National Institute for Health and Care Excellence

FINAL

Chronic heart failure in adults: diagnosis and management

Economic analysis report for chronic heart failure with reduced ejection fraction (HFrEF)

NICE guideline NG106

September 2025

Final

This economic analysis was developed by NICE

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HE1 Introduction

Chronic heart failure (CHF) is a clinical syndrome characterised by typical symptoms (e.g. breathlessness, fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, peripheral oedema), caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

Heart failure with reduced ejection fraction (HFrEF) is defined by a left ventricular ejection fraction (LVEF) ≤40% on imaging. It is often associated with systolic dysfunction due to ischaemic heart disease, hypertension, or dilated cardiomyopathy.

There are currently four pillars of pharmacological treatment for HFrEF (Rees, et al., 2023).

1. One of the following:
    - ACE inhibitor (ACEI),
    - Angiotensin receptor blocker (ARB) or
    - Angiotensin receptor-neprilysin inhibitor (ARNI)
2. Beta-blocker (BB)
3. Mineralocorticoid receptor antagonists (MRAs)
4. Sodium glucose cotransporter-2 inhibitor (SGLT2i)

NICE guideline NG106 recommends the use of ACEI and BB for people with HFrEF and the addition of MRA if people continue to have symptoms. ARNI is recommended as a replacement for ACEI in people who remain symptomatic, according to NICE TA388. SGLT2i is covered in NICE TA679 and NICE TA773, and is recommended as an option for people with symptomatic CHF despite optimised standard care.

Although the TAs currently define the pathway for people to be escalated to more pillars of treatment, it was suggested that initiating three or four pillars immediately after diagnosis could be cost-effective. Therefore, a health economic analysis was undertaken to assess the most cost-effective strategy of initiating people on quadruple therapy after a diagnosis of heart failure with reduced ejection fraction. Several alternative strategies that involve initiating people on a higher number of treatment pillars were compared to current practice, using real-world data from the INTEGRATE study and relative treatment effects from the guideline systematic review.

HE1.1 Decision problem

Table 1: Review questions

Research question	What is the most clinically and cost-effective first line pharmacological treatment approach (using beta-blockers, ACE inhibitors, angiotensin-receptor blockers, angiotensin receptor neprilysin inhibitor, mineralocorticoid receptor antagonists and SGLT2 inhibitors) in adults with chronic heart failure with reduced left ventricular ejection fraction?

Table 2: PICO for review question

Population	Adults diagnosed with heart failure due to left ventricular dysfunction with reduced ejection fraction
Intervention	Pharmacological agents in combination with each other or with standard background therapy including diuretics when indicated: • Angiotensin converting enzyme inhibitor (ACEI) • Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan)

	• Angiotensin receptor blocker (ARB) • Beta-blocker (BB) • Mineralocorticoid receptor antagonist (MRA) • SGLT2 inhibitor (Dapagliflozin or Empagliflozin) • Combinations of the above (e.g. ACEI/ARB/ARNI + BB + MRA + SGLT2i); including different initiation strategies

Comparator	• Different approaches to initiation (e.g., sequential introduction with up-titration of each agent in turn vs more rapid introduction of all initial treatments).
	• Other active treatments in combination with each other or with standard background therapy:
	  ○ Angiotensin converting enzyme inhibitor (ACEI)
	  ○ Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan)
	  ○ Angiotensin receptor blocker (ARB)
	  ○ Beta-blocker (BB)
	  ○ Mineralocorticoid receptor antagonist (MRA)
	  ○ SGLT2 inhibitor (Dapagliflozin or Empagliflozin)
	• Placebo + Usual CHF care or Usual CHF care alone

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • Cardiovascular mortality (time-to-event) • Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value) • Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported) • All cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study, but this will be downgraded for outcome indirectness • Adverse events (recorded as the number of people with at least one event, not the total number of events) • Withdrawal due to drug-related adverse events (dichotomous) • Acute kidney injury – serum creatinine rise of ≥50% over ≤7 days (dichotomous) • Hyponatraemia – serum sodium concentration <135 mmol/L (dichotomous) • Hyperkalaemia – serum potassium concentration ≥5.5 mmol/L (dichotomous) • Falls – number of participants with at least one event (not total number of events) (dichotomous

HE2 Methods

HE2.1 Model overview

The objective of these analyses was to compare the expected benefits, harms, and costs of treatments for people with HFrEF.

HE2.1.1 Population(s)

The population of the model was people with HFrEF, defined as an LVEF ≤40%. The model was run separately for two sub-populations:

1. People with HFrEF who can tolerate ACEI and are initiated to ACEI and BB
2. People with HFrEF who cannot tolerate ACEI and are initiated to ARB and BB

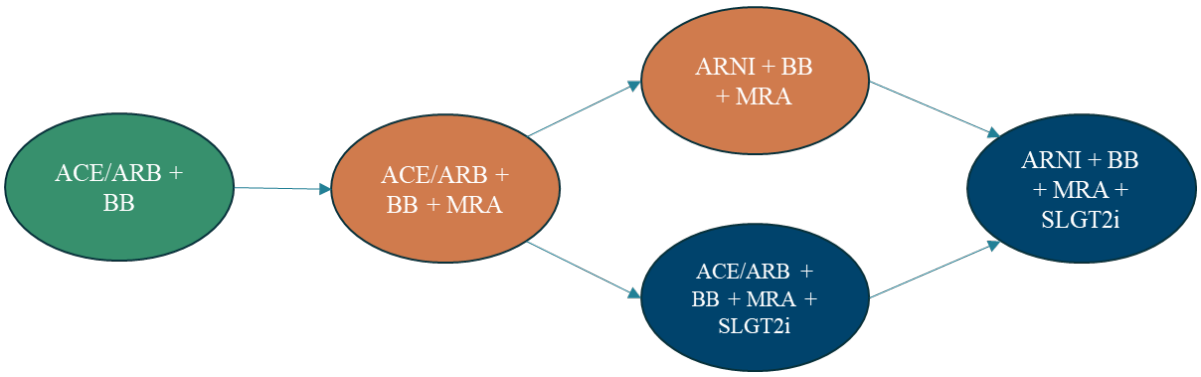
The population was stratified into two groups, as the committee recognised a potential additional benefit in switching people who cannot tolerate ACEI to ARNI, given that ARBs are known to offer less protection against all-cause mortality compared to ACEI.

HE2.1.2 Interventions

The model assessed the following treatment regimens:

1. **Current NICE pathway (Figure 1)**
    1. First-line: ACEI/ARB + BB
    2. Second-line: Add MRA
    3. Third-line: Replace ACEI/ARB with ARNI or add SGLT2i
    4. Fourth-line: ARNI + BB + MRA + SGLT2i

Figure 1: Current NICE pathway



Note: Green = two pillars, orange = three pillars, dark blue = four pillars

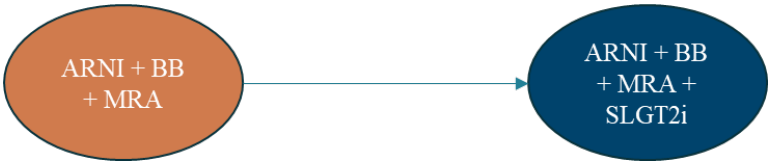
2. **Early MRA (Figure 2)**
    1. First-line: ACEI/ARB + BB + MRA
    2. Second-line: Replace ACEI/ARB with ARNI or add SGLT2i
    3. Third-line: ARNI + BB + MRA + SGLT2i

Figure 2: Early MRA strategy

Note: Orange = three pillars, dark blue = four pillars

3. **Early MRA and early ARNI (Figure 3)**
    1. First-line: ARNI + BB & MRA
    2. Second-line: Add SGLT2i

Figure 3: Early MRA and ARNI strategy



Note: Orange = three pillars, dark blue = four pillars

4. **Early MRA and early SGLT2i (Figure 4)**
    1. First-line: ACEI/ARB + BB + MRA + SGLT2i
    2. Second-line: Replace ACEI/ARB with ARNI

Figure 4: Early MRA and SGLT2

Note: Dark blue = four pillars

5. **Early MRA, early ARNI and early SGLT2i (Figure 5)**
    1. First-line: ARNI + BB + MRA + SGLT2i

Figure 5: Early MRA and early ARNI and SGLT2

Note: Dark blue = four pillars

The strategies align with the current NICE-recommended pathway and those of clinical importance identified by the committee. Strategies 4 and 5 are consistent with the European guidelines (McDonagh, et al., 2021).

HE2.1.3 Type of evaluation, time horizon, perspective and discount rate

A lifetime cost-utility analysis was conducted to reflect all important differences in costs and health outcomes between the interventions compared. Health outcomes were valued in terms of quality adjusted life years (QALYs) estimated by weighting the years of life remaining with a quality of life (utility) score, and the results were presented using incremental cost-effectiveness ratios (ICERs) that express the cost per QALY gained. Net health benefits (NHBs) at a threshold of £20,000 per QALY gained were also presented to provide greater interpretability of the model outputs.

The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in the United Kingdom.

All costs and QALYs were discounted at a rate of 3.5% per year in line with the NICE reference case. Costs are in 2024/2025 UK pounds.

HE2.2 Model structure

A cohort model was developed with a cycle length of 3 months and a lifetime horizon. A half-cycle correction was applied to account for individuals moving between health states within each model cycle, not necessarily at the start or end of each cycle.

A systematic literature review and a review of published NICE TAs was conducted to find relevant economic evidence. Three NICE technology appraisals (TAs) (TA388, TA679 and TA773) were identified for the HFrEF population. All TAs used a Markov model structure, and the majority of models identified in the literature also used this approach. TA388 used a simple Markov model with two health states: alive and dead. A similar model structure was adopted in the current model, where people are either in an alive state (characterised by the treatment strategy they are receiving) and a dead health state. At the time of development, this was the first economic model relevant to the NHS population to compare different strategies for the sequencing of the four pillars of heart failure treatment:

1. ACEI or ARB or ARNI
2. BB
3. MRA
4. SGLT2i

The model allowed people to experience hospitalisations and adverse events within the treatment health states, after which they either remained in the same treatment state, escalated to the next line of treatment, or transitioned to the dead state.

The model included costs associated with treatment, titration, monitoring, hospitalisations, and the management of adverse events. Further information on costs is provided in Section HE2.3.5.

QALYs were accrued by weighting the time spent in each treatment state by the corresponding utility value for that state and adjusting for the utility losses (disutilities) associated with hospitalisations and treatment-related adverse events. An annual utility decrement was also included using data from the trials. Further information on QALYs is provided in Section HE2.3.4.

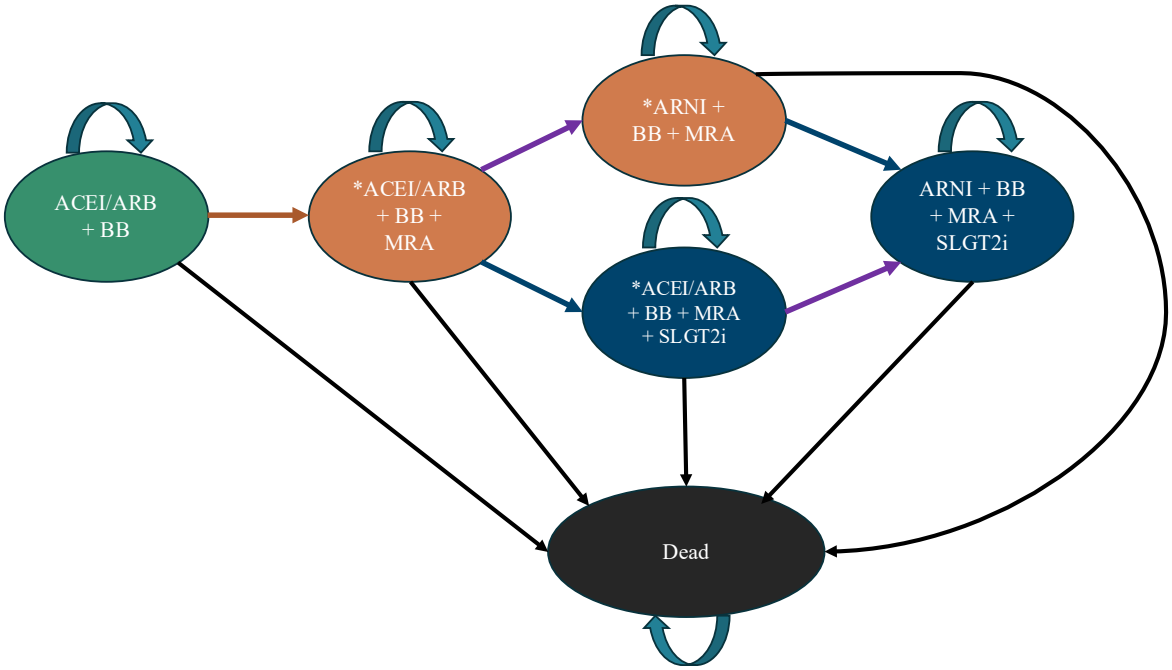
HE2.2.1 Strategies

For each treatment strategy, at the end of a cycle, people either remained on the same line of treatment, escalated to the next line of treatment, or moved to the dead state. Once the final line of treatment was reached, people continued receiving these treatments until they moved to the dead state.

