THE COST-EFFECTIVENESS OF SACUBITRIL/VALSARTAN IN THE TREATMENT OF HEART FAILURE AND REDUCED EJECTION FRACTION

SUPPLEMENTARY MATERIAL

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1. Details of costs

1.1. UK setting

1.1.1. Pharmacological therapies

In the base-case analysis, the daily cost of ACEi is based on the observed enalapril dose from PARADIGM-HF (18.9 mg per day). The daily cost of sacubitril/valsartan is based on the observed dose of sacubitril/valsartan used in PARADIGM-HF (375 mg).

Typical costs of other background medications (including beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA)) are based on recommended doses. Daily costs for primary and background therapies are presented in Table 1. A summary of cost data is provided in Table 2.

Table 1: Daily costs of primary and background therapies

Therapy	Daily cost‡	Daily dose assumptions	Unit costs source
Sacubitril/valsartan*	£3.27	375 mg†	BNF[1]
Enalapril*	£0.07	18.9 mg†	BNF[1]
Carvedilol*	£0.11	Two 25 mg tabs	BNF[1]
Bisoprolol	£0.04	One 10 mg tab	BNF[1]
Spironolactone*	£0.07	One 50 mg tab	BNF[1]
Digoxin*	£0.05	One 62.5 µg or 125 µg tab	BNF[1]
Atorvastatin*	£0.05	One 20 mg tab	BNF[1]
Simvastatin	£0.07	One 80 mg tab	BNF[1]
Furosemide*	£0.03	One 20 mg or 40 mg tab	BNF[1]
Aspirin*	£0.03	One 75 mg tab	BNF[1]
Warfarin*	£0.04	One 5 mg tab	BNF[1]
Clopidogrel*	£0.07	One 75 mg tab	BNF[1]

*Cost used in the base-case

†Average sacubitril/valsartan dose is 375 mg daily in PARADIGM-HF; average enalapril dose is 18.9 mg daily in PARADIGM-HF [2].

‡ Using list prices

Table 2: Summary of cost data

	Total cost - UK	Total cost - Denmark	Total cost - Colombia
Monthly costs			
Sacubitril/valsartan	£99.61	kr. 1,109.30	COP$268,915.31
ACEI (enalapril)	£3.17	kr. 17.19	COP$49,549.09
Background therapy	£7.31	kr. 76.89	COP$57,346.88
Background medical management	£69.31	kr. 75.22	COP$52,562.03
Cost per event			
Hospitalisation	£2,866	kr. 47,760	COP$6,830,157.00
AE – hypotension	£70	kr. 271	COP$51,600.00
AE – cough	£73	kr. 281	COP$72,693.00
AE – angioedema	£221	kr. 1,234	COP$72,964.14
AE – elevated serum creatinine	£73	kr. 281	COP$88,338.00
AE – elevated serum potassium	£73	kr. 281	COP$96,974.00

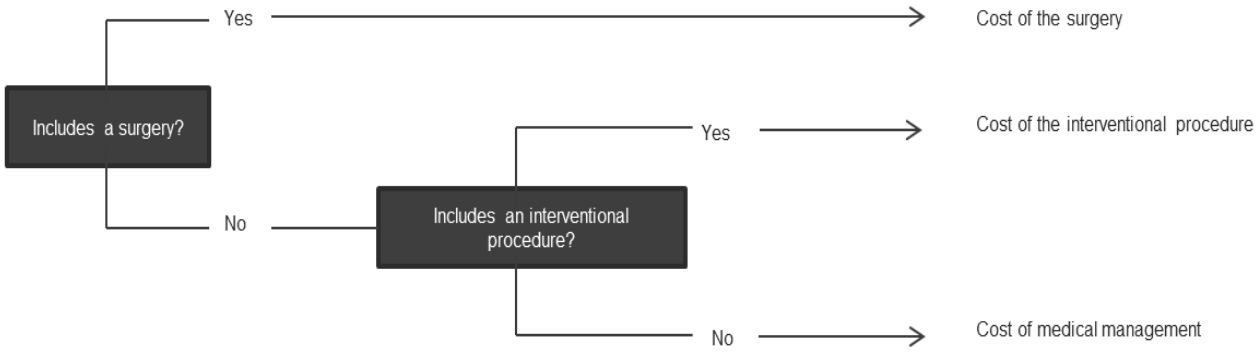
Abbreviations: AE, adverse event; ACEI, angiotensin-converting-enzyme inhibitor

1.1.2. Hospitalisation

Costs for hospitalisation are taken from the NHS National Schedule of Reference Costs 2013–2014[3]. NHS reference costs provide unit costs for a hospitalisation event, and not a cost per day; this method is considered to be aligned with the process through which care is reimbursed in England and Wales.

The proportion of each type of hospitalisation is taken from PARADIGM-HF. A scenario is included in which these proportions are derived from patients in Western Europe, in order to better reflect the kinds of surgical and interventional procedures that are performed in the UK. In the UK, hospitalisations are costed according to HRG code – hospitalisations, including a surgery or interventional procedure, are costed separately and include the costs of medical management incurred before and after the procedure. Hospitalisations observed during PARADIGM-HF are therefore costed according to the algorithm presented in Figure 1.

Figure 1: Algorithm to determine how each hospitalisation is costed



The proportions of each type of hospitalisation are presented in Table 3.

Table 3: Proportions of hospitalisations that are surgeries, interventional procedures and medical management alone

Hospitalisation type	Proportion of hospitalisations
Surgical procedures	3%
Interventional procedures	7%
Medical management	91%

Each hospitalisation type is costed according to hospitalisations as observed in PARADIGM-HF (Table 4); physician reported diagnoses are mapped to the most appropriate HRG codes, and a weighted average is calculated using NHS activity as reported in the NHS National Schedule of Reference Costs

(2013–2014). For simplicity, hospitalisations for medical management were only included where >30 cases had been recorded.

Table 4: Cost per hospitalisation (weighted average of relevant HRG codes)

Event	Cost per event	Source
Hospitalisation	£2,866	NHS National Schedule of Reference Costs, 2013-2014

1.1.3. Background medical resource use

Because of the protocol-driven nature of resource use within PARADIGM-HF, estimates of background resource use are taken from relevant national sources. Levels of background resource use are assumed to be the same between both arms of the model (Table 5).

Estimates of background resource use include A&E referrals, outpatient contacts and GP visits. Mean annual use is taken from a study using data from the Clinical Practice Research Datalink (CPRD) [4]; unit costs are taken from published national sources.

Table 5: Background medical resource use

		Mean annual use†	Unit cost	Source of unit cost
A&E Visits	GP emergency visits	0.14	£35.00	PSSRU 2014 [5]
	A&E referrals	0.01	£123.67	NHS National Schedule of Reference Costs, 2013–2014 [3]
Outpatient office physician visits	GP visits	13.54	£35.00	PSSRU 2014 [5]
	Cardiologist visits	0.05	£130.86	NHS National Schedule of Reference Costs, 2013–2014 [3]
	Other physician visits	0.36	£35.00	PSSRU 2014 [5]
Other GP visits or contacts	GP home visits	1.23	£35.00	PSSRU 2014 [5]
	GP nursing home visits	0.19	£35.00	PSSRU 2014 [5]
	GP residential home visits	0.04	£35.00	PSSRU 2014 [5]
	GP phone calls to patient	0.73	£35.00	PSSRU 2014 [5]
	GP visits with third parties	7.27	£35.00	PSSRU 2014 [5]

Abbreviations: A&E, accident and emergency; GP, general practitioner, NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

†Mean annual use based on CPRD data [4]

1.1.4. Adverse events

The AE profile for enalapril and sacubitril/valsartan (as observed in PARADIGM-HF, and reported by McMurray et al [2]) is presented in Table 6.

Table 6: AE profile for enalapril and sacubitril/valsartan from PARADIGM-HF

Event	Sacubitril/valsartan (N=4187)	Enalapril (N=4212)	p value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids	6 (0.1)	4 (0.1)	0.52

Event	Sacubitril/valsartan (N=4187)	Enalapril (N=4212)	p value
without hospitalisation			
Hospitalisation without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	

All AEs reported by McMurray et al[2] are considered in this analysis. Estimates of resource use associated with AEs were taken from UK clinical opinion, and are as follows:

- Hypotension: patients experiencing hypotension require 2 additional GP visits
- Cough: patients experiencing cough require 2 additional GP visits and a blood test
- Angioedema:
    - Patients experiencing milder angioedema ("no treatment or use of antihistamines only") require 2 outpatient visits in addition to the cost of antihistamines
    - Patients experiencing more severe angioedema ("Use of catecholamines or glucocorticoids without hospitalisation") require an Evisit and a follow-up GP visit in addition to the cost of glucocorticoids
    - Patients hospitalised for angioedema are captured within the hospitalisation model and are not considered here
- Patients with elevated serum creatinine require 2 additional GP visits and a blood test
- Patients with elevated serum potassium require 2 additional GP visits and a blood test
- Unit costs associated with AEs are presented in Table 7.

