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A cost-effectiveness analysis of empagliflozin for heart failure patients across the full spectrum of ejection fraction in Spain: combined results of the EMPEROR-Preserved and EMPEROR-Reduced trials

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ABSTRACT

Background: Heart failure (HF) is a chronic condition with considerable clinical burden for patients and economic burden for healthcare systems. Treatment for HF is typically based on ejection fraction (EF) phenotype. The cost-effectiveness of empagliflozin + standard of care (SoC) compared to SoC has been examined for HF phenotypes below or above 40% EF separately, but not across the full spectrum of EF in Spain.

Methods: The results of two preexisting, validated, and published phenotype-specific Markov cohort models were combined using a population-weighted approach, reflecting the incidence of each phenotype in the total HF population in Spain. A probabilistic sensitivity analysis was performed by sampling each model's probabilistic results.

Results: Empagliflozin + SoC compared to SoC resulted in increased life-years (LYs) (6.48 vs. 6.35), quality-adjusted LYs (QALYs) (4.80 vs. 4.63), and healthcare costs (€19,090 vs. €18,246), over a lifetime time horizon for the combined HF population in Spain. The incremental cost-effectiveness ratio (ICER) was €5,089/QALY. All subgroup, scenario, and probabilistic ICERs were consistently below €10,000/QALY.

Conclusions: Empagliflozin is the first treatment with established efficacy and cost-effectiveness for HF patients across EF from the perspective of healthcare payers in Spain. Empagliflozin also proved to be cost-effective for all subgroups of patients included in the analysis.

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Cost-effectiveness; ejection fraction; empagliflozin; heart failure; SGLT inhibitors; Spain

1. Introduction

Heart failure (HF), as defined by the European Society of Cardiology (ESC), is '*a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise*' [1]. Key risk factors associated with HF include arterial hypertension (high blood pressure), obesity, diabetes mellitus, chronic kidney disease, previous myocardial infarction, and smoking [1]. In 2020, over 15 million people (approximately 2% of the population) were estimated to be living with HF in Europe [2]. The prevalence of HF has been projected to increase in some European countries by 30% in 2035, due to an aging population, higher prevalence of comorbidities, and enhanced treatment options that lead to increased survival for HF patients [3–5]. In Spain, there were more than 750,000 adults with HF in 2019, with an estimated annual incidence of 2.78/1000 individuals per year [6]. A population-based longitudinal study involving 88,195 patients with HF in Catalonia reported a 2.7% prevalence of HF in adults above 44 years of age in 2012 [7].

Besides the clinical burden for healthcare providers and patients, HF imposes a substantial economic burden for the healthcare system. In Spain, HF is the leading cause of hospitalization in patients above 65 years old [8]. From 2015 to 2019, the total HF costs were €15,373 per person in Spain, mainly driven by the costs of HF hospitalization (hHF) (51%) [9]. With the progressive aging of the Spanish population (9.54 million people aged over 65 years in 2022 compared to 6.98 million in 2002) and the increasing prevalence of HF with age, HF-associated costs are expected to rise in the future [10].

According to clinical guidelines, HF can be categorized into three phenotypes based on left ventricular ejection fraction (EF): HF with reduced ejection fraction (HFrEF) for patients with EF ≤ 40%; HF with mildly reduced (HFmrEF) for patients with EF > 40% and ≤ 49%; and HF with preserved EF (HFpEF) for patients with EF ≥ 50 [1,11]. However, facilitating the implementation of a treatment that can be offered across the

