NICE National Institute for Health and Care Excellence

Part 1	No ACIC
Public observer slides	

Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656]

Lead team presentation

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Company: AstraZeneca

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Heart failure with reduced ejection fraction, HFrEF

- **Definition:** Heart cannot pump enough blood to meet body's demands
  - Reduced ejection fraction: % of blood pumped out of the left ventricle of the heart each time it beats defined as ≤40% (normal range 55% to 70%)
- **Causes:** structural or functional abnormalities of the heart
  - Ischaemic heart disease, hypertension and diabetes increase risk
- **Symptoms:** difficulty breathing, fatigue, and ankle swelling, with significant quality of life impact
- **Classification:** NYHA (New York Heart Association) classification used to define severity in clinical practice: 1 being the least severe and 4 being the most severe
- **Prevalence:** 1 in 5 people over 40 years old develop heart failure in their lifetime
  - ~650,000 on UK GP registers of heart failure*, approx. 50% with HFrEF
  - common cause of hospitalisation in people over 65 years
- **Treatment:** chronic condition with no cure, treatment can control symptoms and prolong life
- **Survival:** over 50% of people with heart failure die within 5 years of diagnosis

* *BHF statistics*

NICE guidance

Chronic heart failure in adults: diagnosis and management

NICE guideline [NG106] Published data: 12 September 2018

Guideline includes recommendations on:

- **role of the specialist heart failure multidisciplinary team**
  - multidisciplinary team (MDT) includes:
    - lead physician with subspecialty training in heart failure,
    - specialist heart failure nurse, and a
    - healthcare professional with expertise in specialist prescribing for heart failure
  - MDT is to work collaboratively with primary care team to (among others):
    - diagnose heart failure
    - manage newly diagnosed, recently decompensated or advanced heart failure
    - optimise treatment
    - start new medicines that need specialist supervision
    - manage heart failure not responding to treatment
- **treating heart failure with reduced ejection fraction**
  - 1st-line treatment: angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) + beta blockers + mineralocorticoid receptor antagonist (MRA)
  - specialist treatment: ivabradine [TA267], sacubitril valsartan [TA388], hydralazine in combination with nitrate, digoxin

Related NICE guidance

Ivabradine for treating chronic heart failure [TA267]

Recommended for treating chronic heart failure for people:

- with NYHA class II to IV
- left ventricular ejection fraction ≤35%
- optimised therapy of ACE inhibitors or ARBs
- in sinus rhythm with a heart rate of 75+ beats per minute (bpm)

Should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team.

Dose titration and monitoring should be performed by specialist or primary care with an interest in heart failure

Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction [TA388]

Recommended for treating symptomatic disease:

- NYHA class II to IV symptoms
- left ventricular ejection fraction ≤35%
- already taking a stable dose of ACE inhibitors or ARBs

Should be started by a heart failure specialist with access to a multidisciplinary heart failure team.

Dose titration and monitoring should be performed by the most appropriate team member

Dapagliflozin (Forxiga®, AstraZeneca)

Marketing authorisation indication	European Medicine Agency on 15 Oct 2020 issued positive opinion for: 'adults for the treatment of **symptomatic** chronic heart failure with **reduced** ejection fraction'
	Licensed for adults with type 1 and type 2 diabetes
Population in key trial	'Clinically stable and optimized on heart failure therapies according to local guidelines'
Mechanism of action	- Sodium-glucose co-transporter 2 (SGLT-2) inhibitor - Mechanism of action in HFrEF not yet fully understood
Administration	10 mg oral dapagliflozin once daily
Special warnings and precautions for use	At least annual monitoring of renal function (eGFR) Precautions for use in people with: - high risk of volume depletion/hypotension *- high risk of diabetic ketoacidosis (DKA) in diabetes indications*
Renal function in diabetes indications	*'Forxiga should not be initiated in patients with eGFR < 60 mL/min and should be discontinued at eGFR persistently below 45 mL/min'*
List price	£36.59 for a 28-tablet pack Annual treatment cost of £476.98 No commercial arrangements for dapagliflozin

Patient organisation perspective

Pumping Marvellous Foundation

1. Heart failure affects people in different ways:
   - Major social/psychological implications
   - Debilitating symptoms: breathlessness, fluid accumulation and fatigue
   - Carer and family member quality of life significantly affected
2. Unmet need: Current treatments limited and constrained*:*
   - Primary care not always fully aware of challenges/ best practice for heart failure
   - More options for treating and managing HFrEF essential
3. Primary care administration of new treatment would benefit patients
   - No resource impact on training GPs for prescribing dapagliflozin
   - Requiring specialist referral would restrict access

Professional organisation perspective

British Society for Heart Failure (endorsed by British Cardiovascular Society and Royal College of Physicians)

- Treatment aims: reduce symptom burden, improve clinical outcomes
- Unmet need:
  - high mortality, high hospital admissions and reduced quality of life
- Clinical pathway:
  - well defined but local variation in diagnostic testing / guideline interpretation
  - Initiation of some treatment by heart failure specialists:
    - increased workload for HF specialist teams
    - additional specialist reviews, blood tests and blood pressure monitoring required
    - people with diabetes: collaboration with endocrinology and training required
- Innovative:
  - new drug class for heart failure: Licensed in type 1 and 2 diabetes: dual benefit for people with comorbid diabetes (approx. 25% of heart failure population)

Key issues

Model driver

Where to position dapagliflozin and what is standard care at that point?

- Are ivabradine, hydralazine + nitrate and digoxin relevant comparators?

Would dapagliflozin be offered to people on 'optimised' care?

Should full trial population of DAPA-HF or the European subgroup be used for:

- Baseline characteristics?
- Relative effectiveness?

Is dapagliflozin effective at treating HFrEF?

- When added to first line standard of care treatment options?
- When compared with sacubitril valsartan?
  - is a matching-adjusted indirect comparison (MAIC) or Bucher method preferred for this indirect comparison?
- When added to specialist treatment options?

Who should initiate dapagliflozin? What monitoring is required, by whom?

- Non-specialist primary care or specialist care in primary or secondary care?
- What extra costs and resources are associated with specialist or secondary care?

Are the extrapolations valid?

- What are the most appropriate extrapolations for each population?

How should disease severity be modelled?

- Does KCCQ-TSS accurately model HFrEF disease severity?

Decision problem

Comparator reflects what clinicians would offer in NHS if dapagliflozin were not an option

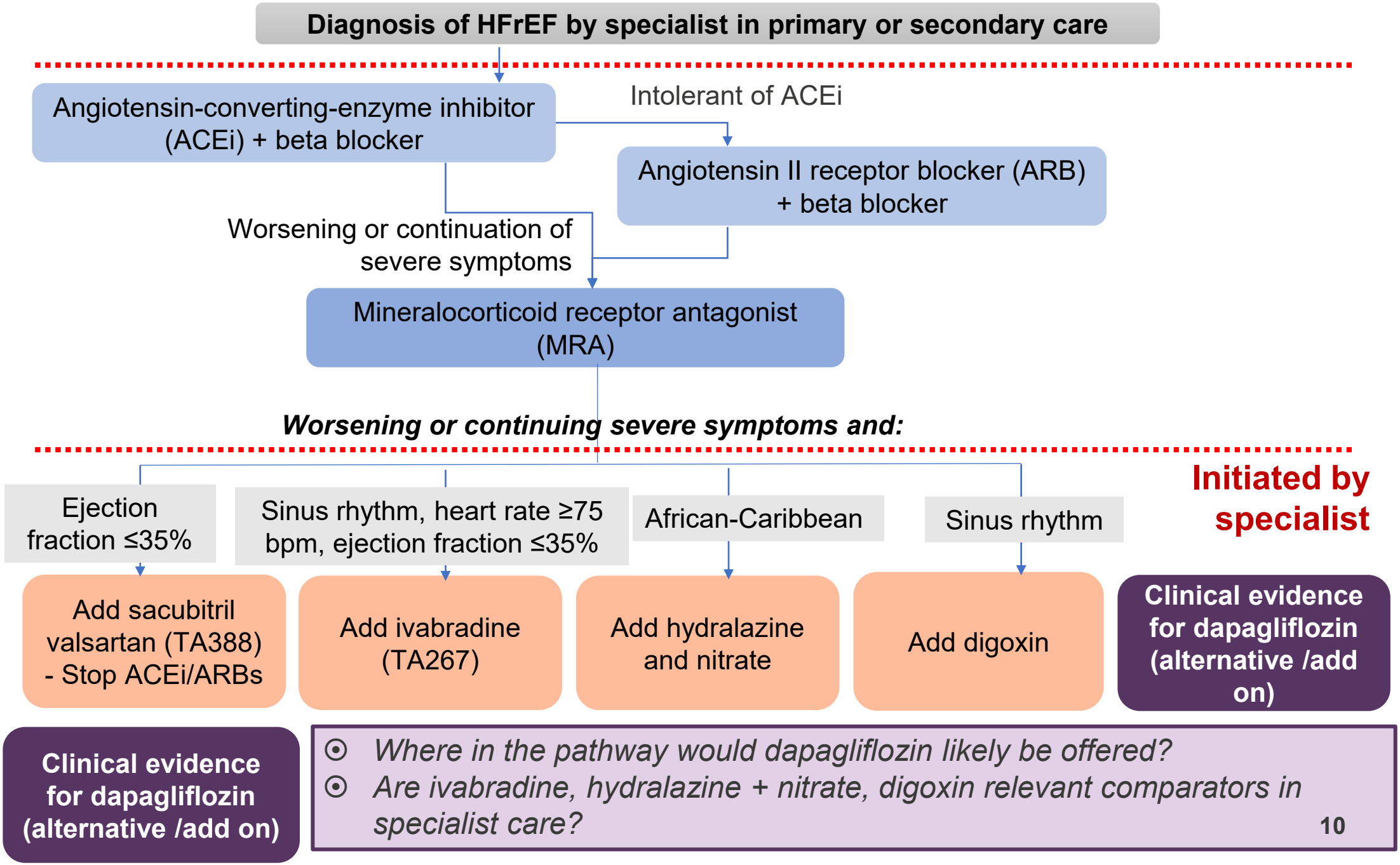
	Final scope issued by NICE	Company submission deviations
Population	Adults with chronic heart failure with reduced ejection fraction	3 sub-populations: • ACEi/ARB-based standard care • ACEi/ARB-based standard care: sacubitril valsartan unsuitable • Sacubitril valsartan-based standard care
Intervention	Dapagliflozin + standard care (see below)	Dapagliflozin + standard care Standard care defined as: 1. (ACEi or ARB) + beta blockers ±MRA 2. Sacubitril valsartan+ beta blockers ±MRA
Comparators	Standard care defined as 1. (ACEi or ARB) + beta blockers ±MRA 2. Sacubitril valsartan+ beta blockers ±MRA	People on standard care (ACEi or ARB) ±MRA) comparators: • Sacubitril valsartan • Placebo if cannot take sacubitril People on standard care (sacubitril valsartan ±MRA) comparators: • Placebo

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid-receptor antagonist

Source: adapted from company submission, table 1, page 12

NICE pathway for HFrEF from guideline

Seek specialist advise after ACEi or ARB and MRAs



- *Where in the pathway would dapagliflozin likely be offered?*
- *Are ivabradine, hydralazine + nitrate, digoxin relevant comparators in specialist care?*

Clinical effectiveness

DAPA-HF clinical trial evidence

Dapagliflozin with standard care vs placebo with standard care. Standard care defined as:

