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RESEARCH ARTICLE

Cost-effectiveness of dapagliflozin for patients with heart failure across the spectrum of ejection fraction: A pooled analysis of DAPA-HF and DELIVER data

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Aim To assess the cost-effectiveness of dapagliflozin in addition to usual care, compared with usual care alone, in a large population of patients with heart failure (HF), spanning the full range of left ventricular ejection fraction (LVEF).

Methods and results Patient-level data were pooled from HF trials (DAPA-HF, DELIVER) to generate a population including HF with reduced, mildly reduced and preserved LVEF, to increase statistical power and enable exploration of interactions among LVEF, renal function and N-terminal pro-B-type natriuretic peptide levels, as they are relevant determinants of health status in this population. Survival and HF recurrent event risk equations were derived and applied to a lifetime horizon Markov model with health states defined by Kansas City Cardiomyopathy Questionnaire total symptom score quartiles; costs and utilities were in the UK setting. The base case incremental cost-effectiveness ratio (ICER) was £6470 per quality-adjusted life year (QALY) gained, well below the UK willingness-to-pay (WTP) threshold of £20 000/QALY gained. In interaction sensitivity analyses, the highest ICER was observed for elderly patients with preserved LVEF (£16 624/QALY gained), and ranged to a region of dominance (increased QALYs, decreased costs) for patients with poorer renal function and reduced/mildly reduced LVEF. Results across the patient characteristic interaction plane were mostly between £5000 and £10 000/QALY gained.

Conclusions Dapagliflozin plus usual care, versus usual care alone, yielded results well below the WTP threshold for the UK across a heterogeneous population of patients with HF including the full spectrum of LVEF, and is likely a cost-effective intervention.

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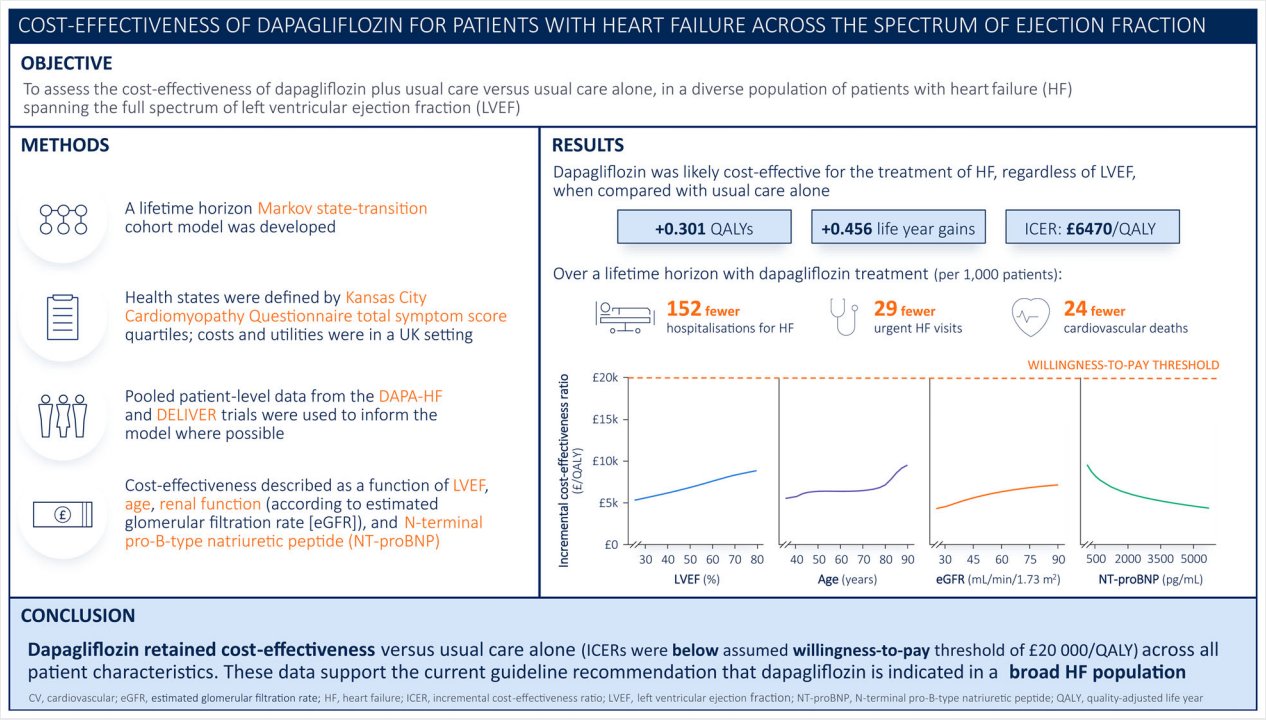
Graphical Abstract



Cost-effectiveness of dapagliflozin for patients with heart failure across the spectrum of ejection fraction.

