Cost effectiveness of Optimal Medical Therapy in Heart Failure with Reduced Ejection Fraction

Main report

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SUMMARY (in Dutch)

De richtlijnen van de *European Society of Cardiology* (ESC) uit 2021 voor de diagnose en behandeling van acuut en chronisch hartfalen definiëren optimale medische therapie (OMT) voor patiënten met HFrEF als viervoudige therapie bestaande uit een ARNi of ACE-remmer, bètablokker, MRA en SGLT2i-remmer. Hoewel betrouwbare cijfers ontbreken, suggereren de beschikbare gegevens en praktijkervaringen dat Nederlandse cardiologen en huisartsen vaak niet volgens deze richtlijnen werken. Hiervoor kunnen verschillende redenen zijn, zoals onbekendheid met de ESC-richtlijnen, zorgen over de tolerantie van patiënten voor bepaalde medicijnen en twijfel over de toegevoegde waarde van OMT voor patiënten. Dit rapport richt zich op de laatste oorzaak en beoogt de onzekerheid rond de waarde van OMT in de Nederlandse context te verkleinen. Hiertoe is een kosteneffectiviteitsanalyse uitgevoerd waarin OMT wordt vergeleken met andere medicamenteuze therapieën. In deze kosteneffectiviteitsanalyse worden factoren die de kosteneffectiviteit van verschillende therapieën beïnvloeden gemodelleerd, zoals sterftecijfers, ziekteverloop en ziekenhuisopnames. De analyse in dit rapport is gebaseerd op een model dat een fictieve groep van 10.000 HFrEF-patiënten volgt tot aan hun overlijden. De kenmerken van de patiënten (zoals geslacht en leeftijd) zijn gebaseerd op de Check-HF studie. Door het cumulatieve aantal voor kwaliteit van leven gecorrigeerde levensjaren (QALYs) van deze groep te berekenen onder verschillende behandelcombinaties, evenals de cumulatieve kosten van hartfalen medicatie, overige zorgkosten (hartfalen gerelateerd en niet-gerelateerd) en kosten van informele zorg, is de kosteneffectiviteit van verschillende behandelcombinaties bepaald.

Uit de analyse blijkt dat viervoudige therapie met een ARNi in plaats van een ACEi voor HFrEF-patiënten kosteneffectief is. Hoewel de kosten per patiënt van een ARNi hoger zijn dan die van een ACE-remmer, zijn ook de gezondheidsvoordelen in termen van overleving en ziekenhuisopname gunstiger met een ARNi dan met een ACE-remmer. De extra gezondheidsvoordelen van een ARNi blijken op te wegen tegen de extra kosten: viervoudige therapie met een ARNi is kosteneffectief bij de drempelwaarde van €50.000 die het Zorginstituut hanteert voor hartfalen. Deze conclusie geldt niet alleen voor de basisanalyse van het rapport, maar ook voor alle subgroepanalyses en gevoeligheidsanalyses (zie rapport en Appendix II). In de meeste subgroepanalyses en gevoeligheidsanalyses is viervoudige therapie met een ARNi ook al kosteneffectief bij een lagere drempelwaarde van €30.000. Als om wat voor reden dan ook viervoudige therapie met een ARNi niet mogelijk is, dan is viervoudige therapie met een ACEi het naast beste alternatief wat betreft kosteneffectiviteit.

Als `bijvangst' van deze kosteneffectiviteitsanalyse zijn de effecten op het aantal ziekenhuisopnames en gewonnen levensjaren bij verschillende behandelcombinaties berekend. Om deze effecten te kunnen vertalen naar de impact voor de gehele Nederlandse HFrEF populatie, zijn gegevens nodig over de huidige combinaties van geneesmiddelen bij HFrEF patiënten en voor elk van de combinaties gegevens over het aantal patiënten dat viervoudige therapie goed kan verdragen. Omdat deze gegevens ontbreken is hiervan een schatting gemaakt op basis van expert opinion van vier cardiologen. Deze schatting is gecombineerd met de berekende effecten op ziekenhuisopnames en gewonnen levensjaren. Deze berekening laat zien dat optimaal inzetten op OMT resulteert in ruim 800 minder ziekenhuisopnames en ruim 300 gewonnen levensjaren per 10.000 HFrEF patiënten in de eerste vijf jaar na start behandeling.

1. Introduction

The 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure define Optimal Medical Therapy (OMT) in patients diagnosed with HFrEF as a quadruple therapy consisting of the following four drug classes: ARNi or ACEi, BB, MRA, and SGLT2i (McDonagh et al. 2022).1 Although exact data are lacking, the available data as well as anecdotal evidence suggest that current Dutch clinical practice is often not in line with OMT. There may be various explanations for this, including a lack of familiarity with the updated ESC guidelines, concerns about patient tolerance for some of the drugs in quadruple therapy, and uncertainty about the added value to patients of adhering to OMT. This report focusses on the last possibility and aims to reduce the uncertainty surrounding the value of OMT in the Dutch context. To this end, a cost effectiveness analysis is carried out in which OMT is compared to other medical therapies. In this cost effectiveness analysis, drivers of differences in cost effectiveness between medical therapies are differences in mortality, disease progression and hospitalization.

The analysis in this report is based on a model that tracks a hypothetical cohort of 10.000 HFrEF patients over time until death. Patient characteristics (such as gender, age, DM2) are based on the Check-HF study (Brunner-La Rocca et al. 2019). By comparing the cumulative number of quality adjusted life years (QALYs) realized by this cohort under the different treatment combinations analysed, as well as the cumulative costs of HF-drugs, other healthcare costs (HF-related and non-HF-related) and costs of informal care, the cost effectiveness of different treatment combinations is determined. Following the Dutch guidelines for pharma-economic analyses, a social perspective is chosen. In this case, this implies that costs of informal care are included. Moreover, in accordance with the recent update of the Dutch guidelines for pharmaco-economic analyses, all costs are discounted by 3 percent per annum while QALYs are discounted by 1.5 percent per annum. Also in accordance with this update, unrelated medical costs are included in the base case. Unrelated medical costs consist of medical costs not related to HFrEF, e.g. costs of nursing home care if this care is unrelated to HFrEF. As will become clear from the results presented below, inclusion or exclusion of unrelated medical costs has a large impact on costs and hence on cost-effectiveness.

[1] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium–glucose co-transporter 2 inhibitor.

2. Literature review

2.1 Cost effectiveness studies of medical treatment of HFrEF

The most recent systematic review of cost effectiveness studies of medical treatment of HFrEF is Di Tanna et al. (2018). A central finding from his review is that a large majority of European studies find the additional costs per QALY gained (i.e. the incremental cost effectiveness ratio or ICER) of HF drugs compared to placebo are well below 10K euro. Two Dutch HF cost-effectiveness studies included in this systematic review are Ramos et al. (2017) and van der Pol et al. (2017). Both studies compare the ARNi sacubitril/valsartan with the ACEi enalapril in adult patients with chronic HFrEF in the Netherlands. Ramos et al. (2017) find that the ICER of sacubitril/valsartan is €17,600 if unrelated medical costs are not included and €28,000 if these cost are included. Van der Pol et al. (2017) arrive at an ICER of €19,100 if unrelated medical costs are not included (they do not report the effect of including costs in life years gained). Of the studies included in the review, 28 were based on a so-called Markov model, often using New York Heart Association (NYHA) disease classifications to establish disease severity. Only 1 very recent study (Dixit et al. 2023) analyses a range of different treatment combinations, which is also the aim of the present report. They include ACE+BB, ACE+BB+MRA and ARNi+BB+MRA+SGLT2i; other treatment combinations such as ACE+BB+MRA+SGLT2i are not included.

Two more recent studies, also not included in the review of Di Tanna et al. (2018), use a different classification than the New York Heart Association (NYHA) disease classifications to establish disease severity, namely the Kansas City Cardiomyopathy Questionnaire (KCCQ). The first of these studies is McEwan et al. (2020), henceforth referred to as MEW, the second Tafazolli et al. (2022), henceforth referred to as TAF. MEW use the KCCQ Total Symptom Score [TSS] to classify patients into KCCQ quartiles, while TAF use the KCCQ Clinical Summary Score [CSS]. TAF motivate their choice as follows:

> "The KCCQ-CSS was selected as the basis for the health states used in the model because the KCCQ tool is an established and prognostically important patient-reported measure of health status in HFrEF [16–19] that health technology assessment bodies regard as appropriate for decision-making, sidestepping issues associated with alternative measures such as New York Heart Association (NYHA) functional classifications (these issues are summarized in the Discussion section). Of note, the KCCQ-CSS is more comprehensive than the measure employed in the aforementioned dapagliflozin study (i.e. the KCCQ Total Symptom Score [TSS]), encompassing not merely symptom burden and frequency, but also physical limitation." (TAF p. 1). [2]

In this report, extensive use is made of the published model parameters in MEW and TAF and in particular their online supplements.3 The reasons for this choice are as follows:

1. By modelling transitions between KCCQ-quartiles, these models explicitly take into account the fact that HFrEF is a progressive disease.4
2. The model of MEW has already been used in a recent cost effectiveness study for The Netherlands (Zorginstituut 2021).

[2] Possibly (partly) due to this difference in the KCCQ score used, transition probabilities between KCCQ-quartiles also differ substantially between the KCCQ quartiles in the two studies (see Appendix I). However, the difference may also be caused by differences in statistical techniques (which are only cursory discussed in both papers). Both papers use different transition probabilities for the short term and longer term(s), but with different time divisions: MEW 0-4 months and >4 months, TAF 0-3, 4-8 and >8 months.
[3] The model by McEwan et al. was also used in the NL analysis presented in the Poster by Kvamme et al. (2023).
[4] The choice of the KCCQ classification rather than the NYHA classification in this report is exclusively based on the availability of transition probabilities and other parameters from published sources (i.e. MEW and TAF).

3. Treatment combinations included in this report

The treatment combinations included in the present study were selected using a combination of data on actual drug use by HF-patients in The Netherlands and expert opinion. This resulted in the following 9 treatment combinations: [5]

1. BB+ARNi+MRA+SGLT2i
2. BB+ACEi+MRA+SGLT2i
3. BB+ARNi+MRA
4. BB+ARNi+SGLT2i
5. BB+MRA+SGLT2i
6. ARNi+MRA+SGLT2i
7. BB+ACEi+MRA
8. BB+ACEi+SGLT2i
9. BB+ACEi

The inclusion of these different (mostly triple) treatment combinations allows pairwise comparisons between OMT and "OMT minus 1", and is informative of the effect of adding a fourth drug (and in the case of BB+ACEi also a third drug) to each of these combinations. All combinations are currently being used in clinical practice. However, the frequency with which the different combinations are currently being used is unknown, because separate data on drug use for the HF subpopulation HFrEF is not available.

