Original article

OPEN

Cost-effectiveness of empagliflozin in heart failure patients irrespective of ejection fraction in England

Spyros Kolovos[a], Leana Bellanca[b], Harinala Groyer[c], Giuseppe Rosano[d], Jennifer Gaultney[e] and Stephan Linden[f]

Aims Heart failure (HF) is a complex syndrome commonly categorized into two main phenotypes [left ventricular ejection fraction (LVEF) below or above 40%], and although empagliflozin is the first approved medication with proven clinical effectiveness for both phenotypes, its cost-effectiveness of treating the entire HF population remains unknown.

Methods The analysis was performed utilizing two preexisting, LVEF phenotype-specific cost-effectiveness models to estimate the cost-effectiveness of empagliflozin in adults for the treatment of symptomatic chronic HF, irrespective of ejection fraction (EF). The results of the phenotype-specific models were combined using a population-weighted approach to estimate the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs).

Results Based on combined results, empagliflozin + standard of care (SoC) is associated with 6.13 life-years (LYs) and 3.92 quality-adjusted life-years (QALYs) compared with 5.98 LYs and 3.76 QALYs for SoC alone over a lifetime, resulting in an incremental difference of 0.15 LYs and 0.16 QALYs, respectively. Total lifetime healthcare costs per patient are £15 246 for empagliflozin + SoC and £13 982 for SoC giving an incremental difference of £1264. The ICER is £7757/QALY, which is substantially lower than the willingness-to-pay (WTP) of £30 000 per QALY used by NICE. The results of the probabilistic sensitivity analyses are in line with the deterministic results.

Conclusion Empagliflozin is the first efficacious, approved, and cost-effective treatment option for all HF patients, irrespective of EF. The combined ICER was consistently below the WTP threshold. Therefore, empagliflozin offers value for money for the treatment of the full HF population in England.

J Cardiovasc Med 2023, 24:758–764

Keywords: cost-effectiveness, economic, ejection fraction, empagliflozin, heart failure

[a]IQVIA, Athens, Greece, [b]Boehringer Ingelheim Ltd., Berkshire, UK, [c]Boehringer Ingelheim France, Paris, [d]IRCCS San Raffaele Pisana Roma, Italy, [e]IQVIA, London, UK and [f]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

Correspondence to Spyros Kolovos, IQVIA, Athens 152 32, Greece
E-mail: spyros.kolovos@iqvia.com

Received 28 October 2022 Revised 12 May 2023
Accepted 24 June 2023

Introduction

Heart failure (HF) is a complex clinical syndrome caused by cardiac dysfunction leading to symptoms such as fatigue, dyspnoea, and orthopnoea.[1,2] Chronic HF affects approximately 2% of all adults with the largest prevalence in those over the age of 55. In the United Kingdom (UK), there are around 1 million HF patients with the expectation that this will increase due to an ageing population.[3] Studies on the cost-of-illness of HF highlight the large worldwide economic burden of this syndrome.[4–7] For instance, lifetime costs of HF are estimated at $126 819 per patient with hospitalizations forming the largest cost component.[6] Specifically for England, available research indicates that around 2% of the annual National Health Service (NHS) budget is spent on HF.[8] Further, HF admissions have risen faster than all other causes of hospital admissions.[9] Due to the predicted increase in the incidence of HF, the burden on the NHS is likely to increase.[10–14]

HF is often categorized into two phenotypes based on the left ventricular ejection fraction (LVEF), which is an indicator of cardiac function: HF with LVEF below or equal to 40% [i.e. HF with reduced ejection fraction (HFrEF)], and HF with LVEF >40% (HF LVEF >40%)].[15,16] However, distinguishing between the different HF phenotypes to provide diagnosis and potentially treatment recommendations is not always straightforward.[17] Therefore, providing a treatment that is shown to be efficacious regardless of the patient's EF would represent a revolution in the clinical management of HF. Empagliflozin has demonstrated efficacy across the HF spectrum in two key clinical trials: EMPEROR-Preserved (NCT03057951) and EMPEROR-Reduced (NCT03057977). EMPEROR-Reduced and EMPEROR-Preserved both demonstrated that patients receiving empagliflozin (10 mg once daily) on top of standard of care (SoC) had a significantly lower risk of hospitalization or death compared with those receiving

 DOI:10.2459/JCM.0000000000001532

placebo on top of SoC.[18,19] Empagliflozin is the first pharmacological intervention to be approved for HF irrespectively of EF by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA),[20,21] and increasing numbers of countries around the world.