1. ACEi/ARB + beta blocker ± MRA treatments
2. Sacubitril valsartan + beta blocker ± MRA

Indirect treatment comparison

Dapagliflozin with standard care vs sacubitril valsartan with standard care

- Matching-adjusted indirect comparison (MAIC)
- Bucher indirect comparison

No evidence provided (not in NICE scope)

Dapagliflozin with standard care vs ivabradine with standard care

Dapagliflozin with standard care vs hydralazine and nitrate with standard care

Dapagliflozin with standard care vs digoxin with standard care

Key trial: DAPA-HF trial

Randomised, double-blind, placebo-controlled, international Phase III trial

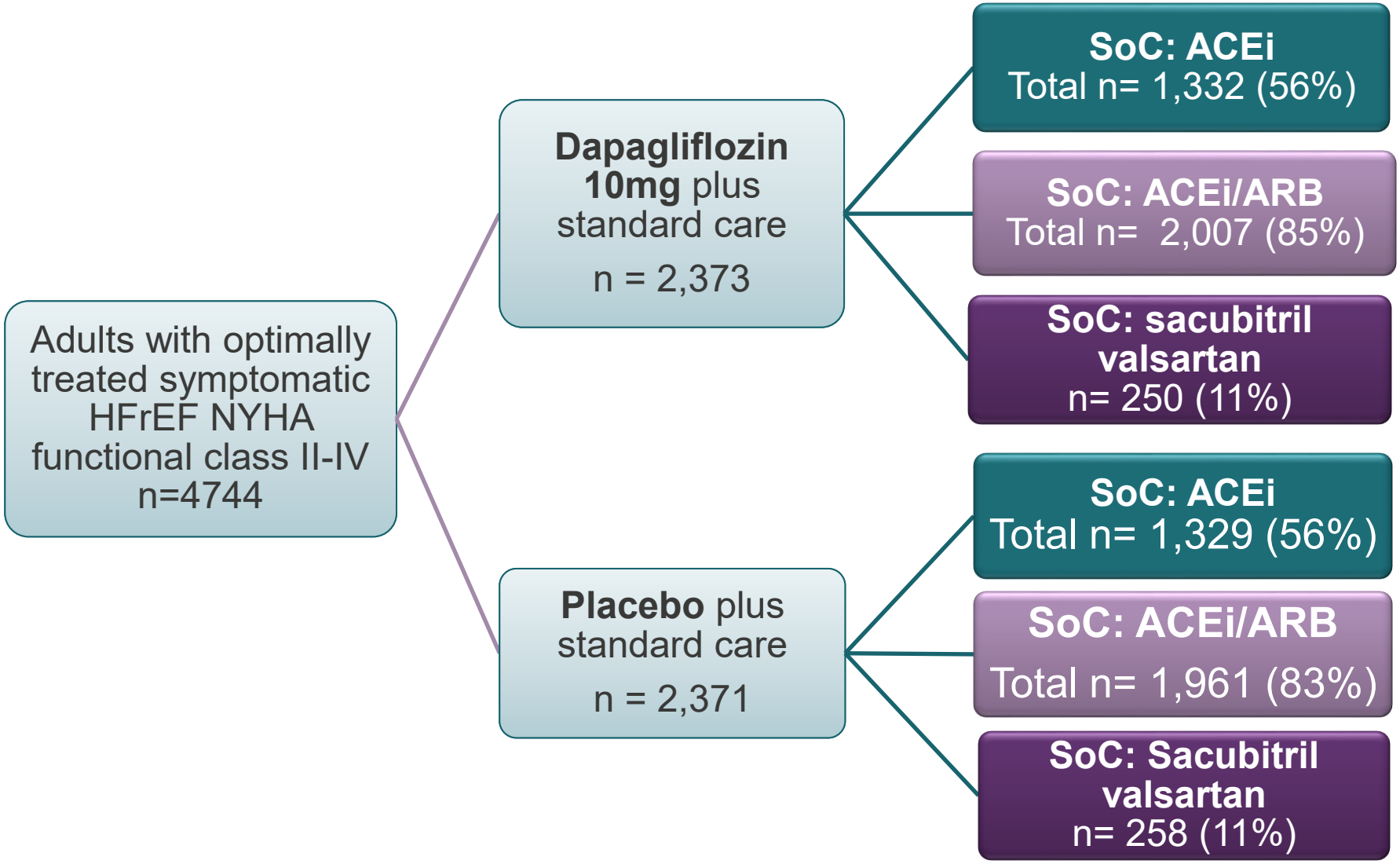
Recruitment	N=4,744; 410 centres worldwide 10 in the UK
Median follow up	18.2 months (range 0 to 27.8 month)
Key inclusion criteria	Adults >18 years with: • Symptomatic HFrEF for ≥2 months (NYHA class II-IV) • LVEF ≤40% • **'Optimally treated with pharmacological and/or device therapy'** • With or without type 2 diabetes • Elevated NT-proBNP level • No type 1 diabetes
1º endpoint	Composite outcome: CV death, hospitalisation for HF; urgent HF visit
2º outcomes	• Time to: death from any cause, CV death or hospitalisation for HF, ≥50% eGFR decline, ESRD or renal death • Change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score: baseline to 8 months
Exploratory endpoints	• Change in EQ-5D-5L score: baseline to 24 months • Change in NYHA class: baseline to 4 and 8 months.

Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

⊙ *Would dapagliflozin only be offered to people on 'optimised' care?*

DAPA-HF trial population breakdown

Company defines subgroups based on baseline treatment: ACE only, ACE or ARB, sacubitril valsartan



NICE Source: adapted from company submission, table 9, page 41

Baseline characteristics from DAPA-HF

ERG proposes that modelling be limited to EU subgroup

Baseline characteristics n (%)		Overall (N=4,744)	Europe (N=2,154)
Age, years, mean ± SD		66 ±11	
Race	White	3,333 (70)	
	Black	226 (5)	
	Asian	1,116 (24)	
	Other	67 (1)	
NYHA functional class	II	3,203 (68)	
	III	1,498 (32)	
	IV	43 (1)	
Medical history	Hospitalisation for HF	2,251 (47)	
	Atrial fibrillation	1,818 (38)	
	Type 2 diabetes mellitus	1,983 (42)	
Principle cause of HF	Ischaemic	2,674 (56)	
	Non-ischaemic	1,687 (36)	
Heart failure medication	Diuretic	4,433 (93)	
	ACEi	2,661 (56)	
	ARB	1,307 (28)	
	Sacubitril-valsartan	508 (11)	
	Beta-blocker	4,558 (96)	
	MRA	3,370 (71)	
	Digitalis	887 (19)	

Younger than expected in UK (av. age at diagnosis 77)

Europe is less ethnically diverse than England

Doses & background therapies differ from NHS (%)

Diuretic	56
ACEi	51
ARB	22
Sac Val	1
BB	64
MRA	22

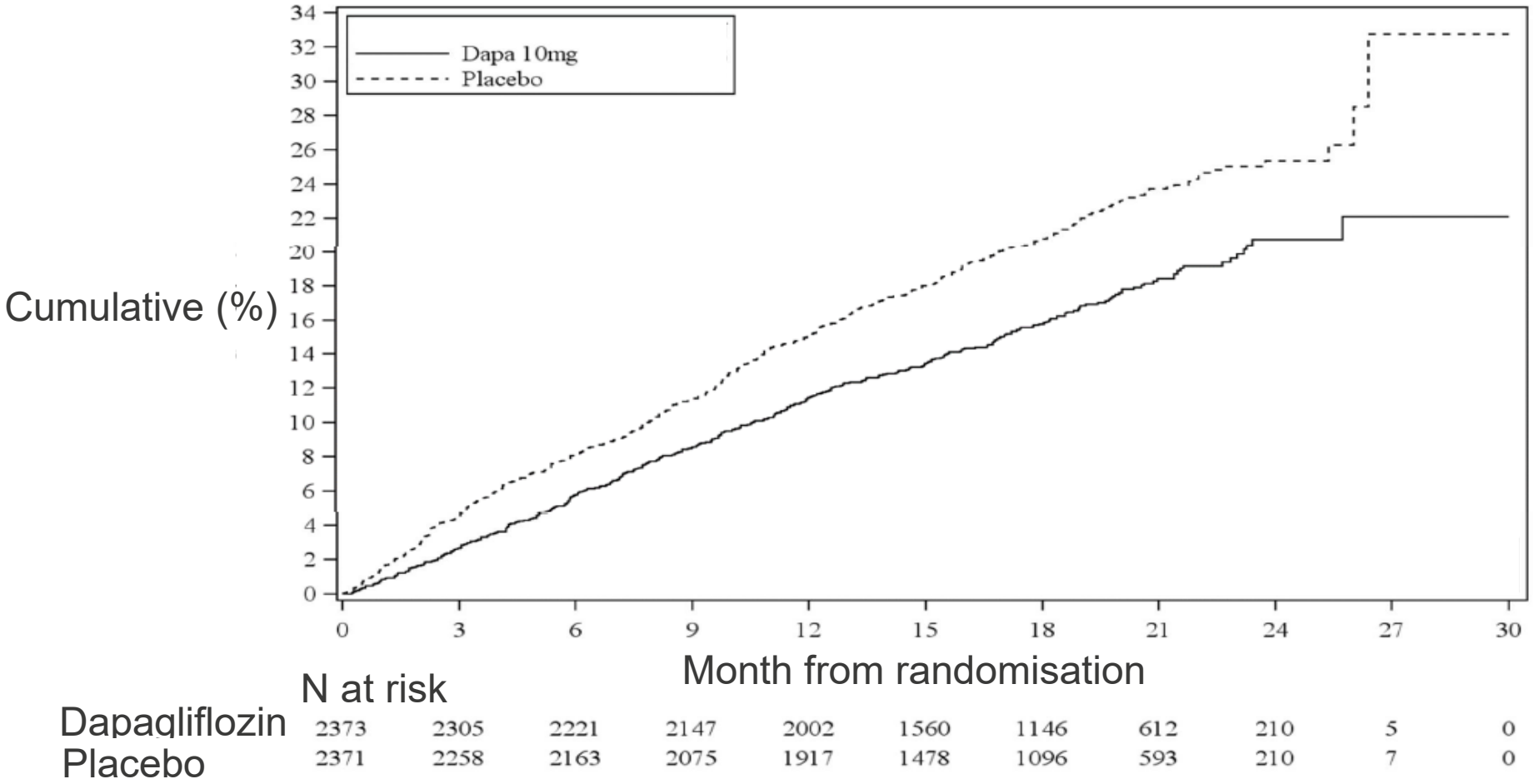
Source: adapted from company submission, table 10, page 42-44

⊙ *Which baseline characteristics are likely to affect baseline rate of dying, and/or by 'effect modifiers'? Which population best reflects the expected characteristics in the NHS?*

DAPA-HF primary outcome result (overall population)

Reduced risk of CV death, hospitalisation, or urgent HF visit versus placebo

DAPA-HF 1º composite endpoint Source: company submission, figure 7, page 48



Primary outcome (median FU 18.2 months)	Dapagliflozin (N=2,373)	Placebo (N=2,371)	Hazard Ratio (95%CI)
Composite endpoint of cardiovascular death, hospitalisation for heart failure, or urgent heart failure visit	386 (16%)	502 (21%)	0.74 (0.65, 0.85)

DAPA-HF key results overall population

Dapagliflozin more effective than placebo in 1º and most 2º outcomes, [redacted]

Outcome	Dapagliflozin (N=2,373)	Placebo (N=2,371)	Hazard Ratio (95% CI)	In model
1º outcome, composite endpoint*	386 (16%)	502 (21%)	0.74 (0.65, 0.85)	No
2º outcomes				
Components of 1º outcome				
- Hospitalisation for heart failure	231 (10%)	318 (13%)	0.70 (0.59, 0.83)	Yes
- Urgent heart failure visit	10 (0%)	23 (1%)	0.43 (0.20, 0.90)	Yes
- Cardiovascular death	227 (10%)	273 (12%)	0.82 (0.69, 0.98)	Survival curves
All-cause mortality	12%	14%	0.83 (0.71, 0.97)	Survival curves
Improvement in KCCQ-TSS: baseline to 8 months	6±19	3±19	NA	Transition probabilities
Explanatory endpoints				
Change in EQ-5D-5L score baseline to 24 months	[redacted]	[redacted]	NA	No

*cardiovascular death, hospitalisation for heart failure or urgent heart failure visit.