[5] In previous drafts of this report, also BB monotherapy was included. However, a panel of 4 cardiologists consulted in an expert meeting (see below) indicated that BB monotherapy occurs very rarely.

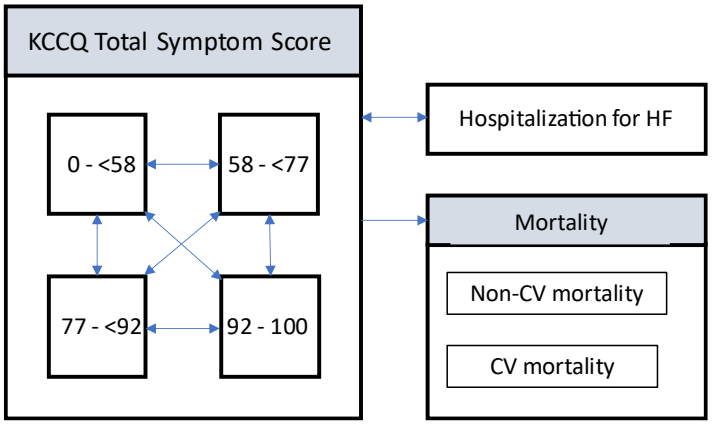
4. Modelling approach: progression as transitions between KCCQ quartiles

Medication which postpones progression of HFrEF also reduces mortality, improves quality of life and reduces the number of adverse events and associated healthcare costs. Therefore, when modelling cost-effectiveness it is important to include the effects of different treatment combinations on progression. Only recently has this become the standard approach in HFrEF cost effectiveness studies (Di Tanna et al. 2018). In these recent models progression is usually modelled as a Markov model with transitions between NYHA or KCCQ quartiles. In these models, the effect of improved pharmacological treatment operates through two channels:

1. by reducing the probability of adverse events, hospitalization and death within each quartile;
2. by slowing down progression to KCCQ-quartiles with higher mortality probabilities.

Figure 1, based on McEwan et al. (2020), illustrates this modelling approach.

Figure 1. Model structure



Source: Based on McEwan et al. (2020)

This report follows the approach of MEW, and models progression as transitions between KCCQ-quartiles. In this type of model, transition probabilities between KCCQ quartiles combined with mortality probabilities by KCCQ quartile determine the evolution over time of the HF population in each KCCQ quartile. Once the HF population in each KCCQ quartile at any given point in time is determined, the monthly number of hospitalizations is computed by applying hospitalization probabilities to each KCCQ-quartile (differentiated between treatment arms). Finally, costs and utilities are computed by multiplying the population in each KCCQ-quartile by the corresponding treatment costs and utilities, taking into account costs and disutility of hospitalization.

5. Data

This section discusses the main aspects of the data used in the analysis. Further details are presented in Appendix I. A number of inputs were validated in an expert session with 4 Dutch cardiologists. When this was the case, this will be indicated below.

5.1 Survival probabilities, transition probabilities and hospitalization: methodology

An important empirical building block for models based on transitions between KCCQ-quartiles are survival probabilities differentiated by KCCQ-quartile. These probabilities (differentiated by age and KCCQ-quartile) can be computed using the published risk equations in the online supplements of MEW and TAF for the Dapa+SoC and Empa+SoC populations in the DAPA-HF and EMPEROR-reduced trials. The resulting survival probabilities correspond to the HF-drugs used in the SoC and treatment arms in these trials, *not* to the treatment combinations analysed in this report. In order to obtain survival probabilities corresponding to the treatment combinations analysed in this report, the risk equations in MEW and TAF were adjusted using relative morality risks (RRs) from the literature, recently summarized in the meta-analysis of different pharmacological treatment combinations in HFrEF by Tromp et al. (2022). This meta-analysis, which serves as the main source for the RRs used in this report, contains RRs for all-cause (AC) and cardiovascular (CV) mortality for different pharmacological treatment options, as well as RRs for the composite outcome CV mortality or (first) hospitalization, but not separately for hospitalization. Moreover, Tromp et al. (2022) do not provide RRs for every treatment combination included in this report. Therefore, in a number of cases the RRs in Tromp et al. (2022) had to be combined to derive the required RRs (see Appendix I for details). Furthermore, if monthly mortality probabilities using these models were lower than monthly mortality probabilities of the overall population of the same age and gender, the latter probabilities were used.[6] Details of these derivations are provided in Appendix I. The resulting survival rates by KCCQ-quartile are presented in table 1.

[6] In one sensitivity analysis, the lowest computed mortality rate across all KCCQ-quartiles and treatment combinations was replaced by the mortality rate of the overall population if the latter was higher, and the relative differences in mortality that follow from the risk models where applied to this series (see Appendix II).

Table 1. Survival

1 year Survival, %				
Treatment combination	KCCQ1	KCCQ2	KCCQ3	KCCQ4
ARNi+BB+MRA+SGLT2i	93.0	95.9	97.3	97.7
ACEi+BB+MRA+SGLT2i	91.3	94.9	96.7	97.1
ARNi+BB+MRA	91.6	95.0	96.8	97.2
ARNi+BB+SGLT2i	90.9	94.6	96.5	97.0
BB+MRA+SGLT2i	90.8	94.5	96.4	96.9
ARNi+MRA+SGLT2i	91.1	94.7	96.6	97.0
BB+ACEi+MRA	90.8	94.5	96.4	96.9
BB+ACEi+SGLT2i	89.9	94.0	96.1	96.6
ACEi+BB	87.9	92.8	95.3	95.9
5 year Survival, %				
Treatment combination	KCCQ1	KCCQ2	KCCQ3	KCCQ4
ARNi+BB+MRA+SGLT2i	67.7	79.7	86.4	87.9
ACEi+BB+MRA+SGLT2i	61.4	75.3	83.3	85.3
ARNi+BB+MRA	62.5	76.1	83.9	85.8
ARNi+BB+SGLT2i	60.0	74.3	82.6	84.7
BB+MRA+SGLT2i	59.4	73.9	82.3	84.4
ARNi+MRA+SGLT2i	60.6	74.7	82.9	85.0
BB+ACEi+MRA	59.4	73.9	82.3	84.4
BB+ACEi+SGLT2i	56.5	71.8	80.8	83.0
ACEi+BB	50.1	66.9	77.2	79.9
10 year Survival, %				
Treatment combination	KCCQ1	KCCQ2	KCCQ3	KCCQ4
ARNi+BB+MRA+SGLT2i	43.5	61.6	70.3	71.5
ACEi+BB+MRA+SGLT2i	35.3	54.6	66.9	69.2
*ARNi+BB+MRA	36.6	55.8	67.6	69.7
ARNi+BB+SGLT2i	33.6	53.1	65.9	68.5
BB+MRA+SGLT2i	32.9	52.4	65.5	68.2
ARNi+MRA+SGLT2i	34.3	53.7	66.4	68.8
BB+ACEi+MRA	32.9	52.4	65.5	68.2
BB+ACEi+SGLT2i	29.5	49.2	63.3	66.5
ACEi+BB	22.8	42.4	57.6	61.8

Source: see text.

5.2 Transition probabilities

A second empirical building block for the analysis in this report consists of transition probabilities between KCCQ-quartiles. Again, these transition probabilities are available only for the DAPA-HF and Emperor-reduced trials (and published in the online materials of MEW and TAF), not for the treatment combinations analysed in this report. Two methods have been used to address this problem. The first method is based on an extrapolation of differences in transition probabilities in the two arms of MEW and TAF. The second method is based on an extrapolation of the *effects* of differences in transition probabilities on the HF-population by KCCQ quartile. Appendix I describes these two methods in more detail. Unexpectedly, the transition probabilities from both MEW and TAF generate a net flow to *healthier* states. However, this is in line with the findings from the DAPA-HF trial, according to which both arms show an improvement in mean KCCQ scores. Kosiborod et al. (2020) interpret this as a placebo effect.[7] The net flow to healthier states is larger in the treatment arm, and the *difference in improvement* is interpreted as the treatment effect.

[7] The following citation from Kosiborod et al. (2020) makes this point explicitly "It should further be noted that the NNT for clinically meaningful improvements in KCCQ observed in the DAPA-HF trial should be interpreted in the context of comparing dapagliflozin-treated patients with those that received placebo (**who also experienced an improvement in health status, consistent with a sizable "placebo effect**," seen in our study, in the DEFINE-HF trial with dapagliflozin, and in placebo-controlled trials of other agents in HFrEF)."(p. 097)

5.3 Treatment discontinuation

The sensitivity analysis presented in Appendix II indicates that discontinuation has only a very small effect on the incremental cost effectiveness ratio (ICER). The reason is that varying the rate of discontinuation has hardly an effect on the distribution of the population over the different KCCQ-quartiles over time. It can be shown in that case, the ICER is also insensitive to the rate of discontinuation. See Appendix II for further details. Still, discontinuation does affect the components which make up the ICER, including life years gained and hospitalizations. Since these are important outcomes in and of themselves, it is important to apply a realistic modelling of discontinuation.

Discontinuation rates during the first year after start treatment are very high for all HFrEF drugs. This was demonstrated in two recent observational studies based on data on patients discharged after HF-hospitalization from Japan, Sweden, UK and US (table 2). Except for ACEi, the two studies arrive at very similar discontinuation rates.[8]

Table 2. Discontinuation after 1 year (%)

	A.	B.
SGLT2i (dapaglifozin)		24
ARNi	27	27
ACEi	55	38
ARB	33	33
BB	24	25
MRA	40	42

Note: the SGLT2i dapaglifozin was included only in the second study.
Sources: A.: Savarese 2021 (Sw, Uk, US), B.: Savarese 2023 (Jap, Sw, US)

Treatment discontinuation for dapaglifozin relatively low according to study B (Savarese (2023)), but still high in absolute terms. These discontinuation rates are much higher than the discontinuation rate used by MEW, who only mention discontinuation in passing: "Patient time on treatment was informed by the annual probability of premature discontinuation derived from DAPA-HF (7% per annum)." (MEW p. 2150). By contrast, Tafazzoli et al. find a rate of discontinuation that is much closer to those in table 2: "KM estimates of time to treatment discontinuation from the EMPEROR-Reduced trial show that the probability of remaining on treatment with empagliflozin at 2 years is approximately 70%. Our model estimates based on the exponential distribution (between 51% for KCCQ Q1 and 80% for KCCQ Q4) are consistent with the trial data."[9]

One year discontinuation rates computed using the TAF model are shown in table 3. These discontinuation rates (transformed into monthly rates) have been used during the first 18 months after initiation of treatment. After 18 months, no further discontinuation is assumed in the base case. In a sensitivity analysis discontinuation is assumed to continue at a slower pace (25% of the discontinuation rate in the first 18 months). These modelling choices were validated in the expert session with cardiologists.