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different phenotypes is more desirable in clinical practice [12]. Until sodium-glucose cotransporter-2 (SGLT2) inhibitors, none of the previous treatments (e.g. angiotensin receptor-neprilysin inhibitor [ARNi] sacubitril – valsartan, angiotensin-converting enzyme inhibitor [ACEi] perindopril, angiotensin receptor blockers [ARB] candesartan and irbesartan, mineralocorticoid receptor antagonist [MRA] spironolactone, and beta blockers [BB] bisoprolol, nebivolol, metoprolol, and carvedilol) that demonstrated efficacy in patients with HFrEF were able to demonstrate efficacy in HF patients with EF above 40% (HF > 40%EF) [13–21]. In the absence of recommendations regarding disease-modifying therapies, the treatment of patients with HF > 40%EF aimed at reducing symptoms, preventing or slowing further damage to the heart, and managing comorbidities [1]. Therefore, a treatment with established efficacy for the overall HF population, across the full spectrum of EF and especially in those with HFpEF and HFmrEF, would be beneficial for the clinical management of HF. The 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF recommended SGLT2 inhibitors for the treatment of patients with HFrEF to reduce the risk of hHF and death (I class of recommendation, A level of evidence) [1]. In the 2023 focused update of the 2021 ESC guidelines, SGLT2 inhibitors were also recommended for the treatment of patients with HFmrEF and HFpEF to reduce the risk of hHF or cardiovascular (CV) death (I class of recommendation, A level of evidence) [22].

Empagliflozin is a SGLT2 inhibitor that has demonstrated efficacy across the HF spectrum in pivotal clinical trials – EMPEROR-Reduced (NCT03057977) for HFrEF patients, and EMPEROR-Preserved (NCT03057951) for HF > 40%EF patients [23,24]. In particular, empagliflozin + standard of care (SoC) has shown a significantly lower risk of hHF or CV death compared to SoC alone. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have approved empagliflozin as the first pharmacological treatment for patients with HF across the EF spectrum, based on the benefits of empagliflozin demonstrated in HF clinical trials [25,26]. Empagliflozin for HF has been extensively evaluated in various Europeans countries including Spain, the United Kingdom (UK), France, Germany, and Italy [27–35]. Its economic benefits have also been evaluated to aid health technology assessment (HTA) across the Asia-pacific region and Australia [36,37]. Empagliflozin has proven to be cost-effective for the treatment of the HFrEF phenotype for payers in Spain, the UK, and France [38]. In addition, empagliflozin was also shown to be the first targeted treatment option that is both clinically effective and cost-effective for patients with HF > 40%EF in Spain, the UK, and France [39].

The economic impact of adding empagliflozin to SoC compared to SoC alone has been previously examined using two Markov-based cost-effectiveness models (CEMs). These models evaluated the healthcare costs and health benefits of empagliflozin over a lifetime time horizon separately for the two distinct phenotypes: HFrEF and HF > 40%EF, which comprises patients with either HFmrEF or HFpEF. The cost-effectiveness models were developed for HFrEF and HF > 40%EF phenotypes, and their design was identical with respect to data inputs, statistical methods used to generate those inputs, and sensitivity and scenario analyses. As indicated in previous studies, the two cost-effectiveness models assessed the healthcare costs and health benefits of empagliflozin for HFrEF and HF > 40%EF independently [38–40]. Recognizing the need for a comprehensive understanding of the cost-effectiveness associated with HF treatment across the EF spectrum, this investigation appraised the cost-effectiveness of empagliflozin in combination with SoC compared to SoC alone. The analysis was conducted from the Spanish healthcare payer perspective.

2. Methods

The cost-effectiveness analysis (CEA) of empagliflozin for HF patients across the full spectrum of EF was conducted in Microsoft® Excel. The results from the two preexisting, phenotype-specific CEMs were combined in this analysis. The phenotype-specific models were developed to estimate the cost-effectiveness of empagliflozin + SoC compared to SoC alone in the treatment of HFrEF and HF > 40%EF, respectively. To combine the total costs and health benefits modeled for each treatment arm (empagliflozin + SoC and SoC) from the two CEMs, population weighting was performed for the aggregated health and cost model outcomes, i.e. life-years (LYs), quality-adjusted life-years (QALYs), and total healthcare costs. Subsequently, the population-weighted results were estimated for the total HF population. More details on the phenotype-specific models and the population-weighted approach are provided in the following sections.

2.1. Overview of phenotype-specific cost-effectiveness models

The two phenotype-specific Markov models were developed to evaluate the cost-effectiveness of empagliflozin in patients with HFrEF and HF > 40%EF, reflecting the results of the EMPEROR-Reduced and EMPEROR-Preserved trials, respectively [23,24]. The analysis was performed from the Spanish healthcare payer perspective. The models were developed in accordance with guidelines from the Society for medical decision making on good modeling practices – the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [41]. Both models underwent evaluations by HTA bodies during technology appraisals to determine their ability to address the use of empagliflozin in patients with HFrEF and HF > 40%EF, respectively, with those evaluations concluding that they were appropriate for the intended purposes [28,42]. Furthermore, the models have been published and have proven empagliflozin to be cost-effective for the treatment of the HFrEF and HF > 40%EF phenotypes separately for payers in Spain, the UK, and France [38,39].

