Dapagliflozin or empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction

Technology appraisal committee C 12 April 2023

Slides for public
ACIC information redacted

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Companies: AstraZeneca (dapagliflozin), Boehringer Ingelheim (empagliflozin)

Abbreviations

AE	Adverse event
CI	Confidence interval
CV	Cardiovascular
DSA	Deterministic sensitivity analysis
EAG	External Assessment Group
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
HF	Heart failure
HFimpEF	Heart failure with an improved ejection fraction
HFmrEF	Heart failure with a mildly reduced ejection fraction
HFpEF	Heart failure with a preserved ejection fraction
HFrEF	Heart failure with a reduced ejection fraction
HHF	Hospitalisation for heart failure
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
KM	Kaplan-Meier
LOCF	Last observation carried forward
LVEF	Left ventricular ejection fraction
NHB	Net health benefit
NYHA	New York Heart Association
PSA	Probabilistic sensitivity analysis
SGLT2i	Sodium-glucose-co-transporter-2 inhibitor
SoC	Standard of care
T2DM	Type 2 diabetes mellitus

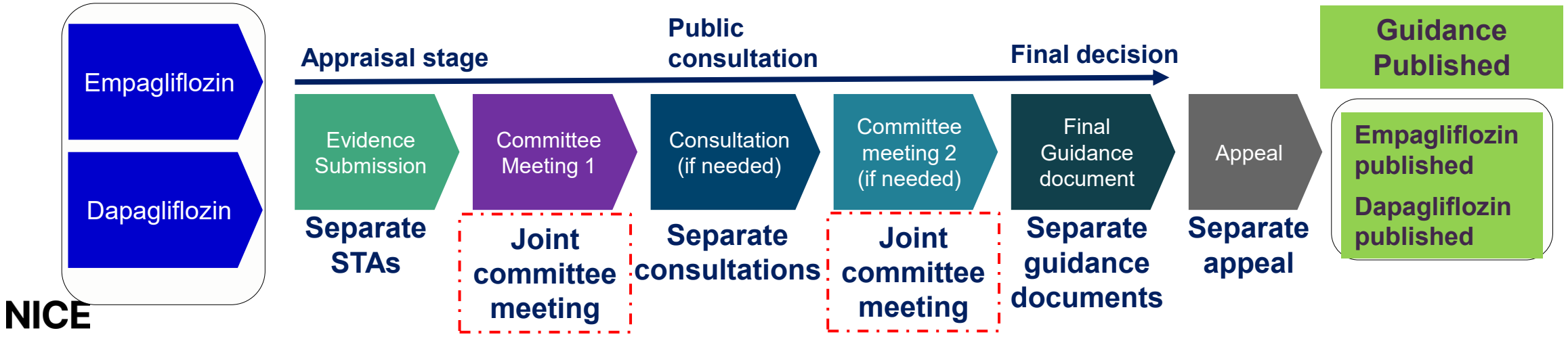
RECAP

Pair appraisals pilot - introduction

Concept

Appraisals pipeline contains topics in same disease area that are likely to be evaluated at similar times.

- Two regular STAs, following STA principles
- Build on **efficiencies and economies of scale by aligning topics and sharing parts of the process** including internal and external aspects (NICE technical team, experts, EAG and committee discussion) to ensure alignment and reduce effort needed
- NICE is not comparing empagliflozin with dapagliflozin



EAG, evidence assessment group; STA, single technology appraisal

Recap of ACM1

Background

Dapagliflozin (ID1648)	Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

RECAP

The technologies are not recommended

Committee decision at ACM1

ID1648 (dapagliflozin)

Dapagliflozin is not recommended for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction (HFpEF or HFmrEF)

- There is uncertainty about the treatment effect on survival and how this was modelled
- The cost-effectiveness estimates are likely above the threshold considered cost-effective by NICE

ID3945 (empagliflozin)

Empagliflozin is not recommended for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction (HFpEF or HFmrEF)

- There is uncertainty about the treatment effect on survival and how this was modelled
- The cost-effectiveness estimates are above the threshold considered cost-effective by NICE

NICE

ACM1, appraisal committee meeting 1; HFmrEF, Heart failure with mildly reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction

Dapagliflozin (Forxiga, AstraZeneca) and empagliflozin (Jardiance, Boehringer Ingelheim)

Technology details for dapagliflozin and empagliflozin

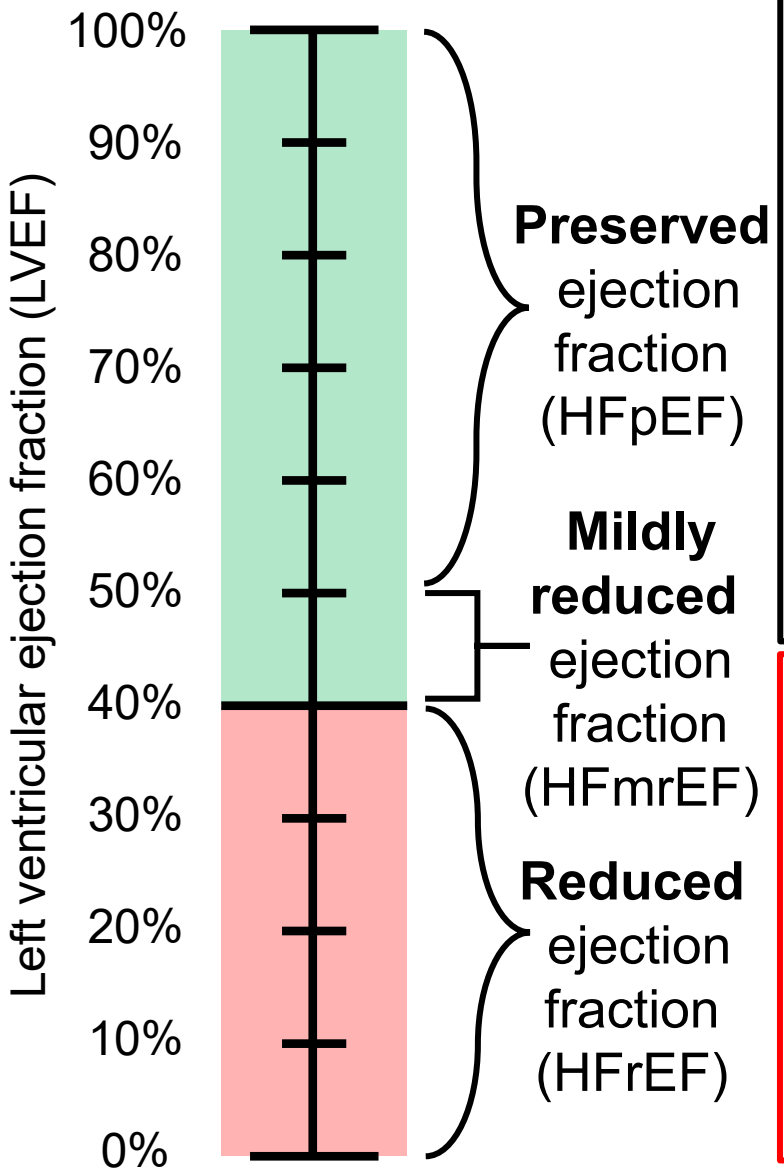
	Dapagliflozin (ID1648)	Empagliflozin (ID3945)
Marketing authorisation	• Adults for the treatment of symptomatic chronic heart failure • Marketing authorisation granted by MHRA in December 2022 • Dapagliflozin is already recommended by NICE for treating chronic heart failure with reduced ejection fraction (TA679)	• Adults for the treatment of symptomatic chronic heart failure • Marketing authorisation granted by MHRA in June 2022 • Empagliflozin is already recommended by NICE for treating chronic heart failure with reduced ejection fraction (TA773)
Mechanism of action	• Highly potent, selective and reversible sodium-glucose co-transporter 2 (SGLT2) inhibitor • Inhibition reduces renal reabsorption of glucose and sodium in the kidney • Mechanism of action in chronic heart failure not yet fully understood	
Administration	Oral	
Price	• List price: £36.59 per pack of 28 x 10 mg tablets • List price: £477.30 per year of treatment • No patient access scheme	• List price: £36.59 per pack of 28 x 10 mg tablets • List price: £477.30 per year of treatment • No patient access scheme