People could experience hospitalisations (either heart failure related or related to cardiovascular disease), adverse events or death in each state, with probabilities depending on the treatment they were receiving and the model cycle.

Figure 6 presents the Markov diagram of the current NICE pathway, in which people started treatment with either an ACEI or ARB (ACEI in the base-case analysis) in combination with BB. When treatment escalation was required to better manage symptoms, an MRA was added to the treatments of ACEI or ARB and BB. In the model, the transition from the first to the second health state was informed by data derived from the INTEGRATE study. People then escalated further by either adding an SGLTi to the other drugs or replacing the ACEI or ARB with an ARNI, in line with the current TA recommendations for SGLT2 inhibitors (TA679 and TA773). Escalation to either ARNI or SGLT2i was based on the INTEGRATE study (see HE2.3.1.1). Finally, people moved to the last health state when either an ARNI or SGLT2i was added to their treatment regimen. Sets of tunnel states were included to ensure that time to escalation to four pillars and ARNI started from the time a person receives three pillars (see HE2.2.2).

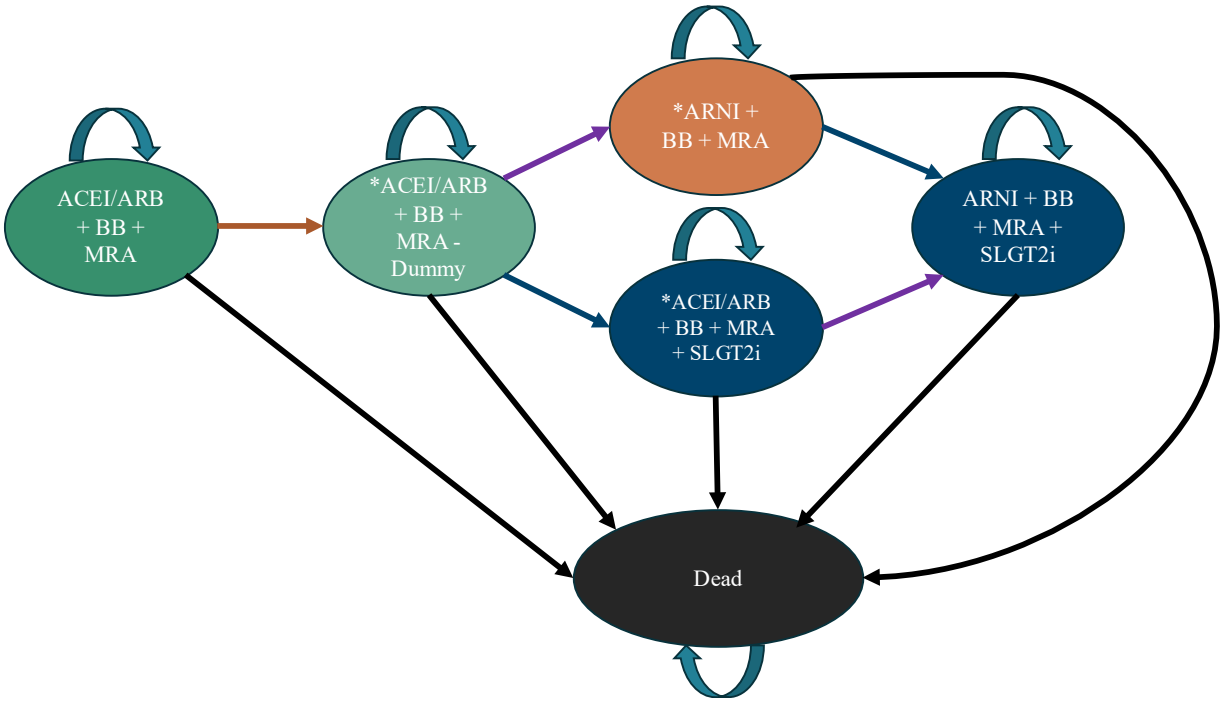
Figure 6: Current NICE pathway – Markov Diagram



Legend: Orange arrow = transition from two to three pillars, blue arrow = transition from three to four pillars, purple arrow = transition from ACEI/ARB to ARNI, black arrow = transition to dead state; states with * include tunnel states

Figure 7 illustrates the Markov diagram 'the early MRA strategy' in which people were assumed to start with three pillars of treatment: an ACEI or ARB, BB and MRA. A dummy state was added after the "ACEI/ARB + BB + MRA" state to ensure that people would escalate to ARNI or to four pillars earlier than in current practice, which would be unrealistic (see HE2.2.2).

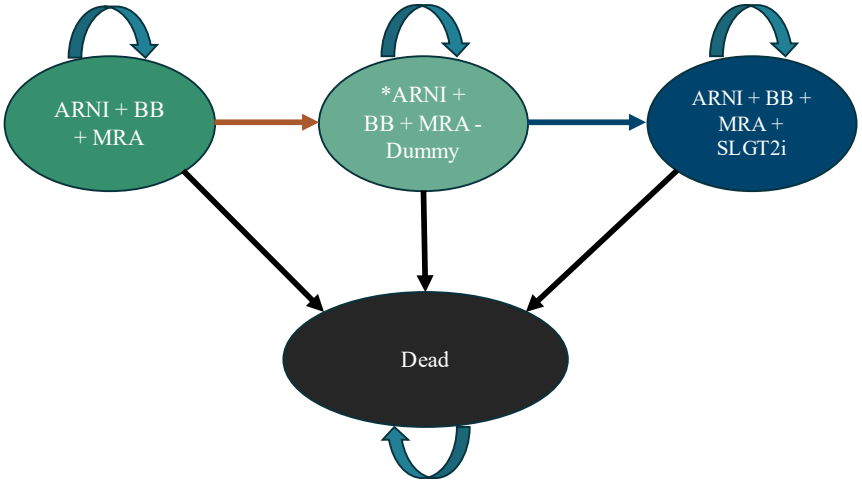
Figure 7: Early MRA – Markov diagram



Legend: Orange arrow = transition from two to three pillars, blue arrow = transition from three to four pillars, purple arrow = transition from ACEI/ARB to ARNI, black arrow = transition to dead state; states with * include tunnel states

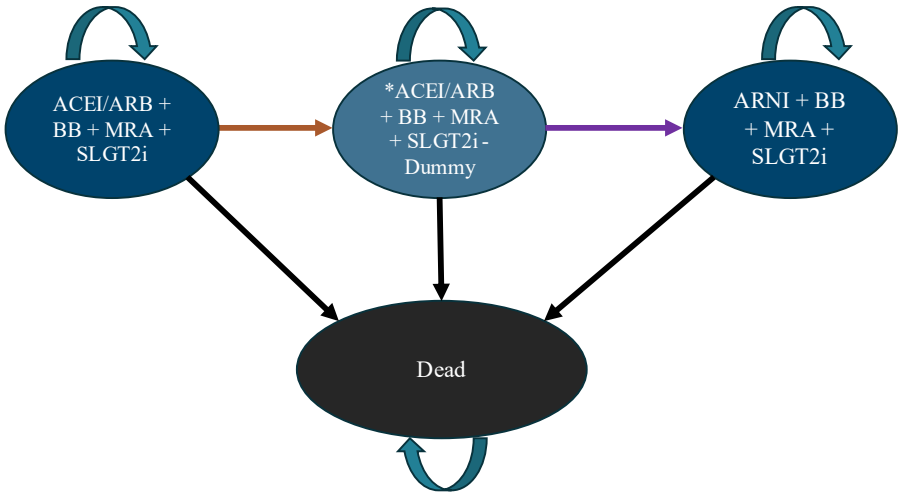
Strategies 3 (Figure 8) and 4 (Figure 9) assumed that all people start with an ARNI and SGLT2i, respectively. These people have only one line of escalation to receive either an SGLT2i or ARNI. As with the previous strategy, dummy staties were included to ensure that the time to escalation would be similar to the one observed in current practice.

Figure 8: Early MRA and ARNI – Markov diagram



Legend: Orange arrow = transition from two to three pillars, blue arrow = transition from three to four pillars, black arrow = transition to dead state; states with * include tunnel states

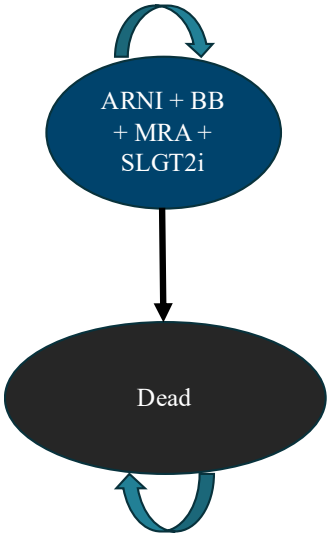
Figure 9: Early MRA and SGLT2 – Markov diagram



Legend: Orange arrow = transition from two to three pillars, purple arrow = transition from ACEI/ARB to ARNI, black arrow = transition to dead state; states with * include tunnel states

In strategy 5, people were assumed to begin treatment with all four pillars, including an ARNI rather than ACEI or ARB. In this strategy, people remained in this state until they moved to the dead state.

Figure 10: Early MRA and early ARNI and SGLT2i – Markov diagram



Legend: Black arrow = transition to dead state; states with * include tunnel states

HE2.2.2 Escalation of treatment

The probability of receiving the next pillar of treatment or having ACEI/ARB substituted with an ARNI was simulated using parametric distribution curves based on Kaplan-Meier curves developed by our collaborators from the INTEGRATE team from the London School of Hygiene & Tropical Medicine (LHSTM) using data from an analysis conducted in the OpenSAFELY data, a dataset of GP records of the entire population of England (Curtis, et al., 2022) (Section HE2.3.1.4). These curves were applied to the usual care strategy to reflect how individuals typically progress through different lines of treatment in current clinical practice.

Following escalation to three treatment pillars (ACEI/ARB, BB and MRA), the probability of further escalation depended on the time spent in this state. To account for this time-

dependency, a series of tunnel states were implemented, allowing people to transition to the next line of therapy based on the number of cycles spent in the three-pillars state.

In the model, escalation to ARNI and escalation to the fourth pillar (SGLT2i) were treated as independent events. This means that initiating one does not affect the probability of initiating the other as both are determined solely by the time elapsed since entry into the three-pillars state.

In strategies where people were initiated to three treatment pillars at diagnosis, dummy tunnel states were used to align the timing of escalation to the fourth pillar or ARNI with the timing that would have occurred if they had initially started on only two pillars. This approach was used to prevent people starting with three pillars from escalating to ARNI or SGLT2i more quickly than in current practice, which would be unrealistic, as initiating more treatments upfront would likely delay further escalation.

HE2.3 Model parameters

Identifying sources of parameters

With the exception of the treatment effects which came from the systematic review conducted for this research question (see below), parameters were identified through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' (Kaltenthaler, et al., 2011)). Searches were conducted in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and Google Scholar.

When searching for quality of life, resource-use and cost parameters in particular, searches were conducted in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED), for example.

The committee was asked to identify papers of relevance. The parameters used in the published cost-utility analyses identified in our systematic review were reviewed (see evidence review A: medicines for heart failure with reduced ejection fraction); during the review, additional articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model were also included.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, data was obtained from unpublished sources; further details are provided below.

Selecting parameters

The overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should come from the UK population).
- All other things being equal, more powerful studies were preferred (based on sample size and/or number of events).
- Where there was no reason to discriminate between multiple possible sources for a given parameter, consideration was given to quantitative synthesis (meta-analysis), to provide a single summary estimate.

HE2.3.1 Baseline characteristics and rates

HE2.3.1.1 INTEGRATE analysis

Baseline characteristics, including age, sex distribution, hospitalisation and mortality rates were informed from a collaborative study of contemporary treatment of heart failure and the impact of COVID upon this. Results were stratified by "pillars" of treatment for HFrEF received (ACEI/ARB/ARNI, BB, MRA, SGLT2i). This was conducted by the INTEGRATE team at LSHTM using the OpenSAFELY platform (Curtis et al., 2022). Primary care records managed by the GP software provider, TPP were linked to the Office of National Statistics (ONS) mortality data through OpenSAFELY, and a cohort of people with HFrEF was identified with outcomes reported as rates per person-year. Although the study overall focussed on the impact of COVID and, for this health economic analysis, only those occurring after the COVID-19 pandemic were included.

Full data will be presented as part of a peer-reviewed publication, currently being prepared.

HE2.3.1.2 Hospitalisation rates

Table 3 shows the hospitalisation rates of people receiving different pillars of treatment for heart failure. The risk of being hospitalised is higher during the first years after diagnosis, but drops to a fairly constant rate around 4-5 years after the diagnosis. Being on more pillars seem to be associated with a lower risk of being hospitalised, particularly in the first year after diagnosis, due to the treatment effect of the medications.

