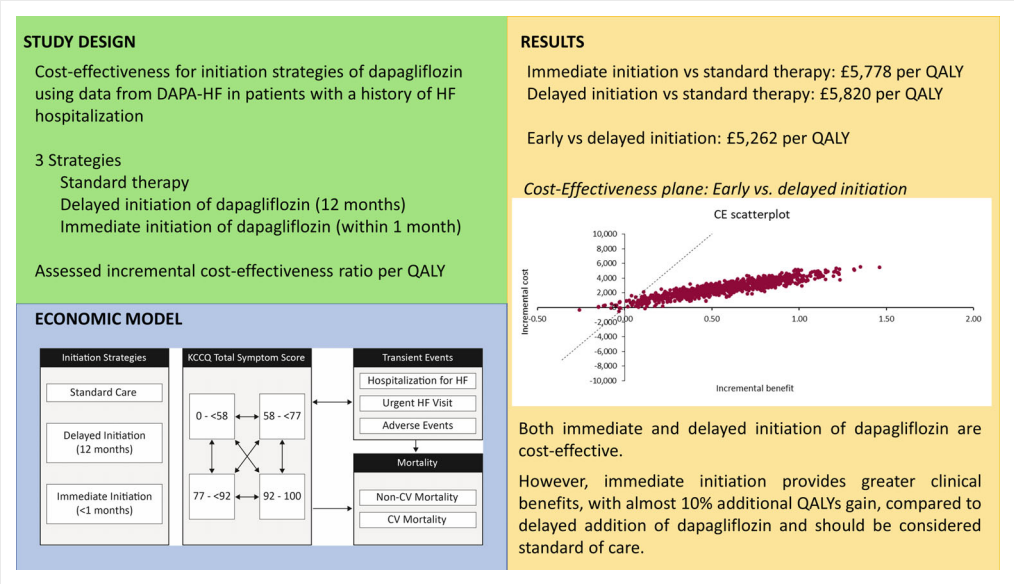
Graphical Abstract



In patients with a history of heart failure (HF) hospitalization, immediate versus delayed initiation of dapagliflozin provides greater clinical benefits and should be considered standard of care. CE, cost-effectiveness; CV, cardiovascular; KCCQ, Kansas City Cardiomyopathy Questionnaire; QALY, quality adjusted life years.

Keywords Pharmacotherapy • Cost-effectiveness • Sodium–glucose cotransporter 2 • Heart failure

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) remains an important cause of morbidity and mortality worldwide.[1] As a result of the high symptom burden and reduced survival, providing medical care for patients with HFrEF is expensive and represents one of the leading demands on healthcare resources globally.[2] In particular, hospitalization for HF (HHF) accounts for a significant proportion of total hospitalizations and is associated with substantial direct healthcare costs.[3]

Recent years have witnessed tremendous improvements in HFrEF medical therapies, with the addition of a number of new agents demonstrating survival benefit. Important among these advancements is the demonstration that the addition of dapagliflozin, a sodium–glucose-contransporter 2 inhibitor (SGLT2i), to standard medical therapy improves outcomes in HFrEF patients.[4] For example, the Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial showed that dapagliflozin 10 mg/day reduces HHF and cardiovascular death when compared with placebo for patients with HFrEF on standard medical therapy.[4] Yet, the risk of adverse events among patients with HFrEF patients remains high, particularly in patients with a history of HHF.[5] Thus, strategies to improve clinical outcomes and maximize health care value are paramount in this population.

Recent economic analyses of the DAPA-HF trial reported that dapagliflozin provided additional health benefits in patients with HFrEF, incurring additional costs which fell within traditional thresholds for good value in health care.[6,7] While prior economic analyses have compared the initiation of dapagliflozin to standard of care, an important clinical consideration is the timing of initiation of dapagliflozin, where immediate initiation of dapagliflozin may be associated with a reduction in risk of cardiovascular death or worsening HF compared to 12-month delayed initiation.[8] Unfortunately, even in dedicated HF clinics, medical therapies are titrated slowly and many patients do not achieve the recommended doses of HF medications.[9] Given the significant early benefits of treatment with dapagliflozin, the cost-effectiveness of immediate versus 12-month delayed dapagliflozin initiation is of clinical and economic relevance. The purpose of this study was to determine whether immediate addition of dapagliflozin to standard therapy was cost-effective compared to a 12-month delay in patients with HFrEF.