The models were mainly populated with data from the EMPEROR-Reduced and EMPEROR-Preserved trials, and where this was not possible, inputs were obtained from published literature or country-specific databases [23,24]. They were developed to be as similar as possible, having the same model structure and model assumptions. Both models used a Markov cohort state transition approach based on patients' subjective disease severity status, defined by the Kansas City

Cardiomyopathy Questionnaire (KCCQ) – clinical summary score (CSS), which measures symptoms, physical and social limitations, and quality of life in patients with HF (Figure S1 in Supplemental Digital Content) [43,44].

The modeled patient population was representative of patients in the EMPERORReduced and EMPERORPreserved trials. From the intention-to-treat (ITT) population of the EMPEROR-Preserved and EMPEROR-Reduced trial data, transition matrices were calculated with a monthly cycle length, over a lifetime time horizon [23,24]. The models tracked the occurrence of hHF and treatment-related adverse events (AEs) as transient events. Death was captured based on two parametric survival equations for CV and all-cause death. All parametric survival equations were derived from statistical analyses of the EMPEROR-Preserved and EMPEROR-Reduced trial data and included KCCQ-CSS health states as time-varying predictors [23,24]. The inclusion of these predictors addressed the dynamic nature of SGLT2 inhibitors' efficacy over time [45]. Various parametric models were explored to extrapolate long-term outcomes based on the trial data, selecting models for base case distributions based on the best fit and most plausible estimates of long-term survival. Additionally, sensitivity analyses explored alternative parametric distributions to demonstrate that the choice of distribution did not significantly affect the results [38,39]. The complete methodology for each phenotype-specific CEM is described in detail in previous articles [38,39]. The SoC therapies modeled reflected the background pharmacological treatments administered to patients in the EMPERORPreserved and EMPERORReduced trials, including ARNi, ACEi, ARB, BB, MRA, and ivabradine (IVA). The proportions for each class of background HF medication are reported in previous studies describing the two phenotype-specific models in detail [38,39].

The costs considered in both CEAs were associated with pharmacological treatment (drug acquisition), management of clinical events and AEs, and disease management (i.e. GP visits, cardiologist visits, and emergency room visits). Unit drug costs, ex-factory prices considering the mandatory deductions (Royal Decree Law 8/2010), for empagliflozin 10 mg and SoC therapies were extracted from the BotPlus Web database for Spain [46].

Patient utilities were measured using EQ-5D-5 L in each respective trial [23,24]. Questionnaires were completed by patients at baseline, post-randomization, at treatment discontinuation, and post-completion. The impact of hHF on health-related quality of life was captured as a one-off utility decrement to the proportion of patients experiencing the event. The disutility associated with AEs was captured as a one-off utility decrement to the proportion of patients who experienced the AEs.

Costs and health outcomes were considered over a lifetime time horizon and discounted at an annual rate of 3.0% [47]. For each phenotype-specific model, LYs, QALYs, total costs, and the incremental cost-effectiveness ratio (ICER) were calculated separately. Furthermore, a probabilistic sensitivity analysis (PSA) with 1,000 iterations was used to explore the uncertainty surrounding the deterministic ICER of each model.