[8] Both studies distinguish between HFrEF and other HF, but the authors state: "One main limitation of our study was the unavailability of ejection fraction assessments, and therefore we could not define whether we enrolled patients with HFrEF rather than with mid-range or preserved ejection fraction. However, the enrolment of new users of HFrEF GDMT following a HHF has been used to minimize the proportion of patients without indication". (Savarese 2021).
[9] Email Reifsnider, coauthor of TAF.

Table 3. Discontinuation after 1 year, conditional on survival

KCCQ-quartile	%
KCCQ TSS Q1: 0-<58	48,8
KCCQ TSS Q2: 58-<77	34,6
KCCQ TSS Q3: 77-<92	21,7
KCCQ TSS Q4: 92—100	16,5

Source: calculated from coefficients in the appendix of Tafazolli et al. (2021)

A consequence of the high rate of treatment discontinuation is that a cohort of patients who start on quadruple therapy, will over time split into a fairly large number of subgroups using various combinations of 3, 2, 1 or 0 of the 4 drugs on which they started. Accounting for this would complicate the model and requires data on discontinuation at a level of detail that is lacking. Therefore, we follow a simplified approach and use the discontinuation data from TAF for all treatment combinations (see table 4). The reason for using the TAF rather than the MEW data in this case, is that only TAF differentiate the discontinuation rate across KCCQ-quartiles. It is assumed that after discontinuation, mortality and hospitalization probabilities of BB + ACEi apply. The latter assumption was validated in the expert session with cardiologists.

Table 4. Monthly discontinuation rates

	Mean (%)	Se	Distribution in used in PSA
KCCQ TSS Q1: 0-<58	2.75	0.28	Beta
KCCQ TSS Q2: 58-<77	1.95	0.17	Beta
KCCQ TSS Q3: 77-<92	1.14	0.10	Beta
KCCQ TSS Q4: 92--100	0.93	0.08	Beta

Sources: Computed from the model in appendix TAF and email Reifsnider (co-author of TAF). The delta method was used to obtain standard errors corresponding to monthly rates (the parameters in TAF refer to daily rates).

5.4 Hospitalization

Hospitalization is the only adverse event included in the analysis in this report, apart from mortality. The reason for this choice is that the studies by MEW and TAF, and also the Dutch cost-effectiveness study based on the MEW model (Zorginstituut 2021), clearly indicate that hospitalization is the only event that results in substantial HF-related treatment costs and utility losses. Data on relative risks of hospitalization by KCCQ-quartile for other treatment combinations than those included in MEW and TAF are not available. However, the earlier mentioned meta-analysis of Tromp et al. (2020) provides RRs for CV mortality and the RR of the composite outcome mortality or (often first) hospitalization for a number of treatment combinations. It is possible to derive from these data the RR of hospitalization; see Appendix I for the methodology and data employed. Table 5 shows the results of this derivation.

Table 5. Annual probability of at least one hospitalization, %

Treatment combination	KCCQ1	KCCQ2	KCCQ3	KCCQ4
BB+ARNi+MRA+SGLT2i	23.8	14.7	8.8	5.6
BB+ACEi+MRA+SGLT2i	30.5	18.7	11.1	7.0
BB+ARNi+MRA	34.5	21.0	12.4	8.0
BB+ARNi+SGLT2i	37.7	22.9	13.5	8.6
BB+MRA+SGLT2i	43.6	26.2	15.4	9.8
ARNi+MRA+SGLT2i	33.5	20.5	12.1	7.7
BB+ACEi+MRA	43.6	26.2	15.4	9.8
BB+ACEi+SGLT2i	68.3	39.9	23.0	14.5
BB+ACEi	68.3	39.9	23.0	14.5

Note: for BB+MRA+SGLT2i hospitalization probabilities of BB+ACEi+MRA are used, see Appendix I.

5.5 Medicine costs

Table 6 presents the data used on medicine costs, including a standard markup for the costs of delivery by an apothecary costs. These costs refer to December 2022. The costs for the various treatment regimens based on these per-drug costs are shown in table 7.

Table 6. Annual cost per patient of individual drugs

Drug class	Annual costs per patient, euro
SGLT2i (dapagilfozin)	521
ACE (enalapril)	50
ARNI (sac/val)	1567
MRA (50/50 mix of eplerenon and spironolacton	138
BB (metoprolol)	65

Source: Z-Index, prices December 2022. For each drug €26 was added for apothecary costs

Table 7. Annual cost per patient of drug combinations

Drug combination	Costs per patient per year
ARNi+BB+MRA+SGLT2i	2290
ACEi+BB+MRA+SGLT2i	774
BB+ARNi+MRA	1770
BB+ARNi+SGLT2i	2152
BB+MRA+SGLT2i	723
ARNi+MRA+SGLT2i	2225
BB+ACEi+MRA	253
BB+ACEi+SGLT2i	254
BB+ACEi	116

Source: calculated from data in table 6.

5.6 Other costs and utilities

Data on costs other than drugs, utilities as well as the distributional assumptions used in the probabilistic sensitivity analysis are shown in table 8.[10] These data are sourced from the aforementioned Dutch cost effectiveness analysis for dapaglifozin (Zorginstituut, 2021). Since the cost data in that report refer to 2019, an inflation correction was applied in order to arrive at the end of 2022 price level. Following the approach in Zorginstituut (2021), the adjustment is based on the CBS consumer price index.[11] This resulted in an upward adjustment of all non-drug prices of 14.3%.

Table 8. Other cost and utilities

Item	Mean	Sd	distribution
Hospitalization costs (per event)	€ 4927	20% of mean	gamma
Background costs HF (annual)	€ 570	20% of mean	gamma
Costs DM2 (annual)	€ 971	20% of mean	gamma
Cost informal care (per hour)	€ 17	20% of mean	gamma
Unrelated medical costs	Age dependent, based on PAID-tool		Not randomized
Costs medication in SoC (DAPA-HF)	€ 250		
Hours informal care (per month)			
KCCQ1	45	10,9	normal
KCCQ2	25	8,0	normal
KCCQ3	9	3,5	normal
KCCQ4	9	3,5	normal
After hospitalization	32	12,9	normal
Utilities			
KCCQ1	0.615	0.016	beta
KCCQ2	0.735	0.016	beta
KCCQ3	0.792	0.016	beta
KCCQ4	0.832	0.016	beta
DM2 (decrement)	-0.017	0.003	beta
Hospitalization (decrement)	-0.246	0.02	beta

Source: Zorginstituut (2021), updated to 2022 using the CBS CPI

Data on unrelated medical cost, i.e. medical costs not related to heart failure, were computed using the online tool PAID 3.0[12]. The weighted average of the costs for men and women was used, using the shares in the study population as weights. Since the costs in this tool are in 2017 prices, an inflation adjustment of 19.4% was applied to these costs data, again using the CBS CPI.

[10] In the PSA, only the items listed in table 8 and the transition probabilities are randomized. This differs from the approach in Zorginstituut (2021) where patient characteristics such as age, gender, comorbidities and items such as NTproBNP are also randomized. The motivation for this choice is that randomization on these items would mix up the sensitivity analysis and the subgroup-analysis.
[11] https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83131ned/table?dl=5D8B
[12] https://imta.shinyapps.io/PAID3code/

6. Study population

Each simulation of the model starts with a hypothetical cohort of 10.000 HFrEF patients in both arms, equally distributed over 4 KCCQ quartiles at the start of treatment (except in one sensitivity analysis in which all patients are assumed to start in the most health KCCQ-quartile). The base case uses extrapolated survival probabilities and transition probabilities from MEW (see Appendix I). Patient characteristics used in the base case (and most other analyses) are shown in table 9. These characteristics were validated in the aforementioned expert session with cardiologists. Patient characteristics are modified in univariate and probabilistic sensitivity analyses. Furthermore, subgroup analyses are carried out for HF patients with DM2, ischemic heart disease, or a diagnosis of heart failure more than 2 years prior to start of the trials on which the data are based (see Appendix II for the result of the subgroup analyses).