Table 3: Heart failure hospitalisation rates per person-year by number of pillars

Year from diagnosis	Two pillars	Three pillars	Four pillars
1	0.161	0.135	0.136
2	0.076	0.075	0.093
3	0.062	0.064	0.080
4	0.058	0.065	0.080
5	0.058	0.066	0.091

However, the committee acknowledged that people on different pillars were not randomised as prescribers consider different patient characteristics before recommending a treatment. To address this, the treatment effects estimated in the clinical review were reversely applied to the hospitalisation risk of people on three or four pillars to extrapolate the risk they would show if they were only on two pillars (Table 4). After the adjustment, people prescribed with more medicines were found to have a higher risk of hospitalisation, suggesting that they have, on average, a more severe form of HFrEF. A pooled rate across the adjusted population was estimated and used as the baseline hospitalisation rate in the base-case scenario. This pooled rate should reflect the average risk of people diagnosed with HFrEF before they are initiated to any treatment. In the scenario analysis, the observed risk of those on two pillars was used (Section HE2.5.1).

Table 4: Heart failure hospitalisation rates per person-year by number of pillars (adjusted)

Year from diagnosis	Two pillars	Three pillars (adjusted)	Four pillars (adjusted)	Pooled
1	0.161	0.231	0.365	0.194
2	0.076	0.129	0.250	0.102
3	0.062	0.109	0.214	0.085
4	0.058	0.110	0.215	0.083

Year from diagnosis	Two pillars	Three pillars (adjusted)	Four pillars (adjusted)	Pooled
5	0.058	0.112	0.244	0.085

Beyond the fifth year, it was assumed that the rate would remain constant, as suggested by the data from years 3, 4, and 5 after diagnosis.

In addition, INTEGRATE data was used to estimate the rate of heart failure related accident and emergency attendances, which were assumed to be affected by treatment in the same way as hospitalisations. INTEGRATE data was also used to estimate rates for CVD hospitalisations, that were pooled across two to four pillars as it was assumed that heart failure drugs would not reduce the probability of CVD hospitalisations. These were used to estimate a background healthcare cost of the population

Table 5: HF A&E and CVD hospitalisation rates per person-year

Year from diagnosis	CVD hospitalisation rate (95% CI)	HF A&E attendance rates (95% CI)
1	0.384 (0.368 to 0.400)	0.086 (0.080 to 0.092)
2	0.198 (0.188 to 0.209)	0.044 (0.040 to 0.048)
3	0.159 (0.15 to 0.168)	0.040 (0.036 to 0.043)
4	0.154 (0.145 to 0.162)	0.038 (0.035 to 0.042)
5 onward	0.151 (0.142 to 0.159)	0.036 (0.033 to 0.039)

Note: All values are mean, 95% confidence intervals are shown in parentheses

HE2.3.1.3 Mortality rates

Table 7 shows the mortality rates per person-year of people on two, three and four pillars. On average, mortality follows a “U” pattern, peaking in the first year after diagnosis, declining around year 2 and 3, and then again increasing in year 4 and 5.

Table 6: Mortality rates per person-year by number of pillars

Year from diagnosis	Two pillars	Three pillars	Four pillars
1	0.104	0.074	0.052
2	0.103	0.072	0.065
3	0.099	0.081	0.067
4	0.103	0.082	0.070
5	0.107	0.082	0.078

The committee noticed that the choice of medications to prescribe after diagnosis is not random, as people with less comorbidities, thus a lower mortality risk, were more likely to receive more drugs compared with people with comorbidities already on multiple medications. Therefore, the rates in Table 7 and Table 8 were re-adjusted using the mortality hazard ratios from the clinical review to estimate the mortality risk of people on three or four pillars had they received only two pillars instead (Table 8). Table 8 shows that, even after the adjustment, people on three or four pillars exhibit a mortality much lower than those on two pillars, particularly during the first 2 years after diagnosis. In the base-case scenario, the pooled rates across the adjusted (three and four pillars) and non-adjusted populations (two pillars) were used, but a scenario analysis using the observed two pillars rate was included (Section HE3.3.1).

Table 7: Mortality rates per person-year by number of pillars (adjusted)

Year from diagnosis	Two pillars	Three pillars (adjusted)	Four pillars (adjusted)	Pooled
1	0.104	0.090	0.078	0.098
2	0.103	0.087	0.097	0.097
3	0.099	0.098	0.099	0.099
4	0.103	0.099	0.105	0.102
5	0.107	0.100	0.115	0.105

HE2.3.1.4 Treatment escalation

Two Kaplan-Meier curves were generated using the INTEGRATE data describing time-to-escalation to three and four pillars (Figure 11: Parametric lognormal survival curve (red) and observed survival curve – escalation from two to three pillars Figure 11 and Figure 12). These curves showed that most escalations occur within the first year after the previous prescription, with around 50% and 60% of individuals being escalated to the next pillar from two and three pillars, respectively.

The numerical data points behind the Kaplan-Meier curves were extracted using WebPlotDigitizer (Rohatgi) and approximated patient-level data was reconstructed using the methodology outlined in Guyot (Guyot, et al., 2012) 2012 and Wei 2017 (Wei, et al., 2017). Several parametric survival curves were fitted to the data using the “survival” package of R studio with the purpose of extrapolating the probability of escalation beyond the last observed follow-up time. The Aikake Information Criterion (AIC) and Bayesian Information Criterion (AIC) are shown in Table 9. The lognormal curve had the lowest AIC and BIC for both survival curves andwas chosen for this analysis.

Table 8: AIC and BIC of six parametric curve fits for the escalation to three and four pillars

Parametric curve	Escalation from two to three pillars		Escalation from three to four pillars	
	AIC	BIC	AIC	BIC
Weibull	102800	102818	40620	40637
Lognormal	**97447**	**97465**	**37925**	**37941**
Exponential	144033	144042	69993	70001
Gompertz	110801	110818	52974	52990
Loglogistic	99947	99965	39208	39224
Gamma	105529	105547	42457	42474

Note: AIC = Aikake Information Criterion; BIC = Bayesian Information Criterion

Figure 11 and Figure 12 show the two parametric curves compared with the observed Kaplan-Meier curves.

Figure 11: Parametric lognormal survival curve (red) and observed survival curve – escalation from two to three pillars

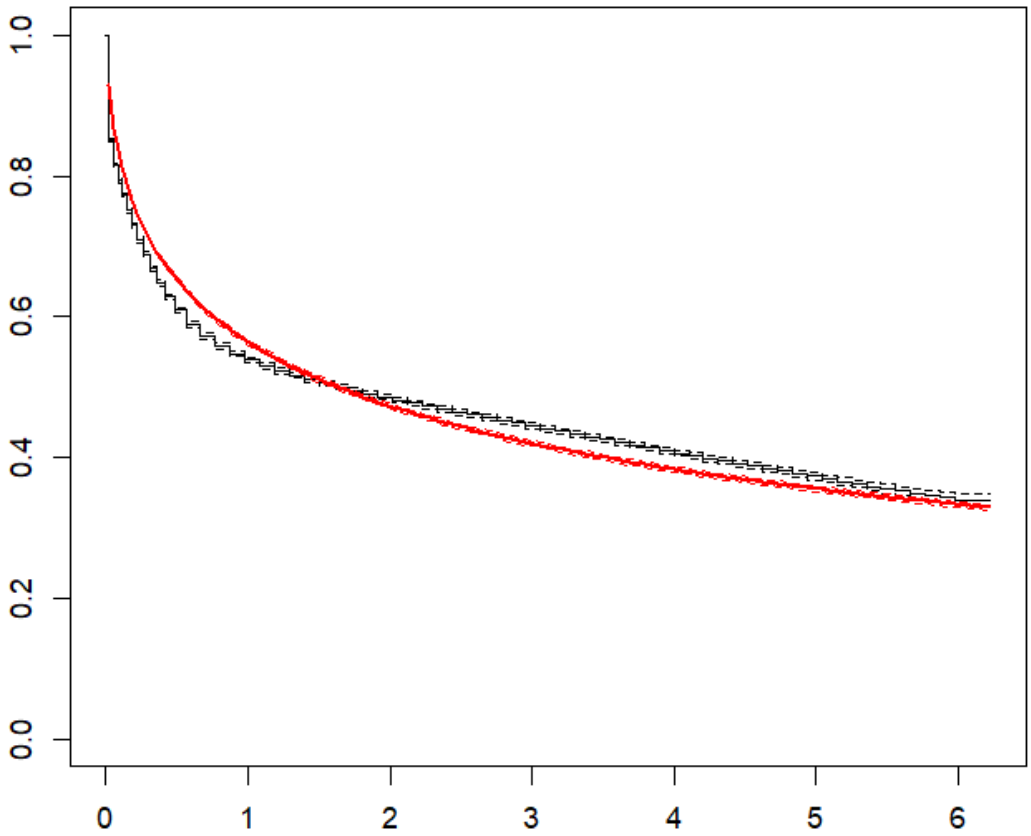
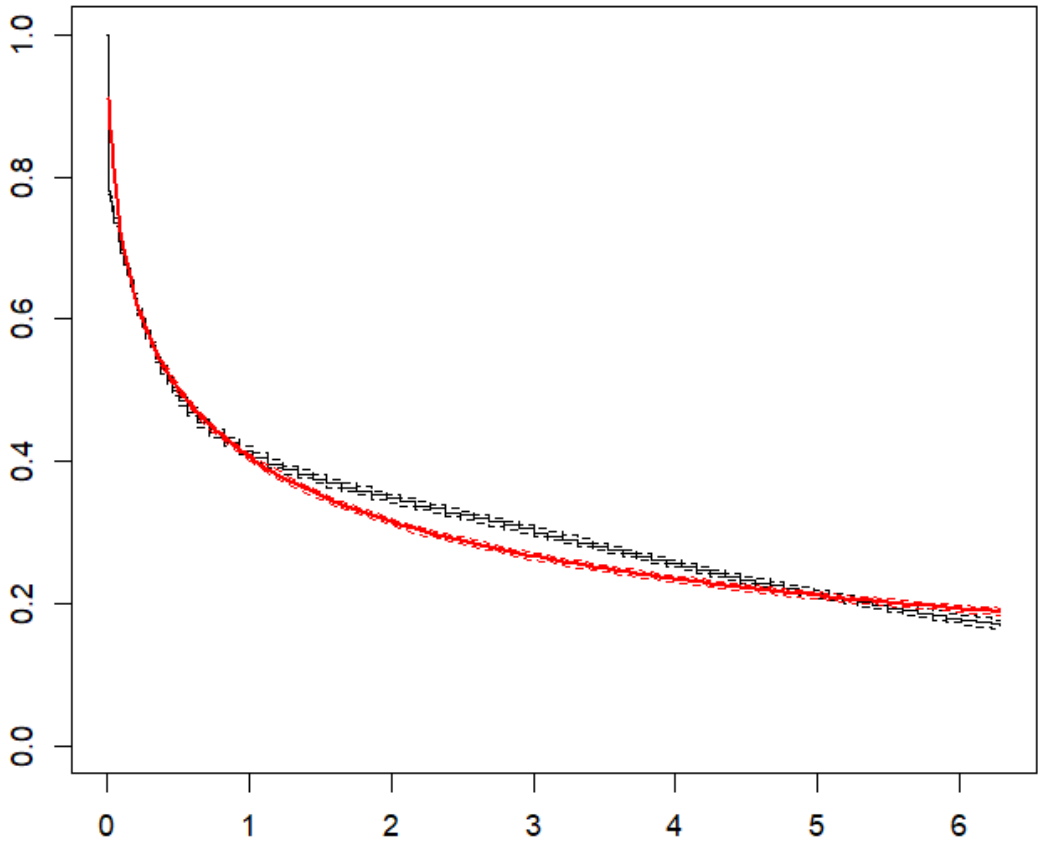


Figure 12: Parametric lognormal survival curve (red) and observed survival curve – escalation from two to three pillars



The INTEGRATE study did not include a time-to-event analysis on switching from ACEI/ARB to ARNI but prevalence data showed that around a quarter of people were on ARNI one year after the diagnosis. Assuming that escalation to ARNI follows a similar pattern to the transition from two to three and four pillars, the scale parameter of the lognormal curve for escalation from two to three pillars was adjusted to ensure that approximately a quarter of people would be on ARNI by year 1. This new curve was then used to extrapolate long-term switching to ARNI.

HE2.3.2 Main treatment effects

The model uses relative treatment effects identified in the guideline update's effectiveness review (evidence review A: medicines for heart failure with reduced ejection fraction). The main treatment effects in the model were all-cause mortality (Table 10) and hospitalisation for heart failure (Table 11). A quality of life benefit was also captured for each treatment (Section HE2.3.4).

