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

## APPENDIX I: extrapolation methods

# Contents

# 1. Introduction

The literature on the pharmacological treatment of HFrEF contains various estimates of mortality risk, transition probabilities to worse health states, and relative risks of hospitalization. However, the available estimates do not always match the data requirements of this study. In particular, the available data often refer to other treatment combinations than those analysed in this report. This appendix describes the methods used to derive the required parameters for his study from the estimates in the literature. Table A1 provides a reading guide for this appendix. In addition, section 5 discusses why ICERs are insensitive to discontinuation (as indicated in the main report).

**Table A1. Reading guide**

| | Relative survival risks | Transition probabilities between KCCQ-classes | Hospitalization |
|---|---|---|---|
| **Sources** | Tromp et al. (2022); McMurray et al. (2014) | MEW+TAF | Tromp et al. (2022) |
| **Brief description** | Tromp et al. (2022) is a network meta-analysis resulting in relative risks of AC and CV mortality. Additional data are obtained form McMurray et al. (2014). | Transition probabilities estimated from the DAPA-HF and EMPEROR-reduced trial respectively | Network meta-analysis resulting in relative risks of composite endpoint CV mortality or (first) hospitalization |
| **Treatment combinations on which source contains data*** | Tromp et al. 2022): ARNI+BB+MRA+SGLT2i; ARNI + BB + MRA; ACEI + BB + MRA; ACE + BB; McMurray et al.: comparison of ACEI + BB + MRA with ARNI + BB + MRA | 1.SoC and 2.dapagifozine/empaglifozine + SoC | ARNI + BB + MRA + SGLT2i; ACEI + ARB + BB + Dig; ACEI + BB + MRA; ACEI+BB |
| **Methodology for obtaining missing data** | Combining available data | 1. Extrapolation of transition probabilities; 2. Extrapolation of results | Combining available data |
| **Section in this appendix** | 2 | 3 | 4 |

* Listed are only those treatment combination which are also included in the present study

# 2. Survival and relative mortality risks

## 2.1. Survival models from MEW and TAF

Survival probabilities differentiated by KCCQ-quartile constitute an important empirical building block for models based on transitions between KCCQ-quartiles. MEW and TAF estimate statistical models to derive these probabilities using data from the DAPA-HF and EMPEROR-reduced trials respectively.[1] These models include treatment regime (MEW: SoC vs SoC + dapaglifozin, TAF: SoC vs SoC empaglifozin) and KCCQ-quartiles as separate regressors (SoC indicates Standard of Care, which differs between the two trials, see below). TAF do not include other regressors beyond treatment and KCCQ-quartile, while MEW also include gender, LVEF (left ventricular ejection fraction), NTproBNP, DM2, Ischemic Heart Disease (ISCH) and HF diagnosed more than 2 years before randomization. Neither MEW nor TAF include age as a regressor; both models implicitly assume that only time since randomization affects survival probabilities.[2] This would imply that mortality rates are age independent, which of course is not correct. Therefore, as starting age for computing survival, age 65 has been used, even if the actual calculations start at age 71.4 in most cases. In the survival model of MEW, most regressors are centered on the mean, which implies that setting these regressors to zero results in the mean survival of the population on which the model was estimated (assuming estimated coefficients are unbiased). However, NTproBNP in the MEW model is entered as an uncentered natural log. In the DAPA-HF trial the median value for NTproBNP was 1446 in the SoC arm and 1428 in the SoC+DAPA and. In the CHECK-HF data, the overall median value for NTproBNP was substantially lower, namely 1039 (Brunner-La Rocca et al. (2019) and private communication). In the mEW survival model, a lower value for NTproBNP results in higher survival. Since cost effectiveness results are quite sensitive to survival, this is an important parameter. Therefore, the sensitivity of the cost effectiveness to variation in NTproBNP was explored in a sensitivity analysis.