Table 7: Unit costs associated with AEs

Resource use	Cost	Source
GP visit (patient contact lasting 11.7 minutes)	£35.00	PSSRU [6]
Lab test (haematology)	£3.00	NHS National Schedule of Reference Costs, 2013–2014 [3]
Outpatient contact	£130.86	PSSRU [6]
Daily cost of antihistamines (cetirizine once daily, 10 mg, assumed taken for 14 days)	£0.04	BNF [1]
ER visit	£123.67	NHS National Schedule of Reference Costs, 2013–2014[3]
Daily cost of glucocorticoids (prednisolone, 40 mg, assumed taken for 5 days)	£0.37	BNF [1]

The cost applied for each AE is presented in Table 8.

Table 8: Cost per AE

Type of AE	Cost per event
Hypotension	£70
Cough	£73
Angioedema	£222
Elevated serum creatinine	£73
Elevated serum potassium	£73

Abbreviations: AE, adverse event.

1.1.5. Initial costs associated with titrating sacubitril/valsartan

One-off costs for titration have been included for sacubitril/valsartan patients. It is assumed that sacubitril/valsartan titration would require two additional outpatient visits. The initial costs associated with titration are £261.72 (see Table 9). No additional monitoring costs are considered.

Table 9: Unit costs associated with titration

Resource use	Cost	Source
Cardiology outpatient contact	£130.86	NHS National Schedule of Reference Costs, 2013-2014 [3]

1.2. Danish setting

1.2.1. Pharmacological therapies

In the base-case analysis, the daily cost of ACEi is based on the observed enalapril dose from PARADIGM-HF (18.9 mg per day). The daily cost of sacubitril/valsartan is based on the observed dose of sacubitril/valsartan used in PARADIGM-HF (375 mg).

Typical costs of other background medications (including BB and MRA) are based on recommended doses. Daily costs for primary and background therapies are presented in Table 10.

Table 10: Daily costs of primary and background therapies

Therapy	Daily cost‡	Daily dose assumptions	Unit costs source
Sacubitril/valsartan*	kr. 36.45	375 mg†	Assumption
Enalapril*	kr. 0.56	18.9 mg†	Lægemiddelstyrelsen [7]
Carvedilol*	kr. 0.77	Two 25 mg tabs	Lægemiddelstyrelsen [7]
Bisoprolol	kr. 0.43	One 10 mg tab	Lægemiddelstyrelsen [7]
Spironolactone*	kr. 0.79	One 50 mg tab	Lægemiddelstyrelsen [7]
Digoxin*	kr. 0.59	One 62.5 µg or 125 µg tab	Lægemiddelstyrelsen [7]
Atorvastatin*	kr. 0.31	One 20 mg tab	Lægemiddelstyrelsen [7]
Simvastatin	kr. 0.42	One 80 mg tab	Lægemiddelstyrelsen [7]
Furosemide*	kr. 0.31	One 20 mg or 40 mg tab	Lægemiddelstyrelsen [7]
Aspirin*	kr. 0.38	One 75 mg tab	Lægemiddelstyrelsen [7]
Warfarin*	kr. 1.56	One 5 mg tab	Lægemiddelstyrelsen [7]
Clopidogrel*	kr. 0.55	One 75 mg tab	Lægemiddelstyrelsen [7]

* Cost used in the base-case

†Average sacubitril/valsartan dose is 375 mg daily in PARADIGM-HF; average enalapril dose is 18.9 mg daily in PARADIGM-HF [2].

‡ Using list prices excluding VAT as per Danish HTA guidelines

1.2.2. Hospitalisation

Hospitalisation costs calculated in a similar manner to the UK, but costs were weighted average of Danish DRG tariffs (weights based on Western European hospitalization type frequency in

PARADIGM-HF). For those categories where there were several DRG tariffs (e.g. “other cardiac surgery”) we used most recent (available) activity as weights (Table 11).

Table 11: Cost per hospitalisation (weighted average of relevant HRG codes)

Event	Cost per event	Source
Hospitalisation	kr. 47,099	DRG-takster 2015[8]

1.2.3. Background medical resource use

In Denmark it was assumed that a patient would incur one outpatient visit and one GP visit per year. The cost of a GP visit was based on the tariff given in the agreement between the Danish Regions and the Danish Medical Association while and the cost of an outpatient consultation was taken from DAGS tariff BG50A.[8] The monthly cost of background medical resource use was estimated to be kr. 75.

1.2.4. Adverse events

Assumptions on the rates of adverse events and their associated resource use are the same as for the UK. Unit costs associated with AEs are presented in Table 12 and Table 7.

Table 7Table 12: Unit costs associated with AEs - Denmark

Resource use	Cost	Source
GP visit (patient contact lasting 11.7 minutes)	kr. 135.64	Basic daytime GP consultation http://www.laeger.dk
Lab test (haematology)	kr. 10.00	Assumption
Outpatient contact	kr. 767.00	DAGS tariff BG50A[8]
Daily cost of antihistamines (cetirizine once daily, 10 mg, assumed taken for 14 days)	kr. 2.80	Lægemiddelstyrelsen [7]
ER visit	kr. 551.00	DAGS tariff AA01C[8]
Daily cost of glucocorticoids (prednisolone, 40 mg, assumed taken for 5 days)	kr. 7.80	Lægemiddelstyrelsen [7]

The cost applied for each AE is presented in Table 13 and Table 8.

Table 13: Cost per AE - Denmark

Type of AE	Cost per event
Hypotension	kr. 271.28
Cough	kr. 281.28
Angioedema	kr. 1,234.18
Elevated serum creatinine	kr. 281.28
Elevated serum potassium	kr. 281.28

Abbreviations: AE, adverse event.

1.2.5. Initial costs associated with titrating sacubitril/valsartan

Titration was included in the base case analysis for Denmark. Titration was assumed to require two additional outpatient visits, costed using DAGS tariff BG50A. [8] The cost of titration used in the model is kr. 1,534.

1.3. Colombian setting

1.3.1. Pharmacological therapies

Therapy	Daily cost‡	Daily dose assumptions	Unit costs source
Sacubitril/valsartan*	COP$8,835.00	400 mg†	Assumption
Enalapril*	COP$1,627.90	20 mg†	SISMED, 2016. Accessed February 2017.
Carvedilol*	COP$4,184.30	Two 25 mg tabs	SISMED, 2016. Accessed February 2017.
Bisoprolol	COP$2,834.44	One 10 mg tab	SISMED, 2016. Accessed February 2017.
Spironolactone*	COP$102.18	Two 25 mg tab	SISMED, 2016. Accessed February 2017.
Digoxin*		One 62.5 µg or 125 µg tab	SISMED, 2016. Accessed February 2017.
Atorvastatin*	COP$84.18	One 20 mg tab	SISMED, 2016. Accessed February 2017.
Simvastatin	COP$3,600.03	One 80 mg tab	SISMED, 2016. Accessed February 2017.

Therapy	Daily cost‡	Daily dose assumptions	Unit costs source
Furosemide*	COP$1,220.09	One 20 mg or 40 mg tab	SISMED, 2016. Accessed February 2017.
Aspirin*	COP$539.83	One 75 mg tab	SISMED, 2016. Accessed February 2017.
Warfarin*	COP$1,068.19	One 5 mg tab	SISMED, 2016. Accessed February 2017.
Clopidogrel*	COP$348.02	One 75 mg tab	SISMED, 2016. Accessed February 2017.

1.3.2. Hospitalisation

The cost of a hospitalisation was taken to be COP$6,830,157, taken from a previous economic evaluation for an exercise based cardiac rehabilitation program in Colombia.{Rincon, 2016 #512} The cost has been exchanged from USD to COP and adjusted to 2015 prices using the World Bank GDP deflator.

1.3.3. Background medical resource use

Background medical resource use was assumed to be the same as in the UK, with costs taken from a burden of disease study performed by Deloitte and from SISMED (data on file).

Resource	Average monthly use	Mean annual use	Unit cost
A&E Visits	GP emergency visits	0.14	$ 77,300.00
	A&E referrals	0.01	$ 37,200.00
Outpatient office physician visits	GP visits	13.54	$ 25,800.00
	Cardiologist visits	0.05	$ 37,200.00
	Other physician visits	0.36	$ 25,800.00
Other GP visits or contacts	GP home visits	1.23	$ 37,158.00
	GP hospital visits	0.19	$ 25,800.00
	GP nursing home visits	0.04	$ 25,800.00
	GP residential home visits	0.04	$ 25,800.00
	GP phone calls to patient	0.73	$ 25,800.00
	GP visits with third parties	7.27	$ 25,800.00

1.3.4. Adverse events

The same resource use assumptions have been applied to cost adverse events in Colombia as were applied in the UK. Costs have been taken from a burden of disease report performed by Deloitte.

Resource use	Cost	Source
GP visit	COP$25,800	Data on file - Deloitte Health Economics. The economic burden of heart conditions-Colombia, 2016. Table B.8, pg 87-89.
Lab test (haematology)	COP$21,093	SISMED. Valorización Insuficiencia Cardiaca Crónica. Abril de 2016
Outpatient contact	COP$25,800	Data on file - Deloitte Health Economics. The economic burden of heart conditions-Colombia, 2016. Table B.8, pg 87-89.
Daily cost of antihistamines (cetirizine once daily, 10mg, assumed taken for 14 days)	COP$71.70	SISMED, 2016. Accessed February 2017.
ER visit	COP$77,300	Data on file - Deloitte Health Economics. The economic burden of heart conditions-Colombia, 2016. Table B.8, pg 87-89.
Daily cost of glucocorticoids (prednisolone, 40mg, assumed taken for 5 days)	COP$80.93	SISMED, 2016. Accessed February 2017.