Methods

We modified a previously developed Markov state-transition cohort model designed to assess the cost-effectiveness of dapagliflozin relative to standard therapy alone (*Figure 1*).[7] The model is informed by the DAPA-HF (study to evaluate the effect of dapagliflozin on the

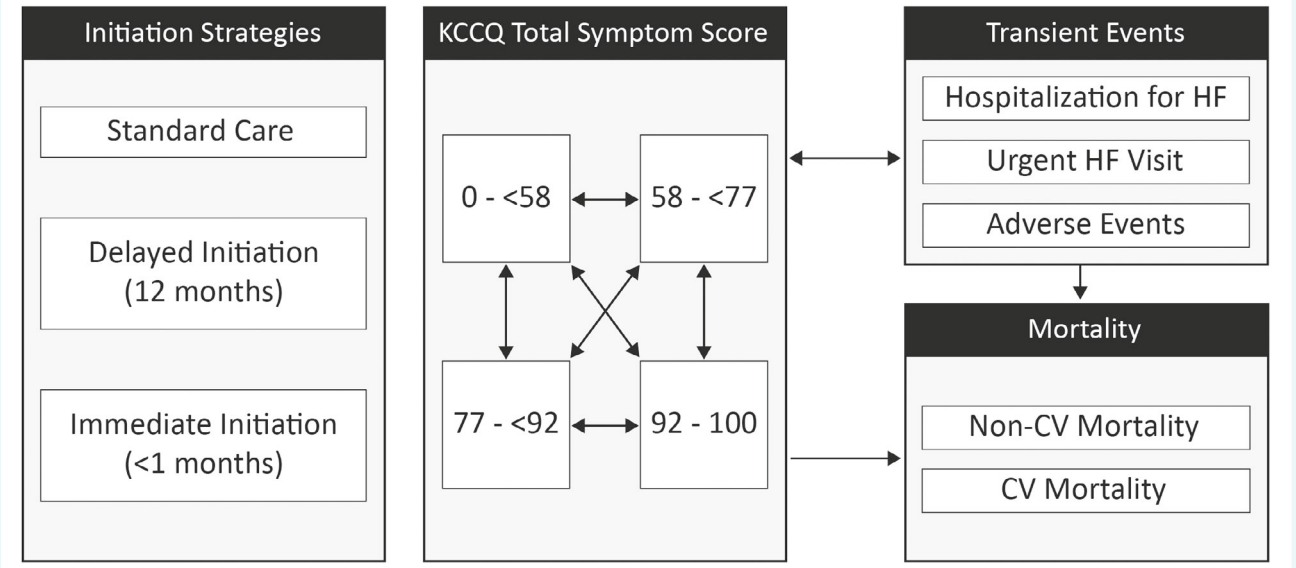


Figure 1 Schematic of economic model. Three initiation strategies were assessed including standard care, 12-month delayed initiation, and immediate initiation of dapagliflozin. CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire.

incidence of worsening HF or cardiovascular death in patients with chronic HF). The study assigned 4744 patients with New York Heart Association class II, III or IV HF and a left ventricular ejection fraction of 40% or less to receive either dapagliflozin 10 mg once daily or placebo, in addition to recommended therapy (ClinicalTrials.gov Identifier NCT03036124).[4,10] Patients were excluded if they had any symptoms of hypotension, a systolic blood pressure >95 mmHg, estimated glomerular filtration rate <30 ml/min/1.73 m^2 (or rapidly declining renal function), or type 1 diabetes mellitus. The trial design, baseline characteristics, and results of the trial have been published.[4,10] The institutional review boards or ethics committees of each of the 410 participating institutions (in 20 countries) approved the protocol, and all patients gave written informed consent.

The key modifications applied to the economic model in this study were as follows. Firstly, our analysis was restricted to the sub-population of DAPA-HF with a history of prior HHF; consequently, all-cause and cardiovascular mortality in addition to risk of HHF were conditional upon this population sub-group. Secondly, we evaluated the cost-effectiveness of dapagliflozin based on timing of initiation in which we compared three treatment strategies: (a) immediate initiation of dapagliflozin (within the first month of HHF), (b) 12-month delayed initiation of dapagliflozin (at 12 months following HHF), and (c) standard therapy without the addition of dapagliflozin. For strategy (a) and (c) the model operates consistently to that previous described[7]; however, for strategy (b) event rates, costs, and transition probabilities for the standard therapy model were applied during the first 12 months with costs and transition probabilities for the dapagliflozin model applied after 12 months. For all scenarios, the model accrues costs and benefits over a lifetime perspective to accommodate the chronic and progressive nature of HF, with a monthly cycle length, consistent with previous HF economic models.[11–13] The primary study endpoint was the incremental cost-effectiveness ratio (ICER), expressed as the cost per quality-adjusted life year (QALY) gained. The primary analysis was conducted from the UK healthcare perspective, with both costs and effects discounted at 3.5% per annum.[14] A secondary analysis was also undertaken, with costs and effects discounted in keeping with country-specific guidelines for economic evaluation (Canada: 1.5%) (Germany and Spain: 3%).[14,15]

Base case and sensitivity analyses

The base case analysis reflected a simulated patient cohort with characteristics consistent with those enrolled in DAPA-HF with prior HHF (online supplementary *Table S1*). Sensitivity analyses were performed in which benefit and cost discounting was varied between 0.0% and 6.0%, health state utilities and costs were varied ± 20%, and effects in sub-populations and various mortality distributions were assessed. Deterministic sensitivity analysis was used to explore the impact of varying input variables on cost-effectiveness and probabilistic sensitivity analysis was used to quantify overall variable uncertainty.[7]

Disease progression

Disease progression was modelled using transitions between discrete health states, characterized by Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) quartiles, as a more precise measure for patient symptoms and a proxy for disease severity.[16] Transition probabilities between health states defined by KCCQ-TSS quartiles were derived using monthly transition count data from DAPA-HF described and summarized previously.[7] Modelled health states were further stratified by baseline type 2 diabetes mellitus (T2DM) status in order to capture reduced quality of life and increased risk and management costs for patients with T2DM.