Using these survival models, monthly probabilities of CV (cardiovascular) and AC (all cause) mortality were computed for each KCCQ-quartile, both for the SoC as the SoC+dapaglifozin/empaglifozin arm. Following Zorginstituut (2022), a floor was applied using overall mortality probabilities from the Dutch statistical agency (CBS): 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. Moreover, in line with Zorginstituut (2022), since Dutch life tables end at age 98, at higher ages mortality probabilities were increased by 10% for each additional year. Comparing figures A1 and A2, the TAF model results in much higher, and at higher ages more plausible mortality rates. Still, both models result in mortality rates at higher ages that are lower than those in the general population.

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[1] Both MEW and TAF use Weibull distributions, based on the empirical distribution in the respective trials. However, the parametrizations differ between MEW and TAF:

MEW: exp(-[no/(coef_scale_`x'*exp(x'B)+coef_kccq`i'_`x')]^coef_shape_`x')

TAF: exp(-coef_scale_`x'*exp(x'B)*no^coef_shape_`x')

[2] Through the scale and shape parameters of the Weibull distributions.

**Figure A1 Survival and mortality based on the MEW survival model**

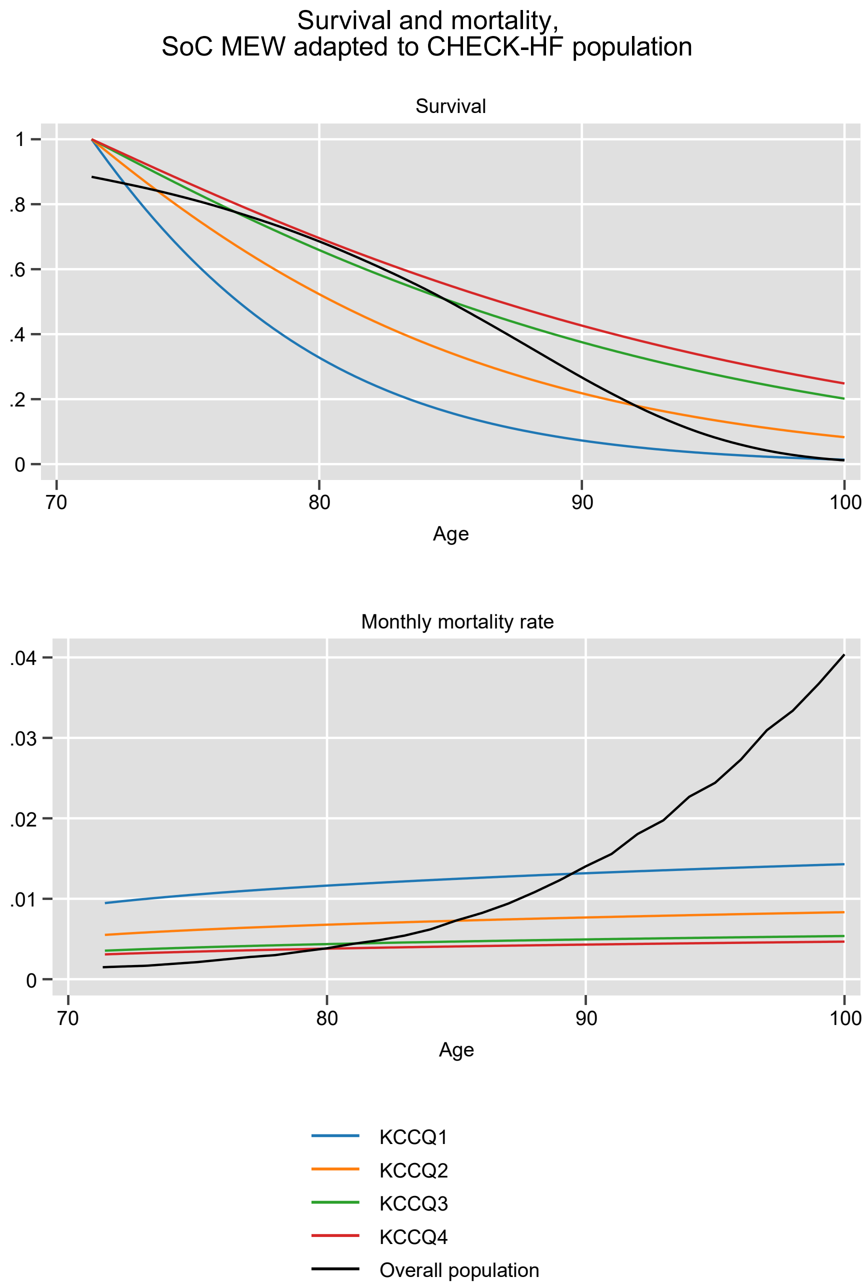
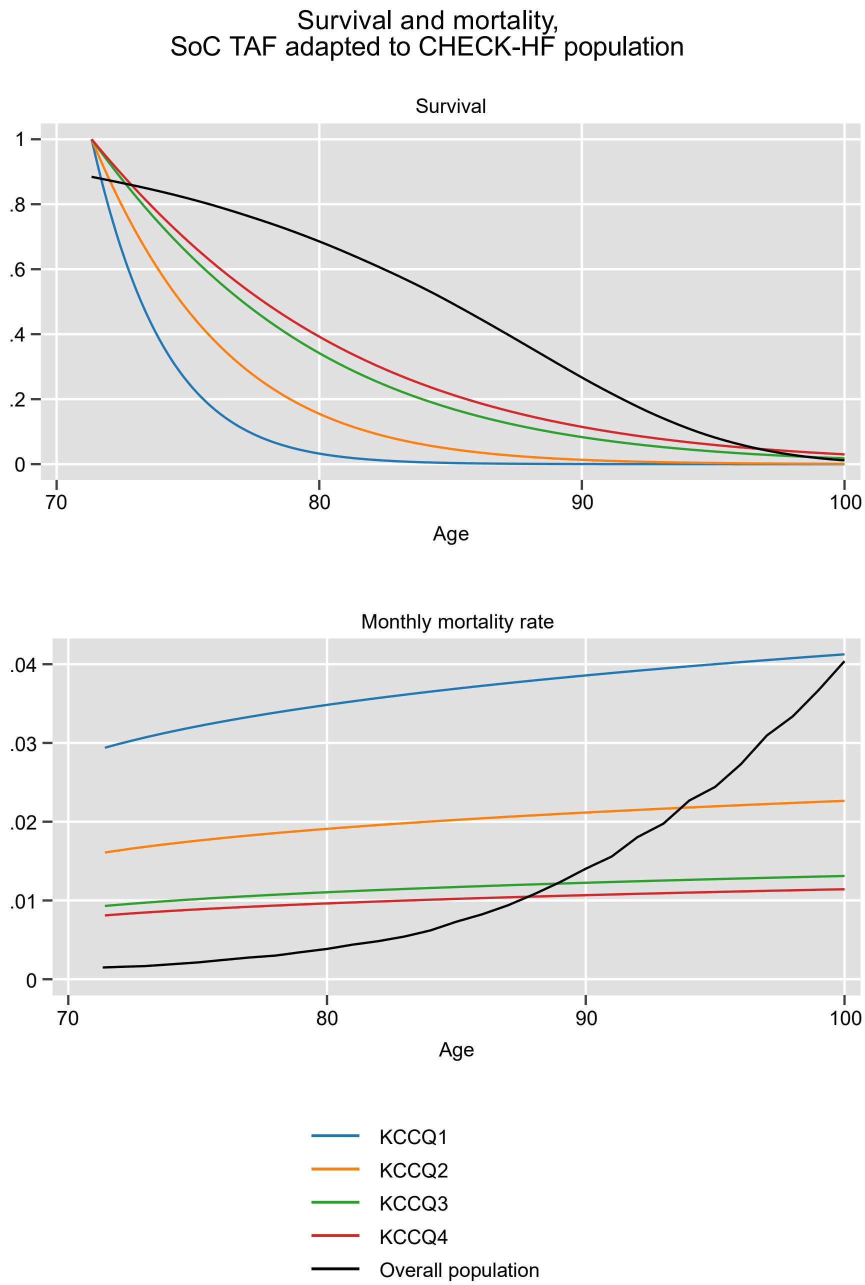