The economic benefits of empagliflozin have also been assessed to facilitate health technology assessment processes (HTA) in England, as well as other countries. For the economic evaluation of empagliflozin, two cost-effectiveness models (CEMs) were developed to examine the cost-effectiveness of empagliflozin for each of the two phenotypes (i.e. HF LVEF >40% and HFrEF, respectively). As the progression of disease in HF is similar irrespective of LVEF phenotype, two phenotype-specific models were developed to reflect the same structure and aligned in terms of inputs, statistical analysis, and subgroup analysis. The two phenotype-specific models investigate whether empagliflozin + SoC is a cost-effective use of NHS England resources against placebo + SoC (hereafter called SoC) separately for each phenotype. However, decision-making by healthcare bodies would be aided by an understanding of the cost-effectiveness of treating HF as a whole, regardless of EF.

The objective of this study was to evaluate the cost-effectiveness of empagliflozin + SoC versus SoC across the HF phenotype spectrum (i.e. HF LVEF>40% and HFrEF) to support decision-making by healthcare bodies and treatment recommendations by clinicians treating HF patients as a whole. For this purpose, the cost-effectiveness of treating the entire HF population (combined HF LVEF > 40% and HFrEF) from the perspective of NHS England was examined.

Method

Analyses were conducted in Microsoft Excel to estimate the cost-effectiveness of empagliflozin in adults for the treatment of HF regardless of ejection fraction (EF). The analysis combined the results from two preexisting, phenotype-specific CEMs, which have been developed to estimate the cost-effectiveness of empagliflozin + SoC compared to SoC in the treatment of HF LVEF>40% and HFrEF, respectively. Population weighting was performed at the results stage to combine the total costs and health benefits modelled for each treatment arm (empagliflozin + SoC and SoC) from the two models. Subsequently, a population-weighted result was computed. Details on the analyses are provided below.

Overview of the preexisting phenotype-specific cost-effectiveness models

The analysis assumed the perspective of the English NHS and Personal Social Services (PSS) in line with the National Institute for Health and Care Excellence (NICE) reference case. The recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good modelling practice guidelines were followed.[22] Both models have been submitted to NICE as part of technology appraisals, where they were reviewed and ultimately accepted as appropriate to address the decision problem for empagliflozin in HF.[23] The two models are currently under peer review pending publication in a scientific journal.

Both models had the same underlying structure and used a Markovian approach with health states based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) CSS, which is a disease-specific health status measure for patients with HF (see Figure S1, Supplemental Digital Content, http://links.lww.com/JCM/A564).[24] Transition matrices were calculated from the intent-to-treat (ITT) population of the EMPEROR-Preserved and EMPEROR-Reduced trial data, respectively, with a monthly cycle length. The clinical outcomes included in the models were hospitalization due to HF (hHF; this includes all hospitalizations), cardiovascular (CV) death, and all-cause mortality, which were modelled using parametric survival analysis, as well as treatment-related adverse events.

Resource use included drug acquisition (i.e. empagliflozin and SoC), hHF management (which included clinical events related to HF), CV death management, treatment-emergent adverse event (AE) management, and disease management. Where resource use was not available from the trial, published evidence from the literature was used. Costs were inflated to 2021 using the Eurostat Harmonized Indices of Consumer Prices values.[25]

Preference-based utility values were derived by mapping the EQ-5D-5L responses collected from the trials to EQ-5D-3L using a mapping algorithm.[26] The impact of hospitalization due to HF and treatment-related adverse events on quality-of-life (QoL) were included as disutilities. Costs and outcomes were considered over a lifetime time horizon and discounted at 3.5%.

Life-years (LYs), total costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER) were calculated independently for each phenotype. The uncertainty surrounding the deterministic ICER of each model was assessed using probabilistic sensitivity analysis (PSA) with 1000 iterations.