Source: ERG report, table 1.1, page 13

⊙ *What is the committee's view on the effectiveness of dapagliflozin vs placebo?*

DAPA-HF Full and European subgroup results

Stat sig and non-stat sig reductions in risk of CV death, hHF or urgent HF visit v placebo

Outcome	Dapagliflozin	Placebo	Hazard Ratio (95% Confidence Interval)
DAPA-HF: Full population			
Primary outcome*	386 (16%)	502 (21%)	0.74 (0.65, 0.85) p<0.001
hHF / urgent HF visit	237 (10%)	326 (14%)	0.70 (0.59, 0.83) p<0.0001
hHF	231 (10%)	318 (13%)	0.70 (0.59, 0.83) p<0.0001
Urgent HF visit	10 (0%)	23 (1%)	0.43 (0.20, 0.90) p=0.0213
CV death	227 (10%)	273 (12%)	0.82 (0.69, 0.98) p=0.0294
DAPA-HF: European subgroup**			
Primary outcome*	[redacted]	[redacted]	[redacted]
hHF / urgent HF visit	[redacted]	[redacted]	[redacted]
hHF	[redacted]	[redacted]	[redacted]
Urgent HF visit	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]

*Composite endpoint of CV death, hHF, or an urgent HF visit.

**European subgroup included different background therapies (combined populations #2 and #3)

Abbreviations: CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure

Source: ERG report, table 1.1, page 15

Treatment effect by geographical region

Company's subgroup analyses show potential difference in efficacy by geographical region

Company

- Subgroups not powered to detect treatment effect
- Company scenarios using European baseline characteristics should apply treatment effect from whole population
- No biological plausibility for effect to differ by location
- Difference in treatment effect not statistically significant based on region

ERG

- Efficacy and safety outcomes differ by region
- Baseline characteristics differ from NHS population:
  - Overestimate dapagliflozin treatment effect

Prefer European subgroup for analyses

Clinical Experts

- Effect of DAPA might be greater in UK versus Europe population:
  - differing care and slightly greater baseline risk.
- Suggest using full population

Stakeholders

- Risk factors similar by region
- Would not expect differences in clinical management based on ethnicity
- **Commentator:** Europe subgroup preferred by committee in TA388 (sacubitril valsartan)

⊙ *Effectiveness estimates based on which subpopulation should be used? Should the same population be used for baseline hazard of dying?*

Clinical effectiveness

DAPA-HF clinical trial evidence

Dapagliflozin with standard care vs placebo with standard care. Standard care defined as:

a) ACEi/ARB + beta blocker + MRA treatments
b) Sacubitril valsartan+ beta blocker + MRA

Indirect treatment comparison

Dapagliflozin with standard care vs sacubitril valsartan with standard care

- Matching-adjusted indirect comparison (MAIC)
- Bucher indirect comparison

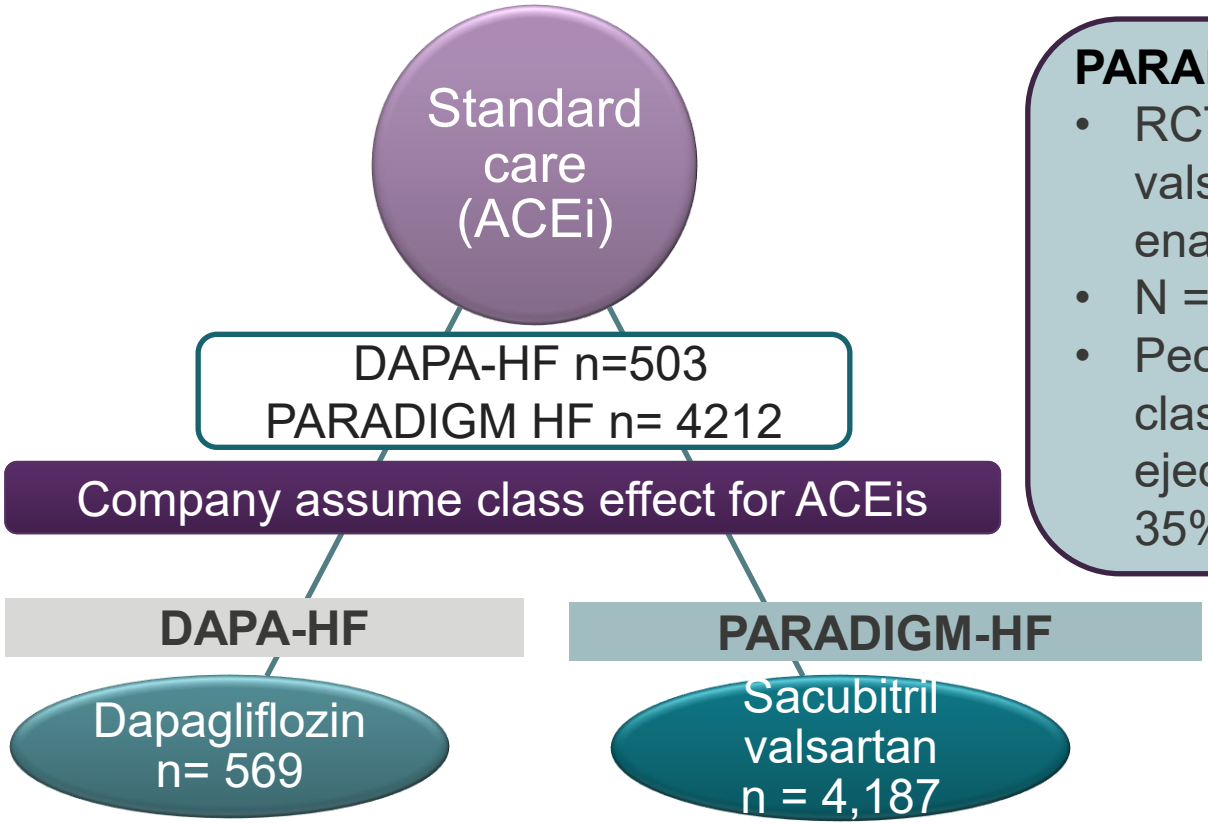
No evidence provided

Dapagliflozin with standard care vs ivabradine with standard care
Dapagliflozin with standard care vs hydralazine and nitrate with standard care
Dapagliflozin with standard care vs digoxin with standard care

Dapagliflozin versus sacubitril valsartan – indirect treatment comparison

No direct trial data: company conducted a matching-adjusted indirect comparison (MAIC)

MAIC 1º outcome: time to first of hospitalisation for HF or cardiovascular death - **not** composite end point to account for overlap between trials



PARADIGM-HF

- RCT: Sacubitril valsartan versus enalapril
- N = 8,442
- People with NYHA class II-IV and ejection fraction of < 35%

Company took DAPA-HF **patient-level** data. Matched it to **study-level** baseline patient characteristics **of PARADIGM-HF** for: age, sex, race, region, blood pressure, heart rate, ischemic heart failure, class of left ventricular ejection fraction, N-terminal pro B-type natriuretic peptide level, NYHA score, diabetes history, cardiac history

⊙ *Are all confounders accounted for? What is missing?*

Bucher method of indirect comparison

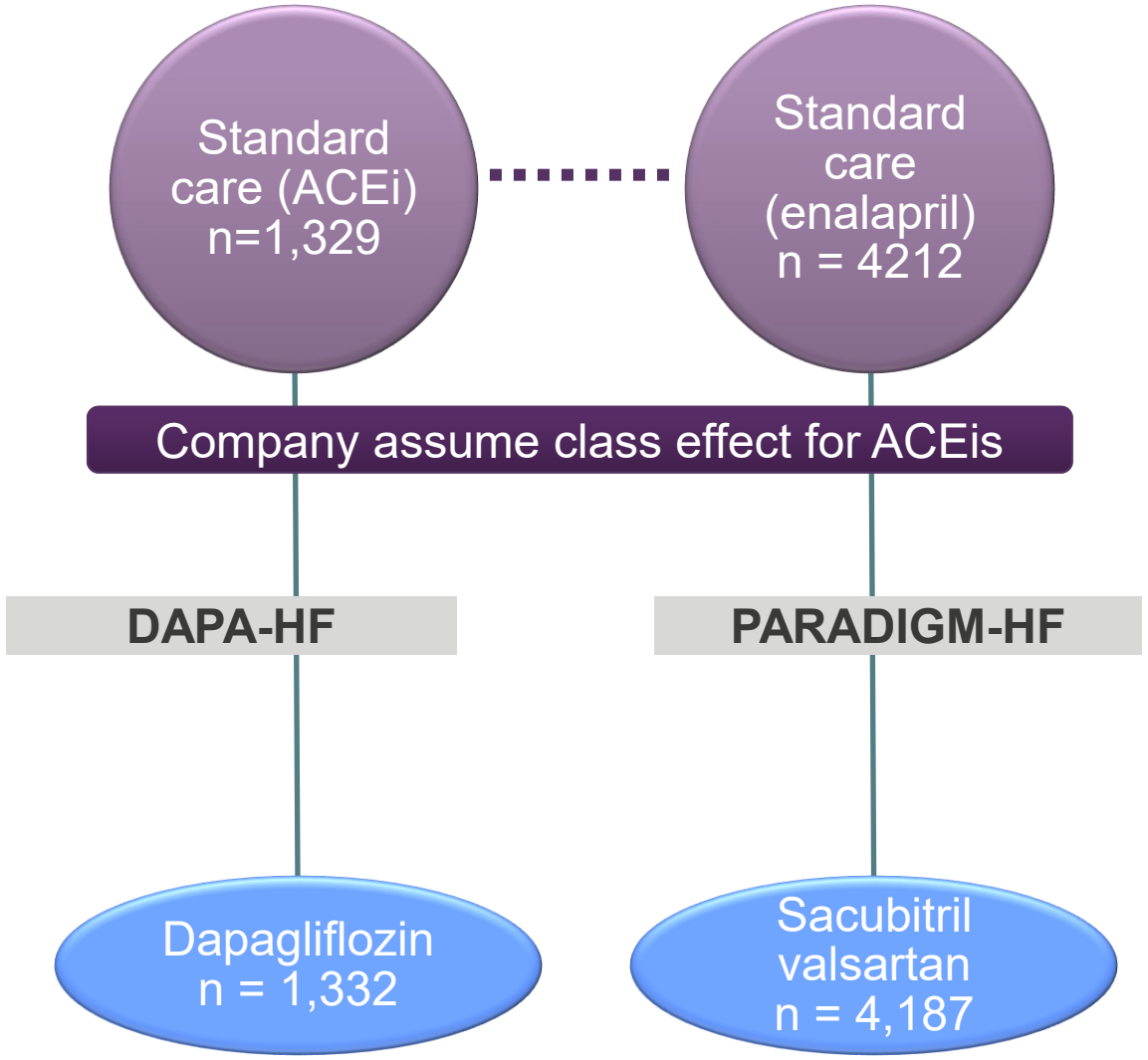
Assumes relative treatment effect is the same across studies

Uses relative effects to compare treatments

Does not address treatment effect modifiers or confounders

Outcomes same as MAIC:

- **1º:** time to first of hospitalisation for HF or cardiovascular death



No adjustment of DAPA-HF patient characteristics to match those in PARADIGM-HF

Effectiveness of dapagliflozin versus sacubitril valsartan

Bucher and MAIC give similar outcomes

Time to hospitalisation for heart failure or CV death using the MAIC and Bucher methods

Population	MAIC effect estimate	Bucher effect estimate
Dapagliflozin + standard care vs. sacubitril valsartan + standard care	HR 0.91 95% CI 0.68 to 1.21	HR 0.94 95% CI 0.77 to 1.15

Source: adapted from ERG report, table 1.3, page 16 -17 and Section 4.4.3 pages 52-54.