Abbreviations: EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Agency Regulatory Agency

Treatment and classification of chronic heart failure (cHF)

RECAP

Heart failure is the inability of the heart to supply sufficient blood flow to meet the body's needs



Treatment pathway

People with chronic heart failure with preserved or mildly reduced ejection fraction (LVEF >40%)

New treatments

Established clinical management (standard care):
- Loop diuretics
- Symptomatic treatments for comorbidities

Dapagliflozin in combination with standard care (ID1648)

Empagliflozin in combination with standard care (ID3945)

Populations of interest for this appraisal:

- Heart failure with **preserved** or **mildly reduced** ejection fraction (LVEF >40%)
- Heart failure with **improved** ejection fraction (HFimpEF) - previously diagnosed HFrEF (LVEF ≤40%) which has now become HFpEF or HFmrEF (LVEF >40%) – included in dapagliflozin trial

ACM1, appraisal committee meeting 1; HFmrEF, Heart failure with mildly reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction

Recap of ACM1

Clinical effectiveness and model structure

Dapagliflozin (ID1648)

NICE National Institute for Health and Care Excellence

Key clinical trial: DELIVER

Clinical trial designs and outcomes

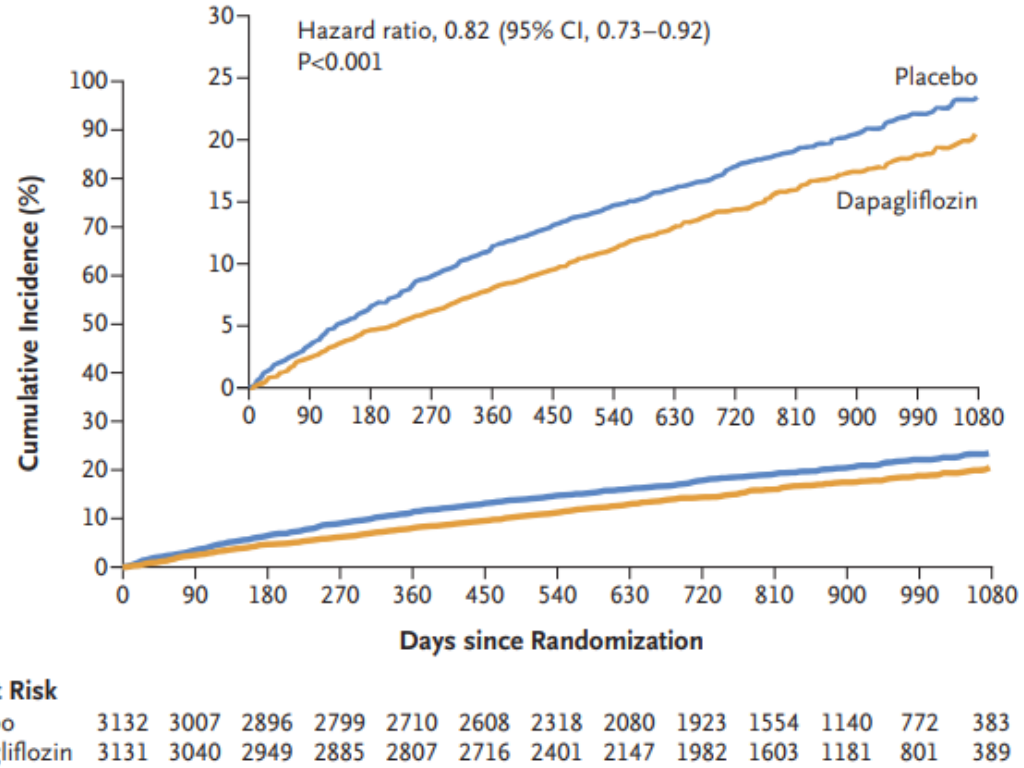
	DELIVER (NCT03619213)
Design	International, phase 3, randomised, double-blind, placebo-controlled trial
Population	Adults (≥40 years) with chronic HF NYHA class II-IV and EF >40%, with or without diabetes (N=6,263)
Intervention	Dapagliflozin, 10 mg taken orally once daily, plus standard of care
Comparator(s)	Placebo plus standard of care
Duration	Event-driven (anticipated duration 39 months), median time in study until primary analysis censoring date was [redacted] months. Study completion date: March 2022
Primary outcome	Time to first event of CV death or HF events (hospitalisation due to heart failure [HHF] or urgent heart failure visit [UHFV])
Key secondary outcomes	Total number of HF events and CV deaths; time to CV death; time to all-cause deaths; adverse events; PRO measured by KCCQ; EQ-5D-5L
Locations	20 countries, including in Europe, Asia, Latin America and North America; no UK patients
Used in model?	Yes

CSS, clinical summary score; CV, cardiovascular; EF, ejection fraction; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; HF, heart failure; HHF, hospitalisation due to heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; QoL, quality of life; NYHA, New York Heart Association

DELIVER results (1/2)

Dapagliflozin reduced combined risk of CV death or HF event compared with placebo

Primary outcome: Composite outcome of CV death or HF event



Key primary and secondary outcomes

Key outcomes	HR (95% CI)
Primary outcome: Composite outcome of CV death or HF event	0.82 (0.73 to 0.92); p<0.001
Composite outcome of CV death or total (first and recurrent) HF events	RR 0.77 (0.67 to 0.89); p<0.001
Recurrent HF events	RR 0.73 (0.62 to 0.87); p=0.0003)
Change in mean KCCQ-TSS at 8 months	Point estimate: +2.4 (1.5, 3.3); p<0.001

NICE

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; RR, relative risk

DELIVER results (2/2)

Dapagliflozin did not significantly reduce all-cause or CV mortality

***KM curves for all-cause deaths in DELIVER**
HR: 0.94; 95% CI: 0.83 to 1.07; p=0.3425

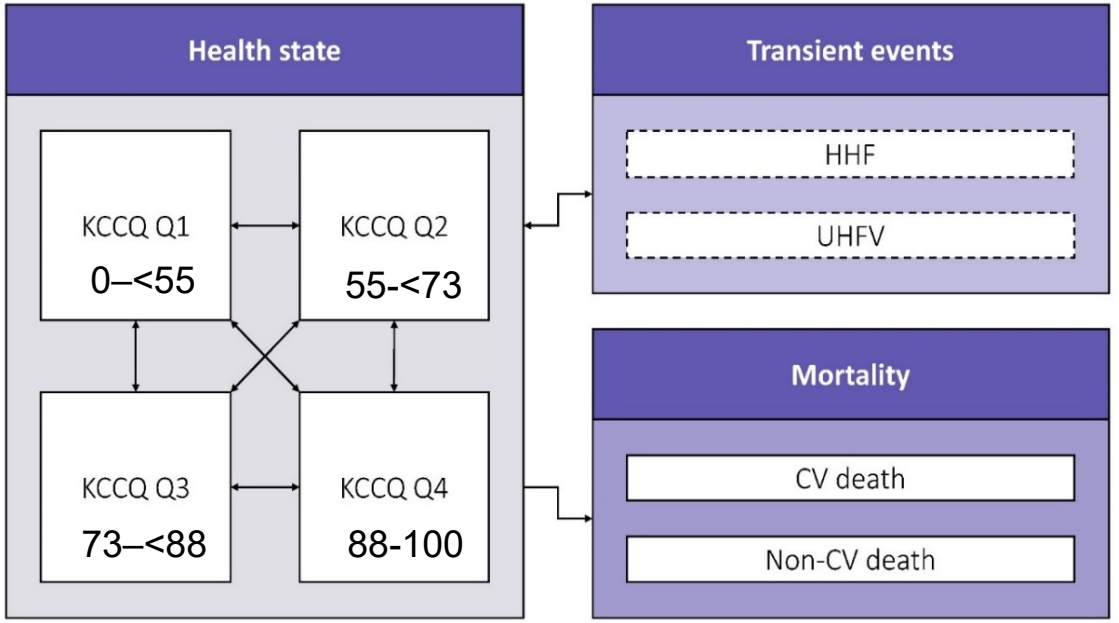
***KM curves for CV deaths in DELIVER**
HR: 0.88; 95% CI: 0.74 to 1.05; p=0.1678