Clinical events

The model captured clinically relevant events including all-cause mortality, first and recurrent HHF, urgent HF visits, and adverse events collected in the case report forms of the DAPA-HF trial.

Using patient-level data,[4] parametric multivariable survival analysis was used to model all-cause mortality and cardiovascular mortality in those with prior HHF; with adjustment for time-updated KCCQ-TSS, baseline patient characteristics and treatment assignment (dapagliflozin or placebo) by intention-to-treat. Mortality was assumed to follow a Weibull distribution, following survival extrapolations compared to previously published long-term projections to ensure plausible extrapolations.[17–19] The proportion of deaths attributable to non-cardiovascular causes was calculated using country-specific life tables, adjusted to remove cardiovascular mortality to avoid double counting.[20,21]

To estimate the incidence of HHF, negative binominal generalized estimating equation models were developed using the full DAPA-HF trial in which prior HHF was included as a covariate. Incidence of urgent HF visits was applied using a constant treatment arm specific incidence rate since only 33 first urgent HF visits were observed in DAPA-HF. Details of the regression models developed for mortality and HHF have been reported previously.[7]

The following treatment-specific adverse events were included in the economic model based on data collected in DAPA-HF: volume depletion, worsening renal function, episodes of major hypoglycaemia, fracture, diabetic ketoacidosis, amputation, and urinary tract infection. The rate of genital infection was not routinely collected in DAPA-HF. Therefore, the modelled incidence rates are based on the dapagliflozin and placebo arms of DECLARE-TIMI 58.[22] Treatment-specific adverse events were modelled assuming a constant hazard.

Health-related quality of life

The DAPA-HF trial prospectively collected health-related quality of life data at baseline, 4, 8, 12 months, and every 12 months thereafter until the end of the study using the KCCQ and EuroQol five-dimensional five-level questionnaire (EQ-5D-5L).[4] Each EQ-5D-5L response was first mapped to EQ-5D-3L scores,[23] then converted to utility index scores using published UK utility values for EQ-5D health states, derived using the time trade-off method.[24] Linear mixed effects regression models were fitted to patient-reported utility values adjusting for KCCQ-TSS, T2DM status, age and sex in addition to the incidence of discrete clinical events.[16] Disutility estimates for major hypoglycaemia, diabetic ketoacidosis and amputation were sourced from published literature,[25–29] since they were not available from DAPA-HF. Health state utility values are summarized in online supplementary *Table S2*.

Medical resource use and costs

Event-specific costs were applied as a one-off cost in the model with each occurrence of an event. Costs describing background resource use associated with HFrEF were applied to all patients and included contact with primary care, cardiologist visits and emergency department referrals with additional costs included for patients with comorbid T2DM. The country-specific cost inputs are reported in online supplementary *Table S3*. The UK costs were sourced using the publicly available National Health Service (NHS) reference costs. The Canadian costs were sourced from publicly available reference inpatient costs from the Canadian Institute for Health Information,[30] supplemented by inpatient and ambulatory care costs from Alberta Health and Wellness, when required.[31] The German and Spanish costs were identical to those utilized in our previous economic analyses of dapagliflozin treatment.[7] Where event costs were not available in the national reference databases, costs were sourced from the published literature.

Dapagliflozin and standard treatment costs were applied while patients remained on dapagliflozin therapy. Upon discontinuation of dapagliflozin, only the costs of standard therapy were continued. We assumed additional monitoring-related costs associated with dapagliflozin, specifically two outpatient visits for patient review and laboratory investigations, which were applied to those receiving dapagliflozin within the first year. Patient time on treatment was informed by the annual probability of premature discontinuation derived from DAPA-HF (7% per annum). UK medication costs were obtained from the Monthly Index of Medical Specialities, a pharmaceutical prescribing reference guide.[32] Canadian medication costs were obtained from reimbursement prices in the Alberta Drug Benefit List.[33] German medication costs were obtained from AstraZeneca (unpublished data). Spanish medication costs were obtained from Vademecum.[34] Costs were evaluated in 2019 British pound (GBP), 2019 Canadian Dollar (CAD), and 2019 Euro (EUR) equivalents, for the respective country healthcare perspectives. Model input values were sampled from distributions around the means of input parameters. Normal distributions were used for patient characteristics, gamma distributions were utilized for costs, and beta distributions for proportions.