Type of AE	Cost per event
Hypotension	COP$51,600.00

Cough	COP$72,693.00
Angioedema	COP$72,964.14
Elevated serum creatinine	COP$88,338.00
Elevated serum potassium	COP$96,974.00

1.3.5. Cost of drug titration

Titration of sacubitril/valsartan was assumed to incur two additional GP visits, costing COP$25,800 each, making the total cost of titration COP$51,600.

2. Statistical model results

Table 14: Results of the Gompertz model of CV mortality

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Sacubitril valsartan	-0.216 (-0.328, -0.104)	-0.215 (-0.327, -0.103)
Age†	-0.092 (-0.128, -0.057)	-0.092 (-0.127, -0.057)
Age^2	0.001 (0.000, 0.001)	0.001 (0.000, 0.001)
Female	-0.357 (-0.508, -0.207)	-0.354 (-0.504, -0.204)
Region - Latin America (vs. North America)	0.625 (0.340, 0.910)	0.628 (0.342, 0.913)
Region - Western Europe (vs. North America)	0.168 (-0.089, 0.424)	0.170 (-0.086, 0.426)
Region - Central Europe (vs. North America)	0.529 (0.270, 0.787)	0.527 (0.269, 0.786)
Region - Asia-Pacific (vs. North America)	-0.187 (-0.809, 0.435)	-0.181 (-0.803, 0.440)
Race - Black (vs. Caucasian)	0.409 (0.126, 0.691)	0.409 (0.127, 0.692)
Race - Asian (vs. Caucasian)	0.962 (0.377, 1.548)	0.959 (0.373, 1.545)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Race - Other (vs. Caucasian)	0.168 (-0.072, 0.409)	0.169 (-0.071, 0.410)
NYHA class III/IV (vs. I/II)	0.296 (0.165, 0.427)	0.300 (0.169, 0.431)
LVEF†	-0.017 (-0.026, -0.008)	-0.017 (-0.026, -0.008)
log(eGFR) †	-0.238 (-0.444, -0.031)	-0.238 (-0.445, -0.032)
log(NT-proBNP) †	0.443 (0.385, 0.502)	0.443 (0.385, 0.502)
Sodium†	-0.027 (-0.046, -0.007)	-0.027 (-0.046, -0.007)
QRS duration†	0.002 (0.001, 0.003)	0.002 (0.001, 0.003)
Diabetes	0.229 (0.111, 0.346)	0.230 (0.112, 0.347)
Beta blocker use	-0.320 (-0.509, -0.131)	-0.321 (-0.510, -0.132)
1-5 years since HF diagnosis (vs. ≤1 year)	0.210 (0.063, 0.356)	0.212 (0.065, 0.358)
>5 years since HF diagnosis (vs. ≤1 year)	0.344 (0.186, 0.502)	0.346 (0.188, 0.503)
Ischaemic aetiology	0.156 (0.033, 0.278)	0.157 (0.035, 0.280)
Previously hospitalised for HF	0.159 (0.038, 0.280)	0.159 (0.038, 0.280)
EQ-5D†	-0.563 (-0.813, -0.313)	-0.659 (-0.980, -0.338)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Constant	-12.665 (-13.934, -11.395)	-12.663 (-13.933, -11.393)
Gamma	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)

Abbreviations: NYHA, New York Heart Asscociation; LVEF, left ventricle ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; HF, Heart failure.

†Variable has been centred on the mean

Table 15: Results of the gompertz model of all-cause mortality

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Sacubitril valsartan	-0.161 (-0.261, -0.061)	-0.160 (-0.260, -0.060)
Age†	-0.102 (-0.134, -0.070)	-0.101 (-0.133, -0.069)
Age^2	0.001 (0.001, 0.001)	0.001 (0.001, 0.001)
Female	-0.384 (-0.520, -0.247)	-0.386 (-0.522, -0.249)
Region - Latin America (vs. North America)	0.542 (0.294, 0.790)	0.529 (0.280, 0.779)
Region - Western Europe (vs. North America)	0.130 (-0.088, 0.349)	0.130 (-0.089, 0.349)
Region - Central Europe (vs. North America)	0.364 (0.140, 0.588)	0.347 (0.122, 0.572)
Region - Asia-Pacific (vs. North	-0.199 (-0.784, 0.386)	-0.206 (-0.791, 0.378)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
America)		
Race - Black (vs. Caucasian)	0.295 (0.040, 0.550)	0.286 (0.030, 0.541)
Race - Asian (vs. Caucasian)	0.715 (0.160, 1.271)	0.707 (0.151, 1.262)
Race - Other (vs. Caucasian)	0.087 (-0.129, 0.302)	0.083 (-0.132, 0.299)
NYHA class III/IV (vs. I/II)	0.214 (0.095, 0.334)	0.206 (0.086, 0.326)
LVEF†	-0.014 (-0.022, -0.005)	-0.014 (-0.022, -0.006)
Heart rate†	0.006 (0.001, 0.010)	0.005 (0.001, 0.010)
log(eGFR) †	-0.228 (-0.415, -0.041)	-0.236 (-0.423, -0.049)
log(NT-proBNP) †	0.391 (0.337, 0.444)	0.387 (0.333, 0.440)
Sodium†	-0.031 (-0.049, -0.014)	-0.031 (-0.048, -0.013)
QRS duration†	0.002 (0.001, 0.003)	0.002 (0.001, 0.003)
Diabetes	0.207 (0.101, 0.313)	0.216 (0.109, 0.322)
Beta blocker use	-0.289 (-0.461, -0.116)	-0.288 (-0.461, -0.115)
Lipid lowering medication use	-	-0.086 (-0.197, 0.025)
1-5 years since HF diagnosis (vs. ≤1 year)	0.204 (0.072, 0.336)	0.207 (0.075, 0.339)
>5 years since HF diagnosis (vs.	0.291 (0.149, 0.434)	0.292 (0.150, 0.434)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
≤1 year)		
Ischaemic aetiology	0.158 (0.047, 0.269)	0.187 (0.071, 0.303)
Prior stroke	0.168 (0.005, 0.330)	0.173 (0.011, 0.335)
Previously hospitalised for HF	0.153 (0.044, 0.261)	0.153 (0.044, 0.261)
EQ-5D†	-0.532 (-0.758, -0.306)	-0.632 (-0.923, -0.342)
Constant	-12.840 (-13.976, -11.705)	-12.761 (-13.903, -11.618)
Gamma	0.000 (0.000, 0.001)	0.000 (0.000, 0.001)

Abbreviations: NYHA, New York Heart Asscociation; LVEF, Left ventricle ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; HF, Heart failure.

†Variable has been centred on the mean

Table 16: Results of negative binomial model for all-cause hospitalisation

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Sacubitril valsartan	-0.173 (-0.247, -0.098)	-0.173 (-0.247, -0.098)
Age†	-0.054 (-0.081, -0.028)	-0.054 (-0.080, -0.028)
Age^2	0.000 (0.000, 0.001)	0.000 (0.000, 0.001)
Female	-0.297 (-0.393, -0.200)	-0.300 (-0.397, -0.204)
Region - Latin America (vs. North	-0.362 (-0.528, -0.197)	-0.361 (-0.526, -0.195)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
America)		
Region - Western Europe (vs. North America)	0.017 (-0.128, 0.162)	0.019 (-0.126, 0.164)
Region - Central Europe (vs. North America)	-0.322 (-0.470, -0.174)	-0.324 (-0.472, -0.177)
Region - Asia-Pacific (vs. North America)	-0.350 (-0.516, -0.183)	-0.345 (-0.511, -0.178)
Heart rate†	0.007 (0.004, 0.010)	0.007 (0.004, 0.010)
log(eGFR) †	-0.477 (-0.618, -0.335)	-0.474 (-0.616, -0.333)
log(NT-proBNP) †	0.228 (0.188, 0.268)	0.228 (0.188, 0.268)
Sodium†	-0.021 (-0.034, -0.008)	-0.021 (-0.034, -0.008)
QRS duration†	0.003 (0.002, 0.004)	0.003 (0.002, 0.004)
Diabetes	0.333 (0.254, 0.412)	0.332 (0.253, 0.411)
Prior use of ACEi	-0.104 (-0.196, -0.013)	-0.104 (-0.196, -0.012)
Beta blocker use	-0.328 (-0.470, -0.185)	-0.327 (-0.469, -0.184)
Lipid lowering medication use	0.073 (-0.012, 0.157)	0.072 (-0.012, 0.156)
1-5 years since HF diagnosis (vs. ≤1 year)	0.265 (0.168, 0.361)	0.265 (0.168, 0.361)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
>5 years since HF diagnosis (vs. ≤1 year)	0.402 (0.300, 0.503)	0.401 (0.299, 0.503)
Ischaemic aetiology	0.085 (-0.002, 0.172)	0.085 (-0.001, 0.172)
Prior stroke	0.147 (0.020, 0.275)	0.148 (0.021, 0.275)
Prior atrial fibrillation/ flutter	0.095 (0.013, 0.176)	0.093 (0.012, 0.175)
Prior cancer	0.164 (-0.008, 0.336)	0.160 (-0.012, 0.331)
Current smoker	0.209 (0.103, 0.314)	0.209 (0.103, 0.314)
Previously hospitalised for HF	0.334 (0.254, 0.413)	0.334 (0.255, 0.413)
EQ-5D†	-0.487 (-0.662, -0.311)	-0.645 (-0.867, -0.422)
Constant	-2.844 (-3.772, -1.917)	-2.840 (-3.767, -1.913)

Abbreviations: NYHA, New York Heart Asscociation; LVEF, Left ventricle ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; HF, Heart failure.