Table 9: Relative treatment effects - All-cause mortality

Comparison	Relative effect (95% CI)	Reference
ACEI/ARB + BB + **MRA** vs ACEI/ARB + BB	HR: 0.76 (0.62 to 0.93)	(Zannad, et al., 2011)
ACEI/ARB + BB + MRA + **SGLT2i** vs ACEI/ARB + BB + MRA	HR: 0.87 (0.77 to 0.98)	Clinical review (McMurray, et al., 2019, Packer, et al., 2020)

Comparison	Relative effect (95% CI)	Reference
ARNI + MRA + BB vs **ACEI** + MRA + BB	HR: 0.84 (0.76 to 0.93)	Clinical review (McMurray, et al., 2014)
ARB + MRA + BB vs **ACEI** + MRA + BB	RR: 1.07 (0.98 to 1.16)	(Park, et al., 2023)

Note: All values are mean, 95% confidence intervals are shown in parentheses

Table 10: Relative treatment effects - Hospitalisation for heart failure

Comparison	Relative effect (95% CI)	Reference
ACEI/ARB + BB + **MRA** vs ACEI/ARB + BB	HR: 0.60 (0.50 to 0.72)	Clinical review (Asakura, et al., 2020, Tsutsui, et al., 2018, Zannad et al., 2011)
ACEI/ARB + BB + MRA + **SGLT2i** vs ACEI/ARB + BB + MRA	HR: 0.70 (0.63 to 0.78)	Clinical review (McMurray et al., 2019, Nassif, et al., 2019, Packer et al., 2020)
ARNI + MRA + BB vs **ACEI** + MRA + BB	HR: 0.80 (0.72 to 0.90)	Clinical review (McMurray et al., 2014)
ARB + MRA + BB vs **ACEI** + MRA + BB	RR: 1	Assumed

Note: All values are mean, 95% confidence intervals are shown in parentheses

The committee acknowledged that although ARB might not be superior to ACEI in terms of preventing hospitalisations, it is associated with a worse mortality outcome. As such, ARNI could potentially be more cost-effective when given to a population using an ARB compared to those using ACEI. To adjust the mortality of those on ACEI, a network meta-analysis by Park et al. 2023 was used. The analysis showed that ACEI was superior to ARB in reducing mortality (RR=1.07), but not in reducing heart failure hospitalisations (RR=1.02). Therefore, the committee agreed to include the mortality treatment effect from the NMA and assumed no difference in hospitalisation rates.

HE2.3.3 Drug-related adverse events

Baseline incidence of hyperkalaemia, acute kidney injury and falls were estimated as part of the INTEGRATE study and the guideline systematic review provided the relative treatment effects (evidence review A: medicines for heart failure with reduced ejection fraction). Where such evidence was not available, adverse event rates were taken from the relevant TA model report.

For the baseline rates of adverse events, the rates per person reported in the placebo arm of the EMPEROR-Reduced trials were used. These represent the rates of adverse events with ACEI, BB and MRA (Table 12). For hyperkalaemia, cough and angioedema, the probabilities reported from other sources were converted into rates.

Table 11: Incidence of drug-related adverse events: ACEI+BB+MRA

Adverse event	Incidence	Reference
Hyperkalaemia	0.106	(Anker, et al., 2021)

Adverse event	Incidence	Reference
Acute Kidney injury	0.090	Tafazzoli/Emperor reduced trial (Tafazzoli, et al., 2023)
Volume depletion	0.088	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Hepatic injury	0.038	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Hypotension	0.077	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Hypoglycaemic events	0.013	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Fracture	0.019	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Urinary tract infection	0.038	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Genital infection	0.005	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Cough	0.076	(McMurray, et al., 2018)
Angioedema	0.001	(McMurray et al., 2018)

Differences in the adverse events rates across the treatments were extracted from various sources, either as hazard ratios or risk ratios, and applied to the baseline rates for people on ACEI, BB and MRA (Table 13). When applied to rates, risk ratios were first converted into hazard ratios using mortality data reported in the trials. An annual rate of 0.001 for diabetic ketoacidosis (DKA) was applied for SGLTi as reported in the DAPA-HF clinical trial (McMurray, et al., 2019), since this adverse event only applies to SGLTi.

Table 12: Adverse events – differences across treatments

Adverse event	Remove MRA (HR)	Add SGLT2i (HR)	Add ARNI (RR)
Hyperkalaemia	0.453	0.887	0.885
Acute Kidney injury	1.091	0.525	0.951
Volume depletion	0	1.057	1
Hepatic injury	0	0.896	1
Hypotension	0.810	1.069	1.910
Hypoglycaemic events	0	0.960	1
Fracture	0	1.063	1
Urinary tract infection	0	1.098	1
Genital infection	0	2.604	1
Cough	1	1	0.793
Angioedema	0	1	2.012
Source	(Zannad et al., 2011)	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)	(McMurray et al., 2018)

HR=hazard ratio; RR=risk ratio

The adverse event profile for ARB was assumed to be similar to ACEI with the exception of cough, which is expected to be less frequent with ARB, and was assumed to be the same as ARNI in the model. The committee noted the importance of hyponatremia, particular as a prognostic factor and a consideration in treatment decisions. However, hyponatremia was not included in the model as it was not reported in the clinical trials or the TA models, and the

committee deemed the rates observed in the INTEGRATE data to be unrealistically low, most likely due to under-reporting.

HE2.3.4 Quality of life

Differences in health-related quality of life across treatments were commonly reported as differences in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS). This is a HF-specific score ranging from 0 to 100, with higher scores indicating better health status. Table 14 shows the values used in this analysis.

Some RCTs comparing SGLT2i and ARNI reported changes in KCCQ-OS, which were subsequently meta-analysed. Overall, the results suggest that SGLT2i and ARNI only slightly improve quality of life compared with placebo.

There were no trials in HFrEF populations that assessed quality of life differences between receiving MRA and those receiving placebo. Therefore, the estimate from the FINEARTS-HF trial, which involved people with mildly reduced ejection fraction (HFmrEF), was used instead. This trial also showed only a very small improvement in quality of life associated with the treatment.

Table 13: KCCQ-OS changes across treatments

Intervention	Trial population	Change in KCCQS-OS (intervention - comparison)	Source
SGLT2i + Usual care vs Placebo + Usual care (ACEI + BB + MRA)	HFrEF	+1.70 (1.67 to 1.73)	Pairwise meta-analysis (fixed effects)(Abraham, et al., 2020), (Butler, et al., 2021), (Nassif et al., 2019), (Jensen, et al., 2021)
ARNI + Usual care vs ACEI/ARB + Usual care (BB + MRA)		+1.68 (0.71 to 2.65)	Pairwise meta-analysis (fixed effects) (McMurray et al., 2014), (Tsutsui, et al., 2021)
MRA + Usual care vs Placebo	HFmrEF	+1.39 (-0.19 to 2.97)	(Docherty, et al., 2025)

Note: All values are mean, 95% confidence intervals are shown in parentheses

As NICE reference case recommends using utility values measured with the EQ-5D-3L, the values had to be mapped accordingly. To achieve this, the mapping algorithm developed by (Thomas, et al., 2021) was used and adjusted to reflect UK population preferences. Two different mapping models were applied in this analysis:

- **A linear model**, where KCCQ-OS scores were directly converted into EQ-5D values using the algorithm.
- **A non-linear model,** where a distribution of KCCQ-OS scores was first generated using a truncated normal distribution, then converted into EQ-5D values and averaged. This approach was recommended by the authors((Thomas et al., 2021) to account for the potential non-linearity in the relationship between EQ-5D and KCCQ-OS.

The Paradigm-HF trial (Lewis, et al., 2017) reported quality of life using both the KCCQ-OS and EQ-5D-3L, making it an ideal candidate for testing the face validity of the two mapping models (Table 15).

Table 14: Observed and mapped EQ-5D-3L in PARADIGM-HF trial

Source	Observed	Mapped – Linear model	Mapped – Non-linear model
PARADIGM-HF – baseline EQ-5D-3L	0.78	0.76	0.73

The linear model produced EQ-5D-3L values closest to the observed data and was therefore chosen for the base-case analysis. A scenario using the non-linear model was included in the scenario analysis. Table 16 shows the values used in the model.

Table 15: Observed and mapped EQ-5D-3L in PARADIGM-HF trial

Source	Change in EQ-5D-3L – linear model	Change in EQ-5D-3L – non-linear model
SGLT2i + Usual care vs Placebo + Usual care (ACEI + BB + MRA)	+0.013	+0.008
ARNI + Usual care vs ACEI/ARB + Usual care (BB + MRA)	+0.012	+0.007
MRA + Usual care vs Placebo	+0.010	+0.008

No trial reported the improvement in quality of life resulting from the simultaneous use of ARNI and SGLT2i, so the highest observed improvement relative to SGLT2i (+0.013) was used in the base-case scenario. In a scenario analysis, the hypothesis that the QoL benefits of ARNI and SGLT2i were addictive (0.013 + 0.012 = 0.025) was tested (Section HE2.5.1).

Hospitalisations in this analysis were considered as one-time events, each incurring a fixed cost and a utility decrement. In addition, an annual utility decrement was applied each year to reflect the natural decline in health due to ageing (Table 17). The values used in NICE TA773 were used in the base-case scenario, with alternative values from different sources tested in the scenario analysis.

Table 16: QALYs decrement used in the model

	QALYs decrement	Source
Hospitalisation	0.019 (0.015 to 0.023)	NICE TA773
Annual utility decrement	0.008 (0.006 to 0.010)	(Berg, et al., 2015)

Note: All values are mean, standard errors are reported in parentheses

Some adverse events (AEs) were associated with a short-term (1 month) EQ-5D reduction. These are listed in Table 18 along with their sources. QALYs decrements were calculated by multiplying the EQ-5D-3L decrements by the assumed duration of the event.

Table 17: EQ-5D-3L decrements with adverse events – 1 month

Adverse events	EQ-5D-3L decrement	Source
Hyperkalaemia	0	Assumed based on clinical consensus
Acute Kidney injury	0.010 (0.012)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Volume depletion	0.018 (0.014)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Hepatic injury	0.016 (0.019)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Hypotension	0.025 (0.003)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)

Adverse events	EQ-5D-3L decrement	Source
Hypoglycaemic events	0.048 (0.033)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Diabetic ketoacidosis	0	NICE TA679
Fracture	0.165 (0.036)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
UTI	0	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Genital infection	0.058 (0.039)	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Cough	0.070 (0.07)	NICE TA388
Angioedema	0	Assumed based on clinical consensus

Note: All values are mean, standard errors are reported in parentheses

HE2.3.5 Cost and healthcare resource use identification, measurement and valuation

HE2.3.5.1 Medicines – acquisition and titration costs

The average cost of each class of drugs across the different formulation was estimated using NHS drug tariff and the Prescription Cost Analysis (Table 19).

Table 18: Cost of drug classes

Drug class	Weighted average Cost for 3 months	Target dose and weights
ACE	£5.47	Enalapril maleate 2.5mg 4% Ramipril 1.25mg 64% Lisinopril 22% Perindopril-erbumine 10%
ARB	£5.17	Candesartan cilexetil 4mg 18% Losartan 82%
ARNI	£298.59	Sacubitril with Valsartan 97/103mg bd
BB	£3.12	Bisoprolol fumarate 91% Carvedilol 8% Nebivolol 1%
MRA	£10.53	Eplerenone 28% Spironolactone 72%
SGLT2i*	£119.33	Dapagliflozin or Empagliflozin

Source=NHS Drug tariff(NHS Business Services Authority, 2025) and NHS Prescription cost analysis(NHS Business Services Authority, 2024)
* Dapagliflozin's patent was ruled invalid in the UK (July 2025), so the average cost of SGLT2is will decrease in future as generics enter the market.

To estimate the cost of titration the following assumptions were made:

- ACEI, ARB, BB and MRAs are initiated by a GP (assuming a 15-minute consultation).
- ARNI and SGLT2i are initiated during a cardiology outpatient visit.
- All subsequent titration visits are conducted by a nurse, assumed to be Band 7 in the base-case scenario, with each visit lasting 30 minutes.

- The number of titration visits is based on the number of dosing steps plus one follow-up visit (Table 20).
- For multiple concurrent treatments, the total number of titration visits is aligned with the treatment requiring the greatest number of visits.
- At each titration visit, a biochemical test (DAPS PATH04) is performed. An additional test is conducted at the initiation of therapy, except for SGLT2 inhibitors, which require two instead (biochemistry and HBA1c)

In the sensitivity analyses the following scenarios were tested:

- A low number of titration visits is required for each treatment.
- A high number of titration visits is required for each treatment.
- ARNI and SGLT2i are initiated by a GP.
- A Band 6 or Band 8a nurse is required for titration.