Keywords Cost-effectiveness • Dapagliflozin • Heart failure • Reduced ejection fraction • Mildly reduced ejection fraction • Preserved ejection fraction

Introduction

Heart failure (HF) is considered the fastest growing cardiovascular (CV) health burden,[1] accounting for up to 2% of total hospital admissions in western countries.[2] Globally, this presents considerable strain on healthcare systems' budget, capacity and resource use, which will only increase alongside the growing prevalence of HF.[3] Sodium–glucose cotransporter 2 (SGLT2) inhibitors such as dapagliflozin, have the potential to partly ease this burden by reducing the risk of CV-related deaths and hospitalizations for patients with HF across the full range of left ventricular ejection fraction (LVEF).[4–6] However, the European Society of Cardiology guidelines state that the implementation of recommendations should not only be based on clinical evidence, but also on cost-effectiveness analyses, which consider expense relative to benefit at a national level.[7]

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[4] and Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure (DELIVER)[5] trials were powered for their primary composite endpoints, meaning important secondary outcomes, such as CV mortality (CVM), were not definitively evaluated. However, further analysis has since demonstrated that through the increased statistical power of pooling clinical trial data, no attenuation of dapagliflozin treatment effect was observed across the broad range of LVEF for CVM and hospitalization for HF (HHF).[6] To build upon these findings, the present study used pooled patient-level data from the DAPA-HF and DELIVER trials to explore the cost-effectiveness of dapagliflozin as a function of LVEF, alongside other patient characteristics such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), age, and renal function (according to estimated glomerular filtration rate [eGFR]). By using a broader set of patient-level data, the model was able to robustly explore the influence of varying clinical parameters on the cost-effectiveness of dapagliflozin in patients with HF, allowing the trajectory of the incremental cost-effectiveness ratio (ICER) to be investigated across a continuum of the clinical variable of interest. Traditional cost-effectiveness studies, in contrast, evaluate sensitivity through one-directional parameter changes. This novel approach has the potential to identify specific sub-populations where dapagliflozin

yields the most value for money, thus supporting healthcare decision-making.

Methods

Overview

Pooled patient-level data from the DAPA-HF and DELIVER trials were used to inform the model, where appropriate. Briefly, the DAPA-HF trial (NCT03036124)[4] was an event-driven, randomized, double-blind, placebo-controlled, phase 3 study in patients with HF and a LVEF ≤40%. The DELIVER trial (NCT03619213)[5] was an event-driven, randomized, double-blind, placebo-controlled study in patients with HF and a LVEF >40%. Further details of the DAPA-HF and DELIVER trial design, including eligibility criteria, ethical approval and informed consent have been previously published.[5,8]

The present analysis follows the approach used in a previously published and validated model of HF,[9] here adapted to a pooled HF population from the perspective of the UK payer. Briefly, after assessment of suitability of merging patient-level data from the DAPA-HF and DELIVER trials, a pooled HF data set was generated consisting of 11 007 patients. As testing of heterogeneity between trial populations was conducted in another study,[6] the applicability of generating statistical models across the pooled population was deemed valid. Following the pre-specified modelling and analysis plan, the pooled data were used to generate adjusted parametric statistical models of survival and recurrent event occurrence for use in a Markov state-transition cohort model for a HF population (online supplementary *Figure S1*) built in Microsoft Excel®.

The purpose of the present analysis was to evaluate the cost-effectiveness of dapagliflozin added to usual care, versus usual care alone, for the treatment of patients with HF. A lifetime horizon with a monthly cycle length was used to reflect the chronic and progressive pathology of HF.[10–12] The ICER was the primary model outcome for this analysis, which was measured according to the cost per quality-adjusted life year (QALY) gained. The willingness-to-pay (WTP) threshold of £20 000/QALY was taken from national guideline recommendations, as was the applied annual discount rate of 3.5% to future value of costs and effects.[13]

The primary analysis consisted of cost-effectiveness outcomes in line with mean baseline characteristics of the pooled HF population (*Table 1*). In addition to the ICER, model outcomes included clinical events (HHF, urgent HF visits [UHFV], and CVM) and overall survival (via all-cause mortality [ACM]). To measure the influence of uncertainty around specific inputs on the model results, probabilistic sensitivity analysis was employed. Furthermore, sensitivity analyses of clinically relevant subgroups including stratification by LVEF, age, eGFR and NT-proBNP were undertaken to determine how the cost-effectiveness outcomes varied as a function of key patient characteristics. Patient characteristics were weighted to target demographics and run through the cost-effectiveness model to generate model outputs. The consolidated health economic evaluation reporting standard (CHEERS 2022) checklist was followed throughout this cost-effectiveness analysis.