2.2. Population-weighted approach

Given the availability of the EMPEROR-Preserved and EMPEROR-Reduced trials, a potential approach to investigate the healthcare costs and health benefits of empagliflozin for the overall HF population (i.e. for patients with either HFrEF or HF > 40%EF) would require the combination of data from both trials and the inclusion of the combined data into a newly developed Markov model [23,24]. However, because of the pronounced heterogeneity ($p = 0.016$ for interaction) among the EMPEROR-Preserved and EMPEROR-Reduced trial cohorts, as demonstrated in a previously conducted study, it was not possible to pool patient-level data from the two trials [48]. Consequently, a population-weighted approach was adopted based on estimates from the study by SicrasMainar et al., particularly the proportion of patients with distinct HF phenotypes [6]. The study reported a prevalence of 51.7% for HFrEF, leading to a calculated proportion of patients with HF > 40%EF of 48.3% [6]. Further details of the approach are available in a previous study, wherein population weighting was used to adjust aggregated healthcare costs and health benefits outcomes for HFrEF and HF > 40%EF patients [40]. This approach was adopted in order to estimate a deterministic ICER for the HF population in Spain, across all levels of EF (Figure 1). All healthcare costs were expressed in 2022 Euros for Spain, adjusted for inflation based on information from the Instituto Nacional de Estadística (INE) when applicable [49].

As reported in a previous study, exploring the uncertainty which surrounded the deterministic ICER involved leveraging

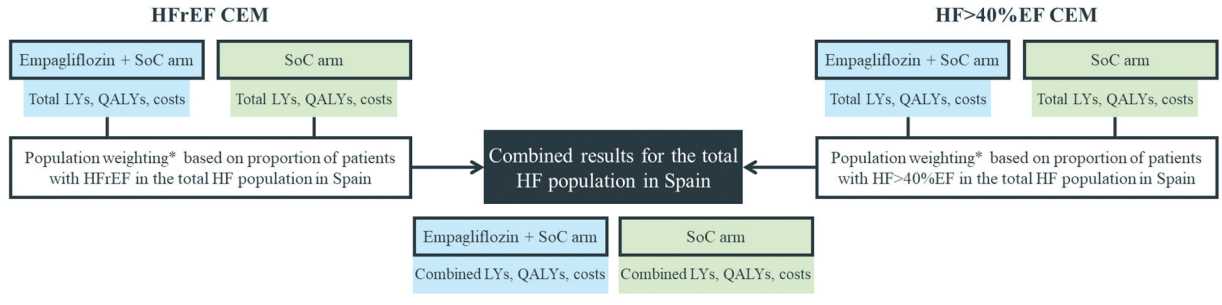

Figure 1. Diagram of the approach to calculate the combined ICER from the base-case results of the two phenotype-specific CEMs.

* Population weighting was performed on the health and cost model outcomes, i.e. LYs, QALYs, and total healthcare costs of each treatment arm (empagliflozin + SoC and SoC), separately. Abbreviations: CEM, cost-effectiveness model; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HF > 40%EF, heart failure with > 40% ejection fraction; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SoC, standard of care.

the PSA outcomes of the two cost effectiveness models that were previously developed and sampling based on the proportion of patients with distinct HF phenotypes [40]. A comprehensive summary of the implemented approach is shown in Figure S2 of Supplemental Digital Content. The total combined 1,000 PSA iterations included 517 randomly picked replications derived from the HFrEF CEM and 483 from the HF > 40%EF CEM. The combined simulations were then utilized to derive a mean probabilistic ICER, a CE plane, and a CE acceptability curve (CEAC). A theoretical €20,000/QALY willingness-to-pay (WTP) threshold was chosen to indicate a cost-effective treatment [50].

2.3. Subgroup and scenario analyses

To investigate the influence of baseline characteristics of patients with HF on the cost-effectiveness results, six additional subgroup analyses were conducted. Pertinent variables influencing treatment outcomes were considered to identify relevant subgroups for analysis, as reported in prior investigations [38–40]. Key patient characteristics considered as potential treatment effect modifiers were patient status in terms of type 2 diabetes mellitus (T2DM) at baseline, patient age at baseline, and recorded glomerular filtration rate (eGFR) (Table S1 and Figure S3 in Supplemental Digital Content). HF has been shown to be related to T2DM; thus, two groups of patients were distinguished: patients with baseline T2DM and patients without. Patient age has also been shown to be associated with prognosis in patients with HF; therefore, subgroup analyses were conducted for patients older or younger than 65 years at baseline. Finally, given the association of eGFR with mortality in patient with HF, subgroup analyses were performed for patients with <60 mL/min/1.73 m^2 at baseline and ≥60 mL/min/1.73 m^2 at baseline.