Population-weighted approach

A potential approach for assessing the cost-effectiveness of HF regardless of EF would have been to pool patient-level data from the EMPEROR-Preserved and EMPEROR-Reduced trials, given the absence of a clinical trial

including all HF patients. However, previous research indicates that pooling patient-level data from the EMPEROR-Preserved and EMPEROR-Reduced trials is not feasible due to significant heterogeneity ($P = 0.016$ for interaction) between the two trial populations.[27] In light of this, a population-weighted approach was used to combine the results of the phenotype specific CEMs. Weighting was based on the percentage of patients with each phenotype in the total HF population, which was sourced from a primary care database analysis of the Clinical Practice Research Datalink (PULSE study) in England reporting 30.4% of patients with HF LVEF>40%, resulting in a percentage of patients with HFrEF equal to 69.6%.[28]

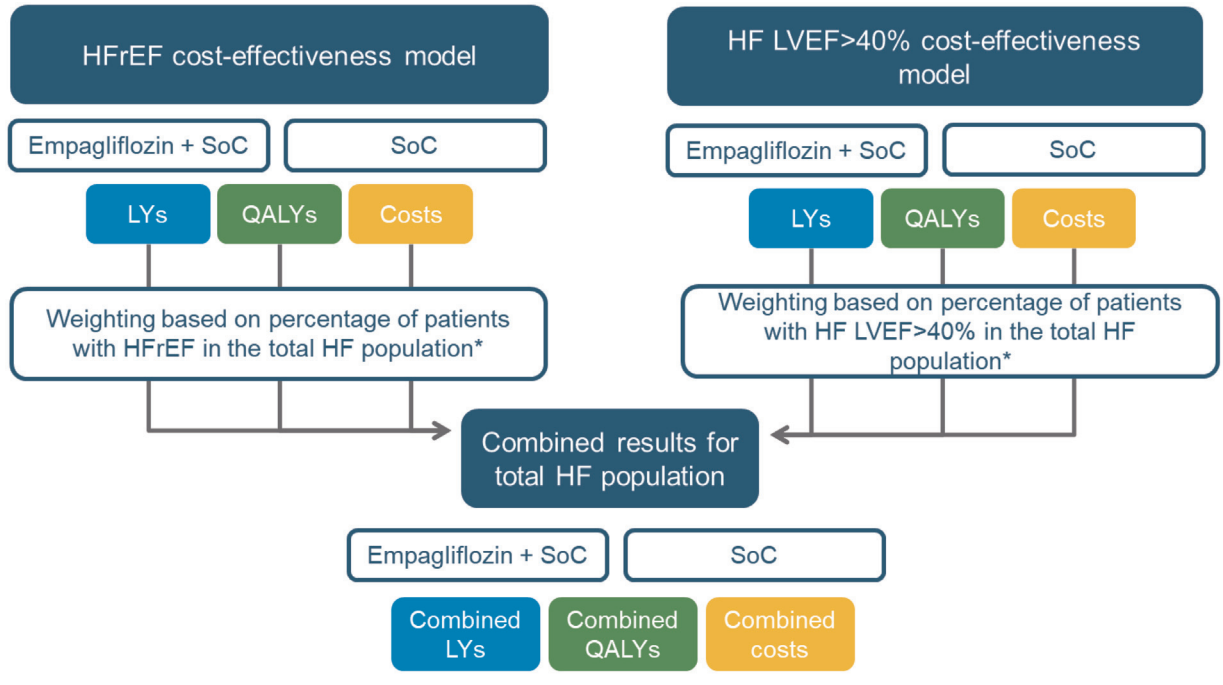
The population weighting was applied to the aggregate results modelled for each phenotype, specifically the LYs, QALYs, and total healthcare costs for each arm (i.e. empagliflozin + SoC, and SoC). Subsequently, the weighted results from each model were combined, enabling a deterministic ICER to be calculated for the overall HF population (Fig. 1).

In order to explore the uncertainty surrounding the deterministic combined ICER, the probabilistic results of the two phenotype-specific CEMs were utilized. Specifically, each phenotype-specific CEM included 1000 Monte Carlo simulated cost and QALY pairs for the respective PSA. Using these pairs, a number of the 1000 simulations was sampled from each model equal to the number used for the population weighting, as described above for the deterministic ICER, and thus, equal to the percentage of patients with each HF phenotype. For instance, given that the number of PSA replications was 1000 for each model, based on the percentage of patients for each phenotype (i.e. 69.6% for HFrEF and 30.4% for HF LVEF>40%), the combined PSA comprised 696 random replications from the HFrEF model's PSA and 304 random replications from the HF LVEF>40% model's PSA, for a total of 1000 combined replications. After this step, the combined PSA simulations were treated like the results of a typical PSA, by calculating a mean probabilistic ICER, creating a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) (see Figure S2, Supplemental Digital Content, http://links.lww.com/JCM/A564).