Table 1 Baseline characteristics of the pooled DAPA-HF and DELIVER population

Parameter	Mean	Standard error
Demographics		
Age (years)	69.37	0.10
Proportion male	0.650	0.005
BMI (kg/m^2)	29.12	0.06
Proportion white	0.706	0.004
Proportion black/African	0.035	0.002
Proportion other race	0.042	0.002
Clinical characteristics		
Proportion in KCCQ-TSS Q1	0.249	0.004
Proportion in KCCQ-TSS Q2	0.243	0.004
Proportion in KCCQ-TSS Q3	0.263	0.004
Proportion in KCCQ-TSS Q4	0.244	0.004
Proportion in NYHA class III/IV	0.281	0.004
LVEF (%)	44.20	0.13
NT-proBNP (pg/ml)	1900.87	23.82
Creatinine (μmol/L)	103.32	0.29
SBP (mmHg)	125.46	0.15
Heart rate (bpm)	71.49	0.11
Medical history		
Proportion with T2DM	0.435	0.005
Proportion with AFF	0.343	0.005
Proportion with most recent HHF >6 months	0.245	0.004
Proportion with most recent HHF ≤6 months	0.190	0.004
Proportion with HF duration >2 years	0.566	0.005
Proportion with prior MI	0.339	0.005

AFF, atrial fibrillation/flutter; BMI, body mass index; HF, heart failure; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Disease progression and health states

The progression of HF was modelled using transitions between discrete health states defined by Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) quartiles, a patient-reported measure spanning symptom burden and frequency, but excluding symptom stability.[14] Between each defined health state, transition probabilities were calculated using monthly transition count data, assuming patients remained in a KCCQ-TSS quartile until an observation which indicated movement. Bayesian analysis was used to estimate the multinomial transition probabilities using a flat Dirichlet prior distribution and Gibbs sampling to provide the posterior probability distribution.[15] Since both the DAPA-HF and DELIVER trials demonstrated statistically significant change in KCCQ-TSS based on dapagliflozin treatment, treatment-specific transition probabilities were considered. The treatment-stratified monthly transition probabilities are presented in online supplementary *Table S1*.

Mortality, heart failure events and adverse events

To predict CVM and ACM over time, multivariable parametric survival models were used. In line with guidelines for the analysis of survival data alongside clinical trials, survival analysis was conducted from

an intention-to-treat perspective.[16,17] A null model consisting of treatment arm and time-updating health state served as the basis for a forward variable selection process with a candidate set of variables, to objectively determine those that contributed to and improved model fit (online supplementary *Table S2*). Candidate variables were selected based on those expected to affect survival or risk of events, available data, and clinical opinion. General population life tables for the UK were adjusted based on data reported by the World Health Organization describing age and sex-stratified UK-specific incident rates of CVM, to estimate non-CVM among the general population. This method was used to minimize the risk of double-counting and to avoid unrealistic survival predictions. Survival extrapolations were validated against published long-term observational studies[18,19] to inform the selection of the Weibull distribution as the base case mortality model, coefficients for which are presented in online supplementary *Table S3*.

The incidence of HF events (HHF and UHFV) were captured as transient events by the model. Given the high frequency of recurrent events, multivariable generalized estimating equations were employed. Similar to the survival analysis, forward variable selection was used to identify adjustment variables in predictive HHF and UHFV models. The coefficients of the regression models are presented in online supplementary *Table S4*.

Serious adverse events (SAEs) in >1% of the pooled DAPA-HF and DELIVER trial populations and adverse events (AEs) of special clinical interest, were included in the model. The model considered the risk of an AE as treatment-dependent, where a constant risk was employed (online supplementary *Table S5*).

A constant risk of discontinuation (6.7% per year) existed for patients receiving dapagliflozin treatment. For modelled patients who discontinued dapagliflozin treatment, the risk of disease progression, mortality, HF events and AEs was assumed equivalent to those receiving usual care alone.

Resource use

Relevant health state costs (inflated to 2022 Pounds Sterling) were assigned to the modelled KCCQ-TSS quartile health states in order to reflect the burden of HF.[20] Across a monthly cycle, the proportion of patients in each health state informed the relevant resource use and included the cost of primary care and cardiologist visits. Resource use was informed by a previous cost-effectiveness analysis, and corresponding costs inflated to net present 2022 values.[20] Upon incidence of a transient event or an AE, a one-off event cost was applied in the model. Patients in receipt of dapagliflozin treatment were subject to treatment-related costs, in addition to the cost of usual care. For those who discontinued dapagliflozin treatment, only the cost of usual care was applied. The cost of usual care was derived by applying the proportions of patients taking classes of medications common in HF (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists and loop diuretics) to costs in the UK setting of representative members of each class (enalapril, candesartan, sacubitril/valsartan, bisoprolol, spironolactone and furosemide, respectively) across the pooled HF population. The cost inputs are reported in *Table 2*.[20–25]

Health-related quality of life

Analysis of patient-level EQ-5D-5L data from the pooled DAPA-HF and DELIVER trials was used to inform modelled utility values. Utility index scores were calculated using a UK value set and guideline-recommended approach of Hernandez-Alava. These scores were subjected to linear mixed effects regression modelling to estimate relevant utilities for health states and transient events. Values assigned to KCCQ-TSS quartile health states were used to capture the impact of disease on health-related quality of life (HRQoL). Relevant utility values were applied to the proportion of patients in each health state per cycle. Upon the occurrence of a transient event or an AE, a one-off utility decrement was applied. The health state utilities and utility decrements applied in the model are reported in *Table 2*.[20–25]