Table 9. Patient characteristics used in the base case

Characteristic	Value used in base case
Age at start treatment	71.4
Gender	33.6% female
Pre-existing comorbidities	None
Median NTproBNP value	1041
Time since diagnosis of HF	<2 year

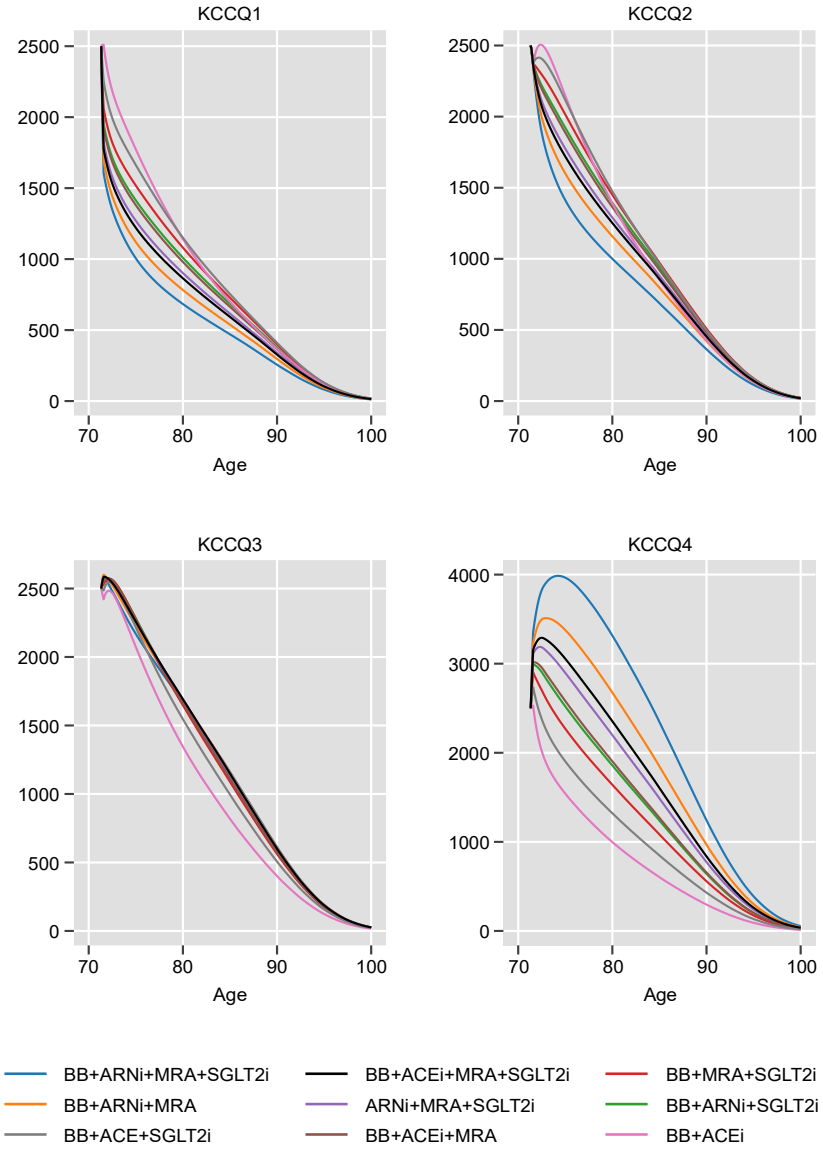
Source: CHECK HF, Brunner-La Rocca et al. (2019) and Brunner-La Rocca, private communication.

7. Results

7.1 Time profiles of the HFrEF population by KCCQ-Quartile

Before turning to the cost effectiveness results, this subsection presents some background outcomes. To start with, figure 2 displays base case results for the HF population by KCCQ-quartile, based on a simulation in which each quartile starts with a population of 2,500 patients. The sharp break a few months after start of the simulation is due to the fact that different transitions probabilities apply during the first four months and later months, following MEW (see Appendix I). Note that initially the population of KCCQ4, the most healthy quartile, increases under most treatment combinations. This unexpected outcome is caused by the fact that the transition probabilities imply a net flow to healthier states (see also section 5.3).

Figure 2. HF-population by KCCQ quartile



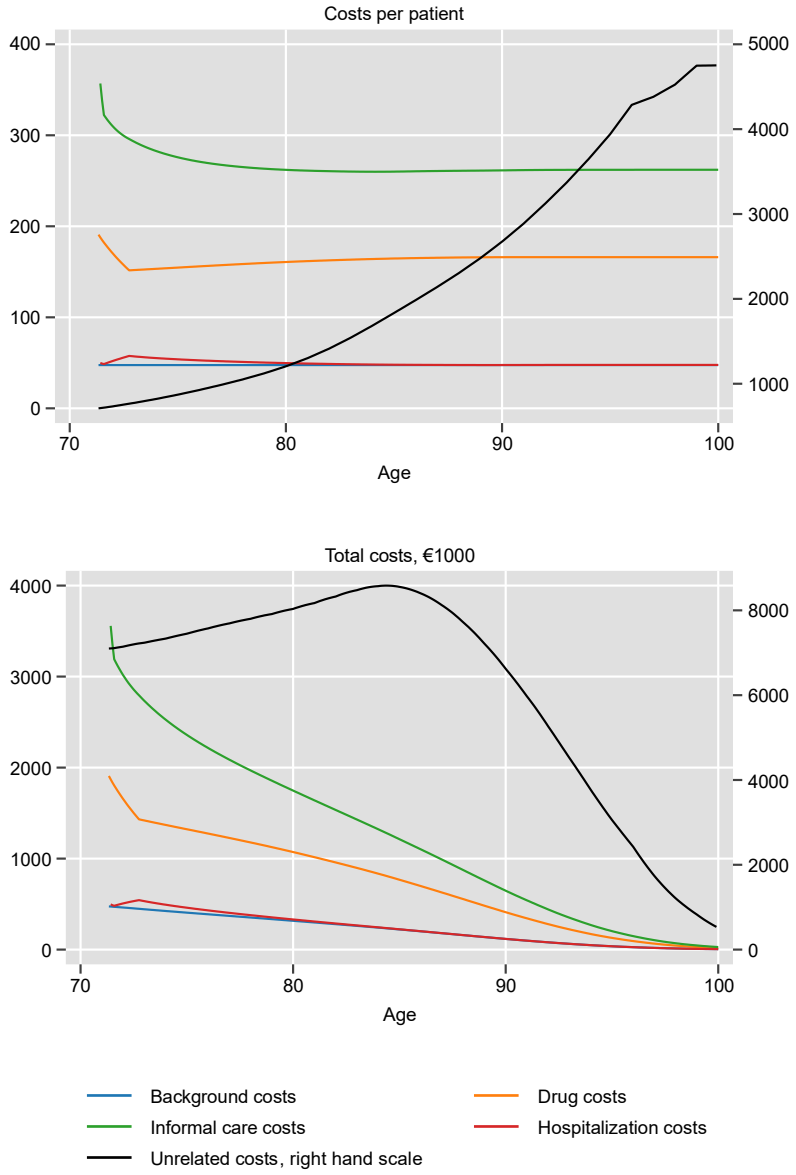
7.2 Time profiles of costs

Figures 3 and 4 show the time profiles of the various cost components included in the study for patients starting on BB+ARNi+MRA+SGLT2i (figure 3) or ACEi+BB (figure 4). Note the very large cost share of unrelated costs (shown on a separate scale). These costs are an important driver of the cost-effectiveness outcomes, as will be shown in a sensitivity analysis that excludes this cost component.

The initial decline in some costs in figure 3 may seem surprising. In the case of informal costs, this is caused by the fact that the per patient costs of informal care depends on KCCQ-quartile in the model. Since the share of the surviving population in the highest KCCQ-quartile increases, this results in a decline of the per patient costs of informal care. Moreover, the break a few months after the start of the simulation is due to the change in transition probabilities after 4 months (this affects informal care costs which depend on the KCCQ-quartile).

For drug costs, the initial fall in costs per patient is caused by discontinuation of treatment, which in the base case only operates during the first 18 months. The slight increase later on is caused by the fact

that the transition probabilities initially result in net increase in the share of the surviving HF population in the healthier KCCQ quartiles, as pointed out in section 5.3.

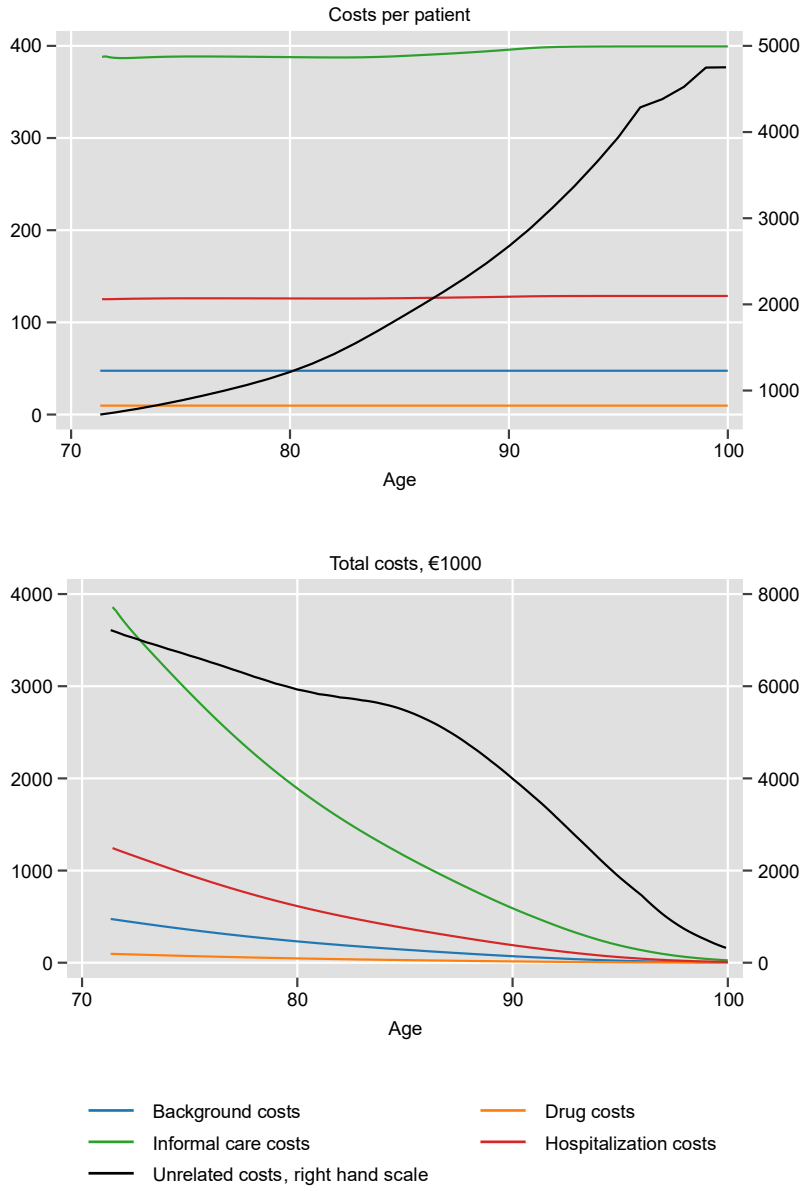


The initial increase in the per patient costs of hospitalization is the net result of two factors. First, discontinuation of treatment, which only operates during the first 18 months, results in an increase in hospitalization. Second, the increase in the share of patients in higher KCCQ-quartiles leads to a lower rate of hospitalization. In the first 18 months, the first effects dominates, while after the first 18 month, only the second effect continues to operate.

Since discontinuation is modelled as a fall back to ACEi+BB, the effect of discontinuation is not present in figure 4. The (small) dynamics in the costs per patient in figure 4 are entirely due to the change in transition probabilities after month 4 and the concentration of the HF population in the lower KCCQ quartiles in later years with BB+ACEi, accounting for a slight rise in the costs of hospitalization and informal care.