A scenario in which the prices for the medications (i.e. empagliflozin and SoC) were based on public price including Value Added Tax (PPI VAT) applying deduction Royal Decree Law 8/2010, as compared to ex-factory prices applying deduction Royal Decree Law 8/2010 in the base case, was also explored. This analysis was performed to explore the impact of different approaches for medication pricing on the results.

3. Results

3.1. Deterministic analysis

Based on the population-weighted results, treatment with empagliflozin + SoC was associated with 6.48 LYs and 4.80 QALYs compared to 6.35 LYs and 4.63 QALYs for SoC alone in patients with chronic HF across the EF spectrum, which amounts to an incremental difference of 0.13 LYs and 0.17 QALYs, respectively, over a lifetime time horizon. These results consistently favored empagliflozin + SoC over SoC alone in terms of health benefit. The total lifetime healthcare costs amounted to €19,090 per patient treated with empagliflozin + SoC and €18,246 per patient treated with SoC alone. This yielded an €843 incremental cost difference per patient, signifying an added expense associated with empagliflozin treatment. The resulting ICER was €5,089/QALY, considerably below a WTP threshold of €20,000/QALY. This indicates empagliflozin + SoC as a cost-effective treatment option compared to SoC alone for chronic HF patients across the full spectrum of EF, from the perspective of the Spanish healthcare system. A summary of the deterministic analysis results is shown in Table 1.

Table 1. Combined deterministic results for the overall ITT population.

Cost-effectiveness measures	Empagliflozin + SoC	SoC
Total LYs	6.48	6.35
Total QALYs	4.80	4.63
Total costs	€19,090	€18,246
ICER (cost/LY gained)	€6,246	
ICER (cost/QALY gained)	€5,089	

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LY, life-year; QALY, quality-adjusted life-year; SoC, standard of care.

Empagliflozin + SoC demonstrated cost reductions for the management of HF, CV death, and AE management compared to SoC alone. This resulted in a lifetime total cost reduction of €609 per patient (Table S2 in Supplemental Digital Content). In contrast, there was an increase in costs of drug acquisition by €1,359 per patient and costs of disease management by €93 per patient. This led to an overall incremental healthcare cost of €843 over a lifetime time horizon (Table S2 in Supplemental Digital Content).

3.2. Probabilistic sensitivity analysis (PSA)

The PSA results for the overall ITT population were aligned with the deterministic results: 0.13 mean incremental LYs, 0.16 mean incremental QALYs, and €847 mean incremental costs, resulting in a probabilistic ICER of €5,135/QALY. The probabilistic results are presented in Table S3 in Supplemental Digital Content. The absolute number of clinical events per patient are presented in Table S4 in Supplemental Digital Content. A visual representation of the PSA results comparing empagliflozin + SoC versus SoC alone is provided in the cost-effectiveness plane in Figure 2. Each dot on the plane corresponds to a specific cost-QALY pair derived from one Monte Carlo simulation. This modeling technique allows for the exploration of the uncertainty in the input parameters. The dispersion of these dots across the plane reflects the variability in cost and effectiveness outcomes. Notably, 76% of the 1,000 simulated cost-and-effect pairs fell in the topright quadrant of the cost-effectiveness plane, indicating a high probability of empagliflozin + SoC being more costly and more effective compared to SoC alone. As shown in the CEAC (Figure 3), empagliflozin + SoC showed a 75% probability of being cost-effective at a WTP threshold of €20,000 per QALY gained.

3.3. Subgroup and scenario analyses

The ICER for each subgroup analysis, including the percentage variation from the base case results, is presented in Table 2. The ICERs for each subgroup were lower than €7,000/QALY, well below the theoretical threshold. Out of all subgroups, the baseline eGFR analyses were shown to have the smallest impact on the ICER in terms of percentage variation. The ICER was lowest