Results

Base case results

Over a lifetime horizon, standard therapy was associated with the lowest cost (£13 244) and the fewest total QALYs (4.023) (*Table 1*). Treatment with dapagliflozin following 12-month delayed initiation was associated with total costs and QALYs of £16 660 and 4.614, respectively. Immediate initiation was associated with the highest total costs and QALYs; £16 912 and 4.662, respectively. Compared to standard therapy, immediate and 12-month delayed initiation of dapagliflozin in addition to standard therapy yielded ICERs of £5778 per QALY gained and £5820 per QALY gained, respectively. When compared to 12-month delayed initiation of dapagliflozin, immediate initiation was associated with an additional cost of £252 and QALY gains of 0.048 resulting in an ICER of £5262 per QALY gained.

Clinical benefit

In the simulated cohort, immediate initiation of dapagliflozin was associated with a reduction in HHF compared to standard therapy (991 vs. 1178 events per 1000 patients, $\Delta = 187$ events). There was also a reduction in urgent HF visits (21 vs. 53 per 1000 patients, $\Delta = 32$ events) and cardiovascular mortality (751 vs. 769 per 1000 patients, $\Delta = 18$ events). Compared to immediate initiation, the strategy of adding dapagliflozin after a12-month delay was associated with a higher rate of HHF ($\Delta = 59$ events), urgent HF visits ($\Delta = 5$ events) and cardiovascular mortality ($\Delta = 4$ events).

The difference in QALYs between immediate and 12-month delayed initiation of dapagliflozin was attributed to a combination of improved survival associated with higher KCCQ scores and an earlier increase in quality of life achieved through immediate dapagliflozin initiation. The latter is illustrated in *Figure 2* and shows the cumulative difference in the number of patients within KCCQ-TSS quartiles over the first 24 months in those initiating dapagliflozin immediately versus a 12-month delay.

Table 1 Base case results (UK healthcare perspective)

	Standard therapy	Standard therapy + dapagliflozin (12-month delayed initiation)	Standard therapy + dapagliflozin (immediate initiation)
Management costs			
Treatment costs (intervention) and monitoring	£964	£3644	£4088
Background medical management	£7416	£8514	£8478
Clinical event costs			
HHF	£2847	£2493	£2346
Urgent HF visit	£18	£9	£7
CV-specific mortality	£1076	£1025	£1022
Adverse event costs	£901	£975	£972
Total costs	**£13 224**	**£16 660**	**£16 912**
QALYs gained by health state			
KCCQ-TSS: 0 to <58	0.5559	0.648	0.539
KCCQ-TSS: 58 to <77	0.9156	1.055	0.937
KCCQ-TSS: 77 to <92	1.2127	1.383	1.363
KCCQ-TSS: 92–100	1.3701	1.555	1.849
Total	4.0544	4.642	4.688
Clinical event disutility			
HHF	−0.027	−0.024	−0.022
Urgent HF visit	−0.000	0.000	0.000
AE-related disutility	−0.004	−0.005	−0.005
Total QALYs	**4.023**	**4.614**	**4.662**
ICERs			
Compared to standard therapy	—	**£5820.51**	**£5778.68**
Compared to 12-month delayed initiation	—	—	**£5262.52**

AE, adverse event; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; ICER, incremental cost-effectiveness ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total summary score; QALY, quality-adjusted life year.

Sub-group analysis and parameter uncertainty

The cost-effectiveness of immediate and 12-month delayed initiation of dapagliflozin compared to standard therapy was stable across a range of deterministic sensitivity analyses (*Figure 3*). The ICER of immediate compared to 12-month delayed initiation of dapagliflozin was most sensitive to benefit and cost discounting parameters as well as intervention costs.

The cost-effectiveness acceptability curve displays the probability of each strategy accruing the best net health benefit at different willingness-to-pay thresholds (*Figure 4*). The cost-effectiveness plane, for immediate versus 12-month delayed initiation of dapagliflozin is shown in *Figure 5*. At a conservative willingness-to-pay threshold of £20 000 per QALY gained, immediate initiation of dapagliflozin was cost-effective in >99% of simulations.

Canadian healthcare perspective

A summary of costs and utility in the Canadian healthcare analysis are shown in online supplementary *Table S4*. The 12-month delayed initiation of dapagliflozin was associated with total discounted lifetime costs and QALYs of $53 839 and 5.079, respectively. Immediate initiation of dapagliflozin was associated with lifetime cost and QALYs; $53 940 and 5.138, respectively. Compared to standard therapy (total lifetime costs of $47 096 and QALYs of 4.373), both immediate and 12-month delayed initiation of dapagliflozin were economically attractive with ICERs of $8945 and $9553 per QALY gained, respectively. Consequently, immediate initiation of dapagliflozin was associated with an additional cost of $101 and QALY gains of 0.059, resulting in an ICER of $1708 per QALY gained.