†Variable has been centred on the mean

Table 17: Results of the mixed effects model for utility

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Sacubitril valsartan	0.011 (0.004, 0.017)	0.009 (0.004, 0.014)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
Age†	-0.001 (-0.001, 0.000)	-0.001 (-0.001, 0.000)
Female	-0.031 (-0.039, -0.023)	-0.025 (-0.031, -0.018)
Region - Latin America (vs. North America)	0.041 (0.027, 0.055)	0.035 (0.023, 0.046)
Region - Western Europe (vs. North America)	0.013 (-0.001, 0.026)	0.009 (-0.001, 0.020)
Region - Central Europe (vs. North America)	0.000 (-0.014, 0.013)	-0.001 (-0.012, 0.009)
Region - Asia-Pacific (vs. North America)	0.041 (0.026, 0.056)	0.036 (0.023, 0.048)
NYHA class II (vs. I)	-0.009 (-0.024, 0.006)	-0.008 (-0.021, 0.004)
NYHA class III (vs. I)	-0.051 (-0.067, -0.034)	-0.041 (-0.055, -0.028)
NYHA class IV (vs. I)	-0.092 (-0.132, -0.051)	-0.058 (-0.090, -0.025)
Heart rate†	0.000 (-0.001, 0.000)	0.000 (0.000, 0.000)
log(NT-proBNP) †	-0.009 (-0.013, -0.006)	-0.007 (-0.010, -0.004)
Sodium†	0.001 (0.000, 0.002)	0.001 (0.000, 0.002)
BMI	-0.002 (-0.003, -0.001)	-0.001 (-0.002, -0.001)
Diabetes	-0.014 (-0.021, -0.007)	-0.011 (-0.016, -0.005)
1-5 years since HF diagnosis (vs. ≤1 year)	-0.017 (-0.024, -0.009)	-0.015 (-0.021, -0.008)

Coefficient	UK & Colombian analysis (coefficient, 95% LCI, 95% UCI)	Danish analysis (coefficient, 95% LCI, 95% UCI)
>5 years since HF diagnosis (vs. ≤1 year)	-0.023 (-0.031, -0.014)	-0.019 (-0.026, -0.012)
Ischaemic aetiology	-0.007 (-0.014, -0.001)	-0.005 (-0.011, 0.000)
Prior stroke	-0.012 (-0.023, -0.001)	-0.008 (-0.017, 0.001)
Current smoker	-0.013 (-0.022, -0.004)	-0.011 (-0.019, -0.004)
EQ-5D†	0.488 (0.473, 0.504)	0.501 (0.486, 0.517)
Hospitalised within previous 30 days	-0.105 (-0.116, -0.094)	-0.081 (-0.090, -0.072)
Hospitalised 30-90 days previously	-0.054 (-0.062, -0.045)	-0.044 (-0.051, -0.038)
Adverse event - cough	-0.028 (-0.041, -0.015)	-0.025 (-0.035, -0.015)
Adverse event - hypotension	-0.029 (-0.042, -0.017)	-0.025 (-0.035, -0.015)
Time (years)	-0.008 (-0.010, -0.006)	-0.006 (-0.007, -0.004)
Constant	0.822 (0.802, 0.843)	0.838 (0.822, 0.855)

Abbreviations: NYHA, New York Heart Asscociation; LVEF, Left ventricle ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; HF, Heart failure.

†Variable has been centred on the mean

3. Cost-effectiveness results using all-cause mortality

Table 18: All-cause mortality cost-effectiveness results in the UK setting estimated over lifetime

Component	ACEI	Sacubitril/valsartan	Incremental
Primary therapy costs	£153	£7,838	£7,685
Background therapy costs	£544	£587	£43
Hospitalisation costs	£7,440	£6,819	-£621
HF management costs	£5,058	£5,458	£400
Adverse events	£92	£98	£6
Titration	£0	£262	£262
Total costs	**£13,287**	**£21,062**	**£7,776**
QALYs	**4.58**	**5.00**	**0.42**
ICER			**£18,507**

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AE, adverse event; ICER, incremental cost-effectiveness ratio; HF, heart failure; QALY, quality-adjusted life-years.

Table 19: All-cause mortality cost-effectiveness results in the Danish setting estimated over lifetime

Component	ACEi	Sacubitril/valsartan	Incremental
Primary therapy	kr. 1,228	kr. 85,733	kr. 84,505
Background therapy	kr. 5,492	kr. 5,942	kr. 450
Hospitalisation	kr. 127,564	kr. 117,284	-kr. 10,280
HF management	kr. 5,373	kr. 5,813	kr. 440
Adverse events	kr. 349	kr. 375	kr. 26
Titration	kr. 0	kr. 1,534	kr. 1,534
Total costs	**kr. 140,006**	**kr. 216,681**	**kr. 76,675**
QALYs	**4.61**	**5.04**	**0.43**
ICER			**kr. 179,939**

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AE, adverse event; ICER, incremental cost-effectiveness ratio; HF, heart failure; QALY, quality-adjusted life-years.

Table 20: All-cause mortality cost-effectiveness results in the Colombian setting estimated over lifetime

Component	ACEi	Sacubitril/valsartan	Incremental
Primary therapy	COP$3,381,980	COP$19,723,125	COP$16,341,146
Background therapy	COP$3,914,218	COP$4,206,007	COP$291,789
Hospitalisation	COP$16,681,836	COP$15,228,645	-COP$1,453,192
HF management	COP$3,587,628	COP$3,855,070	COP$267,443
Adverse events	COP$92,996	COP$93,960	COP$964
Titration	COP$0	COP$51,600	COP$51,600
Total costs	**COP$27,658,658**	**COP$43,158,407**	**COP$15,499,749**
QALYs	**4.31**	**4.68**	**0.37**
ICER			**COP$41,501,493**

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AE, adverse event; ICER, incremental cost-effectiveness ratio; HF, heart failure; QALY, quality-adjusted life-years.

4. Parameter selection and transformations

Covariates for consideration in the model of all-cause mortality were based on pre-specified subgroups in PARADIGM-HF, those reported by a previous economic evaluation in HF and clinical expert opinion.

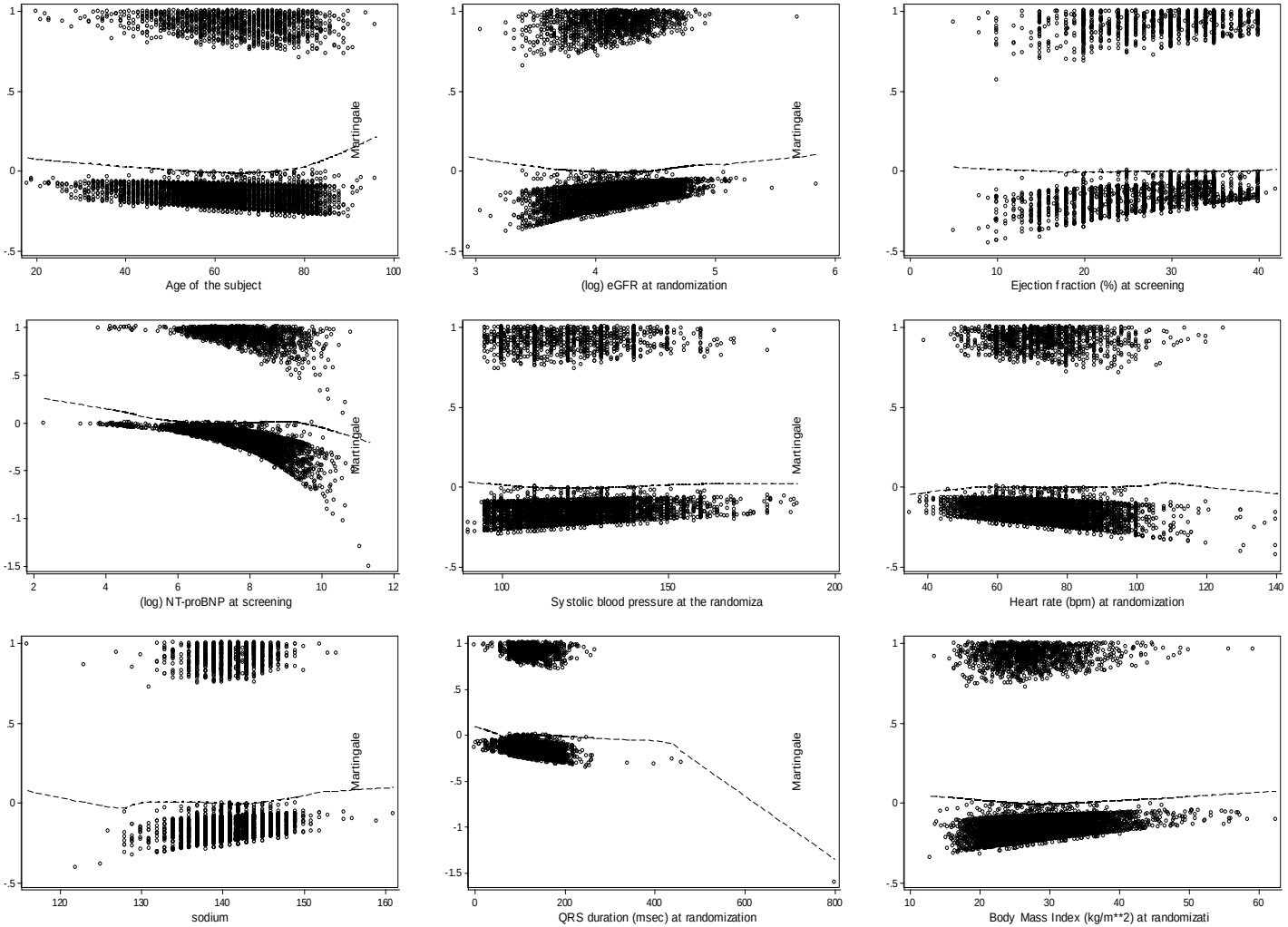
When performing survival analysis, non-linearities in covariates were assessed based on Martingale residuals (Figure 2) and variables were transformed where required. Final covariates for inclusion in the risk equations were selected using a backwards stepwise selection, confirmed using forwards stepwise selection and the resulting model reviewed by clinical experts.