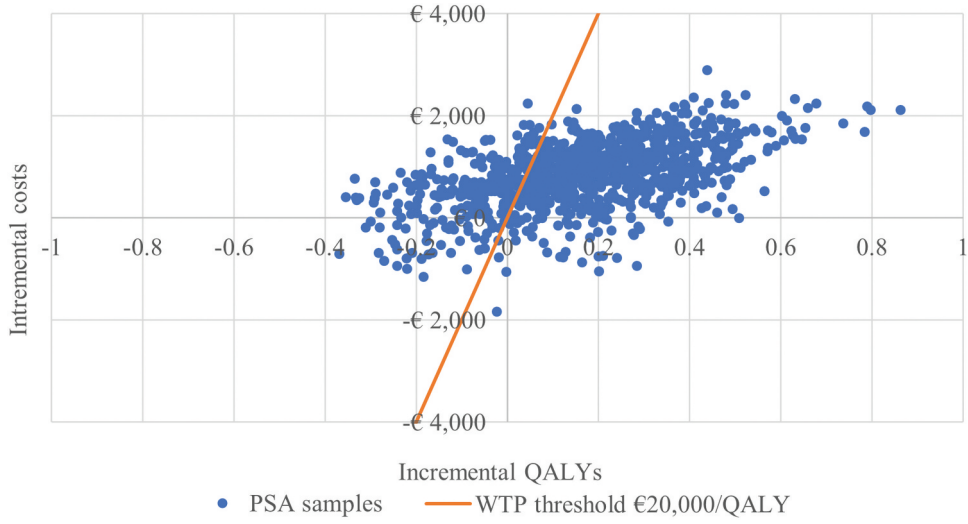

Figure 2. Cost-effectiveness plane for empagliflozin + SoC compared to SoC alone for the overall ITT population. The graph visually represents the incremental differences in costs and QALYs between treatment groups.

Abbreviations: ITT, intention-to-treat; QALY, quality-adjusted life-year; PSA, probabilistic sensitivity analysis; SoC, standard of care; WTP, willingness-to-pay.

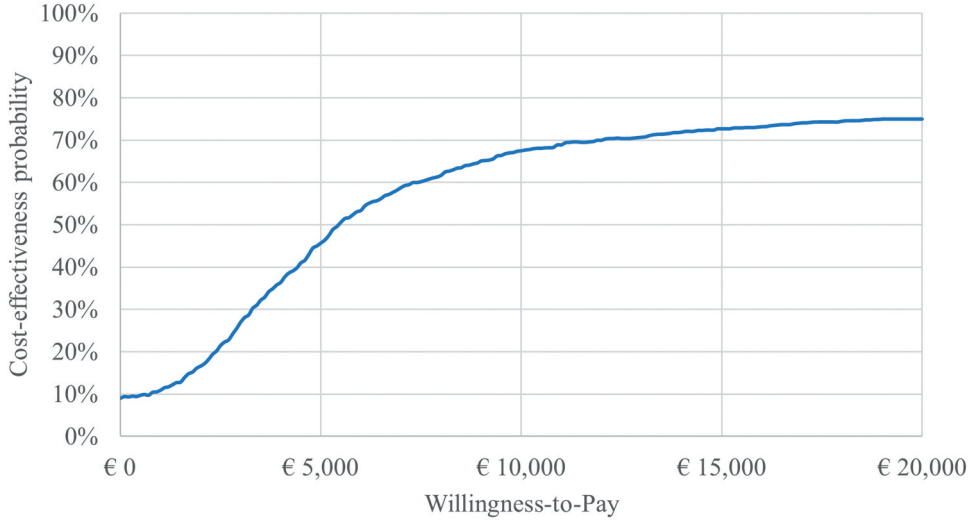

Figure 3. Cost-effectiveness acceptability curve for empagliflozin + SoC compared to SoC alone.

Abbreviations: SoC, standard of care.

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

Subgroup	ICER (cost/QALY gained)	Variation from ITT population (%)
T2DM at baseline	€4,151	−18%
No T2DM at baseline	€5,796	14%
Baseline age <65 years	€4,069	−20%
Baseline age ≥65 years	€6,014	18%
Baseline eGFR <60 mL/min/1.73 m^2	€5,434	7%
Baseline eGFR ≥60 mL/min/1.73 m^2	€4,805	−6%

Abbreviations: eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life-year; T2DM, type 2 diabetes mellitus.

for the subgroup of patients with baseline age <65 years (€4,069/QALY) with a percentage variation of −20% from the ITT population results, while it was highest for the subgroup of patients with baseline age ≥65 years (€6,014/QALY). Furthermore, a diagnosis of T2DM at baseline and no T2DM at baseline gave a cost per QALY of €4,151 and €5,796, respectively. In summary, the subgroup analyses demonstrate that the results are in accordance with the main analysis, regardless of patient characteristics.