Subgroup analysis

Six subgroup analyses were conducted to assess the impact of patient characteristics on the ICER. These subgroups were determined based on potential treatment effect modifiers, such as type 2 diabetes mellitus (T2DM), baseline age, and estimated glomerular filtration rate (eGFR) (see Table S1, Supplemental Digital Content,

Fig. 1



Overview of the approach used to calculate the combined ICER for the overall HF population. * Population weighting was applied separately on the outcomes of each treatment arm (empagliflozin + SoC and SoC). CEM, cost-effectiveness model; HFrEF, heart failure with reduced ejection fraction; HF LVEF >40%, heart failure with >40% ejection fraction; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SoC, standard of care.

http://links.lww.com/JCM/A564). Due to the association of T2DM with HF, a scenario analysis was run for patients diagnosed with T2DM at baseline and patients without T2DM at baseline, respectively. Age is a known prognostic factor of HF; two cohorts were analysed to explore the impact of being >65 years old and <65 years old on the ICER. Similarly, two eGFR cohorts were explored: <60 ml/min/1.73 m^2 and ≥60 ml/min/1.73 m^2.

Scenario analysis

We considered a scenario analysis whereby the HFrEF and HF LVEF >40% population were equally split in order to explore the impact of the prevalence across phenotypes on the cost-effectiveness results, which may vary within and between countries.

Results

Deterministic analysis

Based on the population-weighted results, treatment of HF patients with empagliflozin + SoC is associated with 6.13 LYs and 3.92 QALYs compared with 5.98 LYs and 3.76 QALYs for SoC alone over a lifetime time horizon. This amounts to an incremental difference of 0.15 LYs and 0.16 QALYs, respectively, consistently favouring treatment with empagliflozin. Total lifetime healthcare costs per patient are £15 246 for empagliflozin + SoC and £13 982 for SoC, resulting in an incremental per patient difference of £1264, reflecting an additional cost with treatment of empagliflozin. The resulting ICER of £7,757/QALY is substantially lower than the willingness-to-pay (WTP) threshold of £20 000 to £30 000 per QALY used by NICE for decision-making. The ICER demonstrates that empagliflozin + SoC is a cost-effective use of NHS resources in the treatment of patients with chronic HF regardless of EF. Table 1 presents the results for the deterministic analysis.

Empagliflozin + SoC is associated with reduced costs for hHF management, AE management and CV death compared with SoC alone, resulting in a saving of £482 per patient over a lifetime (see Table S2, Supplemental Digital Content, http://links.lww.com/JCM/A564). Approximately 88% of the cost reduction is due to reduced hHF, equating to a per patient reduction of £422 over a lifetime. However, drug acquisition and disease management costs increase by £1616 and £130, respectively, leading to an incremental cost increase of £1264 over a lifetime.

Probabilistic analysis

The probabilistic results are aligned with the deterministic results. Mean incremental LYs and QALYs are identical to the deterministic output. The mean probabilistic ICER per QALY is £7657, which is below the commonly accepted WTP threshold. Table S3, Supplemental Digital Content, http://links.lww.com/JCM/A564 provides an overview of the combined PSA results for the overall HF population. The probabilistic sampling is presented in a cost-effectiveness plane in Fig. 2. The majority of simulations (82%) lie in the north-east (NE) quadrant, where empagliflozin + SoC is more costly and more effective compared with SoC, with 76% of simulations falling under £25 000. The CEAC demonstrates that empagliflozin + SoC has a probability of 77.5% of being cost-effective at the WTP threshold of £25 000 (Fig. 3).

Subgroup analysis

The ICER for each subgroup analysis is presented in Table 2, including the % change versus the deterministic result. All subgroup ICERs are below the commonly accepted WTP threshold, and even well below £10 000, with the baseline eGFR having the smallest impact on the ICER. A baseline age of <65 years generates the lowest cost per QALY at £6147 with a baseline age of ≥ 65 years providing a cost per QALY of £8772. A diagnosis of T2DM at baseline and no T2DM at baseline gives a cost per QALY of £6974 and £8221, respectively.