Results

The results of the model indicated that dapagliflozin, added to usual care, was likely cost-effective for the treatment of the HF population, regardless of LVEF (*Table 3*). Patients receiving dapagliflozin were forecast to accrue an additional 0.301 discounted QALYs, and an associated ICER of £6470/QALY gained, thus below the WTP threshold for the UK setting. The model predicted that patients treated with dapagliflozin, in addition to usual care, would have 0.456 undiscounted life year gains, versus patients treated with usual care alone. Additionally, patients in receipt of dapagliflozin treatment spent more time in the best KCCQ-TSS quartile when compared with those receiving usual care (38.4 months vs. 33.1 months), and less time in the poorest KCCQ-TSS quartile when compared with those treated with usual care alone (15.1 months vs. 16.6 months). Over a lifetime horizon, the model projected that dapagliflozin treatment, added to usual care, resulted in 152 fewer HHF events, 29 fewer UHFV and 24 fewer CV deaths per 1000 patients, which corresponded to an average reduction of £591 per patient for these events, compared to increases of £2667 for treatment and background maintenance costs associated with increased survival. The robustness of the results was assessed in a probabilistic sensitivity analysis, in which 99.1% of simulations fell within the bounds of cost-effectiveness (online supplementary *Figure S2*).

One-way sensitivity analysis

To understand the influence of clinical characteristics on economic outcomes, clinical scenario analyses are presented (*Figure 1*). Results of this analysis indicated that dapagliflozin retained cost-effectiveness versus usual care alone, where the projected ICERs were well below the WTP threshold for all parameters considered (*Figure 1*). As illustrated in *Figure 1*, minor deviations in the ICER by clinical characteristics were observed and overall, dapagliflozin appeared more cost-effective in subgroups of patients who may be considered higher risk. This included patients with markedly reduced ejection fraction (LVEF 25%, ICER: £5331/QALY gained), advanced renal disease (eGFR 25 ml/min/1.73 m^2, ICER: £4327/QALY gained), and elevated NT-proBNP (6000 pg/ml, ICER: £4367/QALY gained). An exception to this trend was observed in the age dimension, where elderly patients were predicted to have higher ICERs compared with the youngest age sampled. Correspondingly, ICER maxima were observed

Table 2 Model inputs

Parameter	Mean	Standard error	Source
Costs			
Health state costs			
Annual cost in KCCQ-TSS Q1	£953.00	£190.60[a]	Booth et al.[20]
Annual cost in KCCQ-TSS Q2			
Annual cost in KCCQ-TSS Q3			
Annual cost in KCCQ-TSS Q4			
Event costs			
HHF	£4204.34	£840.87[a]	Booth et al.[20]
UHFV	£757.74	£151.55[a]	
CVM	£1811.35	£614.60[a]	
Non-CVM	£0.00	£0.00	Assumption
Treatment costs			
Annual cost of dapagliflozin	£477.30	£0.00	MIMS[21]
Annual cost of usual care	£142.80[b]	£0.00	BNF[22]
AE costs			
Acute kidney injury	£4096.04	£819.21	Booth et al.[20]
Amputation	£17 737.09	£3547.41	
Fracture	£5353.98	£1070.79	
Urinary tract infection	£40.06[c]	£8.01	
Volume depletion	£40.06[c]	£8.01	
Utility			
Health state utilities			
KCCQ-TSS Q1	0.583	0.002	DAPA-HF/DELIVER
KCCQ-TSS Q2	0.698	0.002	
KCCQ-TSS Q3	0.776	0.002	
KCCQ-TSS Q4	0.856	0.002	
Event utility decrements			
HHF	−0.020	0.011	DAPA-HF/DELIVER
UHFV	−0.060	0.035	
AE utility decrements			
Acute kidney injury	−0.073	0.034	DAPA-HF/DELIVER
Amputation	−0.280	0.056	Beaudet et al.[23]
Fracture	−0.278	0.039	DAPA-HF/DELIVER
Urinary tract infection	−0.003	0.001	Barry et al.[24]
Volume depletion	−0.115	0.028	DAPA-HF/DELIVER

Costs were inflated from 2021 values to 2022 values using an inflation factor of 1.027 derived from the Unit Costs of Health and Social Care programme 2022.[25]
AE, adverse event; BNF, British National Formulary; CVM, cardiovascular mortality; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; MIMS, Monthly Index of Medical Specialties; UHFV, urgent heart failure visit.
[a]Standard error assumed to be 20% of the mean value.
[b]The cost of usual care was derived as a weighted average of enalapril, candesartan, sacubitril/valsartan, bisoprolol, spironolactone and furosemide based on the reported proportion of patients receiving the corresponding drug classes in the DELIVER and DAPA-HF trials.
[c]Assumed to be the cost of a general practitioner visit.

for subgroups considered lower risk (aside from age) including normal renal function, increased ejection fraction and lower NT-proBNP, yet all remained well below the applied WTP threshold.

