# An Economic Analysis of Empagliflozin versus Sacubitril/Valsartan in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF) in the United Kingdom (UK)

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## INTRODUCTION

- The sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin and angiotensin receptor neprilysin inhibitor (ARNi) sacubitril/valsartan have both shown to reduce cardiovascular (CV) death or hospitalization for heart failure (HHF) in patients with heart failure with reduced ejection fraction (HFrEF).
- Empagliflozin 10 mg once daily was compared with placebo as an add-on to standard of care (SoC) for HFrEF in the EMPEROR-Reduced trial, demonstrating a 25% (HR: 0.75; 95% confidence interval [CI]: 065–0.86) reduction in the combined relative risk of CV death or HHF, leading to recent authorization by the European Medicines Agency (EMA) in this indication.[1]
  - Effect of empagliflozin + SoC on this outcome was observed irrespective of the use of sacubitril/valsartan at baseline.[1]
  - Risk reduction for CV death or HHF among patients not using sacubitril/valsartan: HR: 0.77; 95% CI: 0.66–0.90.[1]
- Sacubitril/valsartan is authorized for use by EMA for management of HFrEF based on results from the PARADIGM-HF trial.[2]
- Comparative value for money for empagliflozin vs. sacubitril/valsartan in treatment of patients with HFrEF is unknown.

## OBJECTIVE

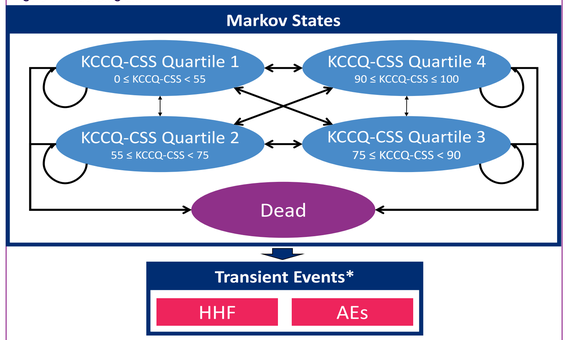
- To conduct a cost-minimization analysis of empagliflozin vs. sacubitril/valsartan in HFrEF patients who were already treated with SoC including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRAs), and/or ivabradine.

## METHODS

### Model Overview

- Cost-minimization analysis was conducted from the United Kingdom (UK) National Health Service (NHS) perspective over a lifetime horizon.
- A Markov cohort state-transition model was used to simulate the clinical course of HFrEF (Figure 1).
- Health states based on Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score (KCCQ-CSS) quartiles tracked patients' disease severity over time.
- At the start of the model, the patient cohort entered following the baseline distribution of KCCQ-CSS quartiles per the EMPEROR-Reduced trial data.
- During each model cycle, patients could transition between KCCQ-CSS health states and/or death (CV or non-CV) and were subject to risk of HHF, treatment-related adverse events (AEs), and treatment discontinuation.
  - First and subsequent HHF and treatment-related AEs were captured as transient events and patients who discontinued treatment with empagliflozin or sacubitril/valsartan were treated with SoC alone.

**Figure 1. Model Diagram**




Abbreviations: AE = adverse event; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Symptom Score; HHF = hospitalization for heart failure
* Transient events may occur in any non-death health state.

## METHODS (CONT.)

### Population

- Modeled population was the same as participants with HFrEF who were not treated with ARNi at baseline in the EMPEROR-Reduced trial (constituting approximately 80.5% of the trial population)
  - Adults with New York Heart Association (NYHA) class II-IV and left ventricular ejection fraction (LVEF) ≤40%. Mean age was 67 years, and 76% of participants were male.
  - Initial proportion of patients distributed in KCCQ-CSS Quartile 1 (0 ≤KCCQ-CSS <55), Quartile 2 (55 ≤KCCQ-CSS <75), Quartile 3 (75 ≤KCCQ-CSS <90), and Quartile 4 (90 ≤KCCQ-CSS ≤100) was 24.6%, 25.7%, 27.0%, and 22.7%, respectively.