*Curves from company model, shared by the EAG

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KM, Kaplan-Meier

Dapagliflozin: Company's model overview

Model structure	Cohort Markov model, with health states defined by KCCQ-TSS quartiles
Population	Adults with symptomatic chronic HF with preserved (HFpEF) or mildly reduced (HFmrEF) LVEF
Intervention	Dapagliflozin + SoC (weighted average of 80% furosemide and 20% bumetanide)
Comparators	SoC (weighted average of 80% furosemide and 20% bumetanide)
Time horizon	Lifetime horizon (to 101 years of age); starting age [redacted] years
Model cycle	One month, with half-cycle correction
Discount rates	3.5% per annum-costs, QALYs and life years
Utility values	EQ-5D-5L mapped to 3L for each KCCQ-TSS quartile
Perspective	NHS and Personal Social Services (PSS)



Used Kansas City Cardiomyopathy Questionnaire – total symptom score (**KCCQ-TSS**)

- A disease-specific, patient-reported, quality of life measurement with scores between 0-100
- Lower scores represent worse outcomes – more frequent and severe symptoms
- **Also used in the HFrEF appraisal (TA679)**

NICE

KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; HF, heart failure; HHF, hospitalisation for heart failure; UHFV, urgent heart failure visits; CV, cardiovascular; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; 3L, 3 levels; LVEF, left ventricular ejection fraction; QALY, quality-adjusted life year; SoC, standard of care

Recap of ACM1

Clinical effectiveness and model structure

Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

Key clinical trial: EMPEROR-Preserved

Clinical trial designs and outcomes

	EMPEROR-Preserved (NCT03057951)
Design	International, phase 3, randomised, double-blind, placebo-controlled trial
Population	Adults (≥18 years) with chronic HF NYHA class II-IV and EF >40%, with or without diabetes (N=5,988)
Intervention	Empagliflozin, 10 mg taken orally once daily, plus standard of care
Comparator(s)	Placebo plus standard of care
Duration	Event-driven, median follow-up 26.2 months. Study completion date: 26 April 2021
Primary outcome	Time to first event of adjudicated CV death or adjudicated hospitalisation due to heart failure (HHF)
Key secondary outcomes	HHF (first and recurrent); decline in renal function; time to first dialysis, renal transplant or sustained reduction of eGFR; time to first HHF; time to CV death; time to all-cause mortality; all-cause hospitalisation; adverse events; PRO measured by KCCQ; EQ-5D-5L
Locations	23 countries, including 25 patients randomised and treated in the UK
Used in model?	Yes

CV, cardiovascular; EF, ejection fraction; eGFR, estimate glomerular filtration rate; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; HF, heart failure; HHF, hospitalisation for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; PRO, patient-reported outcomes; QoL, quality of life;

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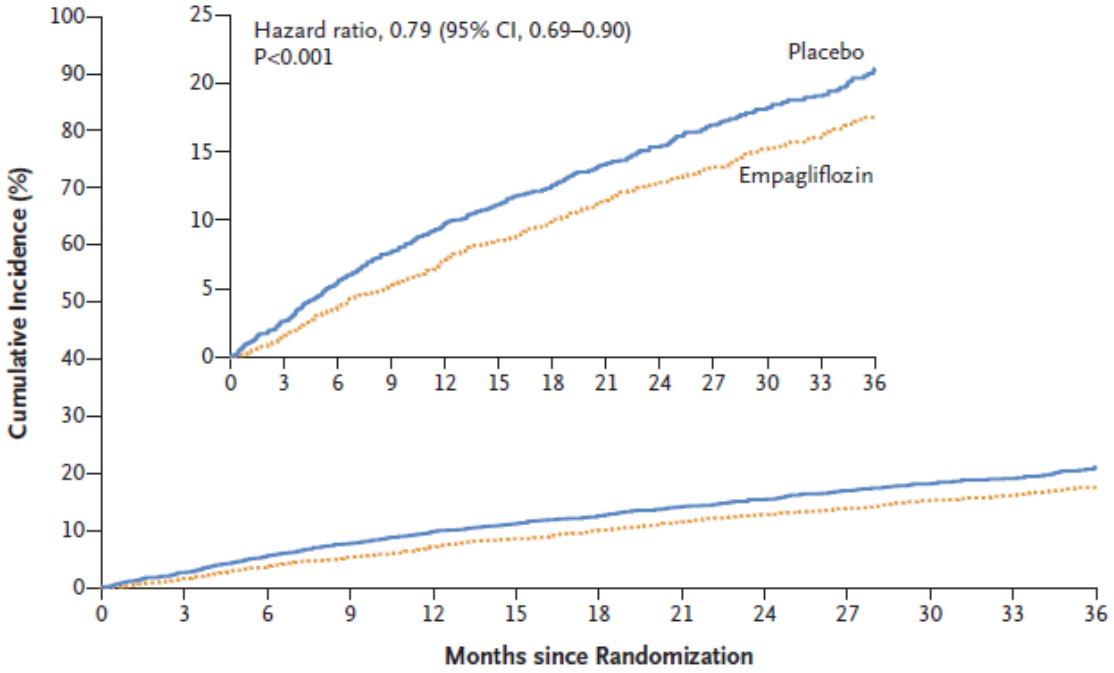
EMPEROR-Preserved results (1/2)

Empagliflozin reduced combined risk of CV death or HHF compared with placebo

Primary outcome: Composite outcome of CV death or HHF



Outcomes in **bold** are statistically significant

Key primary and secondary outcomes

Key outcomes	HR (95% CI)
Primary outcome: Composite outcome of CV death or HHF	**0.79 (0.69 to 0.90)**
Total number of HHF	**0.73 (0.61 to 0.88)**
Deterioration of renal function	**1.36 mL/min/1.73 m² per year (1.06 to 1.66); p<0.0001**
Time to composite renal outcome	0.95 (0.73 to 1.24); nominal p=0.7243
Time to first adjudicated HHF	**0.71 (0.60 to 0.83); nominal p<0.0001**
Time to onset of diabetes in people with pre-diabetes	0.84 (0.65 to 1.07); nominal p=0.15
First and recurrent all-cause hospitalisation	0.93 (0.85 to 1.01); nominal p=0.10

NICE

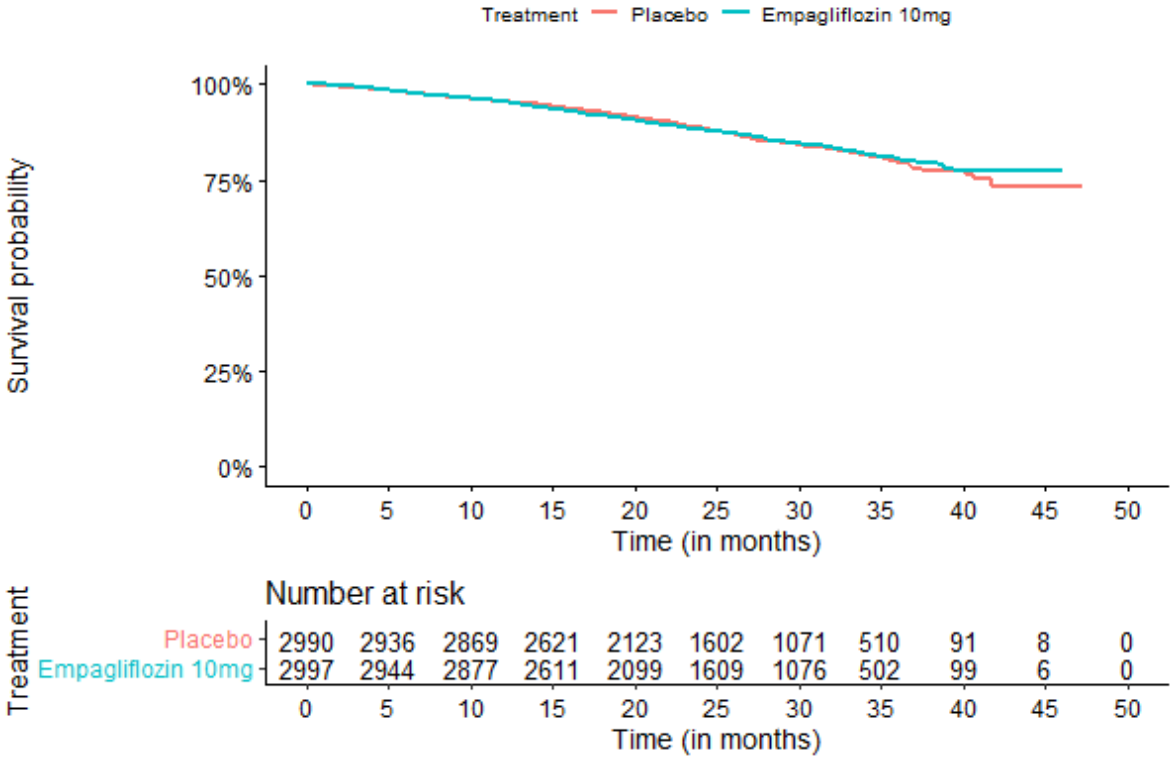
CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio

EMPEROR-Preserved results (2/2)

Empagliflozin did not significantly reduce all-cause or CV mortality

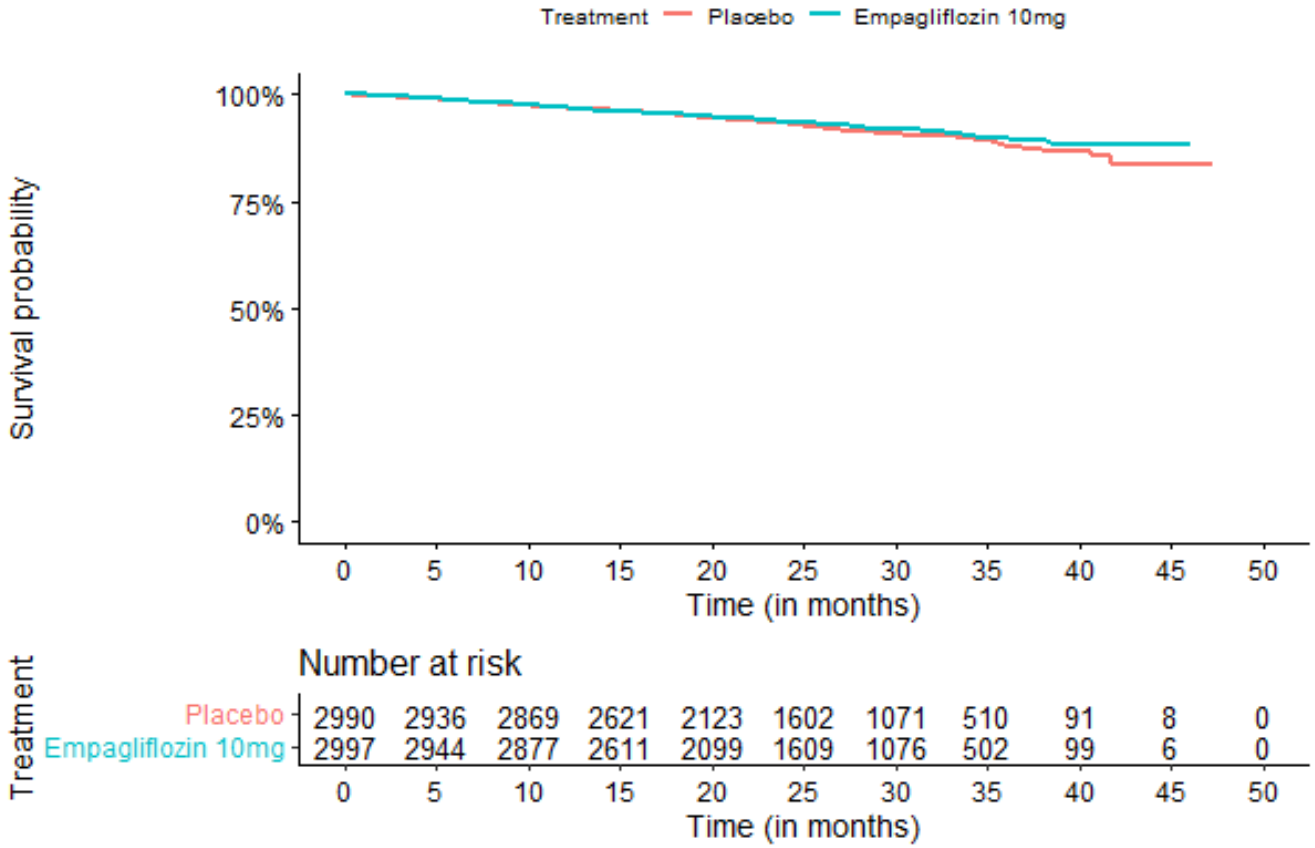
Observed OS data in EMPEROR-Preserved

HR: 1.00; 95% CI: 0.87 to 1.15



Observed CV mortality data in EMPEROR-Preserved

HR: 0.91, 95% CI: 0.76 to 1.09



NICE

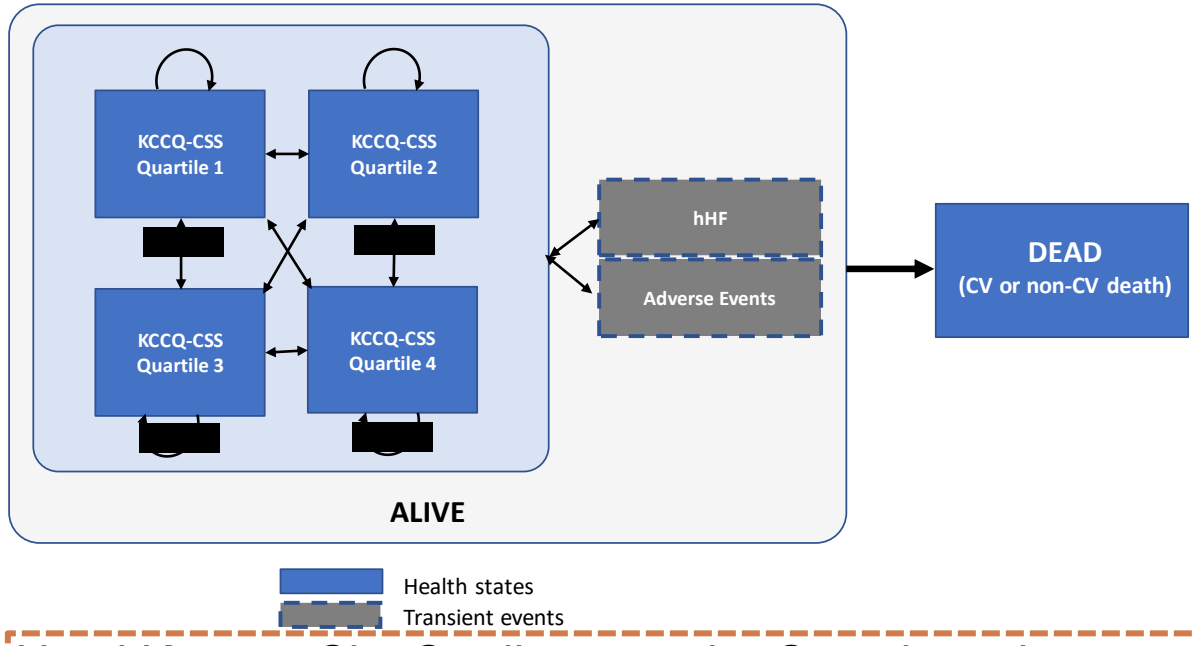
CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio

RECAP

Empagliflozin: Model structure

Model description

Model structure	Cohort Markov model, with health states defined by KCCQ-CSS quartiles
Population	Adults with symptomatic chronic HF with preserved (HFpEF) or mildly reduced (HFmrEF) LVEF
Intervention	Empagliflozin + SoC (ARNIs, ACEIs, BBs, ARBs and MRAs)
Comparators	SoC (ARNIs, ACEIs, BBs, ARBs and MRAs)
Time horizon	Lifetime horizon; starting age 71.89 years
Model cycle	One month, with half cycle applied
Discount rates	3.5% per annum for costs and QALYs and life years
Utility values	EQ-5D-5L mapped to 3L for each KCCQ-CSS quartile
Perspective	NHS and Personal Social Services (PSS)



Used Kansas City Cardiomyopathy Questionnaire – clinical summary score (**KCCQ-CSS**)

- A disease-specific, patient-reported, quality of life measurement with scores between 0-100
- Lower scores represent worse outcomes – more frequent and severe symptoms
- **Also used in the HFrEF appraisal (TA773)**

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta-blockers; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; MRA, mineralocorticoid receptor antagonists; MRA, mineralocorticoid receptor antagonists; SoC, standard of care; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; 3L, 3 levels; LVEF, left ventricular ejection fraction; QALY, quality-adjusted life year; SoC, standard of care

Draft guidance consultation responses

Dapagliflozin (ID1648)

Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

Patient and professional group perspective – DG consultation

Decision to not recommend the treatments is disappointing, due to unmet need

- Decision to not recommend treatments has led to a feeling of great disappointment
- SGLT2is are the first treatments shown to improve symptoms and reduce hospitalisation in this population
- People with HFpEF and HFmrEF have significant symptom burden and physical limitation
- The reduction in mortality is clinically impactful despite not being statistically significant
- Significant benefits for other HF outcomes should not be undermined by mortality results

Feels like a missed opportunity to recommend SGLT2is to a broader group with HF

Many people with HF will have their quality of life affected by this decision

This decision is another blow to people who are often already living a physically & mentally difficult life

Clinical trials have shown SGLT2is are effective…I cannot see why cost would be an issue

DG, Draft guidance; HF, Heart failure; HFmrEF, Heart failure with mildly reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; SGLT2i, sodium-glucose co-transporter 2 inhibitor

Clinical expert perspective on DG consultation

There are currently no disease-modifying treatments for this group and treatments capable of reducing hospitalisation are needed

Invited clinical expert attending first appraisal committee meeting

- Currently no disease-modifying treatment and HF is a leading cause of readmission
- HF admission can be long and costly and benefits of the technologies may not be fully captured in a technology appraisal
- Ability to reduces hospital admission may lead to a reduction in mortality

Clinical expert response by web comment

- HF admission usually requires long hospital stay and readmission is common
- Treatment capable of reducing hospitalisation should be considered in the context of current NHS pressures
- People with HF are more likely to be elderly and at risk of complication when hospitalised

Key issues

Dapagliflozin (ID1648)

NICE National Institute for Health and Care Excellence

Committee preference implemented

Committee preference not implemented

Key issues

Issues for discussion

Issue	Committee preference	Company revised base case	EAG critique	ICER impact
Treatment effect on survival	Uncertainty remains	Direct and indirect effect on CV mortality and all-cause mortality	Insufficient evidence that removal of treatment effect is inappropriate	Large
Appropriate reference costs	Both options plausible, uncertainty remains	NHS Reference Costs (2020/21)	Prefers 2019/20 costs adjusted for inflation	Small
Most appropriate extrapolation	Uncertainty remains	Piecewise Weibull model	None	Small

ACM1, appraisal committee meeting 1; AE, Adverse events; CV, cardiovascular; EAG, external assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio

Key issues

Committee preference implemented

Committee preference not implemented

Issues with committee decision at ACM1

Issue	Committee preference	Company revised base case	EAG critique	ICER impact
Amputation as AE	Should not be included	Excludes amputation as AE	Notes alignment	Small
Validity of AE probabilities	Probabilities from DELIVER trial	Probabilities from DELIVER trial	Notes alignment	Small
Resource use	**HHF events**: 13 day-hospital stay	**HHF events**: 13 day-hospital stay	Notes alignment	Small

ACM1, appraisal committee meeting 1; AE, Adverse events; CV, cardiovascular; EAG, external assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio

Key issue: Impact of dapagliflozin on survival unclear

There is uncertainty surrounding the effect of dapagliflozin on mortality in the appraisal population

ICER impact
Large

Background

- In DELIVER, dapagliflozin reduced CV and all-cause mortality but the difference was not significant
- The company's base case included direct and indirect treatment effect on mortality

Draft guidance

- The model should be able to replicate the observed data
  - Provide scenarios exploring the direct and indirect impact on CV and all-cause deaths
  - Refit model when parameters (such as treatment effect) are excluded

Company

- Provided 2 scenarios removing (i) indirect, and (ii) both direct and indirect treatment effect
- [redacted] in CV and all-cause mortality as standalone endpoints, non-significant p-values reflect [redacted] not lack of dapagliflozin treatment effect

Should modelling of dapagliflozin in this appraisal include a treatment effect on mortality?

CV, cardiovascular; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction

Key issue: Impact of dapagliflozin on survival unclear

There is uncertainty surrounding the effect of dapagliflozin on mortality in the appraisal population

ICER impact
Large

Company

- Scenarios removing treatment effect should not be used for decision making
- Reiterated pooled analysis of DELIVER and DAPA-HF (HFrEF group) from Jhund et al. indicate dapagliflozin reduces CV and all-cause mortality, no evidence that LVEF modifies this effect
- [redacted] reductions in HHF events and improvements in KCCQ score are plausible mechanisms for mortality reductions, based on clinical expert feedback and literature (Johansson et al. 2021)
- NICE manual prefers RCTs to inform treatment effect, previous HFrEF appraisals (TA679 and TA773) did not remove treatment effect
- Probabilistic sensitivity analysis (PSA) already captures uncertainty in treatment effect
- Extrapolations for CV or all-cause mortality in new scenarios not clinically valid compared with DELIVER KM data

Should modelling of dapagliflozin in this appraisal include a treatment effect on mortality?

CV, cardiovascular; EAG, external assessment group; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; KM, Kaplan-Meier; LVEF, left ventricular ejection fraction; RCT, randomised controlled trial; SoC, standard of care

Key issue: Impact of dapagliflozin on survival unclear

There is uncertainty surrounding the effect of dapagliflozin on mortality in the appraisal population

ICER impact
Large

EAG

- [redacted] in DELIVER causes uncertainty in treatment effect, scenarios help explore the uncertainty
- CV mortality reduction in pooled analysis is not statistically significant in the LVEF >40% group
- Unclear if KCCQ score improvements were statistically significant at all time points and uncertain how closely findings from Johansson et al. (2021) matches with DELIVER KCCQ-TSS data
- DELIVER did not show statistically significant difference in mortality compared to SoC, DAPA-HF (HFrEF group) showed significant difference on CV and all-cause mortality
- PSA does not resolve uncertainty around existence of a treatment effect and is limited by correlation of its inputs
- Differences between observed data and all modelled scenarios across timepoints are similar indicating they are of similar clinical validity (although highlights difference in all modelling scenarios over time compared to DELIVER)

Should modelling of dapagliflozin in this appraisal include a treatment effect on mortality?

CV, cardiovascular; EAG, external assessment group; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; KM, Kaplan-Meier; LVEF, left ventricular ejection fraction; RCT, randomised controlled trial; SoC, standard of care

Key issue: Impact of dapagliflozin on survival unclear

ICER impact
Large

Dapagliflozin and SoC mortality extrapolations are closely aligned to each other in mortality scenario 1

Scenario 1 – removal of direct treatment effect

- Removes the direct treatment effect of dapagliflozin by removing treatment with dapagliflozin as a candidate variable in regression modelling of mortality

Scenario 1: CV mortality extrapolations compared with the KM curves from DELIVER

[redacted]

Scenario 1: All-cause mortality extrapolations compared with the KM curves from DELIVER

[redacted]

Are the extrapolations appropriate to predict observed data?