Scenario analysis

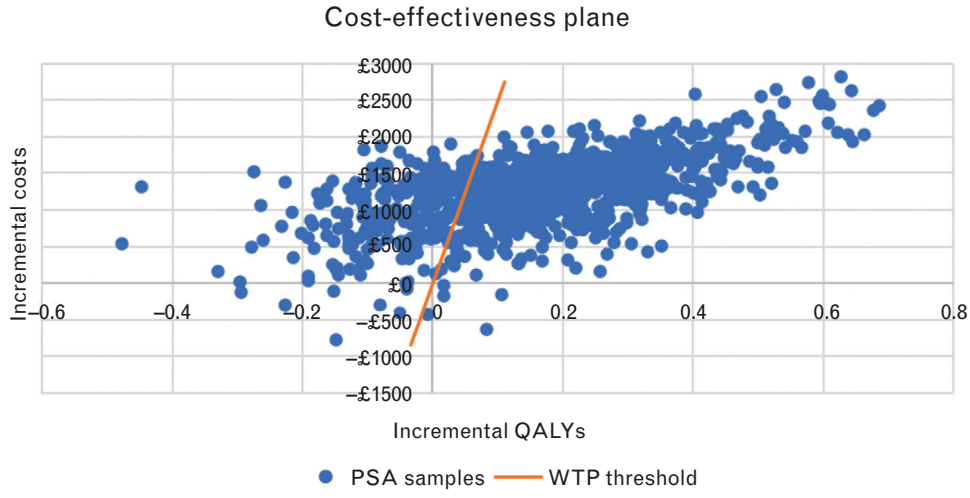
Assuming a 50:50 split in the prevalence across the two phenotypes within the HF population between HFrEF and HF LVEF>40%, empagliflozin + SoC is estimated to result in 6.34 LYs and 4.03 QALYs compared with 6.21 LYs and 3.88 QALYs for SoC alone over a lifetime time horizon (Table S4, Supplemental Digital Content, http://links.lww.com/JCM/A564). Empagliflozin + SoC is, therefore, estimated to generate a gain of 0.13 LYs and 0.14 QALYs per patient over the lifetime. In terms of total lifetime costs, the total cost of treatment in the empagliflozin + SoC arm is

Table 1 Deterministic cost-effectiveness results for the overall HF population

Outcome (per patient)	Empagliflozin + SoC	SoC	Incremental
Total discounted LYs	6.13	5.98	0.15
Total discounted QALYs	3.92	3.76	0.16
Total discounted costs	£15 246	£13 982	£1264
ICER (cost/LY gained)	£8488		
ICER (cost/QALY gained)	£7757		

Note: sums may not add due to rounding. ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality-adjusted life-year.

Fig. 2



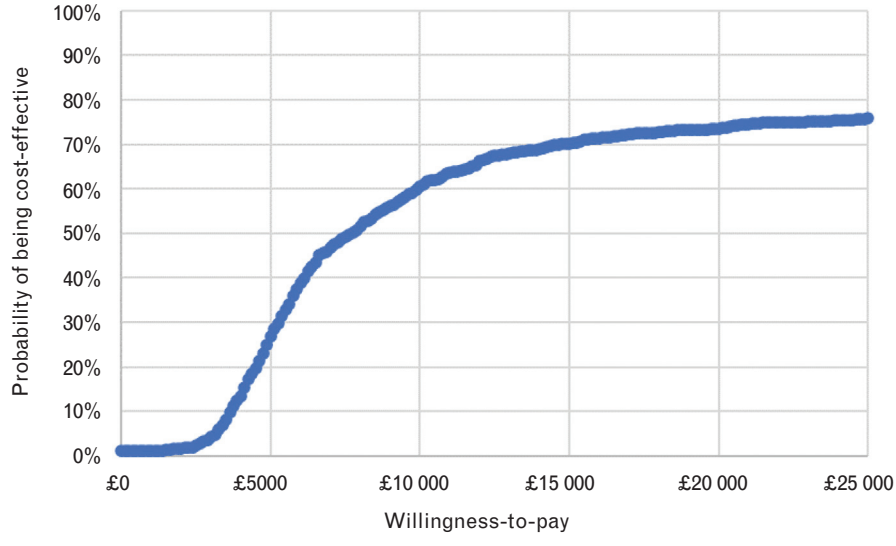
Cost-effectiveness plane for empagliflozin + SoC compared with SoC for the overall HF population. PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

estimated at £14 191 versus £12 887 SoC alone, resulting in an increase in the total healthcare costs for empagliflozin +SoC of £1,304 and an ICER equal to £9074, which is again well below the commonly accepted WTP threshold (Table S5, Supplemental Digital Content, http://links.lww.com/JCM/A564).