For scenario analysis (i.e. using PPI VAT prices for medication), the ICER was €9,670/QALY, indicating that the alternative approach resulted in an increased ICER but that empagliflozin remained cost-effective (Table S5 in Supplemental Digital Content).

4. Discussion

This study is the first to evaluate the cost-effectiveness of empagliflozin or any other SGLT2 inhibitor in combination with SoC for the overall HF population in Spain. The investigation covers the full spectrum of EF and addresses a critical

need for a treatment option that is clinically effective for all HF patients.

The cost-effectiveness of empagliflozin in HF has been explored in various CEA studies in Spain, the UK, France, Australia, China, and the United States, but these have all been phenotype-specific [37–39,51,52]. Overall, those studies have indicated that empagliflozin can provide higher benefits at a higher cost for HFrEF and HF > 40%EF patients separately. However, physicians prefer to prescribe treatments that are clinically effective across the EF spectrum, thereby warranting a therapeutic option that is clinically effective in treating all patients with HF [12,53,54]. Thus, this study fills an important gap by identifying a cost-effective treatment that is suitable for all HF patients across the full spectrum of EF from the perspective of the Spanish healthcare system.

Focusing specifically on Spain, this study contributes to the growing body of evidence on the comprehensive efficacy of SGLT2 inhibitors. Study results are in alignment with other recent studies emphasizing the broader CV benefits of SGLT2 inhibitors, including empagliflozin, and this study reinforces their evolution from primary diabetes treatment to a crucial component in managing HF [55,56].

The current analysis utilized a population-weighted approach to address the lack of a dedicated clinical trial evaluating patients undergoing empagliflozin treatment across the full spectrum of EF. The approach of combining healthcare costs and health benefits has not previously been used in HF research (except for a previous study on empagliflozin), potentially because there were no treatment options that could be suitable for all HF patients until empagliflozin [40]. However, the population-weighted approach has been explored in oncology research, where it was also deemed a transparent and efficient approach to combine cost-effectiveness results [57,58].

The findings of the current study were consistent across all analyses performed, including deterministic, probabilistic, subgroup, and scenario analyses. The results demonstrated that empagliflozin + SoC generated higher health benefits and higher total healthcare costs over a lifetime time horizon compared to SoC alone, resulting in an ICER of €5,089/QALY. The ICER is significantly below a WTP threshold of €20,000/QALY, indicating that empagliflozin can be considered a cost-effective treatment. The PSA results were very similar to the deterministic results. In addition, 76% of all PSA iterations fell in the top-right quadrant of the cost-effectiveness plane, indicating a high likelihood that empagliflozin + SoC would be more costly but also more effective compared to SoC alone. The subgroup analysis results were consistent with the ITT population results, with the percentage difference in ICER between ITT and subgroup analyses ranging from −20% to 18% (Table 2). Thus, patient characteristics did not influence the results, as the ICERs for all subgroup analyses were consistently below €10,000/QALY. The scenario analysis using public price including PPI VAT for the medications' prices resulted in an increased ICER as compared to the base case using ex-factory prices, but still below €10,000/QALY, indicating empagliflozin remained cost-effective. Thus, the uncertainty around the results of the population-weighted approach is limited, and the findings are robust to variation in model inputs (as shown by the PSA results) and not influenced by the effect modifiers tested in the subgroup analyses.

Empagliflozin + SoC was associated with increased health benefits but also total costs compared to SoC alone. The increased health benefits are derived mainly due to the reduced number of hHF events for patients receiving empagliflozin, and also their lower mortality rates. The higher costs in the empagliflozin + SoC arm were largely attributable to treatment costs and longer survival, which led to longer treatment duration. Consistent with the EMPAREG OUTCOME trial results, empagliflozin + SoC reduced the risk of CV mortality by 38% (hazard ratio [HR]: 0.62) and all-cause mortality by 32% (HR: 0.68) over a median observation period of 3.1 years in patients with T2DM and CV disease [59].