KM, Kaplan-Meier; SoC, standard of care

Key issue: Impact of dapagliflozin on survival unclear

ICER impact
Large

Dapagliflozin and SoC mortality extrapolations are identical to each other in mortality scenario 2

Scenario 2 – removal of direct and indirect treatment effect

- Removes the direct treatment effect as in scenario 1 but also removes indirect treatment effect by removing KCCQ stages as potential candidate variables in mortality regression modelling
- By removing direct and indirect effects, mortality is the same for dapagliflozin and SoC

Scenario 2: CV mortality extrapolations compared with the KM curves from DELIVER

[redacted]

Scenario 2: All-cause mortality extrapolations compared with the KM curves from DELIVER

[redacted]

Are the extrapolations appropriate to predict observed data?

KCCQ, Kansas City Cardiomyopathy Questionnaire; KM, Kaplan-Meier; SoC, standard of care

Key issue: Impact of dapagliflozin on survival unclear

Uncertainty if HFimpEF group should be included in the population and impact on mortality estimates

ICER impact: Large

- The EAG note [redacted] between those with and without a prior LVEF ≤40%
- They note clinical expert feedback, which suggests that people with HFimpEF would be eligible for an SGLT2i when their LVEF was <40% (HFrEF) and would be unlikely to stop treatment when their LVEF increased to >40%
- However, [redacted] was observed between those with HFimpEF and those with LVEF consistently >40%

CV mortality and all-cause mortality in HFimpEF vs consistent LVEF >40%

HR (95% CI; p-value)	CV mortality	All-cause mortality
Overall FAS population	0.88 (0.74 to 1.05; p=[redacted]	0.94 (0.83 to 1.07; p=[redacted]
HFimpEF group	[redacted]	[redacted]
Consistent LVEF >40% group	[redacted]	[redacted]
*Interaction p-value	[redacted]	[redacted]

Previously diagnosed with HFrEF (LVEF ≤40%) but have now become HFpEF or HFmrEF (i.e., LVEF >40%)

NICE

Is the HFimpEF group clinically different to the consistent LVEF >40% group?

Key issue: Impact of dapagliflozin on survival unclear

ICER impact: Large

Modelled scenarios show similar mortality increases over time but are overestimated compared to DELIVER

Observed and predicted mortality

	DELIVER study			Cost effectiveness model								
				Company revised base case			Scenario 1			Scenario 2		
	Dapa	SoC	Diff	Dapa	SoC	Diff	Dapa	SoC	Diff	Dapa	SoC	Diff
CV mortality												
Month 26	[redacted]											
Month 36	[redacted]											
Between times	[redacted]											
All-cause mortality												
Month 26	[redacted]											
Month 36	[redacted]											
Between times	[redacted]											

Which scenario aligns most closely with the observed data?

Dapa, dapagliflozin; SoC, standard of care; Diff, difference

Key issue: Appropriate reference costs unclear

ICER impact: Small

There is uncertainty about the most suitable reference costs as a result of COVID

Background

- Company preferred 2020/21 costs while EAG preferred 2019/20 costs adjusted for inflation

Draft guidance

- Committee concluded that both sources of NHS reference costs were plausible, and it was uncertain which NHS reference cost values were most appropriate, given the uncertain impact of the COVID-19 pandemic.

Company

- Unclear if NHS has returned to pre-pandemic conditions given current economic climate and inflation, 2020/21 costs (reflective of COVID-19) may be more appropriate

EAG

- COVID-19 increased demand for hospital resources which likely does not apply going forward
- 2020/21 costs will overestimate costs of non-elective long term hospital stays which will underestimate ICER
- Comparison of costs for HHF and other treatments between 2016/17 and 2020/21 indicate a sharp increase in costs in 2020/21 across all treatments

Are 2020/21 or adjusted 2019/20 costs most appropriate for decision making?

Other considerations (1/2)

Replication of trial data in modelling – draft guidance section 3.13

- EAG compared model results for mortality, HHF and UHFV events, and the proportion of people in each KCCQ-TSS quartile to observed results from DELIVER
- The incremental difference between dapagliflozin and SoC was overestimated in HHF events and mortality
- EAG considers uncertainty present in model's replication of HHF events and mortality observed in DELIVER

Dapagliflozin treatment effect on UHFV events – draft guidance section 3.14

- At ACM1, the EAG considered it uncertain whether dapagliflozin affected rates of UHFV events
- With data provided after draft guidance, the EAG considers this uncertainty addressed with evidence supporting the conclusion that dapagliflozin treatment does not substantially reduce UHFV events compared to SoC

EAG, external assessment group; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; SoC, standard of care; UHFV urgent heart failure visit

Other considerations (2/2)

Model structure contributes to sustained treatment effect– draft guidance section 3.15

- Company noted that sustained treatment effect is not present, because people who discontinue dapagliflozin in the model have the same transition probabilities as people receiving SoC
- EAG considered this did not address committee's concerns as the dapagliflozin arm had a higher proportion of people in higher KCCQ states which had lower transition probabilities and lower mortality rates

Most appropriate survival extrapolation – draft guidance section 3.12

- No further evidence or critique provided for company's mortality base case scenario extrapolation
- Company believes Weibull distribution provides the only clinically plausible extrapolation after validation for both treatment effect scenarios

EAG, external assessment group; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; SoC, standard of care; UHFV urgent heart failure visit

Cost-effectiveness results

Dapagliflozin (ID1648)

Dapagliflozin: Company revised base case results

Deterministic incremental base case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£8,527	4.490	£2,117	0.236	£8,975	0.13	0.17
SoC	£6,410	4.255	-	-	-	-	-

Probabilistic incremental base case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£8,496	4.497	£2,137	0.232	£9,226	0.12	0.15
SoC	£6,359	4.265	-	-	-	-	-

Revised base case assumes both direct and indirect effect on CV and all-cause mortality

DG, draft guidance; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Dapagliflozin: Company deterministic scenario analysis

Scenario 1 (removal of dapagliflozin direct treatment effect from the regression models)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£8,447	4.442	£1,928	0.100	£19,261	0.00	0.04
SoC	£6,518	4.342	-	-	-	-	-

Scenario 2 (removal of direct dapagliflozin treatment effect and indirect effect via KCCQ from the CV and all-cause mortality extrapolations)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£8,586	4.509	£1,922	0.073	£26,435	-0.02	0.01
SoC	£6,663	4.437	-	-	-	-	-

NICE

ICER, incremental cost-effectiveness ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Dapagliflozin: Company deterministic revised base case with EAG assumptions

	Company base case	EAG base case	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Company base case			£8,975	0.13	0.17
Reference costs	2020/21 NHS reference costs	2019/20 NHS reference costs adjusted for inflation	£9,221	0.13	0.16
UHFV treatment effect	Direct UHFV treatment effect included	Direct UHFV treatment effect excluded	£9,011	0.13	0.17
Company base case with EAG preferred assumptions above			£9,250	0.13	0.16

NICE

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care; UHFV, urgent heart failure visit

Dapagliflozin: EAG deterministic base case results

EAG's preferred assumptions:

- 2019/20 NHS reference costs adjusted for inflation
- No direct UHFV treatment effect included

Assumption: Impact of dapagliflozin on CV-related and all-cause deaths

	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
CV-related deaths: Direct and indirect effect **All-cause deaths:** Direct and indirect effect	£9,250	0.127	0.163
CV-related deaths*: Indirect effect **All-cause deaths*:** Indirect effect	£20,068	0.000	0.033
CV-related deaths*: No effect **All-cause deaths*:** No effect	£27,665	-0.028	0.006

*The EAG was unable to provide additional scenarios where no direct or no direct and indirect treatment effect was only applied to either CV or all-cause mortality, as the updated dapagliflozin model only allowed for the exploration of mortality scenarios applied to both CV and all-cause mortality

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; inc., incremental; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QALY, quality-adjusted life year; QoL, quality of life

Key issues

Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

Key issues

Committee preference implemented

Committee preference not implemented

Issues for discussion

Issue	Committee preference	Company revised base case	EAG critique	ICER impact
Treatment effect on survival	Uncertainty remains	• Direct and indirect benefit on CV mortality • Indirect benefit on all-cause mortality	Mortality overestimated	Large
HHF estimation	Uncertainty remains	Assumes constant risk	HHF overestimated	Un-known