German healthcare perspective

A summary of costs and utility in the German healthcare analysis is shown in online supplementary *Table S5*. The 12-month delayed initiation of dapagliflozin was associated with total discounted lifetime costs and QALYs of €26 222 and 4.721, respectively. Immediate initiation of dapagliflozin was associated with lifetime cost and QALYs; €26 257 and 4.772, respectively. Compared to standard therapy (total lifetime costs of €23 020 and QALYs of 4.105), both immediate and 12-month delayed initiation of dapagliflozin were economically attractive with ICERs of €4853 and €5193 per QALY gained, respectively. Consequently, immediate initiation of dapagliflozin was associated with an additional cost of €35 and QALY gains of 0.051, resulting in an ICER of $686 per QALY gained.

Spanish healthcare perspective

A summary of costs and utility in the Spanish healthcare analysis is shown in online supplementary *Table S6*. The 12-month delayed initiation of dapagliflozin was associated with total discounted lifetime costs and QALYs of €25 469 and 4.721, respectively. Immediate initiation of dapagliflozin was associated with lifetime cost and QALYs; €25 809 and 4.772, respectively. Compared to standard therapy (total lifetime costs of €19 832 and QALYs of 4.105), both immediate and 12-month delayed initiation of dapagliflozin were economically attractive with ICERs of €8963 and €9144 per QALY gained, respectively. Consequently, immediate initiation of dapagliflozin was associated with an additional cost of €340 and QALY gains of 0.051, resulting in an ICER of $6733 per QALY gained.

Discussion

In this analysis, we demonstrate the cost-effectiveness of dapagliflozin addition to standard therapy in persistent HFrEF, irrespective of the timing of initiation. However, a strategy of immediate initiation of dapagliflozin is more economically attractive and clinically favourable compared to a 12-month delay; providing an additional 0.048 QALYs, this represents almost 10% additional clinical benefit that is realized at little additional cost (£252). The immediate initiation of dapagliflozin was associated with a minimal increase in patient management costs (£408) compared to initiation after 1 year but was estimated to prevent 59 HHF, 5 urgent HF visits, and 4 cardiovascular deaths for every 1000 patients treated. The increase in management costs is

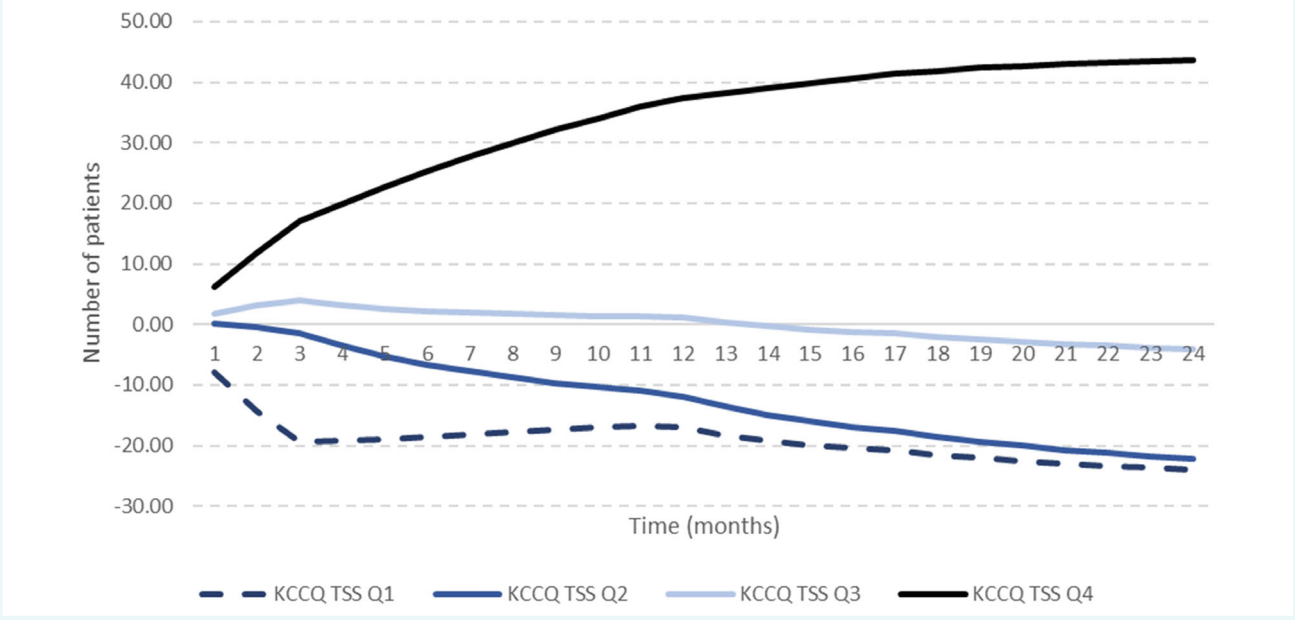


Figure 2 Comparison of difference in number of patients within each Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) quartile comparing treatment with immediate versus 12-month delayed initiation of dapagliflozin. Immediate initiation of dapagliflozin was associated with an early increase in the number of patients in the fourth quartile of KCCQ-TSS, with commensurate decrease in patients in the first two quartiles.

expected to be partially offset by reduced costs associated with these clinical events, while the improvement in QALY is further increased by more time spent in a higher KCCQ class with immediate compared to delayed initiation of dapagliflozin. These results occur with use of a robust costing and evaluation model, fall within accepted willingness-to-pay thresholds, and were similar from a multinational healthcare perspectives and remain valid irrespective of baseline risk or comorbidity. The major driver of cost is the acquisition cost of dapagliflozin, with the clinical benefits including reduction of death, hospitalization and improved health status. These data strongly support inclusion of dapagliflozin to standard HFrEF therapy as soon as possible.