The results of this analysis are in line with a previous study that evaluated the cost-effectiveness of empagliflozin + SoC versus SoC alone across the entire HF population from the perspective of NHS England, which yielded an ICER of £7,757/QALY [40]. The results of the current study also demonstrate consistency with the multinational CEA of empagliflozin + SoC versus SoC alone, which yielded ICERs/QALY of €4,073, £6,152, and €5,511 for HFrEF in Spain, the UK, and France, respectively, and ICERs/QALY of €11,706, £14,851, and €15,447 for HF > 40%EF in Spain, the UK, and France, respectively [38,39]. Overall, the current study adds to the evidence in the literature which shows that empagliflozin is a cost-effective treatment for both HF phenotypes, and also the first treatment to be considered cost-effective across the HF spectrum [40].

4.1. Strengths and limitations

The study has a notable strength in its utilization of a population weighting approach. This approach effectively combines the findings of two cost-effectiveness models, thereby combining evidence from a substantial cohort of over 9,500 patients with HF from two robust multinational phase 3 randomized controlled trials. The approach was chosen due to the lack of a randomized clinical trial comprising patients irrespectively of their EF and the need to pragmatically address concerns about statistical heterogeneity between patients in the two EMPEROR trials. The cost-effectiveness of empagliflozin for patients with HF regardless their EF status can provide valuable insights for both the healthcare system of Spain and clinicians based on the study findings.

Additionally, an inherent strength of this study lies in its use of two established, phenotype-specific models, each deemed suitable for assessing the cost-effectiveness of empagliflozin in patients with HFrEF and HF > 40%EF, respectively.

However, the results of the analysis should be considered in light of several limitations. First, given that the analysis combined the results from two preexisting, phenotype-specific models, the assumptions and limitations of those models are relevant to the results of this study. In particular, the requirement to extrapolate long-term clinical outcomes from a short-term trial data (median follow-up time was 26 and 16 months in the EMPEROR-Preserved and EMPEROR-Reduced trials, respectively) introduced uncertainty, a limitation inherent to all lifetime CEMs. However, the survival estimates of each phenotype-specific model

were validated with the observed rates in the corresponding trial, as described in previous studies [38,39]. Another inherent limitation in the phenotype-specific CEMs is the omission of lower limb amputation and the rare complication of diabetic ketoacidosis associated with SGLT2 inhibitors, which have been subjects of discussion in the literature [60]. This exclusion, while acknowledged, is not anticipated to markedly impact the incremental healthcare costs, as occurrences in the trials were minimal and no imbalance was noted between treatment groups [23,24,38].

Second, although EMPEROR-Preserved and EMPEROR-Reduced are multicenter, international trials, it is assumed that the event rates observed in clinical practice globally, and in Spain specifically, will be similar or even higher compared to those observed in the trial [23,24].

Third, the results of this study are presented based on Spain-specific cost inputs. Although unit costs can be tailored to specific countries, generalizability to other settings outside Spain may be limited due to variations in the financial and organizational structures of healthcare systems in other countries.

Fourth, the current analysis only captured direct medical costs; the costs associated with non-direct medical resources and indirect costs (e.g. productivity loss) were not considered.

5. Conclusions

This study fills a critical gap by providing evidence for the cost-effectiveness of empagliflozin across the full spectrum of EF in Spain, emphasizing its potential as a valuable treatment option across all HF patients. The findings also contribute to the evolving role of SGLT2 inhibitors in managing HF, beyond their primary use in diabetes treatment.

Empagliflozin is the first treatment option to be shown clinically effective and cost-effective for chronic HF population in Spain. The combined ICER was consistently below €10,000 per QALY, including for all subgroups of patients included in the analyses. Therefore, empagliflozin offers value for money for the treatment of HF in Spain, across the EF spectrum.

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Declarations of interest

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Author contributions statement

F. Croci contributed to the design and implementation of the study, to the analysis of the results, and to manuscript writing. X. García Moll and M.A. Calleja-Hernández provided clinical expertise and validation for the manuscript and contributed to its writing. A. Solé contributed to the design and implementation of the study, and manuscript writing. E. Hartgers-Gubbels contributed to manuscript writing. All authors have reviewed and approved the final version of the manuscript, and each has contributed intellectually to its content.

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