Key issues

Committee preference implemented

Committee preference not implemented

Issues with committee decision at ACM1

Issue	Committee preference	Company revised base case	EAG critique	ICER impact
LOCF imputation for KCCQ transition probabilities	Observed data without imputation	LOCF with imputation	Observed data large enough for use	Large
Long term treatment effect	Model structure likely biases results	Assumes long term effect	Not addressed by company	Large
Duration of HHF impact on QoL	6 months	12 months	Additional data supports 6 months	Large
Resource use	**HHF events**: 13 day-hospital stay **CV deaths:** £1,452 (sudden death: £0)	**HHF events**: Average of 53 to 13 day-hospital stay **CV deaths:** £4,295	Maintain committee preference	Small

Key issue: Empagliflozin impact on survival unclear

Uncertain if direct and indirect treatment effect should be included in the model

ICER impact: Large

Background

- Empagliflozin did not significantly reduce CV or all-cause deaths in EMPEROR-Preserved
- The company's base case assumes a direct effect on CV deaths (via treatment effect) and indirect effect on CV and all-cause deaths (via KCCQ state)

Draft guidance

- Model should be able to replicate the observed data
  - Provide scenarios exploring the direct and indirect impact on CV and all-cause deaths
  - Refit model when parameters (such as treatment effect) are excluded

Company

- Refitting risk equation when treatment effect excluded increased ICER by £16
- In revised base case, time-varying treatment hazard ratio was applied for CV mortality, and KM curve was used to estimate survival for the initial 45 months followed by Weibull model
- Indirect treatment effect should be included in the estimates, because higher KCCQ health state in EMPEROR-Preserved related to better survival

CV, cardiovascular; KCCQ, Kansas City Cardiomyopathy Questionnaire

Key issue: Empagliflozin impact on survival unclear

CV deaths predicted by the company and the EAG are different

ICER impact: Large

Company

Survival by KCCQ-CSS level, pooled across empagliflozin and SOC arms

[redacted]

[redacted]

KCCQ, Kansas City Cardio-myopathy Questionnaire

Observed vs predicted CV deaths

*Difference does not always add up due to rounding

Total CV deaths	EMPEROR-Preserved			Model - Company revised base case		
	Empagliflozin + SoC	SoC	**Diff***	Empagliflozin + SoC	SoC	**Diff***
At 26 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue: Empagliflozin impact on survival unclear

Unclear if mortality prediction using company's revised base case appropriate

ICER impact:
Large

EAG comments

- No difference in survival was observed between empagliflozin and SOC in EMPEROR-Preserved, this could mean that treatment effect on KCCQ-CSS health state is insufficient to produce a survival benefit
- Using KM curve for the first 45 months then Weibull model worsens survival prediction, so the EAG base case uses Weibull model to predict survival for the entire duration
- Constant hazard ratio (HR) for CV mortality is preferred in the EAG base case instead of time-varying HR, due to implementation concerns
- Calculation used for prediction of deaths in company's revised base case does not accurately include cumulative events, the EAG has amended this in its prediction analysis

Key issue: Empagliflozin impact on survival unclear

Prediction using company's revised base case with EAG correction overestimates mortality

ICER impact: Large

EAG comments

Observed and predicted mortality

Difference does not always add up due to rounding

#Includes all EAG preferred assumptions

	EMPEROR-Preserved			Model - Company revised base case*			Model - EAG analysis (Scenario A)*#		
	Empa	SoC	**Diff**	Empa	SoC	**Diff**	Empa	SoC	**Diff**
CV mortality									
26 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality									
26 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Models assume direct effect on CV mortality, and indirect effect on CV and all-cause mortality

SOC, standard of care; CV, cardiovascular; diff, difference

Key issue: Empagliflozin impact on survival unclear

Excluding both direct or indirect treatment effect overestimates mortality

ICER impact: Large

EAG comments

Observed and predicted mortality

Difference does not always add up due to rounding

#Includes all EAG preferred assumptions

	EMPEROR-Preserved			Model - EAG analysis (Scenario B)#			Model - EAG analysis (Scenario C)#			Model - EAG analysis (Scenario D)#		
	Empa	SoC	**Diff**	Empa	SoC	**Diff**	Empa	SoC	**Diff**	Empa	SoC	**Diff**
CV mortality												
26 months	[redacted]											
3 years	[redacted]											
3.5 years	[redacted]											
All-cause mortality												
26 months	[redacted]											
3 years	[redacted]											
3.5 years	[redacted]											

Scenario B: Models assume both direct and indirect effect on CV and all-cause mortality
Scenario C: Models assume only indirect effect on CV and all-cause mortality (no direct effect)
Scenario D: Models assume no direct or indirect effect on CV and all-cause mortality

Is empagliflozin likely to impact CV and all-cause mortality? Should indirect treatment effect via KCCQ-CSS health state be included in the cost-effectiveness estimates? Which scenario aligns most closely with the observed data?

SOC, standard of care; CV, cardiovascular; diff, difference

Key issue: Estimation of HHF in the economic model

Unclear if model accurately predicts HHF events

ICER impact Large

Background

- HHF estimated using Poisson model with time varying KCCQ-CSS state and treatment arm as predictors
- Assumes constant risk of HHF and does not differentiate initial and subsequent hospitalisations

Draft guidance

- The committee noted that it is unlikely that the risk of HHF would be constant over time
- Comparison of HHF estimation in the model and observed data is required

Company

- Revised model identified and fixed error, and better predicts HHF events

Observed and predicted HHF events

*Difference does not always add up due to rounding

Total HHF events	EMPEROR-Preserved			Model - Company revised base case		
	Empa	SoC	**Diff***	Empa	SoC	**Diff***
At 26 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE Does the model accurately estimate HHF?

HHF, hospitalisation for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; CE, cost effectiveness

Key issue: Estimation of HHF in the economic model

Unclear if model accurately predicts HHF events

ICER impact
Large

EAG comments

- Company revised base case method does not accurately include cumulative events, correction applied by the EAG but HHF is still overestimated especially over long horizon

Observed and predicted HHF events

Difference does not always add up due to rounding
#Includes all EAG preferred assumptions

	EMPEROR-Preserved			Model – Company revised base case*			EAG analysis*# (Scenario A)		
	Empa	SoC	**Diff**	Empa	SoC	**Diff**	Empa	SoC	**Diff**
26 months	[redacted]								
3 years	[redacted]								
3.5 years	[redacted]								

*Models assume direct effect on CV mortality, and indirect effect on CV and all-cause mortality

Does the model accurately estimate HHF?

Key issue: Estimation of KCCQ-CSS transition probabilities

LOCF maintained in company's revised base case

ICER impact: Large

Background

- Company uses last observation carried forward (LOCF) imputation method – assumes missing observation is identical to previous data point

Draft guidance

- LOCF approach to impute missing values at scheduled visits may introduce bias
- Prefer use of observed values from EMPEROR-Preserved to estimate transition probabilities used in the model

Company

- No clinical reason to expect systematic bias in results due to LOCF, missing data balanced for both arms of trial
- Non-imputed data reduces sample size (from 5,731 to 4,950) and introduces bias

EAG comments

- Missingness not completely at random because baseline [redacted] are shown to be statistically significant predictors of missing data (although 28 other baseline characteristics did not predict missing data)
- Sample size for non-imputed data is sufficient, this carries lower risk of bias than imputed data

Does observed non-imputed data remain the committee's preference?