**Figure A2 Survival and mortality based on the TAF survival model**



## 2.2. Mortality probabilities under placebo

The analysis in this report requires mortality probabilities *under placebo* rather than SoC in the DAPA-HF and EMPEROR-reduced trials. The reason for this requirement is that the meta-analysis of Tromp et al. (2022) only contains relative mortality risks (RRs) compared to placebo.[3] Hence, in order to obtain mortality probabilities for these treatment combinations, mortality probabilities under placebo to which the RRs form Tromp et al. can be applied. The statistical survival models of MEW and TAF described in the previous section produce mortality probabilities for SoC and SoC + dapaglifozin or empaglifozin. SoC in these trial populations consists of various combination of HF-drugs, not placebo. The following calculations were performed to convert the mortality estimates under SoC to mortality probabilities under placebo:

1. Using data on drug use in SoC in MEW and TAF along with RRs from the literature, the RRs of AC and CV mortality under SoC compared to placebo were computed.
2. Using the statistical survival models in MEW and TAF, mortality probabilities under SoC were computed.
3. Mortality probabilities under SoC were divided by the RRs computed in step 1.

These steps may be expressed in the following formula:

$$P_{m,plac} = P_{m,SoC} / RR_{Soc,PLAC} \tag{1}$$

where:

| | | |
|---|---|---|
| $P_{m,plac}$ | = | Mortality probability under placebo |
| $P_{m,SoC}$ | = | Mortality probability under SoC |
| $RR_{Soc,PLAC}$ | = | Relative mortality risk of SoC compared to placebo |

These computations result in a number of time series of monthly mortality probabilities under placebo, differentiated between AC and CV mortality, SoC MEW and SoC TAF and KCCQ-quartiles, for a total of 2×2×4=16 time series. In order to apply the steps outlined above, RRs of AC and CV mortality under SoC compared to placebo are needed (the denominator on the right hand side of (1)). These RRs are not provided in the studies of MEW and TAF. However, both MEW and TAF do provide data on the shares of patients in the respective trials using various HF-drugs. Columns 2 and 3 of table A2 reproduce these shares. For each of these HF-drugs, RRac and RRcv are reproduced from Tromp et al. 2022 when available. In cases where the required RRs were not available in Tromp et al., RRs were computed by combining RRs (`dividing out') as indicated in the notes of table A2. For example, the RRs for adding MRA to ARNI and BB is computed as BB+ ARNI + MRA / BB+ ARNI. Next, for each line in table A2 the weighted RR was computed, defined as $S \times RR + (1 - S) \times 1$, where S indicates the share of patients using the HF-drug in the relevant row of table A2. This computation results in the weighted average of the RR for the corresponding HF-drug multiplied by the share of patients using the drug and an RR of 1 multiplied by the share of patients *not* using the drug. Finally, the weighted RRs for the various drugs are multiplied to give the overall RR of SoC compared to PLAC, shown in the final row of

[3] As pointed out above, Tromp et al. 2022 is the main source for relative mortality risks (RRs) of the treatment combinations included in this study.

table A2.[4] The RRs in the final row of table A2 are used to estimate the time series of mortality under placebo for each KCCQ-quartile in step 3 of the procedure outlined above.

**Table A2. Computing RR SoC / PLAC**

| | Share of patients using this drug | | Crude RR for all cause (AC) and cardiovascular (CV) mortality | | | | Weighted RRs MEW | | Weighted RRs TAF | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Drug** | MEW/ Dapa-HF (% of patients) | TAF/ Emperor-reduced (% of patients) | RRac | | RRcv | | AC | CV | AC | CV |
| **ACE or ARB** | NA | 69,7 | 0,92 | | 0,86 | | NA | NA | 0,94 | 0,90 |
| **ACE** | 56,1 | NA | 0,89 | | 0,83 | | 0,94 | 0,90 | NA | NA |
| **ARB** | 28,4 | NA | 0,95 | | 0,88 | | 0,99 | 0,97 | NA | NA |
| **BB** | 96,0 | 94,7 | 0,78 | | 0,77 | | 0,79 | 0,78 | 0,79 | 0,78 |
| **MRA** | 71,5 | 71,3 | 0,76 | * | 0,73 | **** | 0,83 | 0,81 | 0,83 | 0,81 |
| **ARNI** | 10,5 | 19,5 | 0,74 | ** | 0,67 | ***** | 0,97 | 0,97 | 0,95 | 0,94 |
| **Ivabradine** | NM | 7,0 | 0,92 | *** | 0,91 | *** | NA | NA | 0,99 | 0,99 |
| **Overall weighted RR SoC / PLAC** | | | | | | | 0,59 | 0,53 | 0,58 | 0,53 |