Figure 3. Monthly costs (€), BB+ARNi+MRA+SGLT2i

Figure 4. Monthly costs (€), BB+ARNi



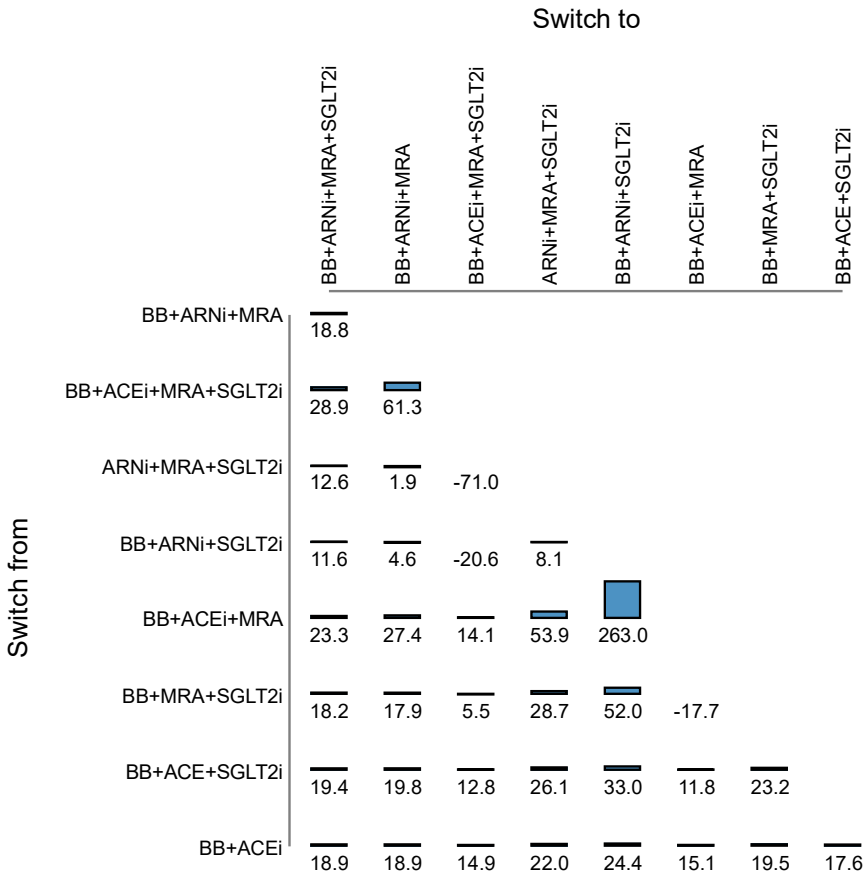
7.3 Base case results: pairwise comparisons of treatment combinations

This section presents pairwise comparisons of all treatment combinations included in the analysis. To start with, figure 5 shows bilateral cost effectiveness ratios (CERs) of all treatment combinations for the base case. These bilateral CERs are defined as the difference in costs between treatment combination A and B, divided by the difference in QALYs between treatment combination A and B. Both costs and QALYs are discounted in this computation (by 3% and 1.5% per annum respectively, in line with the current Dutch guidelines for cost effectiveness analyses). Included in figure 5 are only CERs of moving to a treatment combination that results in a higher number of QALYs. For example, if patients who are currently on BB+ACEi+MRA+SGLT2i switch to BB+ARNi+ARNi+SGLT2i, this leads to additional costs but also to additional QALYs. The additional cost per additional QALY is 28.9 thousand euro.

The following two general conclusions are suggested by figure 6. First, irrespective of the current treatment combination, switching to BB+ARNi+ARNi+SGLT2i is always cost effective. Second, not all switches that result in higher QALYs are cost effective. For example switching from BB+ACEi+MRA to

BB+ARNi+SGLT2i results in more QALYs but at a cost of €263.0 thousand per QALY.

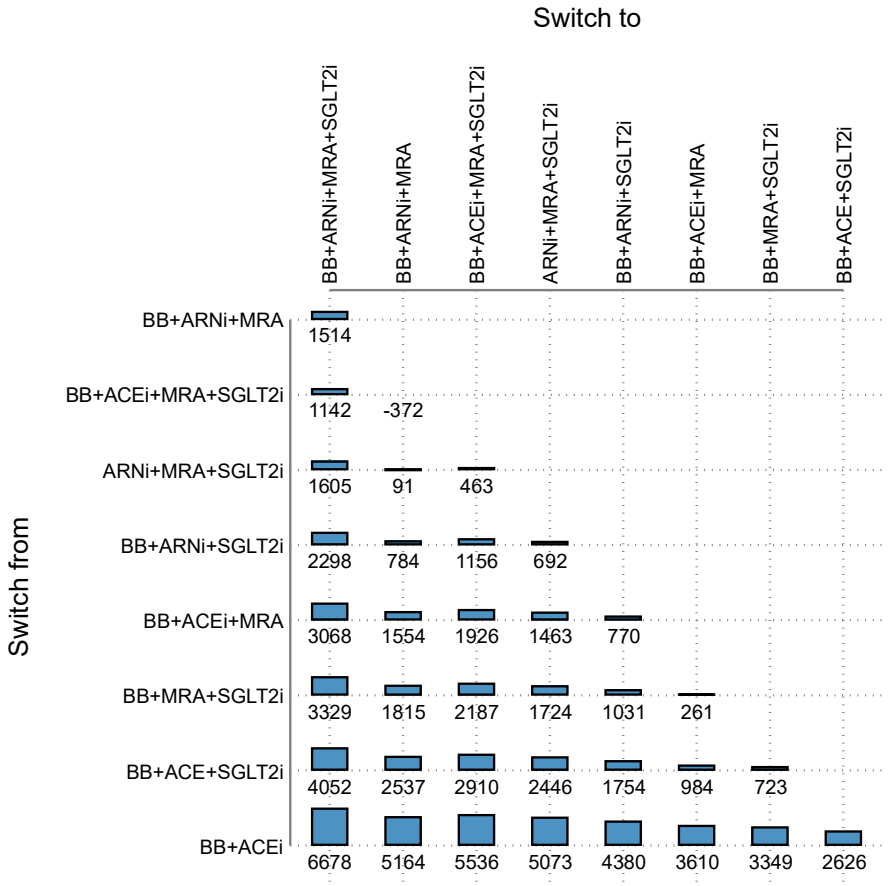
Figure 5. Bilateral cost effectiveness ratios



Note: results for an initial cohort of 10.000 patients equally distributed over KCCQ quartiles.

Some interesting supplementary results that underly these cost effectiveness ratios are shown in figures 6 and 7. Figure 6 shows differences in hospitalizations during the first 5 years after initiation of treatment, for an initial cohort of 10.000 patients equally distributed over KCCQ quartiles. For example, switching form BB+ACEi to BB+ARNi+MRA results in 5164 less hospitalizations.

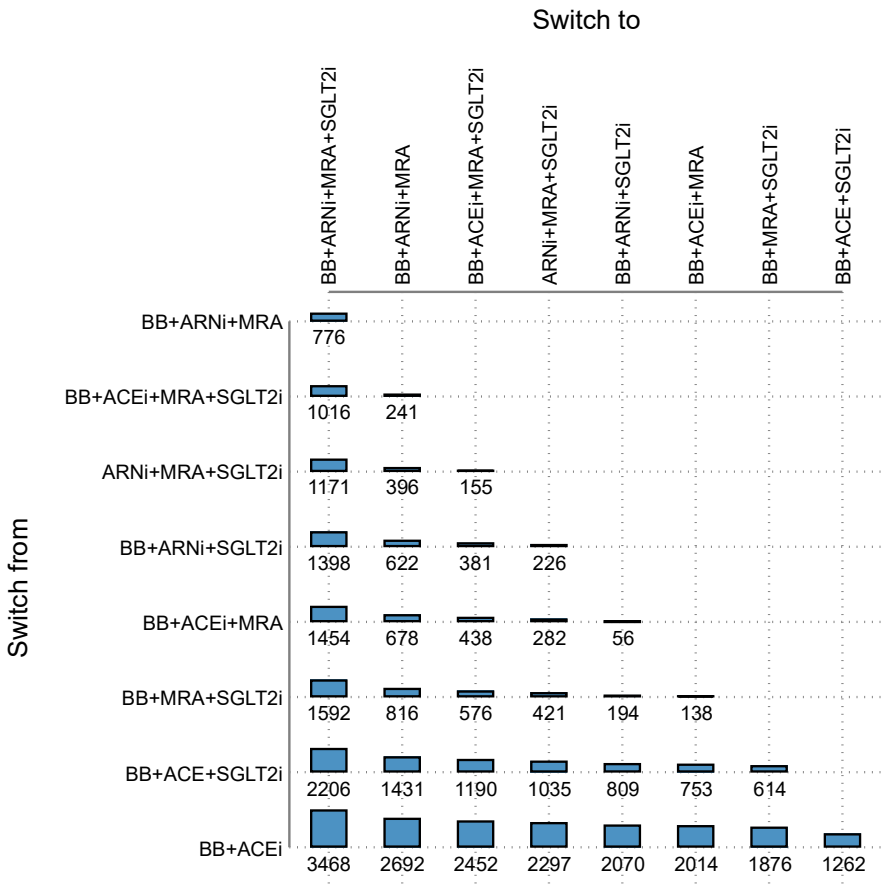
Figure 6. Difference in hospitalizations during the first 5 years after initiation of treatment



Note: results for an initial cohort of 10.000 patients equally distributed over KCCQ quartiles.

Figure 7 shows differences in lifeyears gained during the first 5 years after initiation of treatment, for an initial cohort of 10.000 patients equally distributed over KCCQ quartiles.

Figure 7. Difference in expected lifeyears during the first 5 years after initiation



Note: results for an initial cohort of 10.000 patients equally distributed over KCCQ quartiles.