Table 19: Drugs initial and target dosage

Drug class	Drug	Daily dose at initiation	Target dose & steps	Number of visits for initiation and titration – Base-case (min, max)
ACEI	e.g. Ramipril	1.25mg	Increased if tolerated to 10 mg daily in 1–2 divided doses, increase dose gradually at intervals of 1–2 weeks	6 (3,10)
ARB	e.g. Losartan	12.5mg	Increased if tolerated to up to 150 mg once daily, doses to be increased at weekly intervals	6 (4,10)
BB	e.g. Bisoprolol fumarate	1.25mg	• 2.5 mg for 1 week • 3.75 mg for 1 week • 5 mg for 4 week • 7.5 mg for 4 weeks • 10 mg once daily	5 (4,5)
MRA	Eplerenone/ Spironolactone	25mg	50mg within 4 weeks	3 (2,3)
ARNI (instead of ACEI/ARB)	Sacubitril with Valsartan	24/26mg twice daily for 3-4 weeks	49/51mg twice daily for 3–4 weeks, then increased if tolerated to 97/103 mg twice daily	3 (3,4)
SGLT2i	Dapagliflozin/ Empagliflozin	10mg	10mg	2 (1,2)

Table 20: Healthcare staff and cost

Healthcare professional	Time (minutes)	Cost
GP	15	£74.10
Nurse Band 6	30	£32.00
Nurse Band 7	30	£37.00

Healthcare professional	Time (minutes)	Cost
ANP/Pharmacist Band 8a	30	£41.00
Specialist visit (cardiology)	-	£186.15

Source = PSSRU and NHS cost collection 2023/2024

Based on the information in Table 20 and Table 21, titration costs in the first cycle (Table 22) and following cycles (Table 23) were estimated.
For people starting on ACEI it was assumed based on a 2018 retrospective UK study (Mahmoudpour, et al., 2018):

- Approximately 13.5% of people initiated to ACEI switched to ARB
- These people will require an additional GP visit, 5 titration visits and a blood test at each visit to be fully titrated to the new medication

Table 21: Titration costs in first cycle, by strategy

Treatments	Number of visits for initiation and titration – Base-case (min, max)	Cost* – Base-case (min, max)
ACEI + BB **	6 (3,10)	£307 (£190, £463)
ACEI + BB + MRA **	6 (3,10)	£307 (£190, £463)
ACEI + BB + MRA + SGLT2i **	6 (3,10)	£421 (£304, £577)
ARNI + BB + MRA	5 (4,5)	£344 (£305, £344)
ARNI + BB + MRA + SGLT2i	5 (4,5)	£346 (£307, £346)

*Including the cost of the biochemistry tests
** Including the additional costs associated with switching treatment from ACEI to ARB

Table 22: Titration costs for escalation due to worsening condition

Treatments	Number of visits for initiation and titration – Base-case (min, max)	Cost – Base-case (min, max)
MRA	3 (2, 3)	£153 (£115, £154)
ARNI	3 (3, 4)	£266 (£266, £305)
SGLT2	2 (1, 2)	£229 (£190, £229)

HE2.3.5.2 Monitoring and care costs

It was assumed that monitoring will require 2 visits per year (4 for the 50% with CKD) provided by a nurse Band 7 with an average duration of 30 minutes which includes a renal function test.

The cost of a heart failure hospitalisation was calculated as a weighted average of non-elective short and long stay inpatient using the National Collection Costs 2023/2024. In line with NICE TA679, the cost of an emergency heart failure attendance was estimated using

the weighted average of heart failure day case codes. Finally, to estimate the cost of hospitalisation, a weighted average of long and short stay codes for stroke, angina, myocardial infarction and transient ischaemic attack (TIA) was used.

Table 23: Cost of hospitalisations

Category	Cost	Details
Heart failure hospitalisations	£2,889	Heart failure or shock (EB03A-E with CC score 0-14+) – weighted average of non elective long and short stay (NHS England, 2024)
A&E attendance for heart failure	£653	Weighted average of heart failure day case (NHS England, 2024)
CVD hospitalisations	£3,325	Weighted average of long and short stay of stroke, angina, myocardial infarction and TIA (NHS England, 2024)

Source: NHS cost collection 2023/2024

HE2.3.5.3 Costs associated with drug-related adverse events

The costs of the adverse events were taken from various sources and are illustrated in Table 25.

Table 24: Cost of adverse event

Adverse event	Cost	Details	Source for assumption	Source of unit cost
Hyperkalaemia	£151.24	Two additional GP visits and a blood test	(McMurray et al., 2018)	PSSRU 2023 (Jones, et al., 2022)
Acute Kidney injury	£2,732.43	Weighted average of long and short stay LA07H, LA07J-N, LA07P acute kidney injury	(Tafazzoli et al., 2023)	NHS cost collection 2023/24 (NHS England, 2024)
Volume depletion	£102.10	GP visit and prescription	Guideline committee	PSSRU 2023 (Jones et al., 2022)
Hepatic injury	£3,710.78	Weighted average of long and short stay GC01C-F liver failure disorders	NICE TA679	NHS cost collection 2023/24 (NHS England, 2024)
Hypotension	£176.20	Two GP visits and a prescription	(McMurray et al., 2018)	PSSRU 2023 (Jones et al., 2022)
Hypoglycaemic events	£1,801.48	Weighted average of KA08A-C other endocrine disorders long and short stay with/without interventions	Guideline committee	NHS cost collection 2023/24 (NHS England, 2024)
Diabetic ketoacidosis	£910.65	Weighted average of KB02G-K long and short stay assume 50% hospitalisation, 50% GP visit	NICE TA929	NHS cost collection 2023/24 (NHS England, 2024)
Fracture	£4,071.84	Weighted average of pathological fractures	(Tafazzoli et al., 2023)	NHS cost collection 2023/24 (NHS England, 2024)

Adverse event	Cost	Details	Source for assumption	Source of unit cost
UTI	£74.10	15 minutes GP appointment	(McMurray et al., 2018)	PSSRU 2023(Jones et al., 2022)
Genital infection	£74.10	15 minutes GP appointment	Guideline committee	PSSRU 2023 (Jones et al., 2022)
Cough	£74.10	15 minutes GP appointment	Guideline committee	PSSRU 2023 (Jones et al., 2022)
Angioedema	£434.00	Mild 2 cardiologist outpatient visits, antihistamine Severe (40%) A& E visit, GP visit glucocorticoid treatment)	NICE TA388	NHS cost collection 2023/24 (NHS England, 2024)

HE2.3.6 Summary

All parameters used in the model are summarised in Table 26, including details of the distributions and parameters used in probabilistic analysis.

Table 25: All parameters in original cost-utility model

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
General input				
Mean age	73	Fixed	NA	INTEGRATE
Percentage of males	64.2%	Fixed	NA	INTEGRATE
Discount rate for costs	3.5%	Fixed	NA	NICE reference case
Discount rate for QALYs	3.5%	Fixed	NA	NICE reference case
Baseline rates (ACEI and BB)				
HF hospitalisation (year 0 – 1)	0.194	Gamma	α=1573.719 β=0.0001	INTEGRATE
HF hospitalisation (year 1 – 2)	0.102	Gamma	α=877.721 β=0.0001	INTEGRATE
HF hospitalisation (year 2 – 3)	0.085	Gamma	α=775.721 β=0.0001	INTEGRATE
HF hospitalisation (year 3 – 4)	0.083	Gamma	α=739.721 β=0.0001	INTEGRATE
HF hospitalisation (year 4 – 5)	0.085	Gamma	α=751.721 β=0.0001	INTEGRATE
HF A&E (year 0 – 1)	0.086	Gamma	α=835.721 β=0.0001	INTEGRATE
HF A&E (year 1 – 2)	0.044	Gamma	α=511.721 β=0.0001	INTEGRATE
HF A&E (year 2 – 3)	0.040	Gamma	α=499.721 β=0.0001	INTEGRATE
HF A&E (year 3 – 4)	0.038	Gamma	α=487.722 β=0.0001	INTEGRATE
HF A&E (year 4 – 5)	0.036	Gamma	α=469.721 β=0.0001	INTEGRATE
CV hospitalisation (year 0 – 1)	0.384	Gamma	α=2212.680 β=0.0001	INTEGRATE

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
CV hospitalisation (year 1 – 2)	0.198	Gamma	α=1374.948 β=0.0001	INTEGRATE
CV hospitalisation (year 2 – 3)	0.159	Gamma	α=1198.962 β=0.0001	INTEGRATE
CV hospitalisation (year 3 – 4)	0.154	Gamma	α=1301.489 β=0.0001	INTEGRATE
CV hospitalisation (year 4 – 5)	0.151	Gamma	α=1212.306 β=0.0001	INTEGRATE
All-cause mortality (year 0 – 1)	0.098	Gamma	α=416.193 β=0.0001	INTEGRATE
All-cause mortality (year 1 – 2)	0.097	Gamma	α=700.850 β=0.0001	INTEGRATE
All-cause mortality (year 2 – 3)	0.099	Gamma	α=843.051 β=0.0001	INTEGRATE
All-cause mortality (year 3 – 4)	0.102	Gamma	α=826.296 β=0.0001	INTEGRATE
All-cause mortality (year 4 – 5)	0.105	Gamma	α=800.934 β=0.0001	INTEGRATE
Lognormal – two to three pillars	μ: 0.491 σ: 3.017	Cholesky decomposition	$\begin{pmatrix}0.015 & 0\\ 0.001 & 0.004\end{pmatrix}$	INTEGRATE
Lognormal – three to four pillars	μ: -0.676 σ: 2.848	Cholesky decomposition	$\begin{pmatrix}0.018 & 0\\ 0.001 & 0.005\end{pmatrix}$	INTEGRATE
Proportion of people assumed to switch from ACEI to ARB	13.5%	Fixed	NA	(Mahmoudpour et al., 2018)
Baseline adverse events (MRA)				
Hyperkalaemia	0.106	Gamma	α=496.977 β=0.0001	(Anker et al., 2021)
Acute Kidney injury	0.090	Gamma	α=184.703 β=0.0001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Volume depletion	0.088	Gamma	α=178.868 β=0.0001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Hepatic injury	0.038	Gamma	α=74.195 β=0.001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Hypotension	0.077	Gamma	α=155.200 β=0.0001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Hypoglycaemic events	0.013	Gamma	α=23.582 β=0.001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Fracture	0.019	Gamma	α=35.889 β=0.001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
UTI	0.038	Gamma	α=72.786 β=0.001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Genital infection	0.005	Gamma	α=9.927 β=0.001	Tafazzoli/Emperor reduced trial (Tafazzoli et al., 2023)
Cough	0.076	Gamma	α=343.517 β=0.0001	(McMurray et al., 2018)
Angioedema	0.001	Gamma	α=2.450	(McMurray et al., 2018)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
			β=0.0001	
Treatment effect				
All-cause mortality HR – MRA vs placebo HR	0.76	Lognormal	μ=-0.274 σ=0.103	(Zannad et al., 2011)
All-cause mortality HR – SGLT2i vs placebo	0.87	Lognormal	μ=-0.139 σ=0.062	Clinical review (McMurray et al., 2019, Packer et al., 2020)
All-cause mortality HR – ARNI vs ACEI	0.84	Lognormal	μ=-0.174 σ=0.051	Clinical review (McMurray et al., 2014)
All-cause mortality RR – ARB vs ACEI	1.07	Lognormal	μ=0.068 σ=0.043	(Park et al., 2023)
HF hospitalisation HR – MRA vs placebo	0.60	Lognormal	μ=-0.511 σ=0.093	Clinical review (Asakura et al., 2020, Tsutsui et al., 2018, Zannad et al., 2011)
HF hospitalisation HR – SGLT2i vs placebo	0.70	Lognormal	μ=-0.357 σ=0.061	Clinical review (McMurray et al., 2019, Nassif et al., 2019, Packer et al., 2020)
HF hospitalisation HR – ARNI vs ACEI	0.80	Lognormal	μ=-0.223 σ=0.057	Clinical review (McMurray et al., 2014)
HF hospitalisation RR – ACEI vs ARB	1	Fixed	NA	Assumed
Quality of life				
ACEI/ARB, BB and MRA EQ-5D	0.779	Beta	α=24492 β=6948	PARADIGM-HF (Lewis et al., 2017)
Change with SGLT2i	+0.013	Gamma	α=96.036 β=0.0001	Pairwise meta-analysis (fixed effects) (Abraham et al., 2020), (Butler et al., 2021), (Nassif et al., 2019), (Jensen et al., 2021) converted using mapping algorithm (Thomas et al., 2021)
Change with ARNI	+0.012	Gamma	α=96.036 β=0.0001	Pairwise meta-analysis (fixed effects) (McMurray et al., 2014), (Tsutsui et al., 2021) converted using mapping algorithm (Thomas et al., 2021)
Change without MRA	-0.009	Gamma	α=96.036 β=0.0001	Docherty et al., 2024 FINEARTS-HF Converted using algorithm (Thomas et al., 2021)
HF-related hospitalisation disutility	0.019	Gamma	α=96.036 β=0.0002	NICE TA773
Utility decrement per year	0.008	Gamma	α=96.036 β=0.0001	(Berg et al., 2015)
Hyperkalaemia	0	Fixed	NA	Assumed
Acute Kidney injury	0.010	Gamma	α=0.694 β=0.014	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Volume depletion	0.018	Gamma	α=1.653 β=0.011	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Hepatic injury	0.016	Gamma	α=0.709 β=0.023	Tafazzoli et al., 2023 (Emperor reduced clinical trial)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Hypotension	0.025	Gamma	α=96.036 β=0.0003	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Hypoglycaemic events	0.048	Gamma	α=2.116 β=0.023	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Diabetic ketoacidosis	0	Fixed	NA	NICE TA679
Fracture	0.165	Gamma	α=21.007 β=0.008	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
UTI	0	Fixed	NA	Tafazzoli et al., 2023 (Sullivan 2016)
Genital infection	0.058	Gamma	α=2.212 β=0.026	Tafazzoli et al., 2023 (Emperor reduced clinical trial)
Cough	0.070	Gamma	α=96.036 β=0.001	NICE TA388
Angioedema	0	Fixed	NA	Assumed
Duration of adverse event	1 month	Fixed	NA	Assumed
Costs				
ACEI 3-monthly	£5.47	Fixed	NA	PCA (NHS Business Services Authority, 2024), Drug cost tariff (NHS Business Services Authority, 2025)
ARB 3-monthly	£5.17	Fixed	NA	PCA (NHS Business Services Authority, 2024), Drug cost tariff (NHS Business Services Authority, 2025)
ARNI 3-monthly	£298.59	Fixed	NA	PCA (NHS Business Services Authority, 2024), Drug cost tariff (NHS Business Services Authority, 2025)
BB 3-monthly	£3.12	Fixed	NA	PCA (NHS Business Services Authority, 2024), Drug cost tariff (NHS Business Services Authority, 2025)
MRA 3-monthly	£10.53	Fixed	NA	PCA (NHS Business Services Authority, 2024), Drug cost tariff (NHS Business Services Authority, 2025)
SGLT2i3-monthly	£119.33	Fixed	NA	PCA (NHS Business Services Authority, 2024), Drug cost tariff (NHS Business Services Authority, 2025)
Heart failure hospitalisation	£2,889	Fixed	NA	NHS Collection Cost 2023/24 (NHS England, 2024)
Emergency heart failure visit	£653	Fixed	NA	NHS Collection Cost 2023/24 (NHS England, 2024)
Cardiovascular hospitalisation	£3,325	Fixed	NA	NHS Collection Cost 2023/24 (NHS England, 2024)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
GP appointment	£74.10	Gamma	α=96.036 β=0.772	PSSRU (Jones et al., 2022)
Nurse Band 6	£32.00	Gamma	α=96.036 β=0.333	PSSRU (Jones et al., 2022)
Nurse Band 7	£37.00	Gamma	α=96.036 β=0.385	PSSRU (Jones et al., 2022)
ANP/Pharmacist Band 8a	£41.00	Gamma	α=96.036 β=0.427	PSSRU (Jones et al., 2022)
Specialist visit (cardiology)	£186.15	Gamma	α=96.036 β=1.938	NHS cost collection 2023/2024 (NHS England, 2024) – weighted average of Consultant Led and non-consultant led 320 CL Non-Admitted Face-to-Face Attendance, First WF01B
Haematology test	£3.04	Fixed	NA	NHS cost collection 2023/2024 (NHS England, 2024) – weighted average of haematology DAPS PATH05)
Blood test (biochemistry)	£1.94	Fixed	NA	NHS cost collection 2023/2024 (NHS England, 2024) – weighted average of Clinical biochemistry DAPS PATH04)
Hyperkalaemia	£151	Gamma	α=96.036 β=1.575	PSSRU (Jones et al., 2022)
Acute Kidney injury	£2,732	Gamma	α=96.036 β=28.452	NHS cost collection 2023/24 (NHS England, 2024)
Volume depletion	£102	Gamma	α=96.036 β=1.063	PSSRU 2023 (Jones et al., 2022)
Hepatic injury	£3,711	Gamma	α=96.036 β=38.639	NHS cost collection 2023/24 (NHS England, 2024)
Hypotension	£176	Gamma	α=96.036 β=1.835	PSSRU 2023 (Jones et al., 2022)
Hypoglycaemic events	£1,801	Gamma	α=96.036 β=18.758	NHS cost collection 2023/24 (NHS England, 2024)
Diabetic ketoacidosis	£911	Gamma	α=96.036 β=9.482	NHS cost collection 2023/24 (NHS England, 2024)
Fracture	£4,072	Gamma	α=96.036 β=42.399	NHS cost collection 2023/24 (NHS England, 2024)
UTI	£74	Gamma	α=96.036 β=0.772	PSSRU 2023 (Jones et al., 2022)
Genital infection	£74	Gamma	α=96.036 β=0.772	PSSRU 2023 (Jones et al., 2022)
Cough	£74	Gamma	α=96.036 β=0.772	PSSRU 2023 (Jones et al., 2022)
Angioedema	£434	Gamma	α=96.036 β=4.519	NHS cost collection 2023/24 (NHS England, 2024)