ERG

- No justification for the MAIC and results uncertain:
  - Adjustment excluded ~40% of DAPA-HF population
  - PARADIGM-HF included induction period:
    - treatment could be discontinued before randomisation: may underestimate effectiveness of dapagliflozin

Company updated base case after technical engagement for dapagliflozin versus sacubitril valsartan to use the Bucher method for indirect treatment comparison

- *What are the committee's view on the assumption of a class effect for ACEis?*
- *What is the best estimate to reflect the comparison? Should a model assume they are clinically equivalent (RR = 1)?*

Clinical effectiveness

DAPA-HF clinical trial evidence

Dapagliflozin with standard care vs placebo with standard care. Standard care defined as:

a) ACEi/ARB + beta blocker + MRA treatments
b) Sacubitril valsartan+ beta blocker + MRA

Indirect treatment comparison

Dapagliflozin with standard care vs sacubitril valsartan with standard care

- Matching-adjusted indirect comparison (MAIC)
- Bucher indirect comparison

No evidence provided

Dapagliflozin with standard care vs ivabradine with standard care
Dapagliflozin with standard care vs hydralazine and nitrate with standard care
Dapagliflozin with standard care vs digoxin with standard care

Ivabradine, hydralazine + nitrate, digoxin as comparators

Company states rarely used in clinical practice: should not be considered comparators

Company

Not included as comparators in NICE scope

Ivabradine, hydralazine and nitrate and digoxin with standard care

- Rarely used in clinical practice:
  - Ivabradine: 2.1% HF patients
  - Hydralazine and nitrate: 0.8% HF patients
  - Digoxin: 11.8% HF patients
- Indicated to treat other conditions:
  - Ivabradine: chronic stable angina pectoris
  - Hydralazine and nitrate: moderate to severe hypertension
  - Digoxin: dysrhythmias, including atrial fibrillation
    - Atrial fibrillation: comorbidity in ~40% of HF population in UK

  Use for ***treatment of HF*** likely to be lower than overall HF use

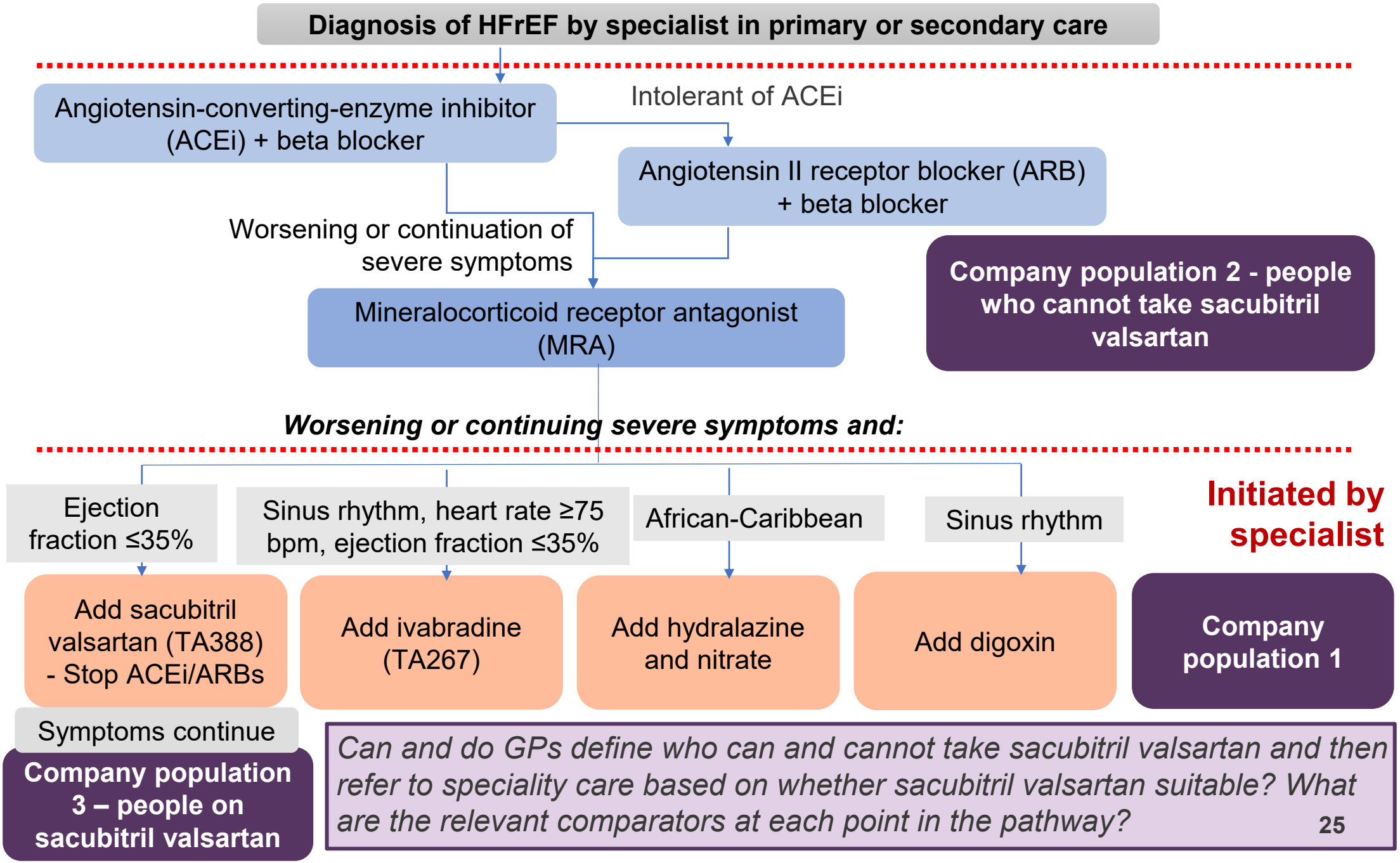
- 4.8% of the whole DAPA-HF population were taking ivabradine at baseline

Clinical Experts:

- Ivabradine is not used frequently in clinical practice

Should ivabradine, hydralazine + nitrate and digoxin be included as comparators?

Positioning of dapagliflozin in context of guideline



Can and do GPs define who can and cannot take sacubitril valsartan and then refer to speciality care based on whether sacubitril valsartan suitable? What are the relevant comparators at each point in the pathway?

Dapagliflozin positioning in the HFrEF pathway

Company

- All patients eligible for sacubitril valsartan also eligible for dapagliflozin: sacubitril valsartan relevant comparator
- Most patients taking sacubitril valsartan continue to have symptoms: reasonable to add dapagliflozin

Clinical Experts/Stakeholders

As an option compared to sacubitril valsartan

- Dapagliflozin and sacubitril valsartan both options.
- Likely preference to use dapagliflozin first:
  - No adjustment based on response
  - Fewer contraindications than sacubitril valsartan
- Dapagliflozin likely to be used earlier in diabetes: dual benefit.

In people who cannot take sacubitril valsartan:

- Sacubitril valsartan unsuitable in some people - low blood pressure or poor renal function (N.B. dapagliflozin also limited to use in people with good renal function)
- Sacubitril valsartan unsuitable in ~10-20% cases: high potassium
- **Commentator:** Specialist should determine if a patient can or cannot take sacubitril valsartan

As an add on to sacubitril valsartan:

- Continue sacubitril valsartan if dapagliflozin introduced

TA388: Committee heard from clinical community that specialists should manage because

'patients should be on stable optimised dose of an ACE inhibitor or an ARB'

'lack of available GPs with a special interest in heart failure and heart failure specialist nurses in the community**'**

Summary: Clinical effectiveness

Dapagliflozin more effective in all populations

Company positioning	Population #1	Population #2	Population #3
Intervention	Dapagliflozin + ACEi/ARB based standard care		Dapagliflozin + sacubitril valsartan based standard care
Comparator	Sacubitril valsartan-based standard care	ACEi/ARB based standard care because sacubitril valsartan unsuitable	Sacubitril valsartan based standard care
Source of data	Bucher ITC	DAPA-HF	
1º outcome*	N/A	0.74 (0.65, 0.85)	
Hospitalisation for HF / urgent HF visit	0.94 (0.77, 1.15)	0.70 (0.59, 0.83)	
Hospitalisation for HF	0.92 (0.71, 1.20)	0.70 (0.59, 0.83)	
Cardiovascular death	0.95 (0.73, 1.22)	0.82 (0.69, 0.98)	

***Composite endpoint of cardiovascular death, hospitalisation for heart failure, or an urgent heart failure visit.** Source: adapted from ERG report, table 4.7, page 39-40 and company response to TE, table 4, page 15

⊙ *Is any clinical effectiveness evidence missing?*

DAPA-HF Adverse Events

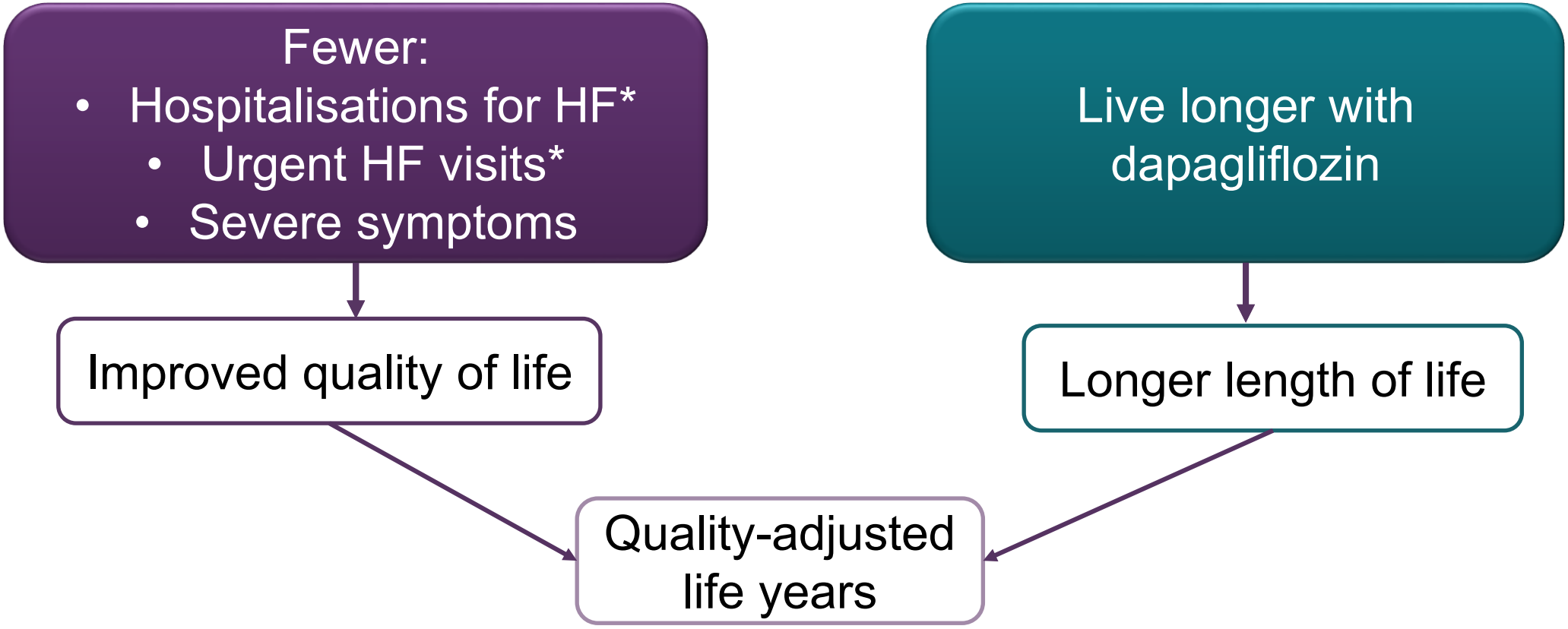
- Proportion with any AE or any SAE typically [redacted] in Europe subgroup than overall population
- Genital infections not recorded: used incidence from DECLARE trial (dapagliflozin 1%, placebo 0%)