Source: MEW+TAF, Tromp et al. 2022;ac; all cause, cv: cardiovascular, RRac: relative risk all cause mortality, RRcv: relative risk cardiovascular mortality, NA = Not Applicable, NM=Not Mentioned
Patients on Ivabradine is only reported in TAF

* BB+ ARNI + MRA / BB+ ARNI
** ARNI + BB / BB
*** ACEI + BB + MRA + IVA / ACEI + BB + MRA
**** ACEI + BB + MRA / ACEI + BB
***** ARNI + BB + MRA /(ACEI + BB + MRA / ACEI)

## 2.3. Mortality RRs for treatment combinations included in this study

In order to obtain time series of mortality probabilities for each of the treatment combinations included in the present study, time series of mortality probabilities under placebo (computed using the approach outlined in the previous subsection) are multiplied by the RR of mortality for the given treatment combination. These RRs are shown in table A2. In a number of cases, Tromp et al. (2022) do not provide RRs; in those cases RRs where derived by combining the RRs that are available in Tromp et al. (2022), as indicated in the notes below table A3.

[4] This method of `multiplying through' RRs for individual drugs in order to estimate the overall RR is quite usual, see e.g. Burger et al. in press 2023 (online appendix), who advice this method in order to estimate RRs at the individual patient level.

**Table A3. Relative risks for ac and cv mortality for each treatment combination included in the analysis, compared to placebo**

| | RRac | RRcv | |
|---|---|---|---|
| **ARNI+BB+MRA+SGLT2i** | 0,39 | 0,33 | |
| **ACEi+BB+MRA+SGLT2i** | 0,49 | 0,41 | |
| **ARNI+BB+MRA** | 0,47 | 0,38 | |
| **ARNI+BB+SGLT2i** | 0,52 | 0,48 | * |
| **BB+MRA+SGLT2i** | 0,52 | 0,52 | ** |
| **ARNI+MRA+SGLT2i** | 0,50 | 0,43 | *** |
| **BB+ACEi+SGLT2i** | 0,57 | 0,59 | **** |
| **ACE+BB+MRA** | 0,52 | 0,47 | |
| **ACE+BB** | 0,69 | 0,68 | |

Note: starred RRs were derived from RRs in Tromp et al (2020) as follows:

* 1.25 * ARNI+BB+MRA+SGLT2i

** ARNI+BB+MRA+SGLT2i / MRA

*** ARNI+BB+MRA+SGLT2i / ARNI

**** ARNI+BB+MRA+SGLT2i / BB

The factor 1.25 under * is based on the RRs found in the Emperor reduced trial.

Figures A3 and A4 show the resulting monthly mortality probabilities for each of the treatment combinations using the risk equations of MEW and TAF respectively. For all treatment combinations except ACEi+BB, calculated mortality rates become lower than those for the general population, in which case the latter is used. This is shown by the black line, which is the mortality probability of the general population from Statistics Netherlands. This `take over' happens at lower ages for higher (i.e. healthier) KCCQ quartiles. A consequence of the use of mortality rates for the general population at higher ages is that there are no differences in mortality between KCCQ-quartiles at higher ages. This may underestimate the true differences between treatment combinations, if in reality such differences continue to exist at higher ages. In a sensitivity analysis, the implications of this possibility are explored. To this end, 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. Figure A5 shows the resulting mortality probabilities. The sensitivity analysis based on these mortality probabilities is included in Appendix II. The results turn out to be insensitive to the differences in mortality rates between figure A3 and A5.