Similar one-way analysis was conducted to assess the effect of varying patient characteristics on the projected event counts for HHF, UHFV and CV death. Across all parameters, treatment with dapagliflozin, added to usual care, was predicted to result in fewer clinical events when compared with patients treated with usual care alone (*Figure 2*). For each arm, the absolute event numbers for HHF increased according to higher risk profiles (markedly reduced ejection fraction, lower eGFR and elevated NT-proBNP), with the exception of age where the fewer events predicted for elderly patients may be attributed to their shorter expected lifespan and therefore less time to experience a recurrent event. The absolute event numbers for UHFV followed a similar trend for age, eGFR and NT-proBNP, however UHFVs were predicted to decrease with reduced LVEF. The absolute event numbers for CV deaths were projected to be highest for patients with reduced ejection fraction or elevated NT-proBNP, whereas in terms of age, the highest counts were predicted for the youngest patients.

Table 3 Base case results

Parameter	Dapagliflozin plus usual care	Usual care	Incremental
Event incidence (per 1000 patients)			
HHF	842.1	994.2	−152.1
UHFV	148.9	177.9	−28.9
CV death	522.4	546.1	−23.7
Cost-effectiveness (per patient)			
Total discounted costs	£14 753	£12 805	£1948
Total discounted QALYs	5.184	4.882	0.301
Total discounted life years	8.597	8.141	0.456
ICER (cost/QALY)			£6470/QALY

CV, cardiovascular; HHF, hospitalization for heart failure; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UHFV, urgent heart failure visit.

Interaction analysis of left ventricular ejection fraction and other patient characteristics

Two-way analysis was conducted to evaluate the impact of the interactions between LVEF and the remaining characteristics on the ICER for treatment with dapagliflozin, added to usual care, versus usual care alone. LVEF was held as a common interaction term as it represents a key characteristic used to categorize patients with HF and in these analyses, was varied in combination with age, eGFR, and NT-proBNP.

The corresponding ICERs for each two-way analysis were compared via contours to identify potential regions where changes in LVEF may interact with changes in other characteristics to affect the resultant ICER (*Figure 3*). Across the contours of ICERs generated by varying cohort characteristics, estimates of cost-effectiveness remain stable, with most modelled ICERs (85.0%) in the range of £5000 to £10 000/QALY gained; extremes ranged from dominant (where the intervention is predicted to both reduce total costs and increase QALYs) up to £16 624, a value still below the WTP threshold of £20 000/QALY. ICER maxima corresponded to lower risk profiles including eGFR 75 ml/min/1.73 m^2 with LVEF 80% (£9171/QALY gained) and NT-proBNP 400 pg/ml with LVEF 80% (£11 402/QALY gained). The overall maximum was predicted for patients aged 90 years with LVEF 80% (£16 624/QALY gained). Conversely, the profiles of highest adverse risk were associated with lower ICERs (dominant for LVEF 25% with age 90 years and dominant for LVEF 25% with eGFR ≤30 ml/min/1.73 m^2; £3835/QALY gained for LVEF 25% with NT-proBNP 6000 pg/ml).

Beyond point estimates of extremes, regions of potential interest that deviate from the relatively flat plane included a region of ICERs ranging from low to dominant, projected for cohorts of moderate to severe renal impairment (eGFR 25–45 ml/min/1.73 m^2) and reduced to mildly reduced LVEF (LVEF 25–50%). A similar region of low ICERs was produced in very elderly patients (age 80 years or older) with reduced LVEF.

Discussion

Based on pooled patient-level data from the DAPA-HF and DELIVER trials, the model results suggest that dapagliflozin, added to usual care, is likely a cost-effective therapy for patients with HF with a wide range of clinical characteristics, compared with usual care alone, illustrated here in the UK setting. These findings were attributed to the increased survival, slowed disease progression, and the reduced incidence of clinical events associated with dapagliflozin, versus usual care alone, which ultimately provided important cost-offsets to the additional cost of dapagliflozin treatment. Results of sensitivity analyses indicated that the cost-effectiveness of dapagliflozin was robust to changes in clinical characteristics, where the ICER remained below the local WTP threshold when LVEF, age, eGFR and NT-proBNP were varied individually and in combination (*Graphical Abstract*).