AE, n(%)	Dapagliflozin (N=2,368)	Placebo (N=2,368)	Cost included in model
AEs of special interest (on and off treatment)			
Any definite/ probable diabetic ketoacidosis	3 (0)	0	Yes
Any major hypoglycaemic event	4 (0)	4 (0)	Yes
Any event of volume depletion symptoms	178 (8)	162 (7)	Yes
Any fracture	49 (2)	50 (2)	Yes
Any renal AE	153 (7)	170 (7)	Yes
Any amputation	13 (1)	12 (1)	Yes
Serious adverse events occurring in ≥1% patients (on and off treatment)			
Cardiac failure	262 (11)	351 (15)	No
Pneumonia	76 (3)	82 (4)	No
Cardiac failure congestive	65 (3)	70 (3)	No
Death	48 (2)	48 (2)	Yes
Acute myocardial infarction	37 (2)	38 (2)	No
Ventricular tachycardia	34 (1)	54 (2)	No
Cardiac failure chronic	27 (1)	33 (1)	No
Atrial fibrillation	26 (1)	39 (2)	No
Ischaemic stroke	24 (1)	26 (1)	No
Acute kidney injury	23 (1)	46 (2)	Yes (any renal AE)
Angina unstable	21 (1)	30 (1)	No
Sudden cardiac death	18 (1)	27 (1)	No

Cost effectiveness

1. *Model differs from previous NICE technology appraisals in HF with reduced ejection fraction*
2. *Company models clinical inputs from DAPA-HF trial for utilities, transition probabilities, baseline characteristics*
3. *Model uses Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score to measure disease severity*
4. *'Validates' projections using clinical opinion*

Overview: How quality adjusted life years accrue

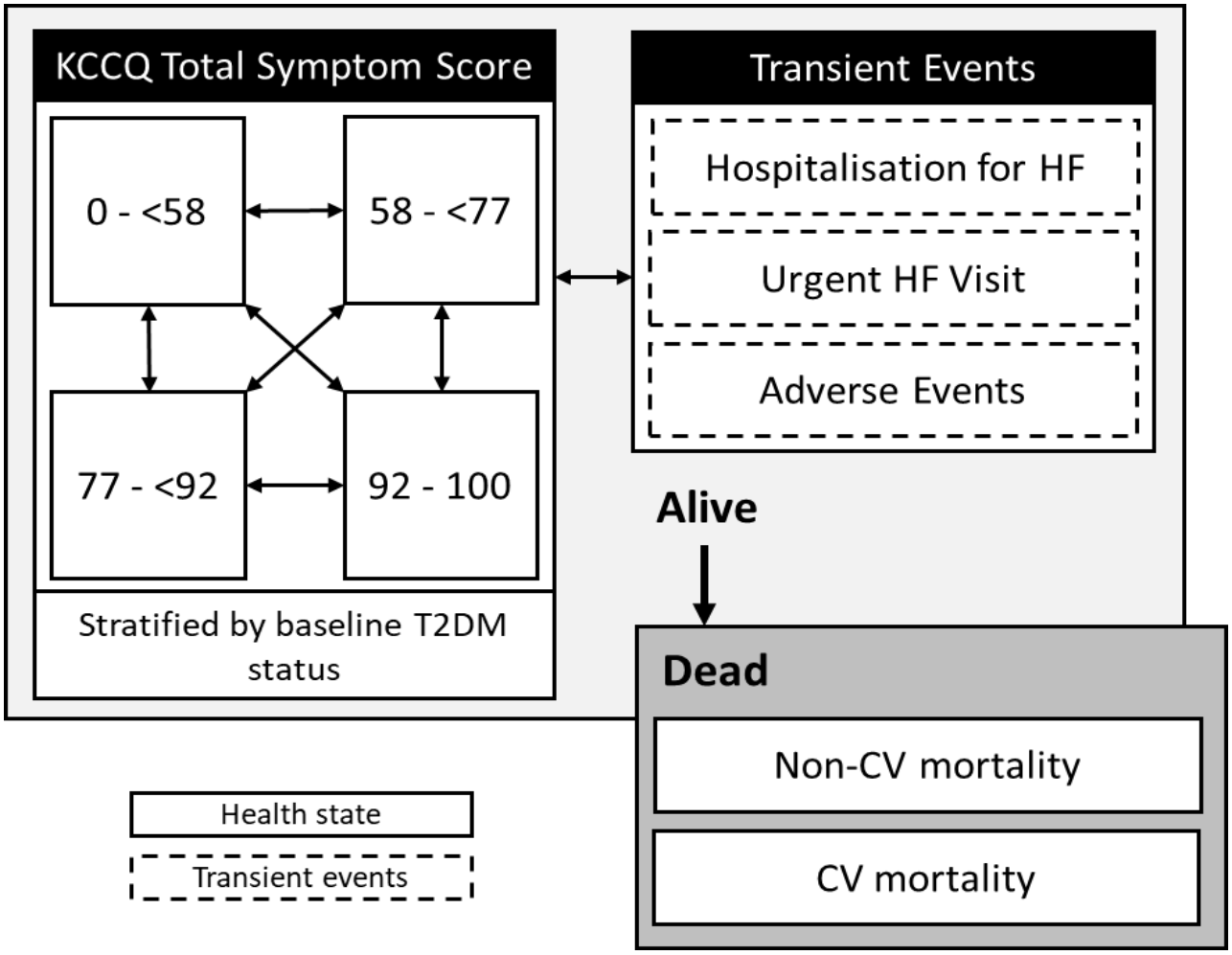


* Main drivers of costs in model

Overview company model: Markov state transition

Uses Kansas City Cardiomyopathy Questionnaire (KCCQ), a disease specific measure of quality of life; 0 to 100, high scores = lower symptom burden

Previous models used NYHA to classify severity



Key features

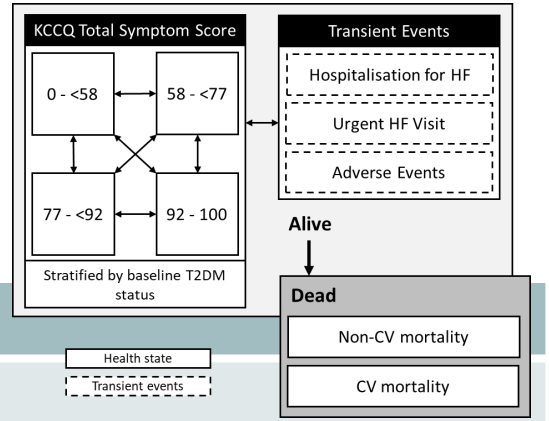
- Discrete health states using KCCQ Total Symptom Score (TSS) quartiles
  - Captures disease severity
  - Utility value for each state from DAPA-HF EQ-5D-5L: mapped to EQ-5D-3L
  - Lifetime horizon, 1-month cycle length, ½ cycle correction
- Background costs constant across quartiles:
  - disease severity captured by rate of hospitalisation for HF

Abbreviations: CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; T2DM, type 2 diabetes mellitus.

Source: company submission, figure 22, page 99

Overview: Company clinical inputs

Clinical evidence comes from the DAPA-HF trial



Input	Evidence Source
Patient baseline characteristics	Whole population from DAPA-HF
Treatment effect of dapagliflozin	Whole population from DAPA-HF: used in survival equations and risk equations for all-cause mortality, CV mortality, hospitalisation for heart failure, urgent heart failure visit
Incidence of hospitalisation for heart failure and urgent heart failure visit	Whole population from DAPA-HF
KCCQ-TSS quartile transition probabilities	Treatment-specific transition probabilities Whole population from DAPA-HF - Robust to different methods of calculating transition probabilities between health states
Cardiovascular and all-cause mortality	DAPA-HF rates with Weibull distribution to extrapolate
Time to stopping treatment	DAPA-HF rates with exponential distribution to extrapolate
Adverse events (AEs)	Most from DAPA-HF Genital infections and urinary tract infections from type 2 diabetes study (DECLARE)

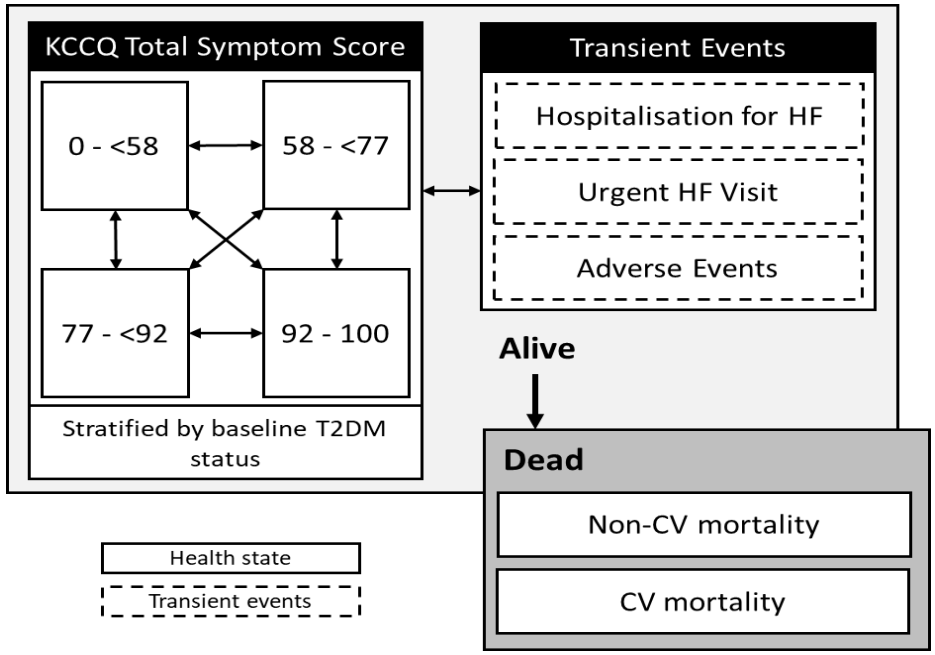
Overview: Company clinical inputs

Patient baseline characteristics

Characteristic	Dapagliflozin vs Sacubitril valsartan (PARADIGM-HF matched population)		Dapagliflozin vs Placebo ACEi/ARB, based care subgroup		Dapagliflozin vs Placebo Sacubitril valsartan-based care subgroup	
	Mean	SE	Mean	SE	Mean	SE
Age (years)	63.8	0.12	66.3	0.16	66.7	0.61
Female	0.2	0.01	0.24	0.01	0.19	0.02
BMI (kg/m2)	28	0.12	28	0.09	30	0.35
KCCQ-TSS Q1: 0-<58	0.23	0.01	0.23	0.01	0.27	0.02
KCCQ-TSS Q2: 58-<77	0.25	0.01	0.25	0.01	0.24	0.02
KCCQ-TSS Q3: 77-<92	0.28	0.01	0.28	0.01	0.25	0.02
KCCQ-TSS Q4: 92-100	0.24	0.01	0.24	0.01	0.24	0.02
NT-proBNP (pg/mL)	234	44	2346	44	2298	212
Ischaemic HF proportion	0.60	0.01	0.57	0.01	0.500	0.03
Duration of HF >2 years proportion	0.62	0.01	0.61	0.01	0.730	0.02
Prior hHF proportion	0.63	0.01	0.48	0.01	0.400	0.03
LVEF (%)	0.30	0.12	0.31	0.00	0.285	0.00
Plasma creatinine (µmol/L)	100	0.29	104	0.46	109	1.64
T2DM proportion	0.35	0.01	0.45	0.01	0.44	0.03