### Clinical Parameters

- Monthly transitions between KCCQ-CSS health states for three time periods (baseline–week 12, week 12–32, and week 32–52) were derived from patient-level EMPEROR-Reduced trial data. Transition probabilities from week 32–52 were used for the remaining model time horizon.
- Risk equations for HHF and death were based on a sub-analysis of patients with HFrEF not treated with ARNi at baseline in the EMPEROR-Reduced trial and included KCCQ-CSS quartiles as time-varying predictors.
  - Rate of first and recurrent HHF was captured using a Poisson model fitted to patient-level data with generalised estimating equations to account for repeated measures.
  - Parametric survival analysis was used to project event-free survival curves for CV death and all-cause death.
  - Proportion of non-CV deaths calculated from the risk equations was compared with UK age- and sex-specific life tables (adjusted to exclude CV deaths), and the least optimistic data was applied.
- Parametric survival analysis of EMPEROR-Reduced trial data informed time to active treatment discontinuation, considering KCCQ-CSS quartiles as time-varying predictors.

### Treatment-related Parameters

- Equal effectiveness was assumed for empagliflozin + SoC and sacubitril/valsartan + SoC based on Bucher indirect treatment comparison (ITC).
  - Comparison of the EMPEROR-Reduced trial subpopulation without ARNi use vs. all patients in PARADIGM-HF was performed.
  - Empagliflozin vs. sacubitril/valsartan on time to CV death or HHF was not statistically significant (HR: 0.96; 0.81–1.15); similarly, no difference in treatment effect was shown on individual outcomes.
- AEs for empagliflozin + SoC reflected EMPEROR-Reduced trial data, and AEs for sacubitril/valsartan were informed by published PARADIGM-HF trial data; AEs were assumed to be constant over time.

### Cost Inputs

- Drug acquisition, clinical event management, and disease management costs in £2021 were derived from public sources[3-6] and discounted at 3.5% per year.
- A weighted average drug acquisition cost was applied for each treatment regimen, adjusted for the utilization of HF medication classes in the EMPEROR-Reduced trial subpopulation without ARNi use at baseline (Table 1).
  - Stable maintenance dosage for each SoC treatment was applied.
- HHF, CV death, and AEs incurred a one-time cost per event in the model (Table 2).
  - AE expenditures were a weighted average based on whether patients were expected to receive outpatient or inpatient care.
- Frequency of use and unit costs for GP visits, cardiologist visits, and accident and emergency referrals were used to estimate the total HF-related disease management cost per patient (Table 3).

**Table 1. Drug Costs by Treatment Regimen (£2021)**

| | Cost[3] (Utilization)* | |
|---|---|---|
| Treatment | Empagliflozin + SoC | Sacubitril/Valsartan + SoC |
| SGLT2i: empagliflozin | £39.78 (100%) | -- |
| ARNI: sacubitril/valsartan | -- | £99.53 (100%) |
| ACEI: captopril, enalapril, lisinopril, ramipril, trandolapril** | £6.03 (41%) | £6.03 (41%) |
| ARB: candesartan, valsartan, losartan** | £11.05 (29%) | £11.05 (29%) |
| MRA: eplerenone | £7.63 (71%) | £7.63 (71%) |
| BB: bisoprolol, carvedilol, metoprolol, nebivolol** | £9.50 (95%) | £9.50 (95%) |
| HCN channel blocker: ivabradine | £4.83 (6%) | £4.83 (6%) |
| **Estimated weighted drug cost per month** | **£60.13** | **£119.89** |

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BB = beta blocker; HCN = hyperpolarization-activated cyclic nucleotide-gated; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor; SoC= standard of care
Note: Cost of SoC alone was estimated to be £20.35.
*Utilization among the subgroup of patients in EMPEROR-Reduced who were not treated with ARNi at baseline.
**Treatments within each class were assumed to be uniformly distributed.

## METHODS (CONT.)

**Table 2. Acute Clinical Event Management Cost (£2021)**

| Event | Cost per Event |
|---|---|
| HHF[a] | £3,072 |
| CV Death[b] | £4,146 |
| Urinary Tract Infection[a#] | £40 |
| Genital Mycotic Infection[a#] | £40 |
| Acute renal failure[a#] | £1,906 |
| Hepatic injury[a,c,§] | £1,274 |
| Volume depletion[a#] | £40 |
| Hypotension[a#] | £40 |
| Hypoglycemic event[a,c,§] | £627 |
| Bone fracture[a#] | £2,710 |
| Hyperkalemia[a#] | £40 |
| Cough[a#] | £40 |
| Dizziness[a#] | £40 |

Abbreviations: CV = cardiovascular; HHF = hospitalization for worsening heart failure
Note: Cost of non-CV death was assumed to be zero.
[a]Patients were assumed to receive outpatient care (per patient contact lasting 9.22 minutes).
[b]Patients were assumed to receive inpatient care (weighted mean by national average unit costs and number of finished consultant episodes).
[c]Patients were assumed to receive outpatient (50%) or inpatient (50%) care.