LOCF, last observation carried forward; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; BMI, body mass index

Key issue: Duration of impact of HHF events on QoL

12 months disutility period maintained in company's revised base case

ICER impact Large

Background

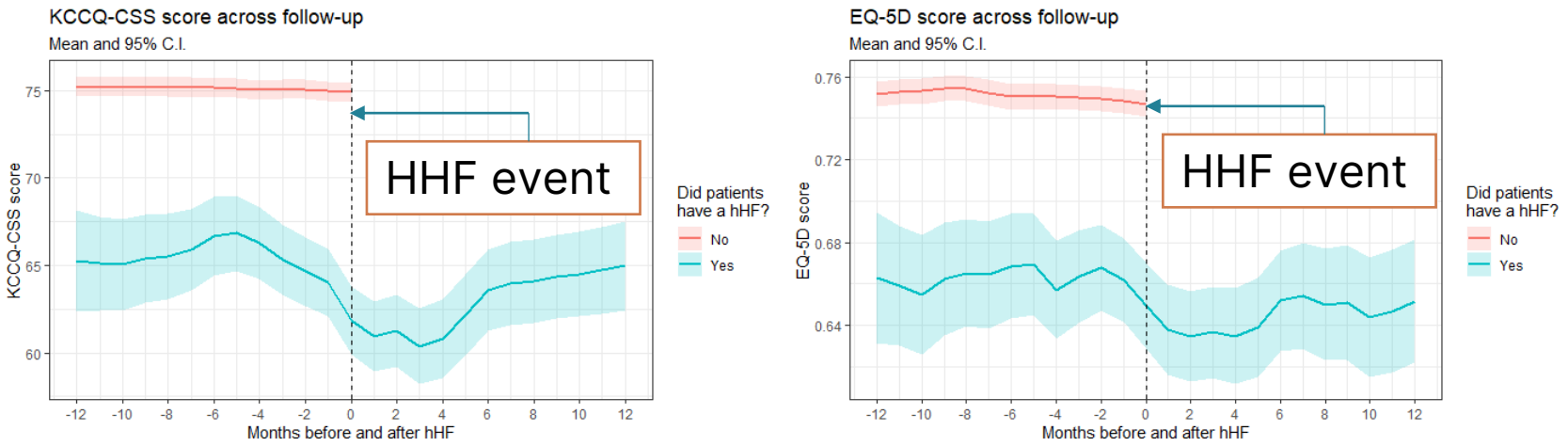
- Company model assumes HHF events impact QoL for 12 months

Draft guidance

- Reasonable to assume QoL impact of 6 month

Company

- EMPEROR-Preserved shows utility 12 months after HHF does not return to same level as 12 months before



EAG comments

- Additional data supports recovery to, and above baseline by 6 months
- Utility (EQ-5D) at month 6 is higher than at month 12
- Literature sources cited by company (PARADIGM-HF and PARAGON-HF) support this
- Unclear if KCCQ-CSS effect removed from EQ-5D scores
- Drop in QoL before HHF should already be captured in KCCQ-CSS scores

Has the committee's preferred HHF disutility period changed?

QoL, quality of life; HHF, hospitalisation for heart failure

Key issue: Costs of HHF events and CV deaths

Company maintained base case costs

ICER impact: Small

Background

- In EMPEROR-Preserved the mean duration for HHF event was 11 days
- Company base case used a weighted average composed of severe (53-day hospital stay) and less severe (13-day hospital stay) HHF
- Cost of CV deaths derived from regression of inpatient costs for T2DM complication (Alva et al.)

Draft guidance

- The committee preferred the use of less severe cost code (13-day hospital stay for HHF), and assumption that the cost of sudden cardiac death is £0

Company

- Average cost chosen because severity and length of hospitalisation for HHF varies
- Some cost likely to be incurred due to sudden CV death e.g. ambulance

Clinical expert

- £0 for sudden death likely an oversimplification

EAG comments

- Scenario with cost of sudden death of £250 for ambulance call increases ICER by £16/QALY

NICE What are the correct cost codes to apply?

HHF, hospitalisation for heart failure; CV, cardiovascular; T2DM, type-2 diabetes mellitus

Cost effectiveness results

Empagliflozin (ID3945)

Empagliflozin: Company revised base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Empagliflozin plus SoC	£9,735	4.02	£1,394	0.10	£13,916	0.03	0.05
SoC	£8,341	3.92	-	-	-	-	-

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Empagliflozin plus SoC	£9,687	4.01	£1,385	0.10	£13,678	0.03	0.06
SoC	£8,302	3.91	-	-	-	-	-

Revised base case assumes direct effect on CV mortality, and indirect effect on CV and all-cause mortality

NICE

ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Empagliflozin: EAG deterministic base case results (1/3)

Assumptions in company and EAG base case

	Company base case	EAG base case	ICER with EAG assumptions (£/QALY)	Cumulative ICER with EAG assumptions (£/QALY)	NHB at £20,000 /QALY*	NHB at £30,000 /QALY*
Company base case			£13,916	-	0.03	0.05
Survival extrapolation	KM curve for 45 months then Weibull	Weibull model throughout	[redacted]	[redacted]	0.02	0.05
CV mortality HR	Time-varying	Constant	[redacted]	[redacted]	0.02	0.05
KCCQ-CSS	LOCF with imputation	Observed without imputation	[redacted]	[redacted]	-0.002	0.02

*refers to cumulative ICER

NICE

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QALY, quality-adjusted life year; QoL, quality of life; NHB, net health benefit; KM, Kaplan-Meier; LOCF, last observation carried forward

Empagliflozin: EAG deterministic base case results (2/3)

Assumptions in company and EAG base case (continued)

	Company base case	EAG base case	ICER with EAG assumptions (£/QALY)	Cumulative ICER with EAG assumptions (£/QALY)	NHB at £20,000 /QALY*	NHB at £30,000 /QALY*
HHF disutility period	12 months	6 months	[redacted]	[redacted]	- 0.01	0.01
HHF costing	Weighted mean (EB03A –E) for HHF events	EB03E code (non-severe HHF)	[redacted]	[redacted]	-0.02	0.01
Cost of CV death and sudden death	**CV death:** £4,295	**CV death:** £1,452 (cost of sudden death: £0)	[redacted]	[redacted]	-0.02	0.01

*refers to cumulative ICER

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QALY, quality-adjusted life year; QoL, quality of life; NHB, net health benefit; KM, Kaplan-Meier; LOCF, last observation carried forward

Empagliflozin: EAG deterministic base case result (3/3)

Additional QALY analysis results also presented

EAG's preferred assumptions
plus
Impact of empagliflozin on CV-related and all-cause deaths

	ICER (£/QALY)	Inc. QALYs	Additional inc. QALYs required for CE at £20,000	Additional inc. QALYs required for CE at £30,000
CV-related deaths: Direct and indirect effect **All-cause deaths:** Direct and indirect effect →	[redacted]	[redacted]	[redacted]	[redacted]
CV-related deaths: Direct and indirect effect **All-cause deaths:** Indirect effect →	[redacted]	[redacted]	[redacted]	[redacted]
CV-related deaths: Indirect effect **All-cause deaths:** Indirect effect →	[redacted]	[redacted]	[redacted]	[redacted]
CV-related deaths: No effect **All-cause deaths:** No effect →	[redacted]	[redacted]	[redacted]	[redacted]

- Including both direct and indirect treatment effect for all-cause deaths increases the ICER considerably
- This is because the coefficient for direct effect of empagliflozin on all-cause deaths is positive which suggests the placebo group had better all-cause survival
- Although the coefficient was not statistically significant, a negative coefficient would have been expected

Equality considerations

No further equality concerns were raised during draft guidance consultation

Background

Equality considerations in ID1648 and ID3945 (HFmrEF and HFpEF):

- People in lower socioeconomic groups may have a higher risk of developing heart failure

Equality considerations in appraisals for HFrEF (TA679 and TA773):

- Meta-analysis showed that SGLT2 inhibitors were more effective in people with a black or Asian family background
- Clinical experts said no reason to restrict SGLT2 inhibitors use based on age or family background

Draft guidance

- The clinical trials did not provide strong evidence of better effectiveness based on family background
    - Although trials are not usually powered to detect these differences
- The recommendations apply to all people with HFmrEF or HFpEF, regardless of family background

HFmrEF; heart failure with a mildly reduced ejection fraction; HFpEF, heart failure with a preserved ejection fraction; HFrEF, heart failure with a reduced ejection fraction; SGLT2, Sodium-glucose-co-transporter-2 inhibitor