⊙ *Do differences in baseline characteristics represent clinical practice?*

Company quality of life inputs



TA388

Baseline utility values for HFrEF population: 0.66-0.72

	Initial base case		ERG preferred values then used by company	
	Value	Source	Value*	Source
KCCQ-TSS: 1 - <58	0.600	DAPA-HF	0.541	Relative differences from DAPA-HF study applied to general population utility for people aged 60-69**
KCCQ-TSS: 58 - <77	0.705	DAPA-HF	0.646	
KCCQ-TSS: 77 - <92	0.773	DAPA-HF	0.714	
KCCQ-TSS: 92 – 100	0.833	DAPA-HF	0.774	General population utility for people aged 60-69**

*Model assumed no change in health state utility based on age

**Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making 2011;31(6):800-4.

Source: Company submission, table 40, page 119 and ERG report, page 72.

⊙ *Do the ERG's preferred values have face-validity?*

Overview: Company's costs inputs

Cost	Annual cost	Source
Treatment costs		
Dapagliflozin	£477	Monthly Index of Medical Specialities
Sacubitril valsartan	£1,194	Monthly Index of Medical Specialities
Standard care population #2 (ACEi/ARB-based standard care)*	£42	DAPA-HF
Standard care population #3 (sacubitril valsartan- based standard care)*	£173	DAPA-HF *NB – Costs for comparison with sacubitril valsartan included ACEi/ARBs in both arms.*
Health state cost/ cost associated with event		
Background heart failure management, including beta blockers & diuretics	£933	McMurray et al. Drug costs: eMIT 2019. Includes specialist care for optimisation.
Type 2 diabetes	£1,091	Alva et al. uplifted to 2018/19
Cardiovascular death	£1,674	
Hospitalisation for heart failure	£2,832	NHS Reference Costs 2017/18; weighted by finished consultant episode
Urgent heart failure visit	£402	
Incidence of AEs (cost per event)		
DAPA-HF	£39 - £13,475	Multiple sources provided
Urinary tract infection/ genital infection	£39	Personal Social Services Research Unit costs 2019: one GP visit per event

*Costs calculated using background therapy proportions from entire population

Source: adapted from company submission, tables 41 – 44, pages 122-124

⊙ *Do these values have face-validity?*

Model based on KCCQ vs. NYHA classification

Company states that KCCQ-TSS quartiles better reflects disease severity

Company

Similar results expected if NYHA class used

- Company chose KCCQ over NHYA class because:
  - KCCQ more accurately measures symptom severity: derived directly from patient
  - KCCQ-TSS data more complete
  - Few with NYHA I or IV at baseline
- Subgroup analyses: [redacted] difference in treatment effect by NYHA class a [redacted]
  - Other markers of disease severity (e.g. LVEF) do not support interaction
  - DAPA-HF not designed to detect differences in subgroups

NYHA classification would overestimate dapagliflozin treatment effect [redacted]

ERG

- Other HFrEF models used NYHA classification
- ERG agrees with company justification for using KCCQ over NYHA:
  - NYHA class has poor reproducibility

Clinical Experts

Use of NYHA classification should make limited difference to modelling

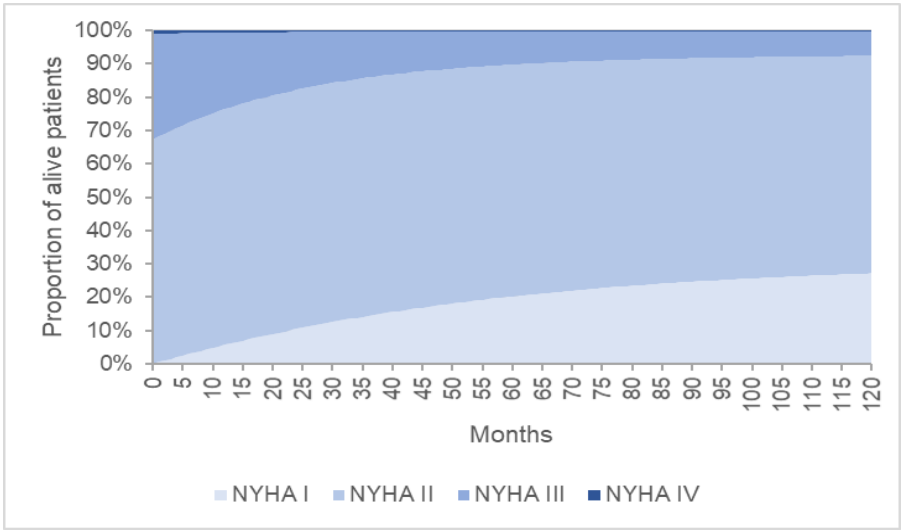
- Both represent disease severity
- NYHA used in clinical practice but subjunctive
- KCCQ more accurately identifies changes: more levels
- KCCQ standard measure of severity in HFrEF clinical trials

⊙ *Is KCCQ a reasonable way to model severity?*

Health state ‘occupancy’ for KCCQ v NYHA class

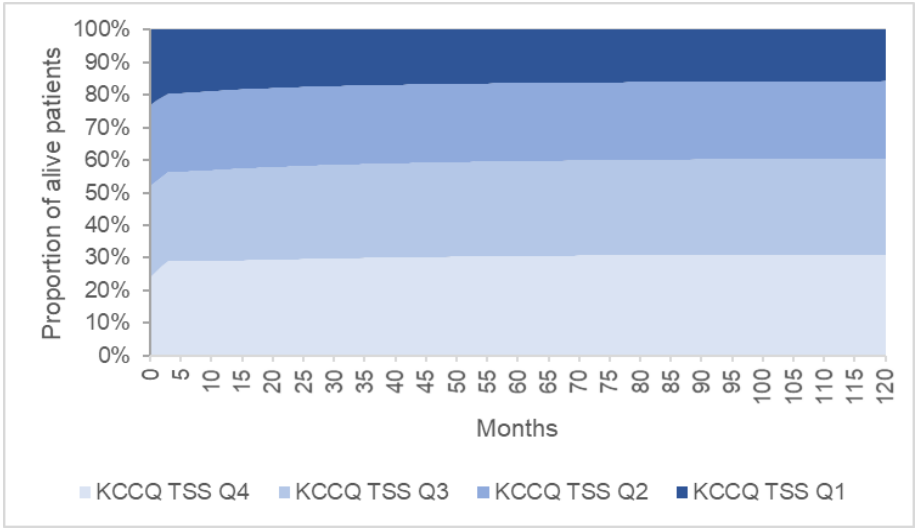
Occupancy over time differs between methods; company states KCCQ better aligned with expected changes in HF symptoms

NYHA class



Source: company response to TE, figure 1, page 8

KCCQ-TSS quartiles



Source: company response to TE, figure 2, page 9

Company

- Increase in NYHA I/II occupancy caused by transition from more severe health states
  - not due to survival effect
- KCCQ-TSS quartiles better aligned with expected symptom changes:
  - Improve for 4-8 months, then ~constant

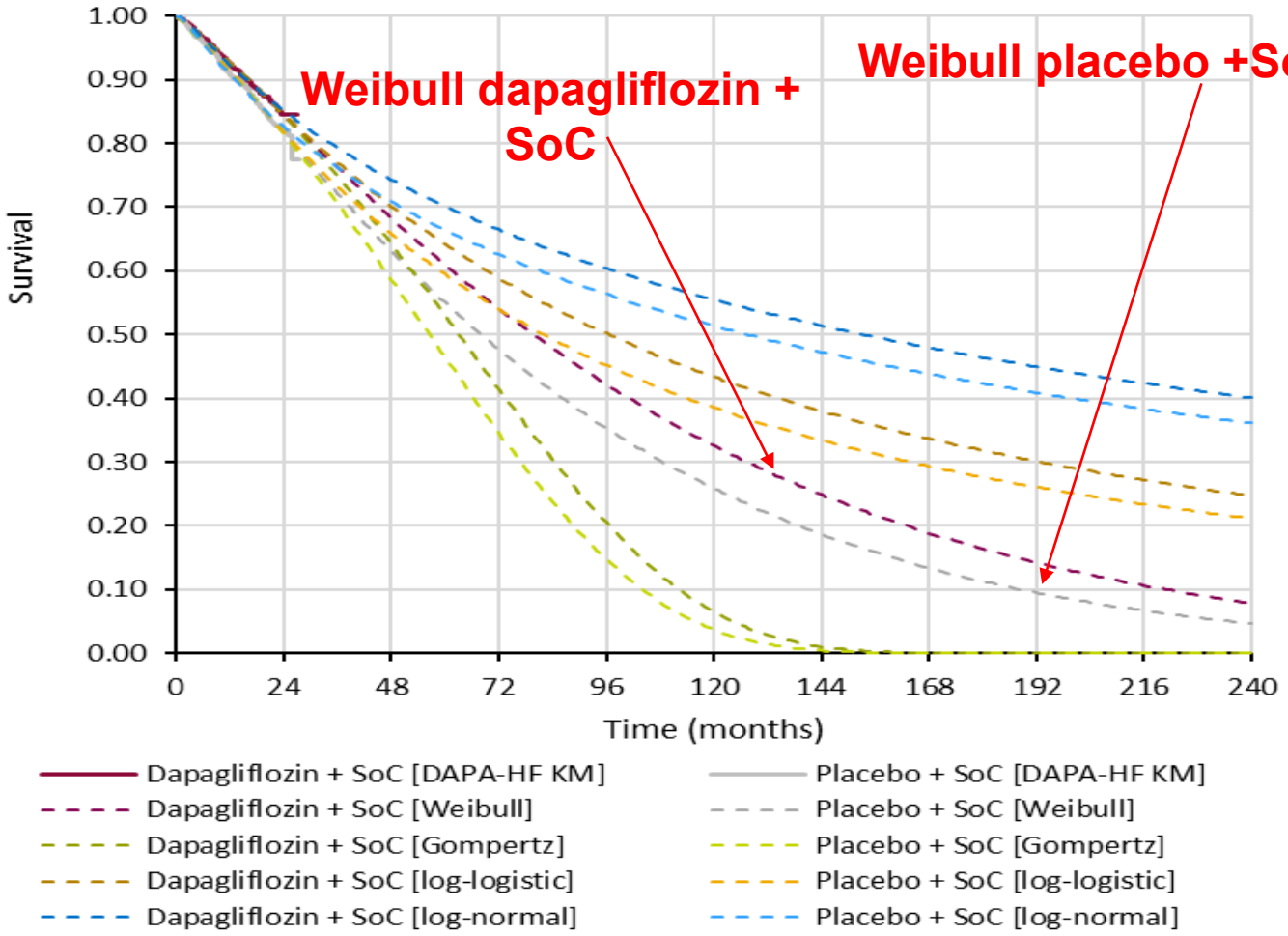
ERG

Company did not provide supporting clinical data on health state occupancy

⊙ *Is KCCQ or NYHA classification more appropriate to use in the model?*

Extrapolating mortality beyond end of trial to estimate average life extension from dapagliflozin

Company chooses Weibull distribution



Source: Company submission, figure 26, page 109.