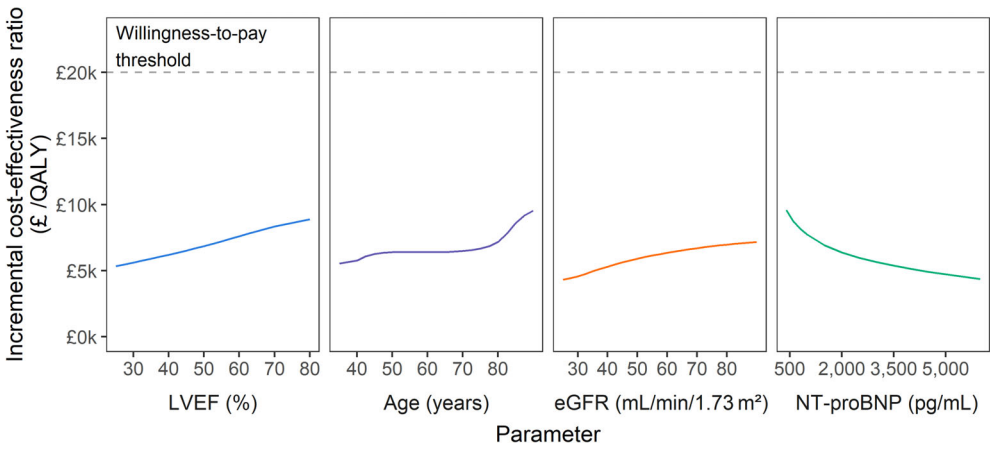


Figure 1 Cost-effectiveness impact of varying patient characteristics. The dashed line indicates the willingness-to-pay threshold in the present analysis. eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QALY, quality-adjusted life year.

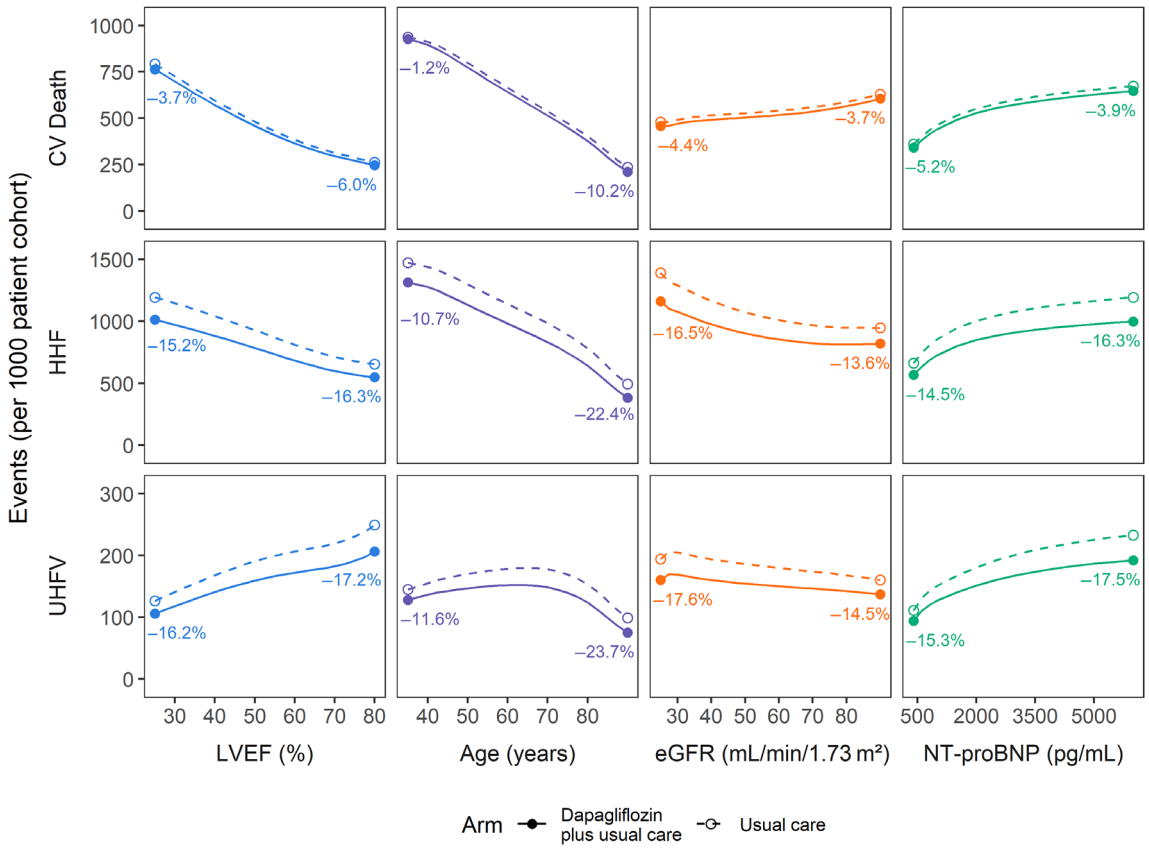


Figure 2 Change in projected event counts by varied patient characteristics. Lines illustrate the trajectory of predicted absolute event counts by treatment arm in cardiovascular (CV) death, hospitalization for heart failure (HHF) and urgent heart failure visit (UHFV) events upon treatment with dapagliflozin plus usual care and usual care alone according to variations in patient characteristics of left ventricular ejection fraction (LVEF), age, estimated glomerular filtration rate (eGFR), and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Points at the extremes of each range are labelled with the relative percent reduction in event count for the dapagliflozin treatment arm relative to usual care alone.