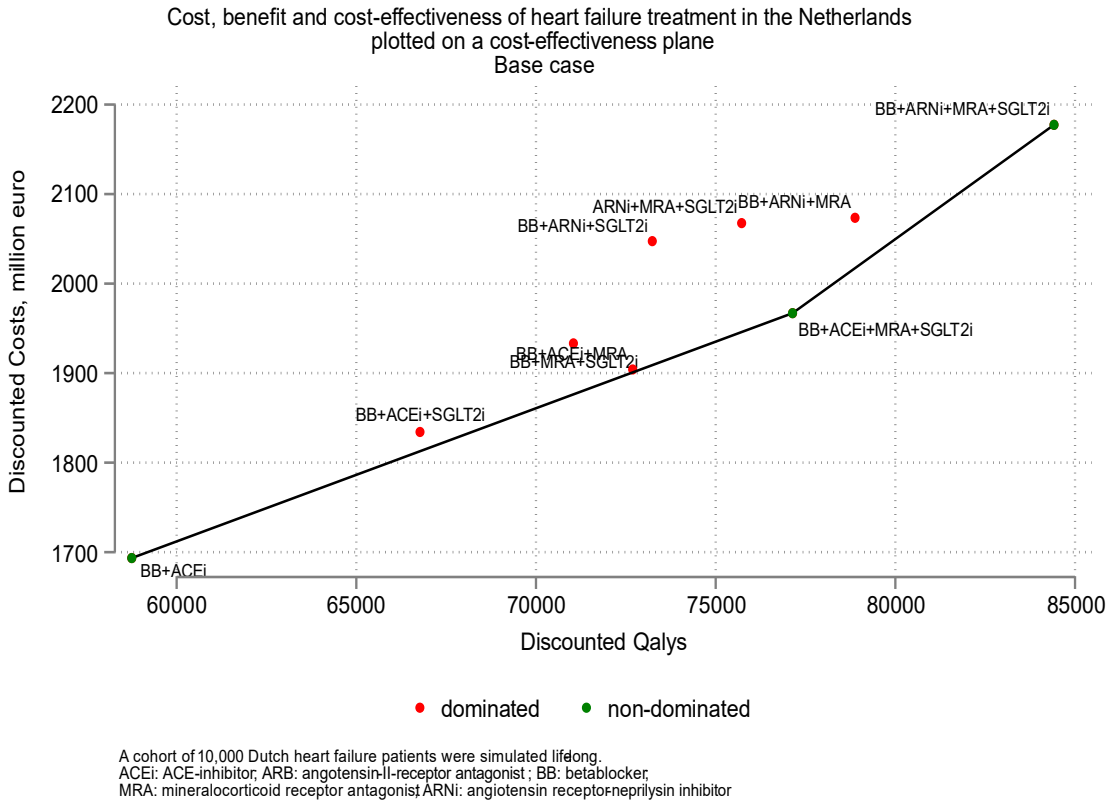
7.4 Base case results: eliminating dominated results

Some of the treatment combinations shown in figures 5-7 in the previous subsection are (extendedly) *dominated* by other treatment combinations. Here, the term *dominated* signifies that the same health gains (as measured by QALYs) can be achieved at lower costs through a combination of other treatment combinations. Table 10 and figure 8 illustrate this for the base case. After elimination of dominated treatment combinations, only two treatment combinations remain, namely the two quadruple therapies (BB+ARNi+MRA+SGLT2i and BB+ACEi+MRA+SGLT2i) and BB+ACEi. Note however that BB+MRA+SGLT2i is almost just as cost effective as BB+ACEi+MRA+SGLT2i. The largest QALY-gain is realized with BB+ARNi+MRA+SGLT2i. AT a 50K € per QALY threshold, the ICER of 28.9K € implies that this treatment combination is cost effective (50K € per QALY is the official threshold used by the Dutch health care institute for heart failure).

Table 10. Costs, QALYs, CERs and ICERs: Base Case

Treatment Combination	Discounted costs, €mln	Discounted QALYs, 1000	CER(1000 €/QALY gained)	ICER(1000 €/QALY gained)
BB+ARNi+MRA+SGLT2i	2177	84.4	18.8	28.9
BB+ARNi+MRA	2074	78.9	61.3	.
BB+ACEi+MRA+SGLT2i	1967	77.1	-71.0	14.9
ARNi+MRA+SGLT2i	2068	75.7	8.1	.
BB+ARNi+SGLT2i	2035	73.2	263.0	.
BB+ACEi+MRA	1904	72.7	-17.7	.
BB+MRA+SGLT2i	1933	71.0	23.2	.
BB+ACEi+SGLT2i	1834	66.8	17.6	.
BB+ACEi	1693	58.8	.	.

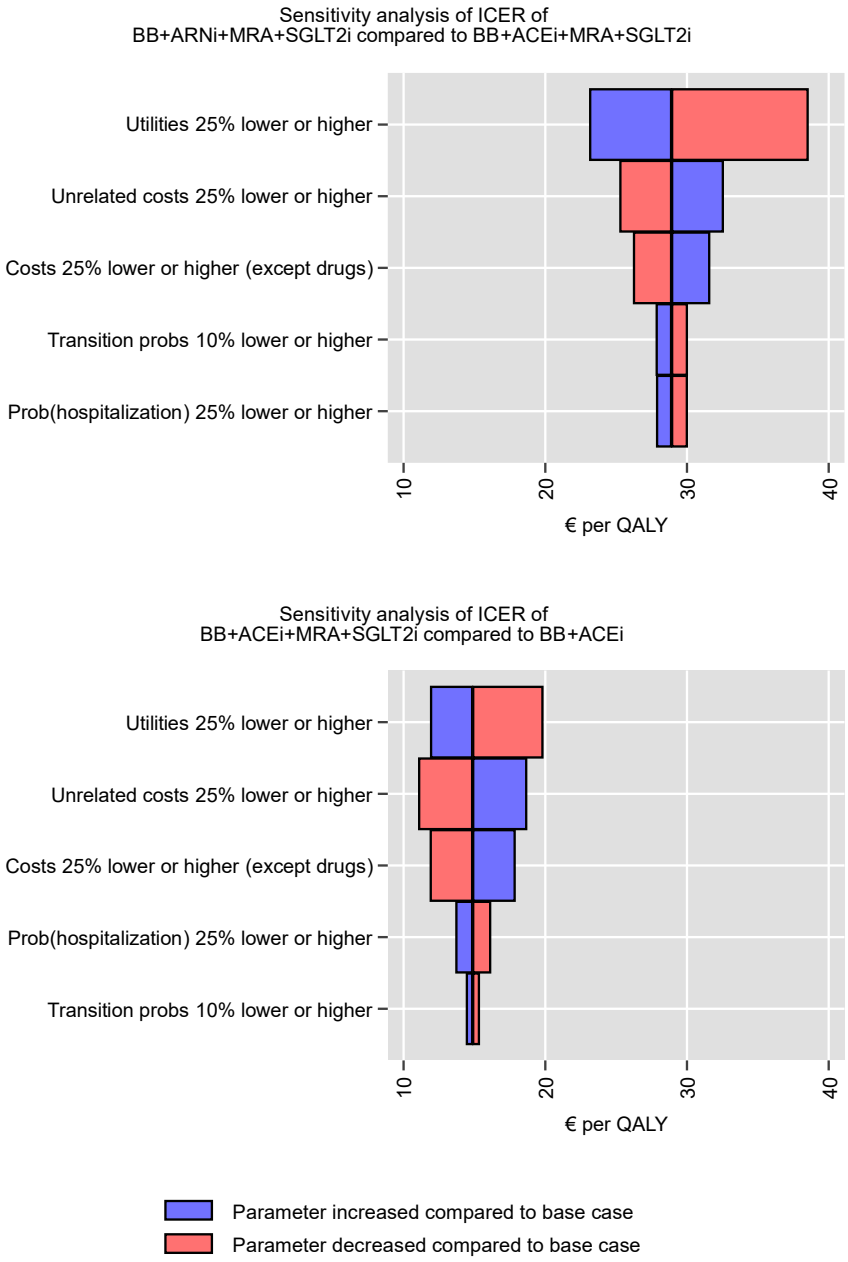
Figure 8. Costs effectiveness shown in the costs-effects plane



A cohort of 10,000 Dutch heart failure patients were simulated lifelong.
ACEi: ACE-inhibitor; ARB: angotensin-II-receptor antagonist ; BB: betablocker;
MRA: mineralocorticoid receptor antagonist; ARNi: angiotensin receptor-neprilysin inhibitor

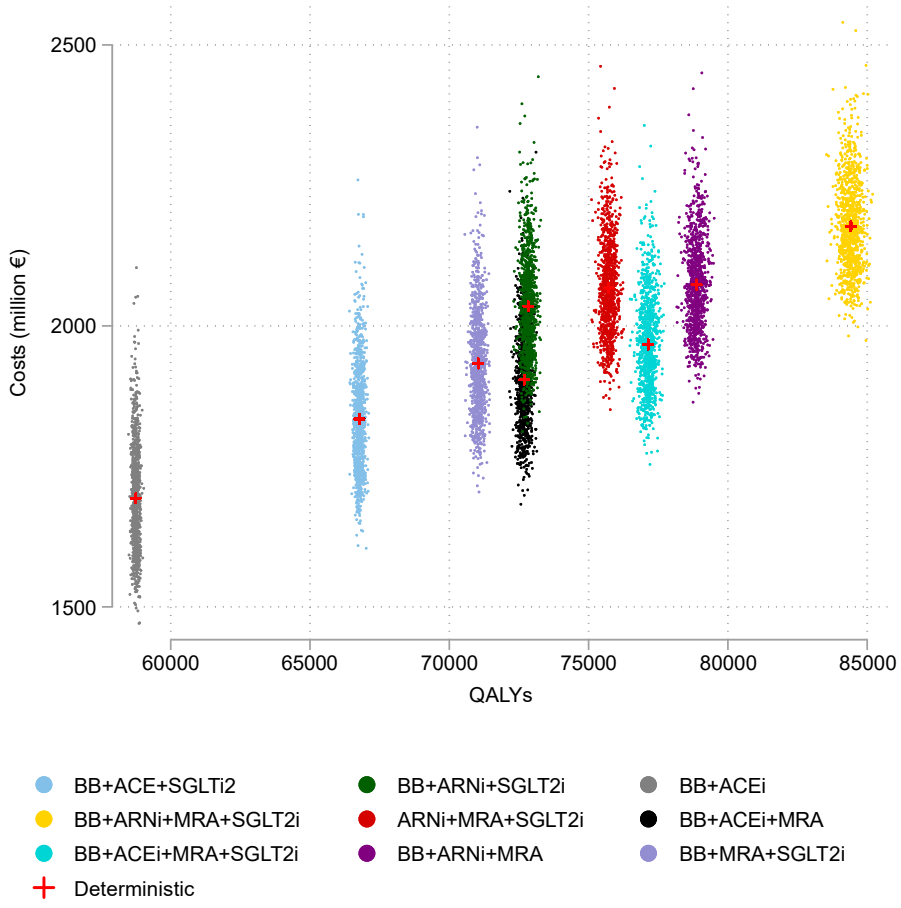
These conclusions are robust to a range of sensitivity analyses and are also valid for various subgroups (see Appendix II). Figure 9 summarizes some of the univariate sensitivity analyses in the form of two tornado diagrams, corresponding to the non-dominated steps in table 10 and figure 8. ICERs in each case are quite sensitive to utilities and cost. However, in all cases the ICERs remain well below the €50K threshold.