Region was pre-specified within the statistical analysis plan (SAP)[21] for analysis of the primary endpoint for PARADIGM-HF and was therefore included in all models. No other variables were identified *a priori* as being of special interest. The primary statistical analysis of PARADIGM-HF did not identify any treatment effect modifiers, and therefore interactions between such variables and the sacubitril/valsartan treatment effect were not considered. The basic covariate identification procedure performed was:

- An initial set of covariates were identified using backwards stepwise elimination (using a p-value of <0.1).
- This was validated using forwards stepwise selection (using a p-value of <0.1).
- The interim statistical model was reviewed by clinical experts at sacubitril/valsartan UK and French advisory boards
    - In addition to suggesting alternative parameters for inclusion, clinical experts recommended that potassium be removed from the predictive model due to unexpected directional effects

For hospitalisation, a negative binomial model was preferred over other possible models (such as a Poisson model), as other models displayed evidence of over dispersion, where the conditional variance of the variable was greater than the conditional mean.

Figure 2: Martingale residuals and LOESS models (dashed line) for CV mortality



5. Quintile analysis

A Cox regression model predicting the risk of experiencing the primary outcome (a composite of CV mortality and HF hospitalisation) was developed using the ACEi patient population and then used to predict the risk for all patients. Patients were then ranked on the basis of the 'risk score' derived from the regression model, and divided into quintiles. Table 21, Table 22 and Table 23 present the results of the model stratified by risk quintile for the UK, Danish and Colombian settings respectively. Patients in the first quintile have the lowest risk and patients in the fifth quintile have the highest risk. In the UK setting, sacubitril/valsartan is associated with a positive net benefit at a willingness-to-pay threshold of £20,000 in all but the lowest risk quintile. In the Danish and Colombian settings sacubitril/valsartan is associate with a positive net benefit in all risk quintiles, using willingness-to-pay thresholds of kr. 250,000 and COP$ 52.4 million respectively. The results of this analysis suggest that the cost-effectiveness of sacubitril/valsartan increases with disease severity, with severity defined here as the multivariate risk of experiencing the primary endpoint of PARADIGM-HF.

Table 21: ICER and NMB by risk quintile in the UK setting

Quintile	Incremental cost	Incremental QALYs	ICER	NMB
1	£11,844	0.55	£22,610	-£785
2	£10,097	0.56	£18,864	£1,091
3	£8,971	0.55	£17,063	£1,984
4	£7,723	0.51	£15,845	£2,467
5	£5,895	0.43	£14,458	£2,691

Abbreviations: ICER, Incremental cost-effectiveness ratio; NMB, Net monetary benefit; QALYs, Quality-adjusted life-years.

Table 22: ICER and NMB by risk quintile in the Danish setting

Quintile	Incremental cost	Incremental QALYs	ICER	NMB
1	kr. 107,120	0.46	kr. 237,069	kr. 8,453
2	kr. 90,864	0.48	kr. 190,370	kr. 30,274
3	kr. 81,156	0.49	kr. 168,265	kr. 40,769
4	kr. 69,692	0.46	kr. 152,275	kr. 46,186
5	kr. 56,787	0.43	kr. 134,924	kr. 50,502

Abbreviations: ICER, Incremental cost-effectiveness ratio; NMB, Net monetary benefit; QALYs, Quality-adjusted life-years.

Table 23: ICER and NMB by risk quintile in the Colombian setting

Quintile	Incremental cost	Incremental QALYs	ICER	NMB
1	COP$21.9 million	0.43	COP$53.7 million	COP$1,275,857
2	COP$18.9 million	0.45	COP$44.1 million	COP$5,246,486
3	COP$16.9 million	0.45	COP$39.3 million	COP$7,269,362
4	COP$14.6 million	0.42	COP$35.9 million	COP$8,378,003
5	COP$11.3 million	0.37	COP$31.7 million	COP$8,883,291

Abbreviations: ICER, Incremental cost-effectiveness ratio; NMB, Net monetary benefit; QALYs, Quality-adjusted life-years.

6. Scenario analyses

6.1. Sensitivity analyses

A Cox regression model predicting the risk of experiencing the primary outcome was developed using the enalapril treated patients and then used to predict the risk of experiencing the primary outcome for all patients. Patients were ranked on the basis of the 'risk score' derived from the regression model, and divided into quintiles, with the lowest risk patients in the first quintile and high risk patients in quintile 5. The model was then run using the baseline characteristics for each patient in PARADIGM-HF and the cost-effectiveness was assessed in each quintile.

Parameter uncertainty was tested using deterministic sensitivity analysis; all model parameters were independently varied over plausible ranges and the ICER was recorded at the upper and lower value for each parameter. A number of scenarios were considered to explore the impact of structural uncertainties and assumptions in the model (see supplementary material for details).

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), where all parameters were assigned distributions and simultaneously varied across 1,000 Monte Carlo simulations. A cost-effectiveness acceptability curve was estimated, presenting the probability that sacubitril/valsartan is cost-effective at a range of willingness-to-pay (WTP) thresholds.[33]

6.2. UK setting

In total, 25 scenario analyses were performed for the UK setting and the results are presented in Table 24.

Table 24: Results of scenario analyses in the UK setting

Scenario	Sacubitril/valsartan	ACEi	ICER

	Costs	QALYs	Costs	QALYs	
Discount rate (costs = 6, outcomes = 1.5)	£20,786	6.29	£13,111	5.66	£12,170
Use weibull model	£26,973	6.28	£16,869	5.71	£17,716
Use exponential model	£27,953	6.49	£17,529	5.92	£18,129
Use all-cause mortality model	£21,062	5.00	£13,287	4.58	£18,507
HRQL time trend halved	£23,720	5.76	£14,814	5.22	£16,328
HRQL time trend doubled	£23,720	5.23	£14,814	4.76	£19,013
No decrease in HRQL over time	£23,720	5.94	£14,814	5.37	£15,597
HRQL constant after 5 years	£23,720	5.73	£14,814	5.19	£16,227
HRQL constant after 10 years	£23,720	5.64	£14,814	5.11	£16,708
No 'Sacubitril valsartan effect' on HRQL	£23,720	5.51	£14,814	5.06	£20,161
Sacubitril valsartan effect applied to HF hosp only	£24,572	5.58	£14,814	5.06	£18,967
Sacubitril valsartan effect applied to CV hosp only	£24,189	5.58	£14,814	5.06	£18,139
Utility decrements for hosp set to zero	£23,720	5.63	£14,814	5.12	£17,257
All Sacubitril valsartan treatment effects cease at year 5	£23,302	5.33	£14,814	5.06	£32,114
All Sacubitril valsartan treatment effects cease at year 10	£23,514	5.47	£14,814	5.06	£21,205
Discontinuation included	£20,917	5.42	£14,822	5.06	£17,215
Disc included; no disc after year 3	£22,235	5.50	£14,818	5.06	£17,117
Disc included, no loss of efficacy	£20,996	5.58	£14,822	5.06	£11,880
Hospitalisation costs doubled	£31,417	5.58	£23,110	5.06	£15,983
Hospitalisation costs halved	£19,871	5.58	£10,666	5.06	£17,710
Hospitalisation proportions derived using Western Europe population	£24,513	5.58	£15,669	5.06	£17,016
All AE rates set to zero	£23,610	5.59	£14,712	5.07	£17,100
Sacubitril valsartan/ ACEi costs using target doses	£23,720	5.58	£14,824	5.06	£17,115
ACEi costed using ramipril	£23,720	5.58	£14,863	5.06	£17,040

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
No titration costs	£23,458	5.58	£14,814	5.06	£16,631

Results are sensitive to discounting, and assumptions around the effect of treatment continuation. The assumption that the treatment effects for sacubitril/valsartan cease at year 5 is associated with an increase of 77% in the ICER, and was the only scenario to generate an ICER exceeding £30,000; however, we note that this represents a highly conservative scenario. Assuming no direct benefit of sacubitril/valsartan on HRQL led to an increase of 20% in the ICER, however other assumptions surrounding the rate of change in EQ-5D over time were less influential; assuming an extreme scenario in which EQ-5D declines at twice the rate of the base-case provided an increase in the ICER of 9%. The inclusion of discontinuation suggested the model was relatively linear to this, with no notable change in the ICER. Only in the extremely optimistic scenario in which discontinuation was associated with a reduction in costs but not efficacy of sacubitril/valsartan was the ICER reduced by 29%.