**Table 3. Disease Management Costs (£2021)**

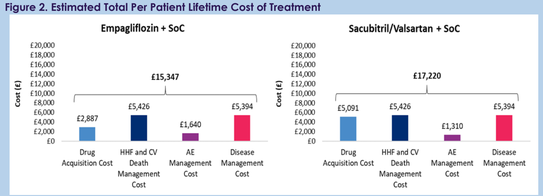
| | KCCQ-CSS Quartile 1–4 | |
|---|---|---|
| Resource | Monthly Frequency | Monthly Unit Cost |
| GP visit[#a] | 1.9283 | £40 |
| Cardiologist visit[#a] | 0.0042 | £140 |
| A&E referral[#a] | 0.0008 | £153 |
| **Estimated total monthly cost per patient** | **£77** | |

Abbreviations: A&E = accident and emergency; GP = general practitioner; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
[a]Outpatient visit with per patient contact lasting 9.22 minutes.
[#]Cardiology, non-admitted, face to face, follow-up visit.
[§]Weighted mean by national average unit costs and number of finished consultant episodes for emergency medicine.

## RESULTS

- In validation, event rates for empagliflozin + SoC vs. SoC estimated by the model over 18 months (available upon request) were consistent with the EMPEROR-Reduced trial results.
- Total discounted costs per patient were £15,347 with empagliflozin and £17,220 with sacubitril/valsartan, resulting in total lifetime cost savings of £1,873/patient which is equivalent to a 12.2% cost reduction (Figure 2).
  - Incremental cost was driven primarily by the lower drug acquisition cost for empagliflozin vs. sacubitril/valsartan
- Empagliflozin remained cost-saving by 10.1% to 22.1% vs. sacubitril/valsartan under a range of sensitivity analyses (Table 4).

**Figure 2. Estimated Total Per Patient Lifetime Cost of Treatment**




Abbreviations: AE = adverse event; CV = cardiovascular; HHF = hospitalization for worsening heart failure; SoC= standard of care

## RESULTS (CONT.)

**Table 4. Sensitivity Analysis Results**

| Scenario | Total Cost: Empagliflozin + SoC | Total Cost: Sacubitril/Valsartan + SoC | Cost Difference | Saving in Annual Cost (%) |
|---|---|---|---|---|
| Base case | £15,347 | £17,220 | -£1,873 | -12.2% |
| Sensitivity Analysis | | | | |
| Exclude treatment discontinuation | £16,228 | £19,820 | -£3,592 | -22.1% |
| Empagliflozin acquisition cost, -20% | £15,054 | £17,220 | -£2,167 | -14.4% |
| Time horizon, 10 years | £13,253 | £15,067 | -£1,814 | -13.7% |
| Treatment discontinuation, alternative distribution* | £15,403 | £17,386 | -£1,983 | -12.9% |
| AE management cost, -20% | £15,019 | £16,959 | -£1,939 | -12.9% |
| Discount rate on cost, 5% | £14,302 | £16,099 | -£1,797 | -12.6% |
| Time horizon, 20 years | £15,160 | £17,032 | -£1,872 | -12.3% |
| AE management cost, +20% | £15,675 | £17,482 | -£1,807 | -11.5% |
| Discount rate on cost, 0% | £18,511 | £20,596 | -£2,085 | -11.3% |
| Empagliflozin acquisition cost, +20% | £15,641 | £17,220 | -£1,580 | -10.1% |

Abbreviations: AE = adverse event; SoC= standard of care
*Weibull instead of exponential in the base case.

## LIMITATIONS

- Analyses were based on the subpopulation of EMPEROR-Reduced not treated with ARNi at baseline, and the trial was not powered to assess treatment benefits in a subgroup.

## CONCLUSIONS

- Treatment with empagliflozin added to SoC resulted in significant cost savings compared to sacubitril/valsartan added to SoC for the management of HFrEF in the UK.
- For decision makers, treatment with empagliflozin may reduce the cost burden of HFrEF.

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