HE2.4 Summary of key assumptions

Table 26: Key assumptions

Category	Assumption	Justification
Treatment effects (including adverse effects)	Treatment effects of each drug are assumed to have a multiplicative effect for each strategy	For example the mortality rate for the Early MRA, early ARNI and early SGLT2i strategy = Baseline rate x HR(MRA) x HR(ARNI) x HR (SGLT2i), where HR (MRA) is the hazard ratio for MRA + Usual care vs Usual care. The SGLT2i trial evidence is from participants with a variety of background treatments including MRA and for some participants ARNI. There is an absence of evidence for MRA or ARNI having or not having an additional benefit over SGLT2i. However, assuming the relative treatment effects are independent of the background treatment is commonly assumed in health economic evaluations.
Treatment effect population	Treatment effects are based on the data extracted from the effectiveness review using the full population of the clinical trial	Although TA388 preferred the use of the European subgroup within the trial, both TA679 and TA773 used the full population from the clinical trials to make their decision. The committee discussed that although participants in the clinical trials were younger than those typically seen in clinical practice, this is a common trend of all clinical trials. The committee were concerned the ethnic distribution of the European subgroups did not reflect the UK population. The committee were also concerned at drawing results from a smaller population rather than the full trial which could lead to greater uncertainty in the values. Overall evidence from the full trial population was used. The European population for ARNI and SGLT2s is used in a scenario analysis.
Treatment effect for ARB	ARB is inferior to ACEI in reducing mortality	Only ARNI compared with ACEI was sourced in the effectiveness review, there was a great deal of uncertainty associated with the values identified for ARNI compared with ARB. The committee considered ACEI to have a greater efficacy in terms of reducing mortality compared with ARB. Using a network meta-analysis from Park et al., 2022 comparing ARNI with ACEI and ARB separately.
Quality of life method	EQ-5D-3L is calculated by using the linear mapping algorithm by Thomas et al 2021 to map quality of life based on KCCQ-OS to EQ-5D-3L	Although the authors expressed there was a non-linear relationship between EQ-5D and KCCQ score when the algorithm was used to map from PARADIGM-HF, the linear value was closest to the observed value, for this reason the linear model was used for the base-case analysis and the non-linear approach was used in a scenario analysis.
Quality of life baseline	Baseline data and the utility decrement over time were sourced from PARADIGM-HF	This was used as the baseline as it was the only dataset containing both KCCQ and EQ-5D data to allow for validation. The values by Berg et al., (2015) were used in a scenario analysis.
Quality of life decrements	Utility decrement of -0.019 used based on NICE TA773 this is	Scenario values based on the sources from TA679 and TA388 to allow for exploration both higher and lower decrements.

Category	Assumption	Justification
following hospitalisation	applied as a one off decrement occurring in the cycle the hospitalisation occurs	
Quality of life benefit associated with treatment	Assume the benefit to be equivalent to the value identified within the SGLT2i trials when people are taking both SGLT2is and ARNIs	This value is tested by a scenario where the value from the ARNI trial was used. A scenario in which both the SGLT2i and ARNI values are used additively was also tested. There was uncertainty regarding the appropriate value to use as no data were available in the literature for both treatments taken together. The committee considered that using both values additively might overestimate the quality of life gains associated with treatment; for this reason, this approach was tested as a scenario only.
Treatment initiation	Assumed GP can initiate the next escalation of treatment with the exception of SGLT2i and ARNI	This is currently based on existing guidance; however, this assumption was tested in a scenario because GPs regularly prescribe SGLT2is for other conditions.
Titration staff	Titration of treatments assumed to occur in visits with a Band 7 nurse specialist	Based on discussions with the committee, titration could potentially be carried out by a Band 6 nurse or a pharmacist. This assumption was tested in scenarios: one scenario assumed Band 6 staff member and the other scenario assumed Band 8a staff member.

HE2.5 Sensitivity analyses

HE2.5.1 Deterministic sensitivity analyses

Table 28 outlines the key parameters used in the base-case analysis and the corresponding alternative assumptions explored in scenario analyses. The base-case generally reflects standard clinical practice and comprehensive data use, while the scenarios test the sensitivity of results to plausible variations in model inputs.

Table 27: Base-case assumptions and scenario analyses

Parameter	Base-case	Scenarios
Population	Full population	European population
Number of visits for titration	Mode	Minimum and maximum based on the values collected from the committee
Clinician initiating treatment for ARNI and SGLT2i	Specialist (Cardiology outpatient)	GP
Specialist staff band	Band 7	Band 6, Band 8a
Baseline rates of mortality and hospitalisation	From all people with HFrEF in INTEGRATE cohort (with rates adjusted for people on three or four pillars using HRs from guideline review)	From people with HFrEF in INTEGRATE cohort on two pillars only
Heart failure hospitalisation cost	Weighted average of NEL and NES	Include elective hospitalisation costs as part of the weighted average
Hospitalisations included	Heart failure only	Both heart failure and CVD
Utility method	Linear conversion	Non-linear conversion

Parameter	Base-case	Scenarios
Baseline utility and constant decrement over time	Paradigm-HF	Berg et al 2015
Utility gain for all treatments combined	SGLT2i only	ARNI only, Summed across SGLT2i and ARNI utilities
Hospitalisation utility decrement source	NICE TA773	TA679, TA388
Adverse event utility decrements source	NICE TA773	TA679

The base-case scenario used treatment effects relative to the entire trial population, whereas the scenario analysis effects based on the European subpopulation only. Notably, the NICE TA committee on ARNI preferred the European subpopulation, although the guideline committee preferred the full trial population, arguing that it better reflected the ethnic distribution within the UK.

As the information for subgroup was redacted in the TA report for ARNI, only data on the composite outcome is publicly available. To estimate the relative reduction in effect for the European subgroup, the composite outcome for this subgroup was divided by the corresponding outcome for the overall trial population. This ratio was then applied within the model. For SGTL2i, both hazard ratios for CV hospitalisation and CV death were available, and these were directly applied in the model to hospitalisation and all-cause mortality rates, respectively. Table 29 include the parameters used in the scenario analysis.

Table 28: European subpopulation analysis parameters

Parameter	Base-case	Source
ARNI vs ACEI/ARB – composite outcome	HR: 0.89	TA679
SGLT2i vs placebo – CV hospitalisation	HR: 0.96	TA773
SGLT2i vs placebo – CV death	HR: 0.98	TA773

In other scenarios, different assumptions for the number of visit for titration, the band of the healthcare professional and the professional needed for initiating the therapy were explored. Different assumption for hospitalisation costs (including elective heart failure hospitalisation and CVD hospitalisation) were also explored.

Finally, several assumptions related to utility estimation were tested. These included using a non-linear method to convert KCCQ scores, varying baseline utility values, summing the quality of life benefits of ARNI and SGLT2i for individuals receiving both treatments, and using alternative sources for hospitalisation and adverse event disutilities.

The results of the scenario analysis are reported in HE3.3.1.

HE2.5.2 Probabilistic sensitivity analyses

The models were configured to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. Probability distributions were specified for all input variables with the exception of drug acquisition costs and unit costs collected from standard national source such as NHS Collection Cost and PSSRU. The type of distribution was selected based on the properties of data of that type (for example, beta distributions were used for probabilities bounded between 0 and 1, and gamma distributions were used for cost parameters that cannot be negative). Where possible, each distribution was parameterised using dispersion data from the source from which the value was obtained. In

the absence of such data, plausible ranges were applied, informed by committee advice and usual properties of similar data.

HE3 Results

HE3.1 Clinical outcomes

Table 30 and Table 31 show the clinical outcomes across the different strategies for people who can and cannot tolerate ACEI, respectively. The difference between the two populations is largely due to variations in mortality, as ACEI is assumed to provide a greater protection against death, resulting in a higher number of people at risk in the first population over the entire time horizon.