The findings of the current analysis indicate that the clinical and economic benefits of dapagliflozin may be realized in a broad HF population, regardless of LVEF. This is particularly important for patients with HF with mildly reduced or preserved ejection fraction, given the limited HF therapies specifically tailored to patients with this phenotype. Meanwhile, these findings may have further clinical implications for healthcare providers. There are several challenges to the current classification of HF, where choice of treatment is largely based on pre-defined subgroups of LVEF.[26] HF is a progressive and heterogeneous disease in which LVEF fluctuates, creating a continuum of HF phenotypes which add difficulty to categorizing patients.[27] The current analysis supports consideration of dapagliflozin as treatment across a spectrum of HF, irrespective of LVEF, thus potentially simplifying treatment decision-making.

Pooling the patient-level trial data from the DAPA-HF and DELIVER trials provided several strengths to this analysis. First, using pooled data allowed for more robust model inputs for this analysis when compared with other pharmacoeconomic studies previously reliant on aggregate trial data. Of particular note, cost-effectiveness modelling often relies on individual components of composite endpoints, differences in which a clinical trial design is not powered to detect. As such, the analysis of pooled data can result in more robust statistical models for implementation in cost-effectiveness modelling, which would result in more certain predictions. Second, having a robust dataset of patients with HF with a breadth of patient characteristics enabled the exploration of model predictions according to varying characteristics, including the key defining characteristic of LVEF, as well as age, eGFR, and NT-proBNP. In doing so, this model captured the heterogeneity within the HF population, while also providing a preliminary estimate of the patient subgroups where dapagliflozin treatment may offer the greatest clinical and economic benefits. This novel approach allows for a more informed interpretation of the relationship between the clinical and economic outcomes observed.

Generally, dapagliflozin achieved lower ICERs (i.e. was more cost-effective) for patient cohorts with higher adverse risk profiles, such as those with reduced ejection fraction, advanced renal disease (lower eGFR) and elevated NT-proBNP. A noteworthy interaction explored in this analysis was that of age and LVEF.