**Figure A3. Mortality probabilities computed from the MEW survival model, adjusted using mortality for the general population**

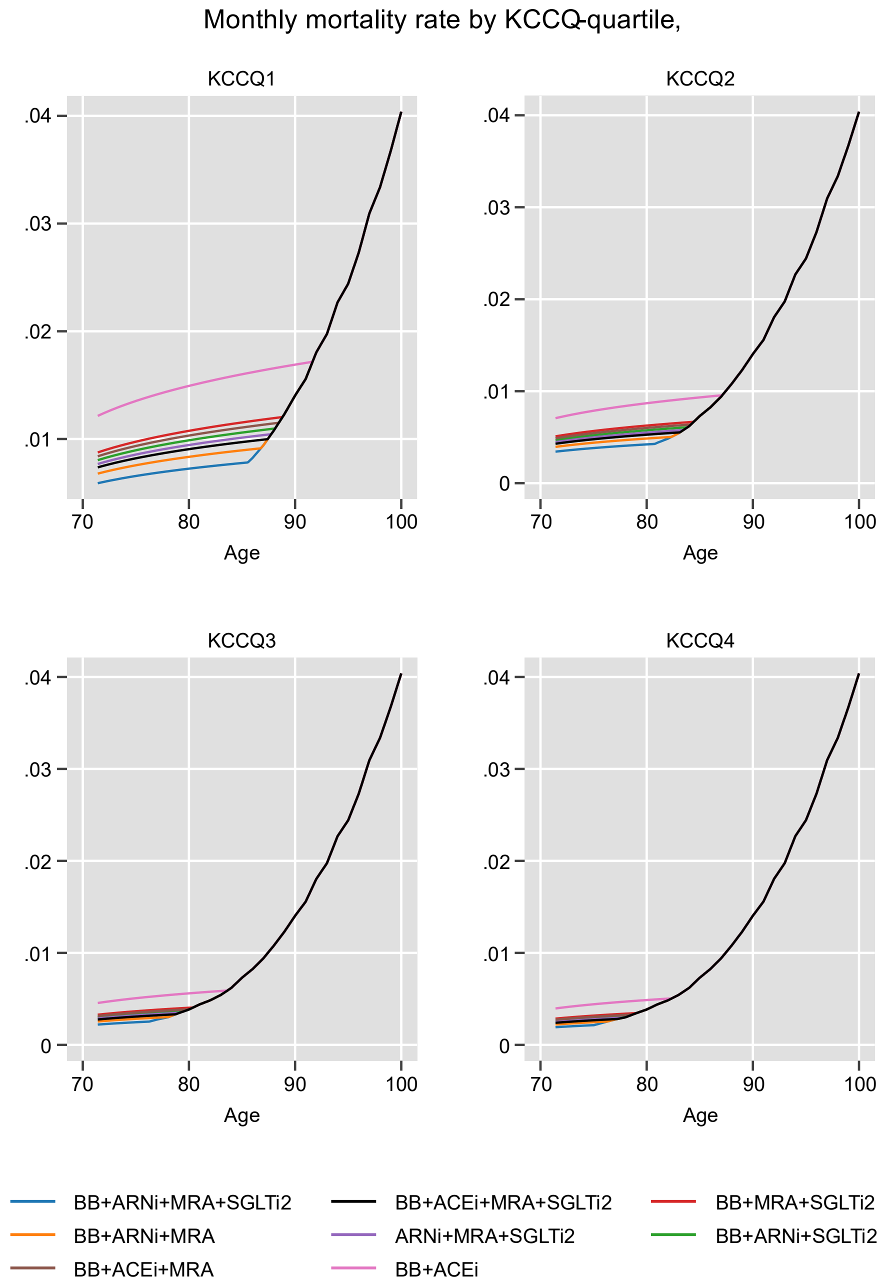


**Figure A4.** **Mortality probabilities computed from the TAF survival model, adjusted using mortality for the general population**