Figure 9. Univariate sensitivity analysis



As a further sensitivity check, figures 10 and 11 show the results of a probabilistic sensitivity analysis (PSA). Figure 10 presents the result of the PSA in the cost effectiveness plane. Also shown are the results for the base case (indicated by red crosses in figure 10).

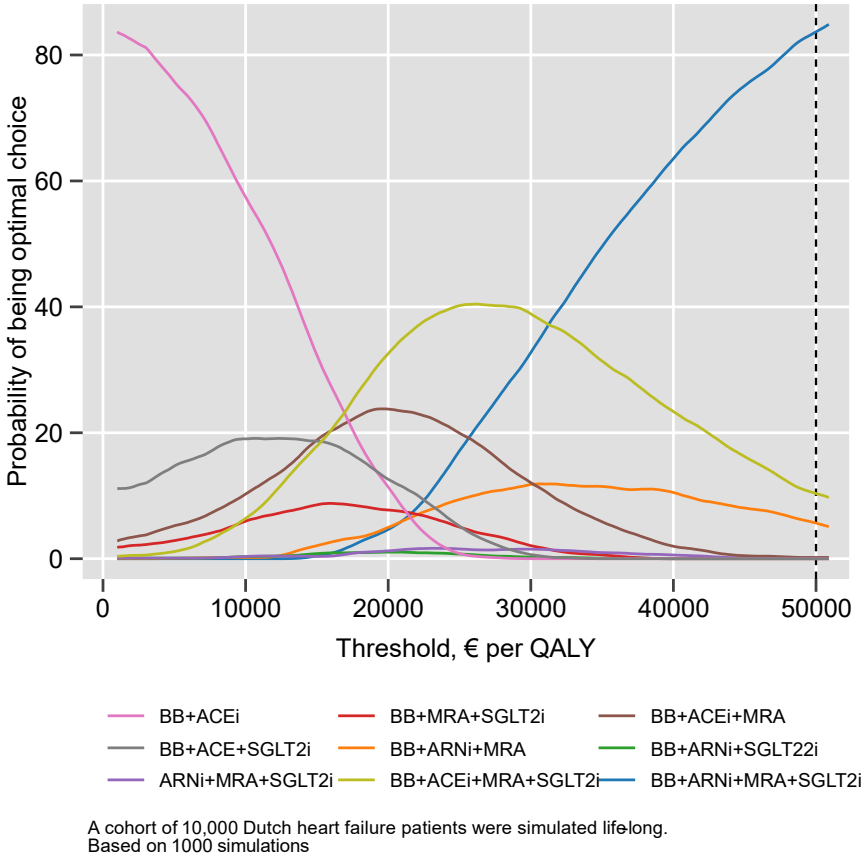
Figure 10. Probabilistic sensitivity analysis in CE-plane*



* Based on 1000 simulations

Figure 11 shown the results of the PSA in the form of a cost effectiveness acceptability curve (CEAC), defined as λ×Qaly minus Cost, where λ represents the threshold value (= willingness to pay for a QALY). At low willingness to pay, ACEi+BB is probably the optimal choice, but at higher willingness to pay, this changes to quadruple therapy. Also drawn is the € 50K threshold. At this threshold value, quadruple therapy with ARNi is the optimal choice with a probability of 80%

Figure 11. Probabilistic sensitivity analysis, CEAC



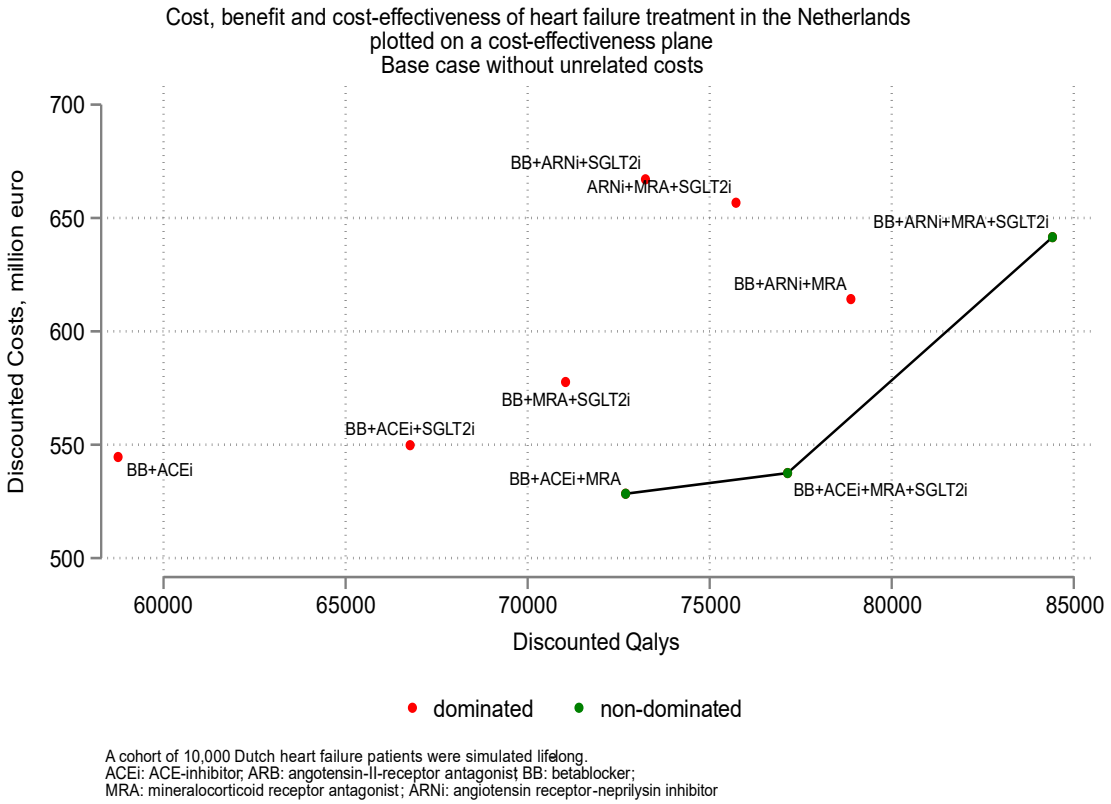
7.5 Base case results without unrelated costs

Since the inclusion of unrelated costs is somewhat controversial, table 10 and figure 12 present results for the base case without these costs. Discounted costs fall by over 50% compared to the base case. As a consequence, the ICER of BB+ARNi+MRA+SGLT2i compared to BB+ACEi+MRA+SGLT2i also drops by about 50%.

Table 10. Costs, QALYs, CERs and ICERs: Base Case without unrelated costs

Treatment Combination	Discounted costs, €mln	Discounted QALYs, 1000	CER(1000 €/QALY gained)	ICER(1000 €/QALY gained)
BB+ARNi+MRA+SGLT2i	642	84.4	4.9	14.3
BB+ARNi+MRA	614	78.9	44.1	.
BB+ACEi+MRA+SGLT2i	538	77.1	-84.1	2.1
ARNi+MRA+SGLT2i	657	75.7	-4.2	.
BB+ARNi+SGLT2i	667	73.2	254.5	.
BB+ACEi+MRA	528	72.7	-29.9	-1.2
BB+MRA+SGLT2i	578	71.0	6.5	.
BB+ACEi+SGLT2i	550	66.8	0.6	.
BB+ACEi	545	58.8	.	.

Figure 12. Base case without unrelated costs



A cohort of 10,000 Dutch heart failure patients were simulated lifelong.
ACEi: ACE-inhibitor; ARB: angotensin-II-receptor antagonist BB: betablocker;
MRA: mineralocorticoid receptor antagonist; ARNi: angiotensin receptor-neprilysin inhibitor

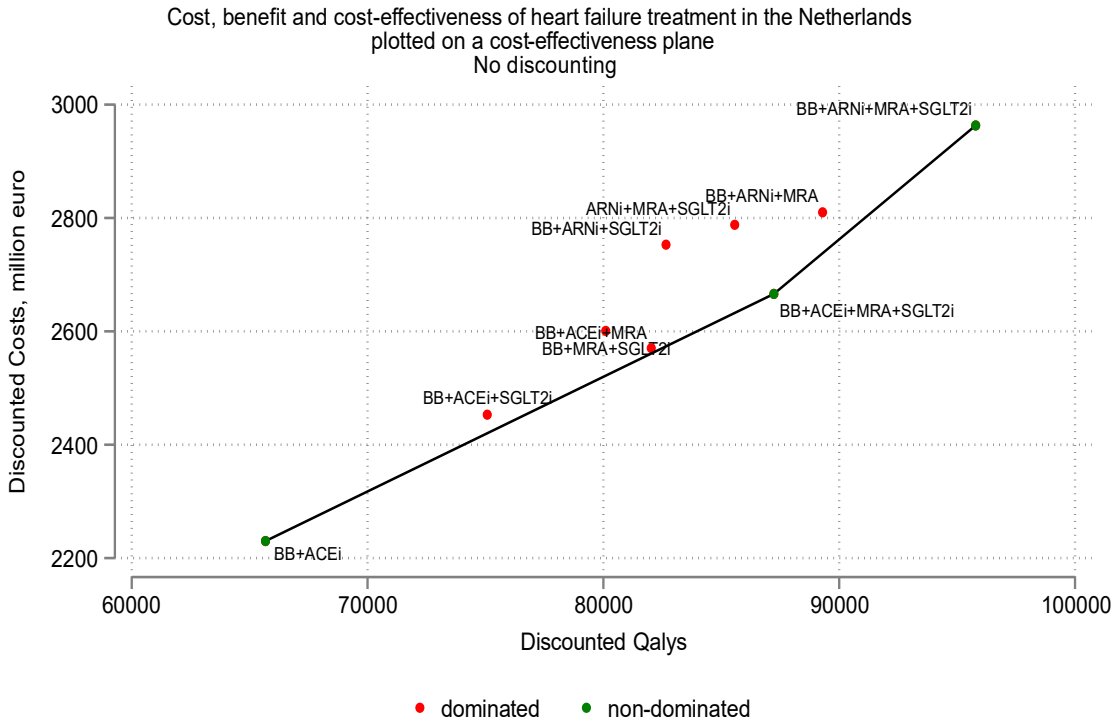
7.6 Base case results without discounting

Table 11 and figure 13 present results for the base case without discounting. Compared to the base case, the same treatment combinations are non-dominated. CERs become somewhat less favourable, which is a consequence of the fact that (in The Netherlands) costs are more heavily discounted than QALYs (3% and 1.5% per annum, respectively).