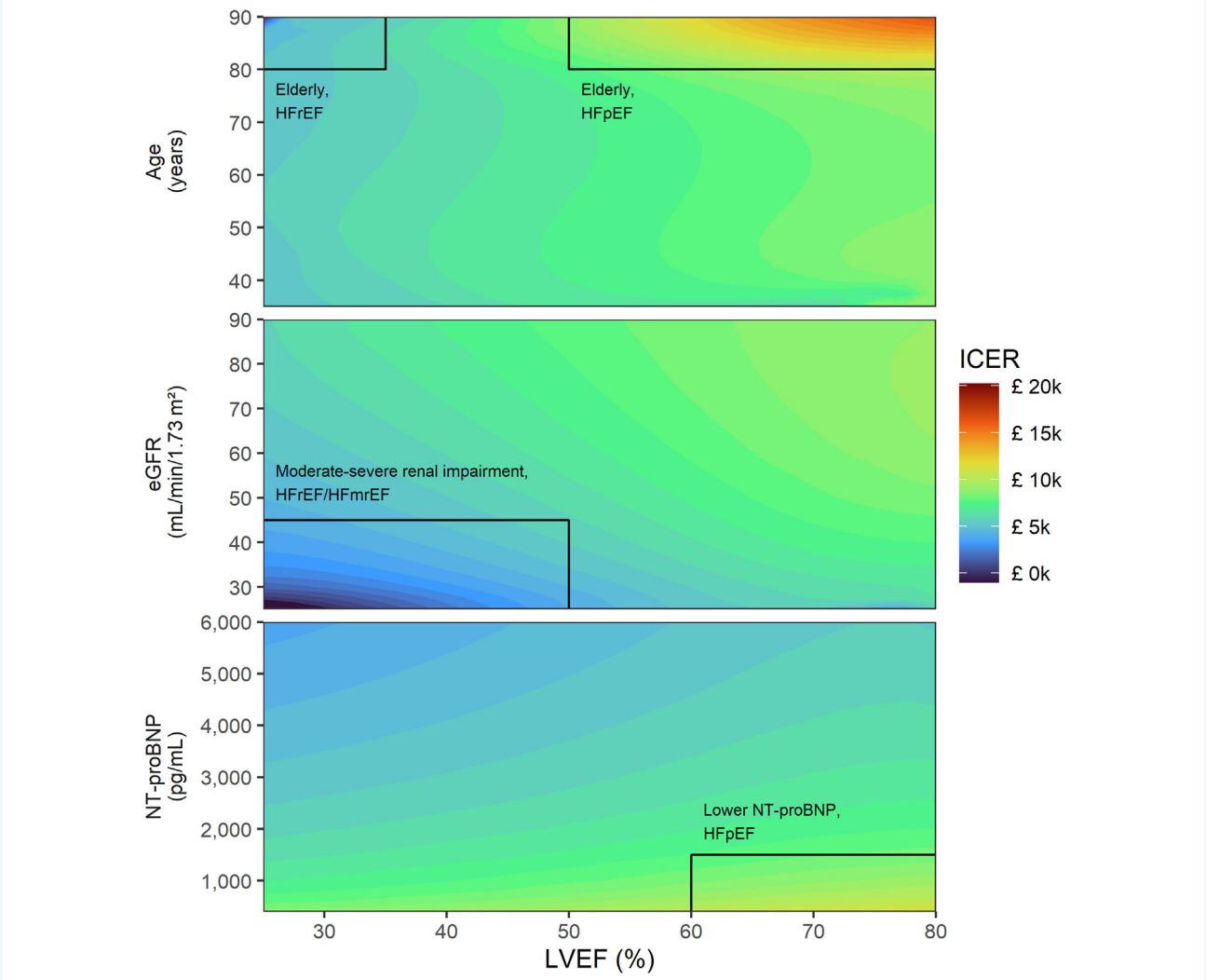


Figure 3 Interaction analysis of left ventricular ejection fraction (LVEF) and other patient characteristics for impact on the incremental cost-effectiveness ratio (ICER). Contours were generated varying LVEF in combination with age, estimated glomerular filtration rate (eGFR) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) with contour levels coloured according to the resulting ICER. Planes are primarily level corresponding to a majority (84.2%) of ICERs between £5000/quality-adjusted life year gained and £10 000/quality-adjusted life year gained. Regions of potential interest outside of this middle range are labelled with a description of patients that would fall within the indicated areas. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

When considering increasing age independently of LVEF, ICERs generally increased (i.e. dapagliflozin was less cost-effective), where it may have been expected that shorter life expectancies would correspondingly reduce the time available for treatment benefits to materialize. However, in combination with LVEF, the present analysis suggested that as age increased, the ICERs decreased towards dominance with lower LVEF. This result may be due to the competing risks of CV death versus non-CV death, such that sufficient decrease in LVEF increases the risk of CV death to be comparable to that of non-CV death, a clinical endpoint for which SGLT2 inhibitor treatment is expected to exhibit benefit, particularly in the HF with reduced ejection fraction population.[4,6]

The predicted ICER for dapagliflozin treatment remained below the WTP threshold of £20 000/QALY gained across the entire range of LVEF, showing the cost-effectiveness of dapagliflozin is robust to this parameter. Nevertheless, the model predicted that the ICER would decrease (i.e. dapagliflozin was more cost-effective) for patients with HF with lower stratifications of LVEF. This finding aligns with the outcomes presented by Tang *et al.*[28] and Hallinen *et al.*[29] in their investigations of empagliflozin across the spectrum of HF, although it is important to note that both studies used separate models for the HF with reduced and preserved ejection fraction populations and weighted averaging to generate a result for the overall HF population. In terms of

clinical events, model predictions according to LVEF were also in line with clinical trial results, where event rates for recurrent HHF and CV death were observed to be higher for HF with reduced ejection fraction than for HF with preserved ejection fraction.[4,30] Outside of LVEF, the results of this study were consistent with a post-hoc analysis of DELIVER, which identified that the effects of treatment with dapagliflozin were improved in patients with increasingly comorbid disease.[31] Cost-effectiveness studies were not identified examining the effect of renal function or NT-proBNP across the entire HF population, although authors have noted that such investigations would be an area of interest for further research.[32,33]

This model has some limitations which should be noted. To predict the outcomes of dapagliflozin over a lifetime horizon, data were extrapolated beyond the observed trial periods and treatment effects were assumed to remain constant; results thus may not capture the true course of dapagliflozin treatment over time. Transition probabilities used to characterize disease progression were not continuously updated according to changes in patient subgroup characteristics, potentially meaning that the evolution of disease may not be fully captured for groups further from the mean. For the scope of the present analyses, we apply this approximation to simplify the results, but future work may seek to implement more complex methodologies to continuously adjust transition probabilities. Disease severity and treatment were used to inform the risk of HF events in the model; however, long-term effects of hospitalization on disease management and rehospitalization on mortality were not captured in the model, thus the results may present a conservative estimate. Although there is some indication that healthcare resource utilization varies according to ejection fraction,[34] suitably granular data were not identified for the present study. As such, this model assumes the same healthcare resource utilization for all patients, regardless of LVEF. Finally, no single cost of treatment for patients with HF exists; the cost of usual care consisted of weighting costs by medication usage across the pooled HF population. This approach may differ from usage in real-world clinical practice.

In conclusion, the model results indicate that dapagliflozin, added to usual care, has the potential to provide important long-term clinical benefits in patients with HF regardless of LVEF, and is very likely to be a cost-effective treatment for HF. The cost-effectiveness of dapagliflozin was maintained regardless of other patient characteristics, including age, eGFR, and NT-proBNP. These data support the current guideline recommendation that dapagliflozin is indicated in a broad HF population.

Supplementary Information

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

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