ERG

- Weibull distribution and assuming proportional hazards plausible based on observed data
- Cost effectiveness results robust to use of alternative distributions.

Clinical Experts

- Weibull most plausible:
  - Aligned with TA388 and published HFrEF survival estimates

Stakeholders

- Weibull survival estimates optimistic

⊙ *Are the company's estimates validated?*

Overall survival estimates by distribution

Months		0	12	24	36	60	120	180	240
People on ACEi or ARB based standard care									
Weibull	Dapagliflozin	100%	93%	85%	76%	61%	33%	16%	8%
	Standard Care	100%	91%	82%	72%	55%	26%	11%	5%
Gompertz	Dapagliflozin	100%	93%	84%	75%	53%	7%	0%	0%
	Standard Care	100%	91%	82%	71%	47%	4%	0%	0%
People on ACEi/ARB based standard care for whom sacubitril valsartan is unsuitable									
Weibull	Dapagliflozin	100%	93%	84%	76%	61%	33%	17%	9%
	Standard Care	100%	91%	82%	72%	56%	27%	12%	5%
Gompertz	Dapagliflozin	100%	93%	84%	75%	54%	9%	0%	0%
	Standard Care	100%	91%	82%	71%	48%	6%	0%	0%
People on sacubitril valsartan-based standard care									
Weibull	Dapagliflozin	100%	95%	86%	76%	56%	19%	5%	1%
	Standard Care	100%	93%	81%	68%	44%	10%	1%	0%
Gompertz	Dapagliflozin	100%	95%	86%	72%	27%	0%	0%	0%
	Standard Care	100%	93%	81%	62%	16%	0%	0%	0%

Source: ERG report, table 5.6, page 70

- *What is the committee's view on the modelling survival for populations on different standard of care treatment regimes?*

Treatment waning with dapagliflozin

Company assumes clinicians won't stop dapagliflozin

Company

- No evidence to suggest treatment waning: none assumed in TA388
- No restrictions to treatment duration in expected marketing authorisation
- No stopping rule in DAPA-HF
- Treatment effect stable in DAPA-HF and DECLARE TIMI58 studies (T2DM trial: median 4.2-year follow-up)
- Scenarios with treatment discontinuation at 3 years (max DAPA-HF follow-up of 28 months) not clinically plausible given the chronic nature of HFrEF

Clinical Experts

- Treatment would continue up to death
  - Sacubitril valsartan only stopped if major deterioration in renal function or death

Stakeholders

- Treatment would be lifelong/ for foreseeable future
- No evidence to support stopping rule
- Might stop as approach end of life: replace with palliative care

ERG

- Cost effectiveness results robust to assumption of treatment waning with 3 years stopping rule and 3-, 5- and 10-year duration of effect

Costs and resources

Company did not model costs of specialist care

ERG

- Use in specialist care could increase costs if extra monitoring required
- Same costs as sacubitril valsartan so incremental costs unchanged

Clinical Experts

- Specialist HF nurses may need training on monitoring people with comorbid diabetes when treated with dapagliflozin

Commentators

- Little training required to prescribe dapagliflozin: simple single dose easy to use in community. Would minimise outpatient specialist care costs.
- Specialist should start and monitor dapagliflozin: standard HF monitoring (BP, renal function, symptoms). Review/dose reduction of diuretics and diabetes drugs. No costs that would not apply to sacubitril valsartan.
- **Commentator:** Only HF specialists can determine who can and cannot take sacubitril valsartan

⊙ *Should additional costs for dapagliflozin in specialist care be included?*

Company deterministic pairwise base cases list prices

Sacubitril offered to NHS at a discount – estimates do not reflect true values

Company updated its base cases at technical engagement

Dapagliflozin as an add on ACEi/ARB-based standard care (SC) compared to sacubitril valsartan plus standard care *same as ERG base case

	Dapagliflozin + SC	Sacubitril valsartan + SC	Incremental	ICER (£/QALY)
QALYs	4.262	4.142	0.120	**Dapagliflozin dominates sacubitril valsartan**
Costs (£)	£14,496	£17,167	-£2,671	

Source: company response to TE, table 15, page 28

Dapagliflozin as an add on to ACEi/ARB-based standard care vs ACEi/ARB-based standard care

	Dapagliflozin + SC	Placebo + SC	Incremental	ICER (£/QALY)
QALYs	4.500	4.095	0.405	**£6,939**
Costs (£)	£15,786	£12,974	£2,813	

Source: company response to TE, table 15, page 29

Dapagliflozin as an add on to sacubitril valsartan-based standard of care

	Dapagliflozin + sacubitril valsartan + SC	Placebo + sacubitril valsartan + SC	Incremental	ICER (£/QALY)
QALYs	4.500	4.095	0.405	**£7,109**
Costs (£)	£16,659	£13,777	£2,882	

Source: company response to TE, table 15, page 30

Summary of differences in cost effectiveness results

Assumptions in ERG versus company base cases

Assumption	ERG base case	Company base case (from technical engagement)
All populations		
Health state utilities	Adjusted relative to general population	Adjusted relative to general population
Dapagliflozin as an add on ACEi/ARB-based standard care compared to sacubitril valsartan plus standard care		
Relative treatment effect	ITC (Bucher method)	
Dapagliflozin as an add on ACEi/ARB-based or sacubitril valsartan standard care compared to placebo plus standard care		
Population	European subgroup	Overall trial population
Relative treatment effect	European subgroup	Overall trial population
Baseline event rate	European subgroup	European subgroup

ERG deterministic pairwise base case

Use of the European treatment effect has a large impact on the ICERs

Dapagliflozin as an add on to ACEi/ARB-based standard care (SC) vs sacubitril valsartan with standard of care (list prices) ***same as company base case**

	Dapagliflozin + SC	Sacubitril valsartan + SC	Incremental	ICER (£/QALY)
QALYs	4.262	4.142	0.120	**Dapagliflozin dominates sacubitril valsartan**
Costs (£)	£14,496	£17,167	-£2,671	

Source: company response to TE, table 15, page 28

Dapagliflozin as an add on to ACEi/ARB-based SC: sacubitril valsartan unsuitable (list prices)

	Dapagliflozin + SC	Placebo + SC	Incremental	ICER (£/QALY)
QALYs	4.217	4.095	0.122	**£18,018**
Costs (£)	£15,179	£12,974	£2,205	

Source: company response to TE, table 15, page 29

Dapagliflozin as an add on to sacubitril valsartan-based SC (list prices)

	Dapagliflozin + sacubitril valsartan + SC	Placebo + sacubitril valsartan + SC	Incremental	ICER (£/QALY)
QALYs	4.217	4.095	0.122	**£18,140**
Costs (£)	£15,998	£13,777	£2,220	

Source: company response to TE, table 15, page 30

Deterministic incremental base case

ICERs considering patient choice to remain on standard care where both dapagliflozin and sacubitril valsartan are options

Dapagliflozin as an add on to ACEi/ARB-based standard care (SC) and sacubitril valsartan plus standard of care against standard care alone (list prices)

Treatment option	Source of baseline characteristics	Cost	QALY	Incremental cost	Incremental QALY	ICER
ACE/ARB based SC	DAPA-HF	£12,974	4.095	-	-	
Dapagliflozin + SC	PARADIGM-HF matched population	£14,496	4.262	Data not comparable	Data not comparable	**Data not comparable**
Sacubitril Valsartan + SC	PARADIGM-HF matched population	£17,167	4.142	£2,671	-0.12	**Dapagliflozin dominates sacubitril valsartan**

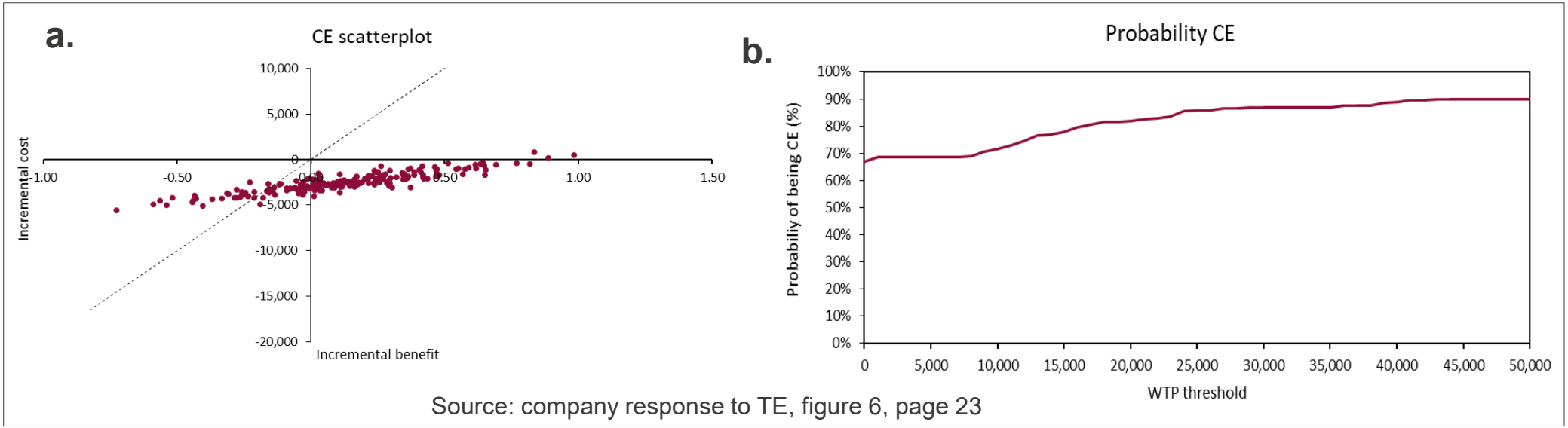
NB: *Incremental analyses calculated by technical team and includes populations with varying baseline characteristics*

- *Should an incremental analysis be presented for patient choice?*
- *What baseline characteristics should these include, should they all be the same?*

Company's Probabilistic Sensitivity Analysis #1

Dapagliflozin v sacubitril valsartan

a. scatterplot of results and b. cost-effectiveness acceptability curve. Results dapagliflozin versus sacubitril valsartan for company base case updated at technical engagement



Source: company response to TE, figure 6, page 23

ERG's Probabilistic base case analysis #1 - dapagliflozin versus sacubitril valsartan