6.3. Danish setting

In addition to the 39 *a priori* defined subgroups in PARADIGM-HF, the cost-effectiveness of sacubitril/valsartan was estimated in the Danish setting for the group of patients that did not have elevated BNP/NT-proBNP at randomization. The result of this subgroup analysis is presented in Table 25 along with the scenario analyses.

Table 25: Results of scenario analyses in the Danish setting

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
Discount rate (costs = 0%, outcomes = 0%)	kr. 267,769	6.29	kr. 169,029	5.67	kr. 159,132
Discount rate (costs = 5%, outcomes = 5%)	kr. 205,091	4.76	kr. 132,951	4.36	kr. 183,880
Include SMR = 2	kr. 199,201	4.68	kr. 128,561	4.30	kr. 185,649
Include SMR = 3	kr. 181,141	4.28	kr. 117,212	3.95	kr. 194,019
Use all-cause mortality model	kr. 216,681	5.04	kr. 140,006	4.61	kr. 179,939
HRQL time trend halved	kr. 226,330	5.38	kr. 145,346	4.90	kr. 168,636
HRQL time trend doubled	kr. 226,330	5.06	kr. 145,346	4.62	kr. 185,802
No decrease in HRQL over time	kr. 226,330	5.49	kr. 145,346	4.99	kr. 163,598
HRQL constant after 5 years	kr. 226,330	5.36	kr. 145,346	4.88	kr. 168,158
HRQL constant after 10 years	kr. 226,330	5.30	kr. 145,346	4.83	kr. 171,400
No 'LCZ696 effect' on HRQL	kr. 226,330	5.21	kr. 145,346	4.81	kr. 200,064
LCZ696 effect applied to HF hosp only	kr. 239,879	5.27	kr. 145,346	4.81	kr. 204,251
LCZ696 effect applied to CV hosp only	kr. 233,806	5.27	kr. 145,346	4.81	kr. 190,647
Utility decrements for hosp set to zero	kr. 226,330	5.30	kr. 145,346	4.83	kr. 174,552
All LCZ696 treatment effects cease at year 5	kr. 226,375	5.06	kr. 145,346	4.81	kr. 325,647
All LCZ696 treatment effects cease at year 10	kr. 226,010	5.18	kr. 145,346	4.81	kr. 213,986
Discontinuation included	kr. 201,134	5.13	kr. 145,546	4.81	kr. 174,440
Disc included; no disc after year 3	kr. 212,505	5.19	kr. 145,460	4.81	kr. 173,694
Disc included, no loss of efficacy	kr. 198,892	5.27	kr. 145,546	4.81	kr. 114,614
Hospitalisation costs doubled	kr. 348,597	5.27	kr. 277,714	4.81	kr. 152,291
Hospitalisation costs halved	kr. 165,197	5.27	kr. 79,162	4.81	kr. 184,846
All AE rates set to zero	kr. 225,937	5.28	kr. 144,982	4.81	kr. 173,808
No weighting of PARADIGM-HF	kr. 242,916	5.77	kr. 153,393	5.25	kr. 169,580

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
Full compliance, patients receive 400mg of LCZ per day	kr. 232,318	5.27	kr. 145,346	4.81	kr. 186,860
Subgroup analysis for patients with non-elevated BNP/NT-proBNP at randomization	kr. 261,365	6.39	kr. 165,170	5.95	kr. 214,604

6.4. Colombian setting

Table 26: Results of scenario analyses in the Colombian setting

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
Discount rate (costs = 6, outcomes = 1.5)	COP$43,779,744	6.01	COP$27,982,617	5.43	COP$27,138,595
Include SMR = 2	COP$40,933,310	4.43	COP$26,247,480	4.08	COP$42,114,355
Include SMR = 3	COP$37,211,867	4.05	COP$23,979,188	3.75	COP$44,224,000
Use all-cause mortality model	COP$43,158,407	4.68	COP$27,658,658	4.31	COP$41,501,493
HRQL time trend halved	COP$46,008,231	5.09	COP$29,284,724	4.65	COP$37,810,530
HRQL time trend doubled	COP$46,008,231	4.66	COP$29,284,724	4.28	COP$43,460,192
No decrease in HRQL over time	COP$46,008,231	5.23	COP$29,284,724	4.77	COP$36,247,798
HRQL constant after 5 years	COP$46,008,231	5.06	COP$29,284,724	4.62	COP$37,677,247
HRQL constant after 10 years	COP$46,008,231	4.98	COP$29,284,724	4.55	COP$38,709,238
No 'Sacubitril/valsartan effect' on HRQL	COP$46,008,231	4.88	COP$29,284,724	4.52	COP$47,228,642
Sacubitril/valsartan effect applied to HF hosp only	COP$47,810,228	4.94	COP$29,284,724	4.52	COP$44,110,472
Sacubitril/valsartan effect applied to CV hosp only	COP$47,001,164	4.95	COP$29,284,724	4.52	COP$42,042,164
Utility decrements for hosp set to zero	COP$46,008,231	4.98	COP$29,284,724	4.55	COP$39,704,928
All Sacubitril/valsartan treatment effects cease at year 5	COP$45,485,841	4.76	COP$29,284,724	4.52	COP$69,832,595

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
All Sacubitril/valsartan treatment effects cease at year 10	COP$45,748,604	4.87	COP$29,284,724	4.52	COP$47,351,165
Discontinuation included	COP$40,965,087	4.82	COP$31,381,334	4.52	COP$32,353,101
Disc included; no disc after year 3	COP$43,221,701	4.88	COP$30,485,413	4.52	COP$35,963,470
Disc included, no loss of efficacy	COP$40,966,011	4.95	COP$31,381,334	4.52	COP$22,651,519
Hospitalisation costs doubled	COP$62,281,600	4.95	COP$46,964424	4.52	COP$36,199,163
Hospitalisation costs halved	COP$37,871,546	4.95	COP$20,444,874	4.52	COP$41,184,549
All AE rates set to zero	COP$45,908,187	4.95	COP$29,186,406	4.53	COP$39,483,848
Sacubitril/valsartan/ ACEi costs using target doses	COP$46,008,231	4.95	COP$25,709,194	4.52	COP$47,972,823
Re-weighting of PARADIGM-HF	COP$40,315,555	4.19	COP$25,975,330	3.86	COP$43,374,255
Titration costs set to zero	COP$45,956,631	4.95	COP$29,284,724	4.52	COP$39,400,807
Discount rate (costs = 6, outcomes = 1.5)	$ 38,290,190	5.93	$ 22,479,350	5.26	$ 23,609,917
Include SMR = 2	$ 36,696,166	4.59	$ 21,664,294	4.17	$ 35,710,131
Include SMR = 3	$ 33,884,210	4.25	$ 20,154,861	3.89	$ 37,901,378
Use all-cause mortality model	$ 35,397,546	4.45	$ 21,012,812	4.06	$ 37,118,201
HRQL time trend halved	$ 40,093,744	5.12	$ 23,449,678	4.60	$ 32,097,936
HRQL time trend doubled	$ 40,093,744	4.75	$ 23,449,678	4.29	$ 36,414,209

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
No decrease in HRQL over time	$ 40,093,744	5.24	$ 23,449,678	4.70	$ 30,877,922
HRQL constant after 5 years	$ 40,093,744	5.08	$ 23,449,678	4.56	$ 32,084,822
HRQL constant after 10 years	$ 40,093,744	5.02	$ 23,449,678	4.51	$ 32,930,958
No 'Sacubitril/valsartan effect' on HRQL	$ 40,093,744	4.93	$ 23,449,678	4.50	$ 38,537,322
Sacubitril/valsartan effect applied to HF hosp only	$ 41,393,961	4.99	$ 23,449,678	4.50	$ 36,193,811
Sacubitril/valsartan effect applied to CV hosp only	$ 40,809,803	5.00	$ 23,449,678	4.50	$ 34,943,712
Utility decrements for hosp set to zero	$ 40,093,744	5.02	$ 23,449,678	4.52	$ 33,494,458
All Sacubitril/valsartan treatment effects cease at year 5	$ 39,236,958	4.78	$ 23,449,678	4.50	$ 55,839,640
All Sacubitril/valsartan treatment effects cease at year 10	$ 39,764,559	4.93	$ 23,449,678	4.50	$ 38,269,205
Discontinuation included	$ 34,927,014	4.84	$ 25,431,852	4.50	$ 27,657,067
Disc included; no disc after year 3	$ 37,117,721	4.91	$ 24,636,708	4.50	$ 30,281,290
Disc included, no loss of efficacy	$ 35,195,294	5.00	$ 25,431,852	4.50	$ 19,603,253
Hospitalisation costs doubled	$ 40,093,744	5.00	$ 23,449,678	4.50	$ 33,418,323
Hospitalisation costs halved	$ 40,093,744	5.00	$ 23,449,678	4.50	$ 33,418,323
Hospitalisation proportions derived using Western Europe population	$ 40,093,744	5.00	$ 23,449,678	4.50	$ 33,418,323
All AE rates set to zero	$ 39,997,891	5.00	$ 23,356,991	4.50	$ 33,385,681