In our previous analysis, we evaluated the cost-effectiveness of dapagliflozin across several sub-groups including those with/without prior HHF, HF duration and age. Across all subgroups, the cost-effectiveness results (assessed over a lifetime) were stable, with only modest numerical differences. Our current analysis indicates that the benefits accruing from the use of dapagliflozin over the short term (1 year) justify the acquisition cost of the drug over the same period, at conventional willingness-to-pay thresholds. Consequently, and from a health economics standpoint, there appears to be little justification for delaying the use of dapagliflozin in patients with HF.

Timeliness of initiation of goal-directed medical therapy for HFrEF has often been overlooked in deference to establishment of optimal baseline treatment prior to addition of newer agents. This has likely contributed to a climate of clinical inertia and consequent delays in both initiation and titration of medical therapy. As has been shown in numerous clinical HF registries,[9,35] delays in medical optimization may take weeks or months, and penetration of effective therapies at a population level may occur over several years. This clinical inertia leaves patients undertreated and at unnecessarily high risk of adverse events.[36] In particular, our analysis suggests that initiation of dapagliflozin should occur immediately following HHF rather than waiting for a period of time or subsequent events.

The urgency of medical treatment optimization has taken a central role in HF management due to the development of novel therapies showing early and substantial clinical benefit.[36,37] It is therefore timely to describe the healthcare value of early initiation of efficacious therapies, quantified through economic analysis. To our knowledge, the cost-effectiveness of dapagliflozin based on timing of initiation has not been previously described. We demonstrate that immediate initiation of dapagliflozin was cost-effective compared to a 12-month delay, with an estimated ICER well within conventional willingness-to-pay thresholds from the perspectives of four different national healthcare systems. Few economic evaluations comparing dapagliflozin to placebo are available. In prior analysis conducted by our group, there were small variances in the estimates of QALYs and ICERs with the addition of dapagliflozin; however, these differences are related to adjusting the model to account for timing of initiation.[7] Parizo *et al.*[6] estimated a higher ICER ($83 650 per QALY gained) for use of dapagliflozin from the perspective of the US healthcare system. While comparisons of ICERs are limited by country-specific contexts, it is worth noting that the authors used drug list prices in their base case which are typically double (or greater) the net drug price.[38] Consistent with our analysis, the estimated ICER was sensitive to drug costs.