	Dapagliflozin + SC (total)	Sacubitril valsartan + SC (total)	Incremental	ICER (£/QALY)
QALYs	4.086	3.961	0.125	**Dapagliflozin dominates sacubitril valsartan**
Costs (£)	£13,928	£16,470	-£2,543	

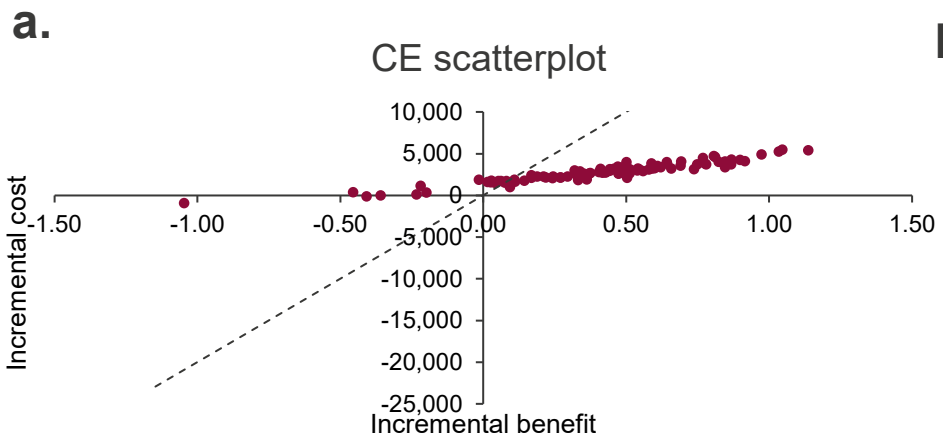
Source: ERG report, page 85

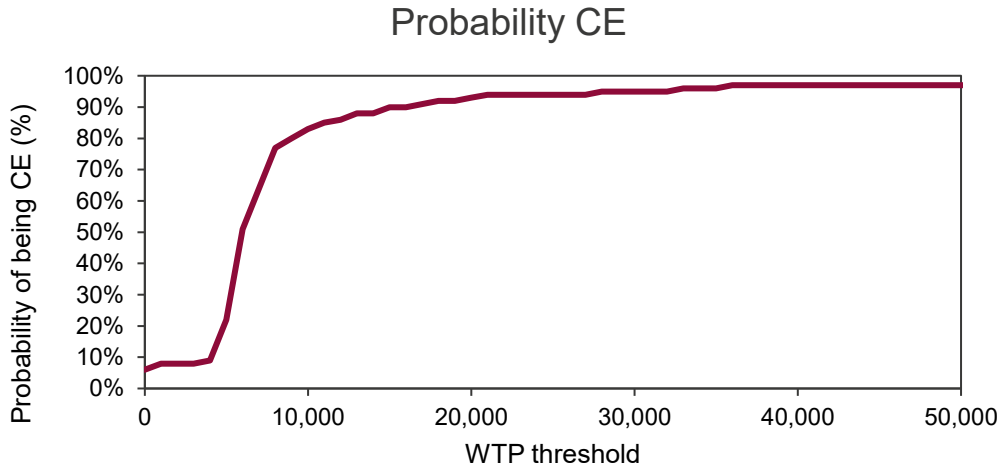
* Company uses model v0.3 and list prices for dapagliflozin and sacubitril valsartan

ERG's Probabilistic Sensitivity Analysis #2

Dapagliflozin v placebo (ACEi/ARB-based standard care)

a. scatterplot of results and b. cost-effectiveness acceptability curve. Results versus placebo (population #2, sacubitril valsartan unsuitable) for company base case updated at technical engagement





Source: ERG CEM TE response #2, PSA tab

Probabilistic base case analysis #2 - dapagliflozin versus placebo (ACEi/ARB based standard care, sacubitril valsartan unsuitable)

	Dapagliflozin + SC (total)	Placebo+ SC (total)	Incremental	ICER (£/QALY)
QALYs	4.339	3.929	0.410	**£6,761**
Costs (£)	£15,290	£12,519	£2,771	

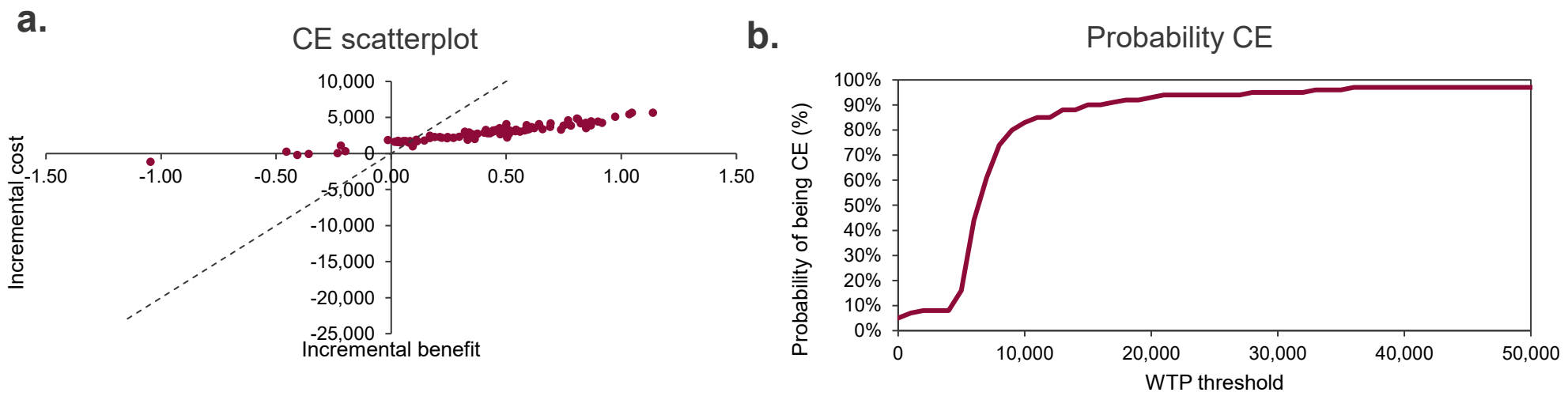
Source: ERG CEM TE response #2, PSA tab

NICE * Company uses model v0.3 and list price for dapagliflozin

ERG's Probabilistic Sensitivity Analysis #3

Dapagliflozin v placebo (sacubitril valsartan-based standard care)

a. scatterplot of PSA results and b. cost-effectiveness acceptability curve. Results versus placebo (population #3) for company base case updated at technical engagement



Source: ERG CEM TE response #3, PSA tab

Probabilistic base case analysis #3 - dapagliflozin versus placebo (sacubitril valsartan-based standard care)

	Dapagliflozin + SC (total)	Placebo + SC (total)	Incremental	ICER (£/QALY)
QALYs	4.339	3.929	0.410	**£6,933**
Costs (£)	£16,132	£13,290	£2,842	

Source: ERG CEM TE response #3, PSA tab

NICE * Company uses model v0.3 and list prices for dapagliflozin and sacubitril valsartan

Cost effectiveness scenarios: Company

Dapagliflozin dominates sacubitril valsartan in all company and ERG scenarios

Scenarios	Change in costs	Change in QALYs	ICER
Comparison with sacubitril valsartan: ACEi/ARB-based standard care			
Using non-statistically significant treatment effect from unadjusted (Bucher) analysis **(base case)**	-£2,671	0.130	**Dapagliflozin dominates sacubitril valsartan**
Assuming relative risk =1 (clinical equivalence)	-£3,131	0	
Using non-statistically significant treatment effect from MAIC analysis	-£2,701	0.171	

Source: adapted from company submission, table 46, page 132 and response to clarification, tables 9-10, pages 25-26

Cost effectiveness scenarios: Company

Deterministic pairwise ICERs for company scenarios: comparison with placebo

Scenarios	ICER	Change from base case
ACEi/ARB-based standard care	**Base case: £5,830**	
Base case using model v0.3	£5,835	+£5
Age >65 subgroup	£5,944	+£114
Gompertz distribution: CV and all-cause mortality	£7,264	+£1434
Europe subgroup: baseline characteristics	£5,819	-£11
Pooled Europe + North America subgroup	£8,809	+£2979
Unadjusted survival analyses (background therapy: ACEi/ARB-based SC)	£6,492	+£662
ITT treatment effect with Europe subgroup baseline event rate	£6,449	+£619
Including costs of GP renal function monitoring for people without T2DM*	£5,898	+£68
Sacubitril valsartan-based standard care	**Base case: £5,866**	
Base case using model v0.3	£5,872	+£6
Age >65 subgroup	£6,103	+£237
Gompertz distribution: CV and all-cause mortality	£7,162	+1296
Europe subgroup: baseline characteristics	£5,980	+£114
Pooled Europe + North America subgroup	£8,958	+£3092
Unadjusted survival analyses (background therapy: sacubitril valsartan-based SC)	£4,553	-£1313
ITT treatment effect with Europe subgroup baseline event rate	£6,607	+£741
Including costs of GP renal function monitoring for people without T2DM*	£5,934	+£68

*Company: eGFR routinely monitored by HF specialists (or GPs for type 2 diabetes). No additional monitoring required for dapagliflozin versus SC.

Source: adapted from company submission, table 56, pages 149-152 and company response to TE, tables 2-3 and 8-11, pages 12 and 21-22

Innovation

Company

Dapagliflozin innovative in HFrEF:

- First in class for heart failure
- Simple administration: no dose adjustment based on response - initiated at recommended dose with early benefits
- Not associated with hypotension and hyperkalaemia: limit use of current standard care.
- Single-dose, once-daily treatment: easy to initiate and for patients to adhere.
- Offers clinical benefits for patients with HFrEF regardless of current treatment: helps ease burden of HFrEF on NHS.
- Exact mechanism of action in HFrEF is currently unknown: likely to be new and innovative
- Initiation in primary care reduces need for outpatient visits in COVID-19 pandemic

⊙ *Should dapagliflozin be considered innovative for HFrEF?*

Equalities

Stakeholders

- Dapagliflozin prescribed in primary care for diabetes, heart failure patients should have access in this setting.
  - Specialist care limitation denies access to people with HF but not comorbid diabetes
  - GP's have expertise in prescribing SGLT2i drugs without specialist involvement
  - Equal access for HFrEF with or without diabetes.
- Also noted that dapagliflozin would be beneficial in people with preserved ejection fraction.
  - *NB: outside of remit of appraisal.*

- *Should current practice in one disease dictate the recommendations for another?*
- *Is excluding hydralazine as a comparator - recommended for people of Afro-Caribbean descent - an equalities issue?*

Key issues

Model driver

Where to position dapagliflozin and what is standard care at that point?

- Are ivabradine, hydralazine + nitrate and digoxin relevant comparators?

Would dapagliflozin be offered to people on 'optimised' care?

Should full trial population of DAPA-HF or the European subgroup be used for:

- Baseline characteristics?
- Relative effectiveness?

Is dapagliflozin effective at treating HFrEF?

- When added to first line standard of care treatment options?
- When compared with sacubitril valsartan?
  - is a matching-adjusted indirect comparison (MAIC) or Bucher method preferred for this indirect comparison?
- When added to specialist treatment options?

Who should initiate dapagliflozin? What monitoring is required, by whom?

- Primary care or specialist care?
- What extra costs and resources are associated with specialist care?

Are the extrapolations valid?

- What are the most appropriate extrapolations for each population?

How should disease severity be modelled?

- Does KCCQ-TSS accurately model HFrEF disease severity?