Scenario	Sacubitril/valsartan		ACEi		ICER
	Costs	QALYs	Costs	QALYs	
Sacubitril/valsartan/ ACEi costs using target doses	$ 40,093,744	5.00	$ 20,078,935	4.50	$ 40,186,176
Re-weighting of PARADIGM-HF	$ 29,246,578	4.14	$ 15,914,196	3.87	$ 49,874,549
Titration costs set to zero	$ 40,042,144.04	5.00	$ 23,449,678.05	4.50	$ 33,314,720

6.5. Subgroup analysis

Table 27: UK setting, results of subgroup analysis

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
1	**Full analysis set**	**£8,906**	**0.520**	**£17,134**	**0%**
2	Baseline age < 65 years	£9,996	0.610	£16,399	-4%
3	Baseline age ≥ 65 years	£7,774	0.427	£18,225	6%
4	Baseline age < 75 years	£9,504	0.563	£16,892	-1%
5	Baseline age ≥ 75 years	£6,287	0.332	£18,926	10%
6	Region - North America	£8,966	0.486	£18,443	8%
7	Region - Latin America	£8,560	0.554	£15,456	-10%
8	Region - Western €pe	£9,159	0.492	£18,634	9%
9	Region - Central €pe	£8,864	0.484	£18,299	7%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
10	Region - Asia-Pacific	£8,945	0.607	£14,743	-14%
11	Baseline NYHA class I/ II	£9,306	0.548	£16,992	-1%
12	Baseline NYHA III/ IV	£7,687	0.435	£17,677	3%
13	Baseline LVEF ≤ median	£8,624	0.536	£16,105	-6%
14	Baseline LVEF > median	£9,233	0.501	£18,413	7%
15	Baseline SBP ≤ median	£8,903	0.537	£16,566	-3%
16	Baseline SBP > median	£8,910	0.498	£17,874	4%
17	Baseline eGFR < 60	£7,851	0.467	£16,825	-2%
18	Baseline eGFR ≥ 60	£9,510	0.550	£17,285	1%
19	Baseline NT-proBNP ≤ median	£10,250	0.546	£18,790	10%
20	Baseline NT-proBNP > median	£7,457	0.492	£15,156	-12%
21	Diabetes at baseline	£8,275	0.501	£16,518	-4%
22	No diabetes at baseline	£9,239	0.530	£17,442	2%
23	Hypertension at baseline	£8,763	0.501	£17,477	2%
24	No hypertension at baseline	£9,250	0.564	£16,399	-4%
25	Prior use of ACEi	£8,967	0.520	£17,250	1%
26	Prior use of ARB	£8,684	0.519	£16,741	-2%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
27	Use of beta blocker at baseline	£9,007	0.522	£17,263	1%
28	No use of beta blocker at baseline	£7,559	0.493	£15,324	-11%
29	Use of MRA at baseline	£8,924	0.533	£16,755	-2%
30	No use of MRA at baseline	£8,883	0.504	£17,637	3%
31	≤ 1 year since diagnosis of HF	£10,008	0.566	£17,674	3%
32	1-5 years since diagnosis of HF	£8,677	0.513	£16,923	-1%
33	> 5 years since diagnosis of HF	£8,133	0.484	£16,805	-2%
34	Ischaemic aetiology	£8,581	0.497	£17,262	1%
35	Non-ischaemic aetiology	£9,392	0.554	£16,962	-1%
36	Prior atrial fibrillation at baseline	£8,371	0.477	£17,555	2%
37	No prior atrial fibrillation at baseline	£9,217	0.545	£16,920	-1%
38	Prior HF hospitalisation	£8,685	0.521	£16,666	-3%
39	No prior HF hospitalisation	£9,278	0.517	£17,929	5%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALYs, quality-adjusted life years; SBP, systolic blood pressure.

Table 28: Danish setting, results of subgroup analysis

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
1	**Full analysis set**	kr. 80,984	0.465	kr. 174,295	0%
2	Baseline age < 65 years	kr. 70,306	0.439	kr, 160,204	-8%
3	Baseline age ≥ 65 years	kr. 92,074	0.493	kr. 187,350	7%
4	Baseline age < 75 years	kr. 76,760	0.456	kr. 168,443	-3%
5	Baseline age ≥ 75 years	kr. 99,460	0.505	kr. 197,411	13%
6	Region - North America	kr. 80,335	0.455	kr. 177,075	2%
7	Region - Latin America	kr. 87,233	0.544	kr. 160,511	-8%
8	Region - Western €pe	kr. 87,430	0.468	kr. 187,495	8%
9	Region - Central €pe	kr. 75,230	0.398	kr. 189,137	9%
10	Region - Asia-Pacific	kr. 77,271	0.519	kr. 149,159	-14%
11	Baseline NYHA class I/ II	kr. 85,984	0.498	kr. 172,852	-1%
12	Baseline NYHA III/ IV	kr. 65,775	0.365	kr. 180,277	3%
13	Baseline LVEF ≤ median	kr. 76,863	0.483	kr. 159,230	-9%
14	Baseline LVEF > median	kr. 85,774	0.444	kr. 193,343	11%
15	Baseline SBP ≤ median	kr. 78,615	0.472	kr. 166,734	-4%
16	Baseline SBP > median	kr. 83,848	0.457	kr. 183,738	5%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
17	Baseline eGFR < 60	kr. 77,909	0.460	kr. 169,924	-3%
18	Baseline eGFR ≥ 60	kr. 82,747	0.469	kr. 176,751	1%
19	Baseline NT-proBNP ≤ median	kr. 90,547	0.467	kr. 194,375	12%
20	Baseline NT-proBNP > median	kr. 70,680	0.464	kr. 152,545	-12%
21	Diabetes at baseline	kr. 72,317	0.441	kr. 164,515	-6%
22	No diabetes at baseline	kr. 85,545	0.479	kr. 179,032	3%
23	Hypertension at baseline	kr. 80,883	0.456	kr. 177,702	2%
24	No hypertension at baseline	kr. 81,229	0.488	kr. 166,607	-4%
25	Prior use of ACEI	kr. 80,069	0.458	kr. 175,182	1%
26	Prior use of ARB	kr. 84,294	0.492	kr. 171,758	-1%
27	Use of beta blocker at baseline	kr. 81,531	0.465	kr. 175,781	1%
28	No use of beta blocker at baseline	kr. 73,722	0.476	kr. 155,043	-11%
29	Use of MRA at baseline	kr. 76,459	0.455	kr. 168,141	-4%
30	No use of MRA at baseline	kr. 86,654	0.478	kr. 181,641	4%
31	≤ 1 year since diagnosis of HF	kr. 89,177	0.488	kr. 182,899	5%
32	1-5 years since diagnosis of HF	kr. 78,898	0.459	kr. 172,007	-1%
33	> 5 years since diagnosis of HF	kr. 75,716	0.451	kr. 168,257	-3%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
34	Ischaemic aetiology	kr. 78,172	0.446	kr. 175,612	1%
35	Non-ischaemic aetiology	kr. 85,195	kr. 0	kr. 172,517	-1%
36	Prior atrial fibrillation at baseline	kr. 79,203	0.441	kr. 179,834	3%
37	No prior atrial fibrillation at baseline	kr. 82,021	0.479	kr. 171,325	-2%
38	Prior HF hospitalisation	kr. 76,834	0.458	kr. 168,101	-4%
39	No prior HF hospitalisation	kr. 87,988	0.478	kr. 184,305	6%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALYs, quality-adjusted life years; SBP, systolic blood pressure.