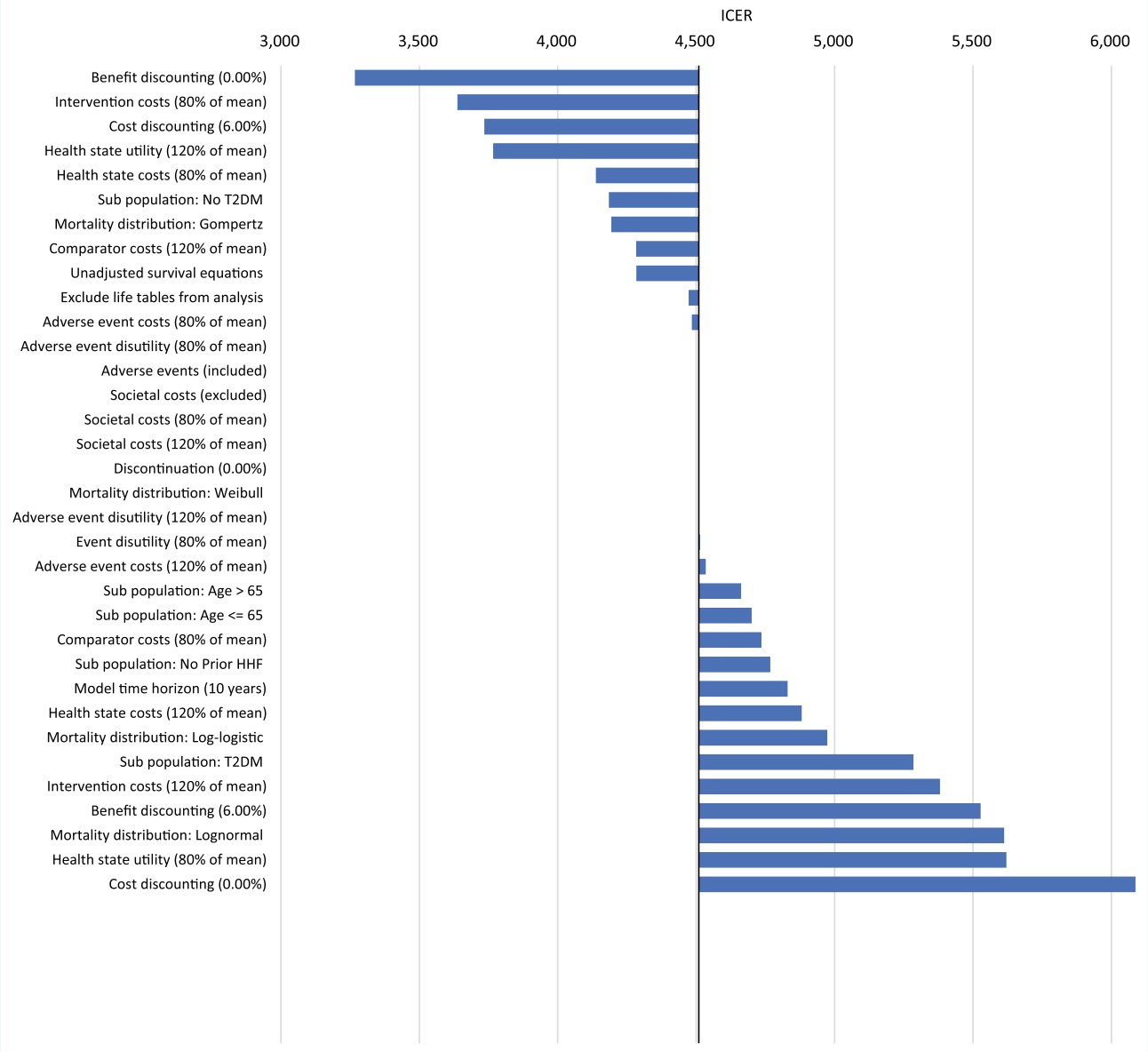


Figure 3 Tornado diagram outlining the incremental cost-effectiveness ratio (ICER) of immediate initiation compared to 12-month delayed initiation of dapagliflozin across a variety of sensitivity analyses. HHF, hospitalization for heart failure; T2DM, type 2 diabetes mellitus.

There is clinical interest in even earlier initiation of SGLT2i while patients are in hospital with acutely decompensated HF as the result of two studies demonstrating the safety of early initiation.[39] Bhatt *et al.*[40] demonstrated that initiation of the SGLT1/2i sotagliflozin prior to discharge in patients with diabetes admitted for worsening HF decreased rates of cardiovascular death, HHF, and urgent HF visits. Voors *et al.*[41] also reported benefits of early initiation of empagliflozin in patients hospitalized for worsening HF. It will be increasingly important to determine the clinical and cost benefits (if any) for patients hospitalized with decompensated HF as they represent a vulnerable HF subgroup, where event trajectories are accelerated early on, before clinical stabilization and a return to linear event rates.

The cost-effectiveness related to timing of initiation of other HF therapies has been previously studied. For example, sacubitril/valsartan has been shown to be cost-effective when administered early.[11,42] Grant *et al.*[11] showed, using published data from the PARADIGM-HF trial, that *de novo* administration (or immediate initiation) of sacubitril/valsartan was associated with a lifetime total 5.697 QALYs compared to 5.628 QALYs with a strategy of initiating sacubitril/valsartan following a 12-month delay. In this analysis, the *de novo* strategy resulted in nearly 25% of the overall QALY benefit of sacubitril/valsartan over angiotensin-converting enzyme inhibitor therapy for a total cost of CAD $24 426 (or £14 189.67).[11] Gaziano *et al.*[42] evaluated cost-effectiveness of sacubitril/valsartan in the acute hospital period using patient-level