Discussion

This study evaluated the cost-effectiveness of empagliflozin + SoC versus SoC across the HF phenotype spectrum. The results demonstrate that empagliflozin is a cost-effective treatment for adult patients with chronic HF regardless of EF, with the ICER being substantially lower (i.e. £7757/QALY) than the WTP threshold of £20 000–£30 000 per QALY commonly used by NICE. The importance of understanding the cost-effectiveness of empagliflozin in adults regardless of EF is highlighted by the challenges of effectively determining the EF for each HF patient in the clinical setting, and the preference of clinicians for prescribing therapies that are effective across the EF spectrum.

Fig. 3



CEAC for empagliflozin + SoC compared with SoC. CEAC, cost-effectiveness acceptability curve; SoC, standard of care.

Table 2 Results (in terms of ICER) of subgroup analyses

Subgroup	ICER (cost/QALY gained)	% Change from deterministic ICER
T2DM at baseline	£6974	−10%
No T2DM at baseline	£8221	6%
Baseline age <65 years	£6147	−21%
Baseline age ≥65 years	£8772	13%
Baseline eGFR <60 ml/min/1.73 m^2	£7905	2%
Baseline eGFR ≥60 ml/min/1.73 m^2	£7851	1%

AE, adverse events; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; HF, heart failure; hHF, hospitalization for heart failure; QALY, quality-adjusted life-year; SoC, standard of care; T2DM, type II diabetesmellitus.

Empagliflozin + SoC is associated with higher LYs and QALYs compared with SoC alone over a lifetime time horizon. However, empagliflozin + SoC is also associated with higher drug acquisition and disease management costs leading to higher overall healthcare costs (£15 246 versus £13 982) compared with SoC. This increase in costs is driven by the cost of empagliflozin as an add-on to SoC, although it should be noted that empagliflozin leads to reductions in healthcare costs attributed to fewer hHF, AE and CV death costs. The prevalence of hHF, AE and CV death is in accordance with the findings of the two clinical trials, indicating the face validity of the analysis. Similarly, the PSA results demonstrate that the cost-effectiveness of empagliflozin (mean ICER of £7657/QALY) is in line with the deterministic findings. In addition, subgroup analyses are consistent with the deterministic results, with the difference in ICER between deterministic and subgroup analyses ranging from −21% to 13%, and all subgroup ICERs consistently being below £10 000. When considering a scenario with an equal split across the LVEF>40% and HFrEF phenotype spectrum, empagliflozin + SoC remains a cost-effective treatment option.

Given that to date there is no clinical trial assessing patients under treatment with empagliflozin with both HF phenotypes, the approach taken in this study applied a pragmatic approach based on population weighting of the results generated independently for each phenotype to establish the cost-effectiveness at the HF population level. This is an approach that has previously been used in oncology research successfully.[29,30] However, to the best of our knowledge, population weighting to combine cost-effectiveness results across indications has not been previously performed in HF research. This is likely due to empagliflozin being the first treatment that has been proven and approved to be clinically effective for both HF with LVEF >40% and HFrEF.[18,19]

Strengths and limitations

One of the strengths of this study is that it used population weighting to combine the results of two CEMs, combining data on >15 000 patients in two large multinational randomized controlled trials, given the absence of a clinical trial including patients regardless of EF. This meant that it was possible to overcome the concerns around statistical heterogeneity in a pragmatic way. This can inform the healthcare systems and clinicians about the cost-effectiveness of empagliflozin for the overall HF population.

This study has some limitations that are worth mentioning. Given that the analysis combined the results from two existing CEMs, the assumptions and limitations of those models are also reflected in the results of the current study. For instance, the clinical outcomes in the models that were extrapolated using parametric distributions due to the relatively short-term trials' follow-up (the median follow-up time was 16 and 26 months in the EMPEROR-Reduced and EMPEROR-Preserved trials, respectively) could have introduced some uncertainty, though typical for lifetime economic evaluations. Finally, the analysis was conducted based on direct medical costs to align with the NICE reference case, while indirect costs (i.e. productivity loss, etc.) reflecting a broader societal perspective may be influential but were not considered given the perspective of this analysis.

In conclusion, empagliflozin is the first efficacious and cost-effective treatment option for all HF patients, regardless of EF. The combined ICER, after population weighting, was consistently below £10 000 per QALY including for subgroups as well as the equal phenotype split. Therefore, empagliflozin offers value for money for the treatment of the full HF population in England.