Table 29: Base-case deterministic results events per 1,000 people over their lifetime – people who can tolerate ACEI

Outcome	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
HF Hospitalisation	550	440	400	370	330
CVD (non-HF) hospitalisation	1570	1660	1770	1730	1830
Hyperkalaemia	660	880	870	860	850
Acute Kidney injury	750	770	790	760	780
Volume depletion	530	830	890	890	950
Hepatic injury	200	330	360	330	350
Hypotension	860	950	1480	1020	1600
Hypoglycaemic events	70	110	120	120	120
Fracture	110	180	190	190	210
UTI	230	360	390	400	420
Genital infection	70	90	90	130	140
Cough	600	640	570	670	590
Angioedema	10	10	10	10	10

Table 30: Base-case deterministic results - events per 1,000 people over the lifetime – people who cannot tolerate ACEI

Outcome	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
HF Hospitalisations	530	430	400	360	330
CVD (non-HF) hospitalisations	1530	1620	1770	1690	1830
Hyperkalaemia	640	860	870	840	850
Acute Kidney injury	720	750	790	740	780

Outcome	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
Volume depletion	510	800	890	870	950
Hepatic injury	200	320	360	320	350
Hypotension	840	930	1480	1000	1600
Hypoglycaemic events	70	110	120	110	120
Fracture	110	170	190	190	210
UTI	230	350	390	390	420
Genital infection	70	80	90	130	140
Cough	580	620	570	650	590
Angioedema	0	10	10	10	10

HE3.2 Base-case cost-utility results

The base-case deterministic cost-effectiveness results for people who can and cannot tolerate ACEI are presented in Table 32 and Table 33 respectively.

Table 31: Base-case deterministic cost-utility results – people who can tolerate ACEI

Strategies in ascending order of cost	Cost per person	QALYs per person	Incr. costs*	Incr. QALYs*	Incr. cost per QALY*	NHB
Current NICE Pathway (ACEI + BB)	£10,225	5.142	-	-	-	4.63
Early MRA	£10,999	5.464	£774	0.322	£2,400	4.91
Early MRA and early SGLT2i	£12,987	5.717	£1,989	0.253	£7,865	5.07
Early MRA and early ARNI	£17,703	5.836	£4,716	0.119	Extendedly dominated	4.95
Early MRA and early SGLT2i and early ARNI	£19,858	6.042	£6,870	0.325	£21,148	5.05

Note: Abbreviations: NHB = Net health benefit, which is defined as QALYs per person – (Cost per person /£20,000); QALYs = quality-adjusted life-years.
* Compared with the next non-dominated row above

Table 32: Base-case deterministic cost-utility results – people who cannot tolerate ACEI

Strategies in ascending order of cost	Cost per person	QALYs per person	Incr. costs*	Incr. QALYs*	Incr. cost per QALY*	NHB
Current NICE Pathway (ARB + BB)	£9,962	5.011	-	-	-	4.51
Early MRA	£10,726	5.335	£764	0.324	£2,360	4.80
Early MRA and early SGLT2i	£12,680	5.588	£1,954	0.253	£7,710	4.95
Early MRA and early ARNI	£17,703	5.836	£5,024	0.247	Extendedly dominated	4.95

Strategies in ascending order of cost	Cost per person	QALYs per person	Incr. costs*	Incr. QALYs*	Incr. cost per QALY*	NHB
Early MRA and early SGLT2i and early ARNI	£19,858	6.042	£7,178	0.453	£15,838	5.05

Note: NHB = Net health benefit, which is defined as: 'QALYs per person – (Cost per person /£20,000)'; QALYs = quality-adjusted life-years.

* Compared with the next non-dominated row above

In people who can tolerate ACEI, the combination of early MRA and early SGLT2i was the most cost-effective strategy, with a net health benefit of 5.07 and a cost per QALY compared to early MRA of £7,865 that is well below NICE's lower cost-effectiveness threshold of £20,000 per QALY. The combination of early MRA, SGLT2i and ARNI was not cost-effective at the £20,000 threshold but became cost-effective at NICE's upper threshold of £30,000 per QALY. This was because, although more effective, ARNI was the most expensive treatment among those compared.

In people who cannot tolerate ACEI, the combination of early MRA, early SGLT2i and early ARNI was the most cost-effective strategy, with a net health benefit of 5.05 and a cost per QALY compared to early MRA and SGLT2i of £15,838. Early MRA, early ARNI and early SGLT2 was found to be cost-effective in this population as ARNI was associated with a greater mortality benefit.

HE3.3 Sensitivity analysis

HE3.3.1 Deterministic sensitivity analysis

The scenario analyses for people who can and cannot tolerate ACEI are presented in Table 34 and Table 35, respectively. In people who can tolerate ACEI, the combination of early MRA and early SGLT2i was cost-effective in most scenarios. However, when treatment effects from the European sub-population were used, SGTLT2i ceased being cost-effective and early MRA became the most cost-effective strategy. When the improvement in quality of life from the simultaneous prescription of ARNI and SGLT2i was assumed to be additive, the combination of early MRA, early SGLT2i and early ARNI emerged as the strategy with the highest net health benefit.

Table 33: Deterministic scenario analysis NHB – people who can tolerate ACEI

Scenario	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
Base-case	4.630	4.914	4.950	5.067	5.049
European subpopulation	4.445	4.724	4.589	4.708	4.537
Number of visits for titration (minimum)	4.637	4.920	4.953	5.072	5.051
Number of visits for titration (maximum)	4.623	4.907	4.950	5.060	5.049
Disutility source adverse events (TA679)	4.631	4.914	4.951	5.068	5.050

Scenario	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
No specialist for treatment initiation (ARNI)	4.632	4.916	4.955	5.069	5.054
No specialist for treatment initiation (SGLT2)	4.633	4.917	4.953	5.072	5.049
Hospitalisation disutility source (T6A79)	4.627	4.911	4.948	5.065	5.047
Hospitalisation disutility source (TA388)	4.631	4.915	4.951	5.068	5.049
Staff level for titration (Band 6)	4.632	4.915	4.951	5.069	5.050
Staff level for titration (Band 8a)	4.629	4.913	4.950	5.066	5.048
Utility method (non-linear)	4.609	4.895	4.910	5.031	5.010
Utility for all treatments (ARNI)	4.630	4.914	4.950	5.067	5.049
Utility for all treatments (ARNI + SGLT2i)	4.651	4.935	4.994	5.096	5.148
Baseline utility/ decrement over time source (Berg et al 2015)	4.295	4.561	4.579	4.703	4.666
Integrate data source (two pillars)	4.584	4.867	4.907	5.020	5.005
Include elective HF hospitalisations	4.630	4.914	4.950	5.067	5.049
Include CVD hospitalisations	4.411	4.684	4.708	4.829	4.799

In people who cannot tolerate ACEI, the combination of early MRA and early SGLT2i and early ARNI remained the most cost-effective strategy in most scenarios based on net health benefit, with one exception: when treatment effects for the European population were used, early MRA alone was the most cost-effective strategy.

Table 34: Deterministic scenario analysis – people who cannot tolerate ACEI

Scenario	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
Base-case	4.513	4.799	4.950	4.954	5.049
European subpopulation	4.330	4.611	4.589	4.596	4.537

Scenario	Current NICE Pathway	Early MRA	Early MRA and early ARNI	Early MRA and early SGLT2i	Early MRA and early SGLT2i and early ARNI
Number of visits for titration (minimum)	4.520	4.805	4.953	4.959	5.051
Number of visits for titration (maximum)	4.506	4.791	4.950	4.947	5.049
Disutility source adverse events (TA679)	4.513	4.799	4.951	4.955	5.050
No specialist for treatment initiation (ARNI)	4.515	4.800	4.955	4.956	5.054
No specialist for treatment initiation (SGLT2)	4.516	4.801	4.953	4.959	5.049
Hospitalisation disutility source (TA679)	4.510	4.796	4.948	4.952	5.047
Hospitalisation disutility source (TA388)	4.514	4.799	4.951	4.955	5.049
Staff level for titration (Band 6)	4.515	4.800	4.951	4.956	5.050
Staff level for titration (Band 8a)	4.512	4.798	4.950	4.953	5.048
Utility method (non-linear)	4.492	4.780	4.910	4.919	5.010
Utility for all treatments (ARNI + SGLT2i)	4.513	4.799	4.950	4.954	5.049
Utility for all treatments (combined)	4.533	4.819	4.994	4.983	5.148
Baseline utility/ decrement over time source (Berg et al 2015)	4.186	4.453	4.579	4.597	4.666
Integrate data source (two pillars)	4.465	4.750	4.907	4.906	5.005
Include elective HF hospitalisations	4.513	4.799	4.950	4.954	5.049
Include CVD hospitalisations	4.299	4.573	4.708	4.721	4.799

HE3.3.2 Probabilistic sensitivity analysis

A total of 5,000 Monte Carlo simulations were conducted separately for each of the two populations in the analysis. Table 36 and Table 37 present the base-case probabilistic cost-utility results for people who can and cannot tolerate ACEI, respectively.

In people who can tolerate ACEI, the combination of early MRA and early ARNI was the most cost-effective strategy in 56% of the simulations. The second-ranked strategy, the combination of early MRA, early SGLT2i and early ARNI was the most cost-effective strategy in 37% of the simulations. This result is likely due to its cost per QALY ratio, which was approximately £21,000; very close to NICE's lower threshold of £20,000 per QALY.

Table 35: Base-case probabilistic cost-utility results – people who can tolerate ACEI

Strategy*	Cost per person	QALYs per person	Incremental cost per QALY gained**	Mean NHB*** (95% CI)	Mean Rank*** (95% CI)	Probability 1st rank***
Current NICE Pathway	£9,504	5.144	-	4.67 (4.35 to 5.00)	5.0 (5,5)	0.0%
Early MRA	£10,188	5.468	£2,109	4.96 (4.46 to 5.48)	3.5 (2,4)	1.3%
Early MRA and early SGLT2i	£12,124	5.720	£7,699	5.11 (4.55 to 5.70)	1.6 (1,3)	55.8%
Early MRA and early ARNI	£16,860	5.839	Extendedly dominated	5.00 (4.45 to 5.55)	3.1 (1,4)	5.8%
Early MRA and early SGLT2i and early ARNI	£18,959	6.044	£21,070	5.10 (4.52 to 5.68)	1.8 (1,4)	37.1%

Note: All values are mean, 95% confidence intervals are shown in parentheses. NHB = Net health benefit, which is defined as: 'QALYs per person – (Cost per person /£20,000)'; QALYs = quality-adjusted life-years.

* In ascending order of cost

** Compared with the next non-dominated row above

*** At £20,000 per QALY

In people who cannot tolerate ACEI, the combination of early MRA, early SGLT2i and early ARNI was found to be the most cost-effective strategy in around 71% of simulations. The second most cost-effective strategy, the combination of early MRA and early SGLT2i was cost-effective in only 20% of the simulations. This was because of the higher relative effectiveness of ARNI compared to ARB in reducing all-cause mortality.

Table 36: Base-case probabilistic cost-utility results – people who cannot tolerate ACEI

Strategy*	Cost per person	QALYs per person	Incremental cost per QALY gained**	Mean NHB*** (95% CI)	Mean Rank*** (95% CI)	Probability 1st rank***
Current NICE Pathway	£9,256	5.014	-	4.55 (4.19 to 4.92)	5.0 (5,5)	0.0%
Early MRA	£9,933	5.339	£2,083	4.84 (4.31 to 5.38)	3.8 (2, 4)	0.2%
Early MRA and early SGLT2i	£11,842	5.592	£7,532	5.00 (4.40 to 5.60)	2.3 (1, 4)	20.0%

Strategy*	Cost per person	QALYs per person	Incremental cost per QALY gained**	Mean NHB*** (95% CI)	Mean Rank*** (95% CI)	Probability 1st rank***
Early MRA and early ARNI	£16,843	5.835	Extendedly dominated	4.99 (4.45 to 5.53)	2.5 (1, 4)	9.1%
Early MRA and early SGLT2i and early ARNI	£18,950	6.041	£15,821	5.09 (4.50 to 5.67)	1.3 (1, 3)	70.6%

Note: All values are mean, 95% confidence intervals are shown in parentheses. NHB = Net health benefit, which is defined as: 'QALYs per person – (Cost per person /£20,000)'; QALYs = quality-adjusted life-years.

* In ascending order of cost

** Compared with the next non-dominated row above

*** At £20,000 per QALY

Figure 13 and Figure 14 depict the probabilistic cost-utility plane for the two populations. In Figure **13**, early MRA and early ARNI, and early MRA, early SGLT2i, and early ARNI lie above the cost-effectiveness threshold, indicating they are not cost-effective. In contrast, Figure 13 shows the intervention below the threshold, suggesting they are cost-effective in people who cannot tolerate ACEI.