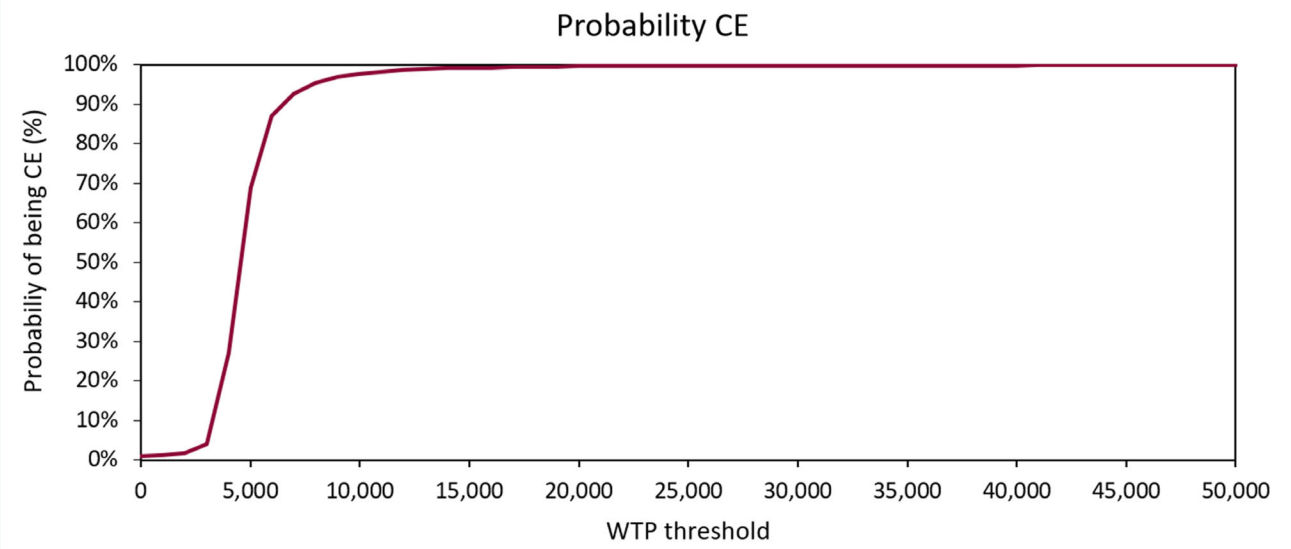


Figure 4 Cost-effectiveness (CE) acceptability curve showing the probability of a strategy being cost-effective over a range of willingness-to-pay (WTP) thresholds.

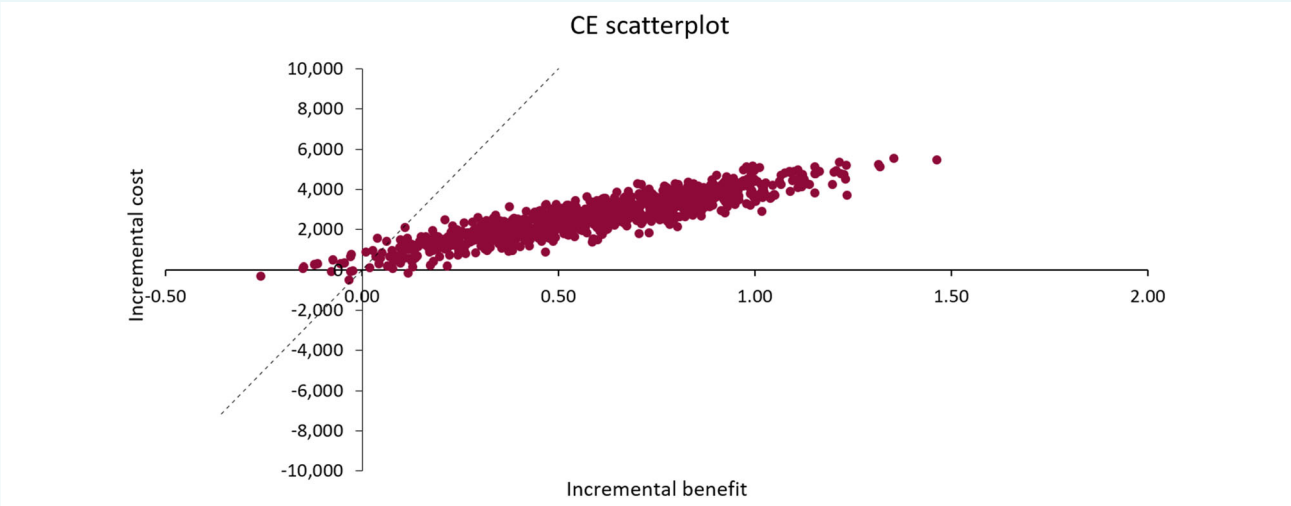


Figure 5 Incremental cost-effectiveness (CE) plane comparing immediate initiation to 12-month delayed initiation of dapagliflozin.

data from the PIONEER HF trial. In this analysis, in-hospital initiation (as per protocol) was compared with a 2-month delay. The authors reported a large 0.27 increase in QALYs which was almost completely driven by fewer repeat hospitalizations observed in the in-hospital administration.[42] Thus, it is quite likely that cost-effectiveness will not only vary with timing of therapy, but also with baseline risk of the target population.

There are several limitations of the present study. The use of a lifetime Markov model required extrapolations of event rates beyond the actual 18-month median follow-up period observed in the DAPA-HF trial. However, previously these model assumptions have generally aligned with outcomes observed during long-term follow-up in similar trials. We calculated ICERs for specific healthcare perspectives, but the DAPA-HF trial included patients from multiple countries. However, there were no country-specific interaction with drug efficacy observed in DAPA-HF. Finally, all patients were exposed to the study drug at randomization visit. This analysis assumed that the beneficial effect of dapagliflozin would be the same after initiation irrespective of timing. In response, we imputed the effect of the drug on outcomes and health status in response to addition of dapagliflozin at both baseline and after 12-month delay, hypothesizing a similar differential effect on KCCQ score. This may not actually be the case which may have introduced error into the health status inputs.

Immediate or 12-month delayed initiation of dapagliflozin in addition to standard therapy is cost-effective from a multinational

healthcare perspective. However, immediate initiation is associated with rapid improvement in patient symptoms and reduction in HF events leading to almost 10% greater QALY gains for minimal additional cost. These data strongly support inclusion of dapagliflozin to standard HFrEF therapy as soon as possible.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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