Table 29: Colombian setting, results of subgroup analysis

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
1	**Full analysis set**	COP$16,723,507	0.42	COP$39,522,754	0
2	Baseline age < 65 years	COP$18,853,013	0.49	COP$38,099,512	-4%
3	Baseline age ≥ 65 years	COP$14,511,818	0.35	COP$41,620,590	5%
4	Baseline age < 75 years	COP$17,792,183	0.45	COP$39,187,590	-1%
5	Baseline age ≥ 75 years	COP$12,049,499	0.29	COP$41,833,409	6%
6	Region - North America	COP$16,575,622	0.39	COP$42,424,381	7%
7	Region - Latin America	COP$16,264,964	0.46	COP$35,629,374	-10%
8	Region - Western €pe	COP$16,949,053	0.39	COP$43,083,517	9%
9	Region - Central €pe	COP$16,658,707	0.39	COP$42,293,957	7%
10	Region - Asia-Pacific	COP$17,037,325	0.50	COP$34,025,362	-14%
11	Baseline NYHA class I/ II	COP$17,431,831	0.44	COP$39,358,683	0%
12	Baseline NYHA III/ IV	COP$14,568,880	0.36	COP$40,131,639	2%
13	Baseline LVEF ≤ median	COP$16,255,758	0.44	COP$37,003,692	-6%
14	Baseline LVEF > median	COP$17,267,246	0.40	COP$42,704,220	8%
15	Baseline SBP ≤ median	COP$16,742,042	0.44	COP$38,178,311	-3%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
16	Baseline SBP > median	COP$16,701,096	0.40	COP$41,284,903	4%
17	Baseline eGFR < 60	COP$14,723,501	0.38	COP$38,328,033	-3%
18	Baseline eGFR ≥ 60	COP$17,870,382	0.45	COP$40,113,502	1%
19	Baseline NT-proBNP ≤ median	COP$19,106,429	0.43	COP$44,072,811	12%
20	Baseline NT-proBNP > median	COP$14,156,104	0.41	COP$34,363,742	-13%
21	Diabetes at baseline	COP$15,504,400	0.41	COP$37,790,398	-4%
22	No diabetes at baseline	COP$17,368,799	0.43	COP$40,397,763	2%
23	Hypertension at baseline	COP$16,434,013	0.41	COP$40,280,882	2%
24	No hypertension at baseline	COP$17,422,812	0.46	COP$37,897,548	-4%
25	Prior use of ACEI	COP$16,828,890	0.42	COP$39,823,524	1%
26	Prior use of ARB	COP$16,339,620	0.42	COP$38,503,390	-3%
27	Use of beta blocker at baseline	COP$16,906,269	0.42	COP$39,873,063	1%
28	No use of beta blocker at baseline	COP$14,295,688	0.41	COP$34,729,385	-12%
29	Use of MRA at baseline	COP$16,787,870	0.43	COP$38,637,083	-2%
30	No use of MRA at baseline	COP$16,642,863	0.41	COP$40,701,946	3%
31	≤ 1 year since diagnosis of HF	COP$18,810,155	0.46	COP$41,247,846	4%

#	Subgroup	Δ Costs	Δ QALYs	ICER	% change from full analysis set
32	1-5 years since diagnosis of HF	COP$16,326,639	0.42	COP$38,922,232	-2%
33	> 5 years since diagnosis of HF	COP$15,217,480	0.40	COP$38,405,313	-3%
34	Ischaemic aetiology	COP$16,087,182	0.40	COP$39,736,088	1%
35	Non-ischaemic aetiology	COP$17,676,386	0.45	COP$39,235,675	-1%
36	Prior atrial fibrillation at baseline	COP$15,661,181	0.39	COP$40,283,198	2%
37	No prior atrial fibrillation at baseline	COP$17,342,130	0.44	COP$39,134,254	-1%
38	Prior HF hospitalisation	COP$16,309,618	0.43	COP$38,311,417	-3%
39	No prior HF hospitalisation	COP$17,422,019	0.42	COP$41,600,894	5%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QALYs, quality-adjusted life years; SBP, systolic blood pressure.

7. Re-weighting of the PARADIGM-HF population in the UK setting

The PARADIGM-HF population is younger, with a higher proportion of males than the general UK heart failure population. The CPRD database was accessed to assess the generalisability of the PARADIGM-HF population to the UK heart failure population[22]. The objective of this cohort study was to generate evidence on burden of illness of HF using a real world NHS database (CPRD). The analysis allowed the identification of subjects with HFrEF to determine the generalisability of PARADIGM-HF to UK clinical practice. Subjects in PARADIGM-HF were generally younger, more likely to be male, and more likely to be current smokers than those in CPRD (Table 30).

These differences have consequences for estimating, amongst other things, the baseline mortality rate. Because cost-effectiveness is determined by absolute differences in costs and effects, this may affect the cost-effectiveness of sacubitril/valsartan in clinical practice. In order to provide estimates of cost-effectiveness more representative of clinical practice, several scenario analyses are included in which the cohort of subjects in PARADIGM-HF is sampled or weighted in such a way as to make them more generalisable. For the UK analysis, this requires over-sampling of older and female subjects.

Raking (or sample-balancing) adjusts sampling weights across subjects such that the marginal totals of the adjusted weights on specified characteristics agree with the corresponding totals for the population. All propensity-score methods assume that balance of the observed variables leads to balance across unobserved variables i.e. there are no unobserved confounding factors that remain unbalanced.

Table 30 presents baseline characteristics prior to and following raking. The weights generated are based on age, gender, current smoking status, prior stroke and eGFR <60 mL/min. The resulting distribution of subjects after weighting closely resembles that of the CPRD HFrEF cohort. These weights are used to reweight the estimated costs and effects across the PARADIGM-HF population.

Table 30: Comparison of PARADIGM-HF and CPRD characteristics and model characteristic after reweighting of subjects

Variable	PARADIGM-HF	CPRD	Re-weighted PARADIGM-HF
18–49 years	11	3†	3
50–54 years	9	3†	3
55–64 years	32	13†	12
65–69 years	16	10†	10
70–74 years	15	14†	14
75–84 years	17	35†	35
85+ years	1	22†	22
Mean age (SD)	63.8 (11)	74.8 (12)†	73.9 (11)
Gender (% female)	22	41†	41
Prior stroke (%)	8.6	5.2‡	5.2
eGFR <60 mL/min (%)	36.4	22.6‡	22.6
Current smoker (%)	14.4	8.2‡	8.2

Abbreviations: CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; HF, heart failure.

† New HF patients and LVSD within 6 months of HF diagnosis in CPRD, 2005-2013 (n=18,028)

‡ Characteristics of patients with HF and LVSD, based on CPRD-HES linked data set, 2005-2013, at index date (n=10,646)

The effect of re-weighting is to assume alternative baseline characteristics of the sampled cohort. Table 31 presents the results when the re-weighted population is run through the model.

Table 31: Cost-effectiveness results with the re-weighted population

Therapy	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ACEi	£12,869	4.251			
Sacubitril valsartan	£20,370	4.644	£7,501	0.393	£19,102

8. Inclusion of the PARADIGM-HF run-in phase

PARADIGM-HF contained two run-in phases, a two-week run-in phase for enalapril during which all patients took enalapril and a four-week run-in phase for sacubitril/valsartan during which all patients took sacubitril/valsartan.[23] These allowed patients to reach target doses of each drug and provided investigators with short-term safety data on sacubitril/valsartan. This led to a proportion of patients discontinuing the study prior to the randomised phase and these discontinuations are not captured in the model. During the enalapril run-in, 1,102 of 10,513 (10.5%) patients discontinued the study. During the sacubitril/valsartan run-in 977 of 9,419 (10.4%) patients discontinued the study.[2]

In order to assess whether these discontinuations will affect the cost-effectiveness of sacubitril/valsartan a scenario analysis has been performed using the UK model. This scenario accounts for the run-in phase by assuming that 10.5% of ACEi patients and 19.7% of sacubitril/valsartan patients will discontinue during the first cycle of the model. This scenario also accounts for discontinuation during the randomised phase and assumes discontinuation requires an outpatient contact, thus incurs a cost.

Table 32: Results of the scenario modelling the run-in phase

Component	ACEi	Sacubitril valsartan	Incremental
Primary therapy	£180	£4,852	£4,672
Background therapy	£607	£637	£30
Hospitalisation	£8,296	£7,992	-£303
HF management	£5,639	£5,918	£279
Adverse events	£102	£107	£4
Titration	£0	£262	£262
Total costs	**£14,881**	**£19,831**	**£4,949**
QALYs	**5.06**	**5.35**	**0.29**
ICER			**£17,246**

Table 33: Results of the scenario considering randomised phase discontinuation only

Component	ACEi	Sacubitril valsartan	Incremental
Primary therapy	£173	£7,046	£6,873
Background therapy	£607	£651	£45
Hospitalisation	£8,296	£7,834	-£461
HF management	£5,639	£6,054	£415
Adverse events	£102	£109	£6
Titration	£0	£262	£262
Total costs	**£14,830**	**£21,981**	**£7,151**
QALYs	**5.06**	**5.48**	**0.42**
ICER			**£17,082**

Table 32 presents the results of this scenario and Table 33 presents the results of the scenario where only randomised phase discontinuation is considered. Modelling the run-in phase is associated with a decrease in both incremental costs and incremental QALY and results in a small increase in the ICER. These results suggest that the inclusion of a run-in phase in unlikely to affect the cost-effectiveness of sacubitril/valsartan.

9. Comparison of sacubitril/valsartan with ARBs in the UK setting

Presented below are the results of an analysis comparing sacubitril/valsartan to ARBs in the UK setting. The same model structure was applied as in the base case and the efficacy of ARBs was defined relative to ACEi. There were assumed to be equally effective on reducing CV mortality and to have a rate ratio of 0.90 compared to ACEi for all-cause hospitalisation. The monthly cost of ARB was assumed to be £2.39 (one 100 mg tab and one 50 mg tab of candesartan is taken daily). Adverse event rates were assumed to be equal to those for sacubitril/valsartan.

Component	ARB	Sacubitril valsartan	Incremental
Primary therapy	£195	£8,836	£8,641
Background therapy	£607	£662	£55
Hospitalisation	£7,493	£7,697	£204
HF management	£5,639	£6,153	£514
Adverse events	£101	£110	£9
Titration costs	£0	£262	£262
Total costs	**£14,034**	**£23,720**	**£9,685**
QALYs	**5.07**	**5.58**	**0.52**
ICER			**£18,298**

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