Table 11. Costs, QALYs, CERs and ICERs: Base Case, undiscounted

Treatment Combination	Discounted costs, €mln	Discounted QALYs, 1000	CER(1000 €/QALY gained)	ICER(1000 €/QALY gained)
BB+ARNi+MRA+SGLT2i	2963	95.8	23.6	34.7
BB+ARNi+MRA	2810	89.3	69.7	.
BB+ACEi+MRA+SGLT2i	2666	87.2	-73.4	20.2
ARNi+MRA+SGLT2i	2788	85.6	12.0	.
BB+ARNi+SGLT2i	2753	82.7	292.3	.
BB+ACEi+MRA	2570	82.0	-15.8	.
BB+MRA+SGLT2i	2601	80.1	29.4	.
BB+ACEi+SGLT2i	2453	75.1	23.7	.
BB+ACEi	2230	65.7	.	.

Figure 13. Base case without discounting

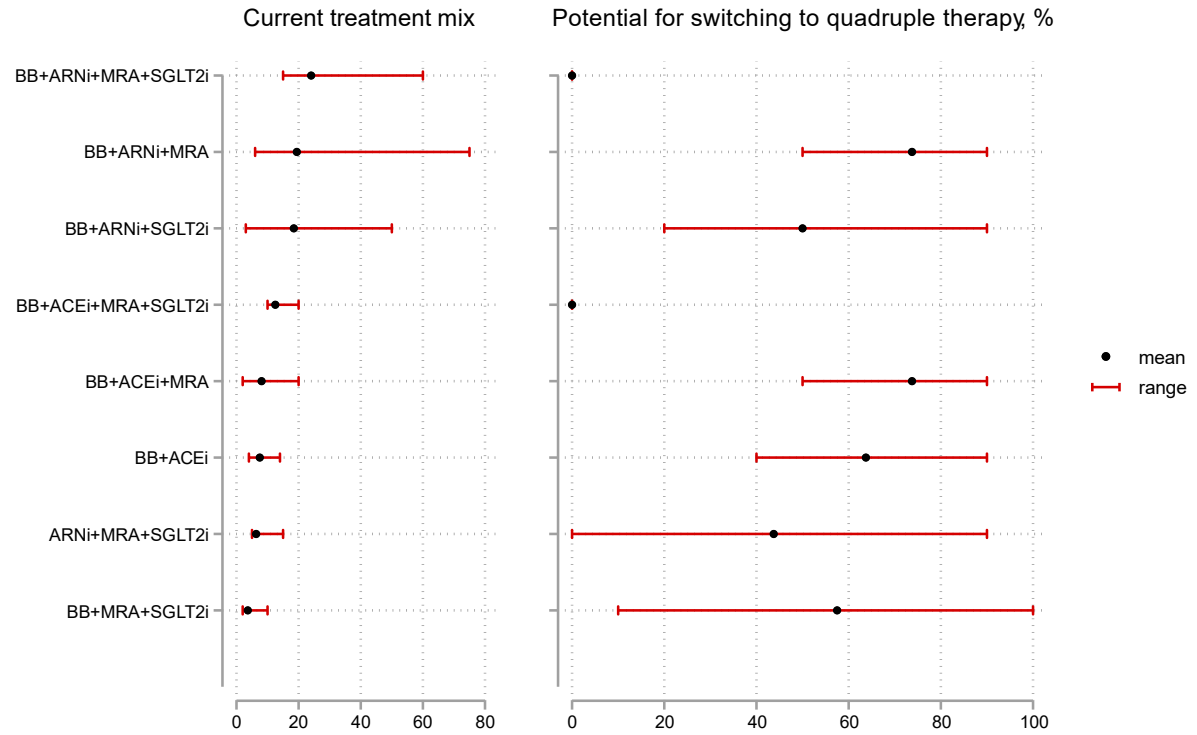


A cohort of 10,000 Dutch heart failure patients were simulated lifelong.
ACEi: ACE-inhibitor; ARB: angotensin-II-receptor antagonist ; BB: betablocker;
MRA: mineralocorticoid receptor antagonist; ARNi: angiotensin receptor-neprilysin inhibitor

7.7 Scenario analysis

Given the findings reported in the previous subsections, it is interesting to assess the effects of moving from the current pharmacological treatment mix in the Dutch HFrEF population to a realistic scenario in with a substantially higher share of patients on quadruple therapy. However, such an analysis requires data on the current pharmacological treatment mix of the Dutch HFrEF population. These data are not available; data from IQVIA, the most important source of this type of data, refers to all HF patients and do not allow zooming in on the HFrEF population. As a partial remedy for this lack of data, the panel of 4 Dutch cardiologists already mentioned in earlier sections was asked to give an indication of both the current treatment mix as well as the potential for switching to quadruple therapy. The answers are summarized in figure 14.

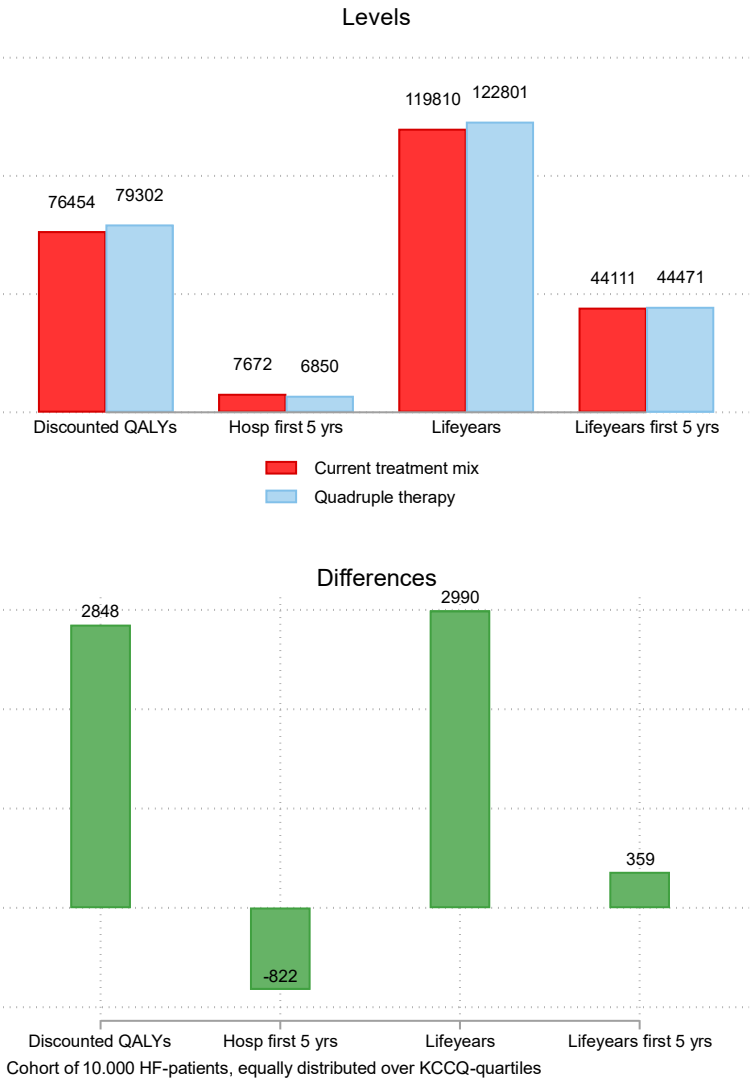
Figure 14. Inputs for scenario analysis



Based on a panel of 4 Dutch cardiologists

Combining the mean values in figure 14 with the results of the base case reported earlier, the effect of switching to quadruple therapy to the extent deemed possible by the panel of 4 cardiologists was determined for various outcomes, for a cohort of 10.000 HFrEF patients. Results are shown in figure 15. The upper panel shows, both for the current treatment mix and the treatment with maximum use of quadruple therapy, the number of QALYs, hospitalizations in the first 5 years after start treatment, life years gained over the whole remaining lifetime and life years gained during the first 5 years after start of treatment. In this analysis, it is assumed that quadruple consists of an equal mix of quadruple therapy including and ACEi and ARNi. The bottom panel of figure 15 shows the differences between the current treatment mix and the maximum potential switch to quadruple therapy. With the caveat that these results are based on expert opinion on the current treatment mix (and not on more solid data), figure 15 makes it clear that switching towards quadruple therapy has substantial benefits in terms of quality of life, hospitalization and life expectancy for HFrEF patients.

Figure 15. Scenario-analysis: effect of switching to OMT, levels



8. Conclusions

The main finding of this report may be briefly summarized as follows: quadruple pharmaceutical therapy including an ARNi, a BB, an MRA and an SGLT2i is cost-effective for HFrEF patients in The Netherlands at the threshold value of €50K used by the Dutch Health Care Institute (Zorginstituut) for HF. This is true not only for the base case in the analysis, but also for all subgroup analyses and sensitivity analyses included in this report (see also Appendix II). In most subgroup analyses and sensitivity analyses, quadruple therapy with an ARNi is also cost effective at a lower threshold value of €30K.

Extrapolation of these results to the Dutch HFrEF population is hindered by a lack of data on the current mix of pharmacological treatments in this population. A tentative scenario analysis, based on expert opinion of a panel of 4 Dutch cardiologists, points to substantial benefits in terms of quality of life, hospitalization and life expectancy for HFrEF patients. This conclusion may be corroborated when more solid data on the current mix of pharmacological treatments in the Dutch HFrEF population become available.

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