Figure 13: Base-case probabilistic cost-utility plane – people who can tolerate ACEI

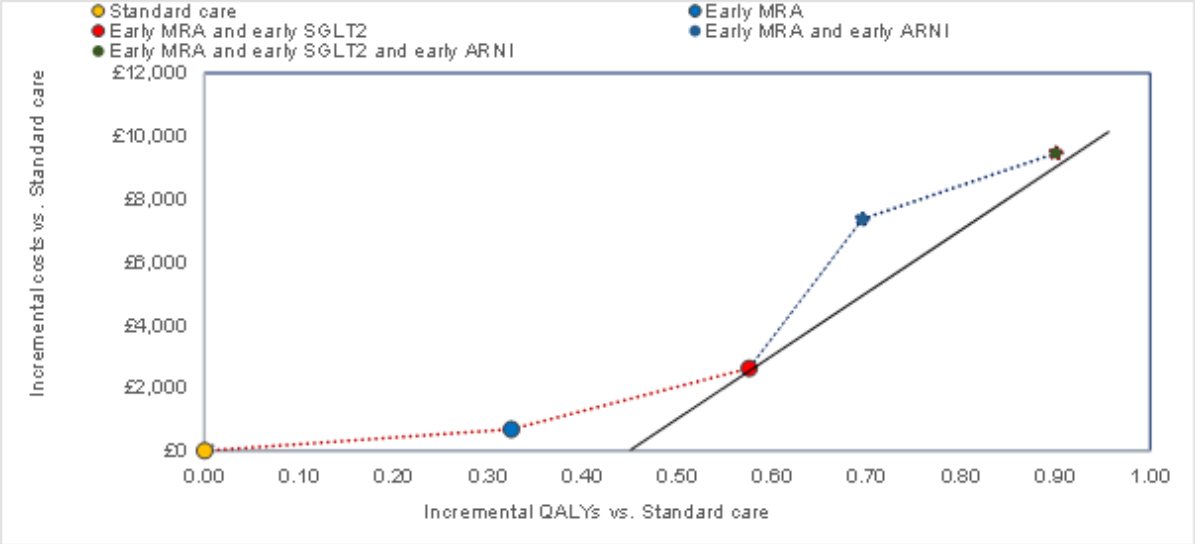
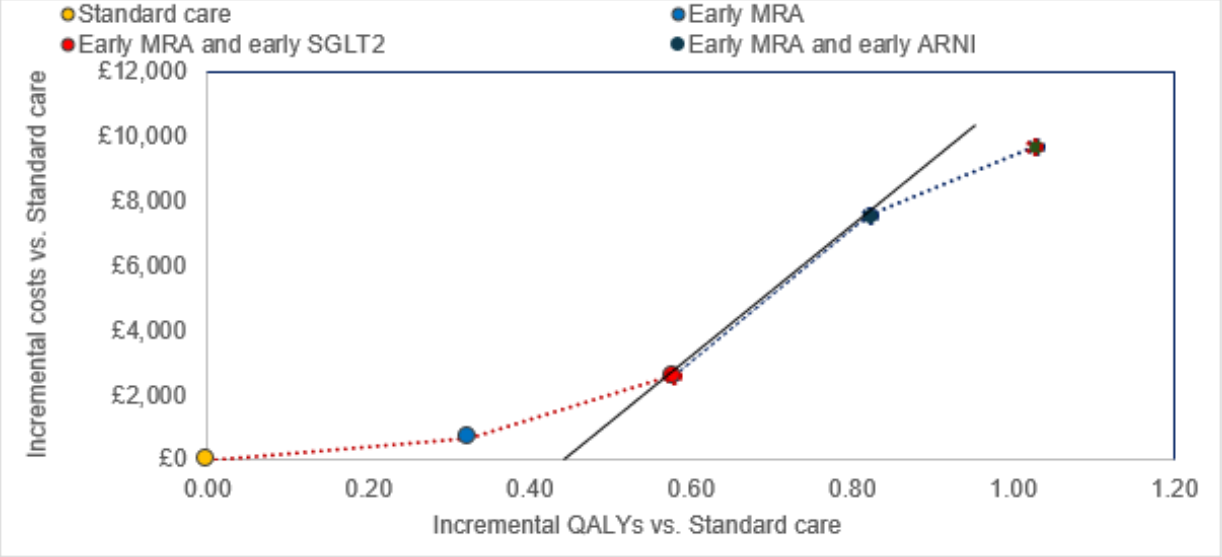


Figure 14: Base-case probabilistic cost-utility plane – people who cannot tolerate ACEI



HE3.4 Discussion

HE3.4.1 Principal findings

This analysis found that:

- In people who can tolerate ACEI, the combination of early MRA and early SGLT2i was cost-effective at a threshold of £20,000 per QALY, with a 56% probability of being cost-effective.
- In people who cannot tolerate ACEI, the combination of early MRA, early SGLT2i and early ARNI was cost-effective at a threshold of £20,000 per QALY, with a 71% probability of being cost-effective.

These results were consistent across most alternative scenario analyses. The exceptions were:

- Early MRA, early ARNI and early SGLT2i became cost-effective when the quality of life improvement of each was assumed to be additive.
- Early MRA, early ARNI and early SGLT2i became cost-effective when the cost-effectiveness threshold was increased to £30,000 per QALY.
- In both populations, early MRA, SGLT2i and ARNI ceased being cost-effective when the relative treatment effects from the European subgroups of the key trials were applied. This was the preferred analysis of the TA committee that appraised Sacubitril-Valsartan. However, the guideline update committee preferred the full trial analysis to estimate the relative treatment effects for each medicine.

Since the economic analysis was run, the UK court ruled that the dapagliflozin patent was no longer valid. It is expected that generic versions may soon enter the market, which would likely reduce the average price of SGLT2 in England, further increasing the cost-effectiveness of providing it first-line.

HE3.4.2 Strengths of the analysis

This analysis has several strengths. Treatment effects were estimated from a clinical systematic review of randomised trials conducted for this guideline. These treatment effects were applied to baseline rates estimated through collaboration with the INTEGRATE study,

which used real-world data to represent the risk for people with HFrEF in England. Likewise, the transitions of people across two, three and four pillars of therapy were estimated using a survival analysis based on real-world evidence from the same population. Overall, this enhanced the applicability of the analysis to the NHS setting and the English population.

In addition to using care assumptions based on current NHS practice, this analysis included unit cost estimates from standard UK sources and resource use assumptions informed by expert clinicians on the guideline committee.

The model was developed using several tunnel states to ensure that movement across pillars is based on the time people spend in a particular treatment regimen. Furthermore, for strategies where people are initiated to a higher number of treatment pillars, the model introduces dummy states to ensure that escalation to the next line of treatment occurs over the same duration as in the current NICE pathway. This approach ensured that transitions between treatment pillars are realistic across all strategies evaluated.

HE3.4.3 Weaknesses of the analysis

The analysis has some limitations. Firstly, the relative treatment effects were derived from trials that did not specifically evaluate the early use of medications. In the key trials, participants were optimally titrated on BB and ACEI or ARB, but remained symptomatic at the start of each trial. While some trials investigated the de novo use of ARNI and SGLT2i, these were conducted in the context of acute heart failure rather than specifically in chronic heart failure. For example, in the PIONEER-HF trial, “the composite of rehospitalisation for heart failure and death occurred in 22.9% of the patients in the Sacubitril/Valsartan group compared to 32.6% in the ACEI/ARB group (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.52–0.97) after a mean follow-up period of 11.8 months” (Chen, et al., 2021). Although this treatment effect was not included in the model, as it fell outside the scope of the guideline review, it does suggest that early use may be both effective and safe.

The treatment effect for ARNI was informed by clinical trials that focused on populations with chronic heart failure and reduced LVEF of less than 35% based on the enrolment criteria of studies comparing ARNI to either ACEI or ARB. This differs from the population with an LVEF of 40% or lower, which was in the focus of this analysis. However, the committee did not expect this population difference to significantly impact the results, particularly given the margin of error associated with measurement, making it unlikely to affect treatment decisions.

As previously mentioned, the model assumed that movement across treatment pillars was consistent across all strategies. In reality, people who receive more treatments early in the course of heart failure may require less escalation later, as their condition is better managed over time. However, no data were available to support this.

Although the proportion of people on ARNI at year 1 was reported in the INTEGRATE study, no survival analysis was available to model the transition to ARNI over time. Therefore, the survival curve for the transition between pillars two and three was calibrated to align with the known ARNI data point, under the assumption that escalation to the third pillar or to ARNI would follow the same trajectory.

Quality of life is rarely reported using the EQ-5D-3L instrument in heart failure clinical trials as disease-specific scores such as the KCCQ are generally preferred. However, this analysis used a published algorithm (Thomas et al., 2021) to convert changes in KCCQ into EQ-5D-3L values and tested two different conversion methods. The algorithm demonstrated strong predictive accuracy, with R^2 values ranging from 48.4% to 50.5% for internal validation and 33.7% to 45.6% for external validation. It has also been used in several other cost-utility analyses (Parizo, et al., 2021).

The analysis could not be stratified by age, frailty, sex or other subgroups for two reasons. Firstly, the treatment effects extracted from the clinical review represent the effect on the entire population enrolled in the trials and, except for people with diabetes, other stratifications were not included. Moreover, although baseline hospitalisation rates and mortality were stratified by age and frailty in the INTEGRATE study, these rates were not further stratified for number of pillars, so they could not be used in the analysis.

HE3.4.4 Comparison with other cost-utility analyses

Only one cost-utility study (Van, et al., 2024) comparing different pharmacological strategies for people with heart failure was identified in the literature. This Canadian study examined 12 different strategies for initiating and titrating the four pillars of HFrEF treatment: ACEI/ARB/ARNI, BB, MRA and SGLT2i. The study found that the simultaneous initiation of all four pillars was cost-effective in Canada, compared to alternative strategies involving fewer initial medications followed by sequential escalation. These findings align with this analysis, which also found early initiation of all four pillars to be cost-effective.

Nine cost-utility studies compared single therapies versus placebo or another therapy were identified in the review. A 2014 cost-utility analysis (Lee, et al., 2014) from a UK perspective found that adding an MRA is cost-effective in people with HFrEF, which is consistent with the findings of this analysis that also supports the inclusion of MRA as part of the four treatment pillars. Four cost-utility analyses compared ARNI versus either ACEI or ARB in different settings: UK (McMurray et al., 2018), South Korea (Park, et al., 2019), Germany (van der Pol, et al., 2019) and Canada (Grant, et al., 2020). Overall, ARNI was found to be potentially cost-effective compared to either ACEI or ARB, although its cost per QALY compared to ACEI was very close to the £20,000 threshold and, in one case, exceeded it. Notably, the cost per QALYs of ARNI versus ARB was lower compared to ARNI versus ACEI, which aligns with the findings of this analysis. Finally, four analyses compared SGLT2i against placebo and found the medication to be cost-effective, with a cost per QALY around £5,000 to £6,000, which is consistent with the findings of this analysis.

As mentioned earlier, NICE published three TAs for this population, which used a Markov model with a similar structure to assess the cost-effectiveness of ARNI (TA388) and SGLT2i (TA679 and TA773). In TA388, a two-state Markov model was developed using clinical data from the PARADIGM-HF trial. The analysis found ARNI to be cost-effective, with an estimated cost per QALY of £18,818 for people on ACEI and £17,599 for people on ARBs. The current analysis found a higher cost per QALY in people who can tolerate ACE when early ARNI, early MRA and early SGLT2i were compared to early MRA and early SGLT2i. This is because, unlike in the TA, the comparison group is receiving four pillars representing a higher standard of care. The estimated cost per QALY of early ARNI in people receiving only three pillars was £18,075, which aligns closely with the estimate from TA679.

TA679 included a more complex Markov model with nine states to capture symptom severity and found that SGLT2i is cost-effective as an add-on to optimised care, with a cost per QALY of £6,939. This closely aligns with the results of this analysis, which estimated a cost per QALY of £7,782 of early MRA and SGLT2i compared to early MRA only. TA773 analysis used a Markov model with five health states based on KCCQ-CSS quartiles and a Dead state and found SGLT2i to be cost-effective as an add-on to standard care of ACEI/ARB + BB + MRA with a cost per QALY of £4,804. Whilst this ICER is lower than the results of this analysis, the analysis from TA773 is based on only one SGLT2i rather than a class effect and allows for symptoms to be taken into account based on the KCCQ-CSS quartiles which was not available for this analysis.

HE3.5 Conclusions

This analysis assessed different pharmacological interventions in people with HFrEF and found that:

- For people who can tolerate ACEI, initiating ACEI, BB, MRA and SGLT2i would be cost-effective in England at a £20,000 per QALY threshold.
- For people who cannot tolerate ACEI, initiating ARNI, BB, MRA and SGLT2i would be cost-effective in England at a £20,000 per QALY threshold.

The findings of this analysis are consistent with published literature demonstrating that initiating people with HFrEF to four pillars of treatment is cost-effective compared to a delayed and sequenced approach.

However, subgroup analyses from the European population in the DAPA-HF trial and the Western European in the PARADIGM-HF trial showed smaller benefits compared to the overall trial populations. While these subgroups have limitations and were not preferred by the guideline committee, they suggest that the cost per QALY gained in these analyses could be underestimated in the context of the UK NHS. If this is the case, then greater caution may be warranted about the early use of ARNI, given its higher cost per QALY gained relative to early use of SGLT2 inhibitors.

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