Acknowledgements

We would like to acknowledge Francesco Croci and Nermina Ferizović for their contribution to this work.

Conflicts of interest

This study was supported by Boehringer Ingelheim Intl GmbH. L.B., H.G., and S.L. are employees of BII GmbH. S.K., G.M.C.R., and J.G. have received consultancy fees from BII GmbH.

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

The authors did not receive payment related to the development of the manuscript.

B.I. was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

References

1 Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; **93**:1137–1146.
2 Tanai E, Frantz S. Pathophysiology of heart failure. *Compr Physiol* 2015; **6**:187–214.
3 Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. *Heart* 2015; **101**:1182–1189.
4 Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014; **171**:368–376.
5 Urbich M, Globe G, Pantiri K, *et al.* A systematic review of medical costs associated with heart failure in the USA (2014–2020). *Pharmacoeconomics* 2020; **38**:1219–1236.
6 Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. *BMC Cardiovasc Disord* 2018; **18**:74.
7 Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. *Eur J Heart Fail* 2001; **3**:283–291.
8 Gielen V, Alexopoulos S, Hudson P, Mitchell S. PCV143 – resource use in chronic heart failure in the UK: a systematic review. *Value Health* 2016; **19**:A662.
9 Foundation BH. Heart failure hospital admissions rise by a third in five years. 2022. https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2019/november/heart-failure-hospital-admissions-rise-by-a-third-in-five-years. [Accessed 22 August 2022]
10 Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J* 2020; **25**:5.
11 Conrad N, Judge A, Tran J, *et al.* Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018; **391**:572–580.
12 Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present, and future. *Curr Heart Fail Rep* 2014; **11**:404–415.
13 Roth GA, Forouzanfar MH, Moran AE, *et al.* Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015; **372**:1333–1341.
14 Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017; **3**:7–11.
15 Beggs SAS, McDonagh TA, Gardner RS. Chronic heart failure: epidemiology, investigation and management. *Medicine* 2018; **46**:594–600.
16 Hajouli S, Ludhwani D. *Heart failure and ejection fraction*. StatPearls: StatPearls Publishing; 2022.
17 Aldaas OM, Igata S, Raisinghani A, Kraushaar M, DeMaria AN. Accuracy of left ventricular ejection fraction determined by automated analysis of handheld echocardiograms: a comparison of experienced and novice examiners. *Echocardiography* 2019; **36**:2145–2151.
18 Anker SD, Butler J, Filippatos G, *et al.* Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385**:1451–1461.
19 Packer M, Anker SD, Butler J, *et al.* Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**:1413–1424.
20 EMA. Jardiance: summary of product characteristics. https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance. [Accessed 27 July 2022]
21 FDA. Jardiance. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204629s033lbl.pdf. [Accessed 22 August 2022]
22 Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices–overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Med Decis Making* 2012; **32**:667–677.
23 NICE. Empagliflozin for treating chronic heart failure with reduced ejection fraction. https://www.nice.org.uk/guidance/ta773/chapter/1-Recommendations. [Accessed 27 July 2022]
24 Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000; **35**:1245–1255.
25 Eurostat. Harmonised Index of Consumer Prices. 2022. https://ec.europa.eu/eurostat/web/hicp/data/main-tables. [Accessed 27 July 2022]
26 NICE. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/estimating-the-relationship-betweenE-Q-5D-5L-and-EQ-5D-3L.pdf. [Accessed 22 August 2022]
27 Packer M, Butler J, Zannad F, *et al.* Empagliflozin and major renal outcomes in heart failure. *N Engl J Med* 2021; **385**:1531–1533.
28 CPRD. Incidence, prevalence, resource use and clinical outcomes of heart failure in England: a linked descriptive analysis of primary and secondary care (PULSE). https://cprd.com/protocol/incidence-prevalence-resource-use-and-clinical-outcomes-heart-failure-england-linked. [Accessed 27 July 2022]
29 Wu E, Pellissier J, Kvamme M, Irgens K. A holistic approach to evaluate the cost-effectiveness of pembrolizumab with multiple indications: a Norway-based example. *Value Health* 2018; **21**:S7.
30 Jakobsen M, Holst-Kristensen A. PDG40: the potential of a weighted average ICER as a supplementary decision tool when assessing the cost-effectiveness of MULTI-Indication Pharmaceuticals. *Value Health* 2020; **23**:S526.