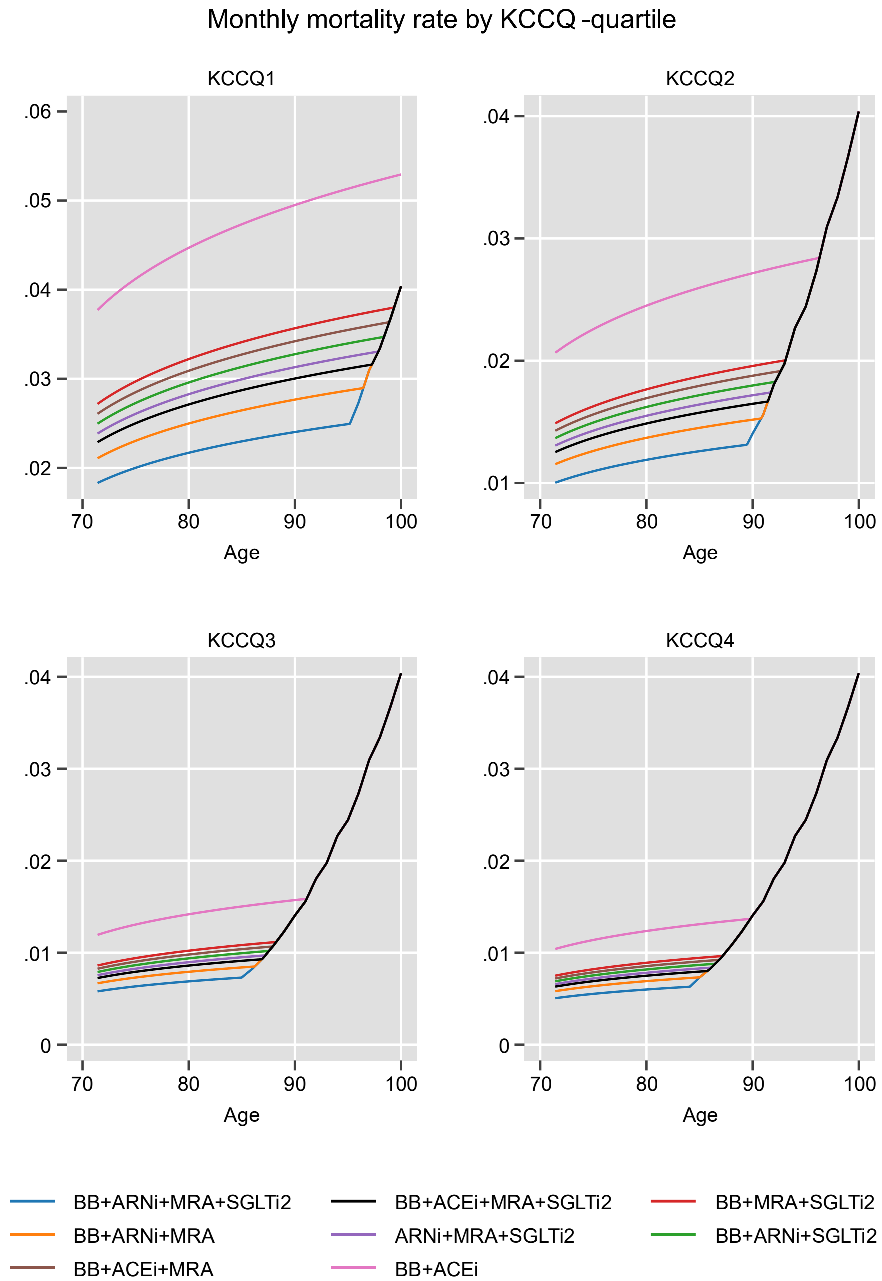
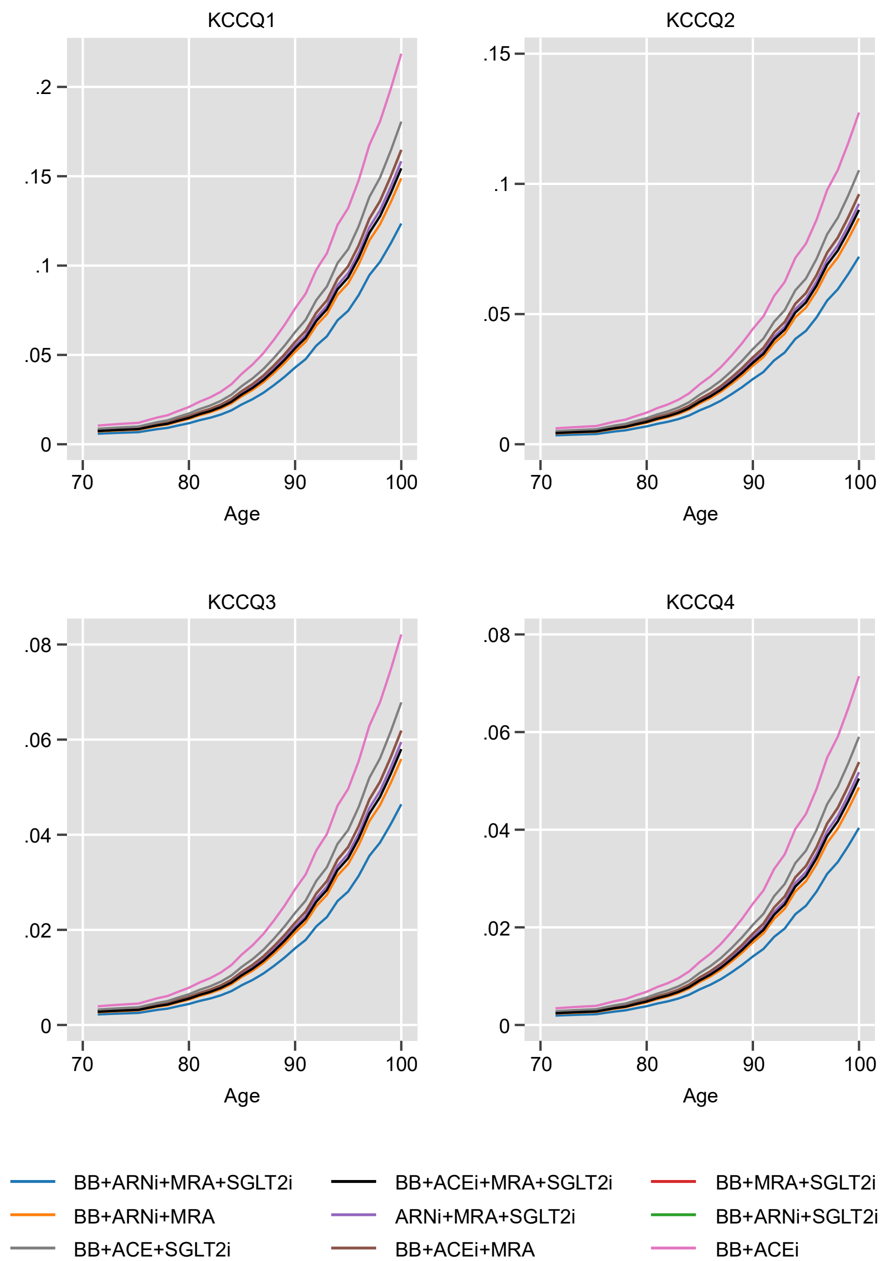


**Figure A5.** **Mortality probabilities computed from the MEW survival model, adjusted using mortality for the general population, *separate adjustments for each KCCQ-quartile and each treatment combination.***



# 3. Transition probabilities

## 3.1. Data

Transition probabilities between KCCQ quartiles are available only for SoC and SoC + dapagliflozin  from the DAPA-HF trial (MEW), and for SoC and SoC + empagliflozin from the EMPEROR-reduced trail (TAF). The two sets of probabilities refer to different subcategories of KCCQ-scores and also to different time periods after initiation of treatment. As indicated in the main report, both sets of transition probabilities imply progression in both arms was negative, i.e. the KCCQ score improved over time, but faster in the SoC+dapa/empa arm than in the SoC-arm. This difference indicated the treatment effect.

Transition probabilities between KCCQ quartiles are shown in tables A4 and A5. The probabilities in table A4 correspond to those used in MEW, who in turn estimated these probabilities on the basis of the DAPA-HF trial. The probabilities in table A5 correspond to those used in TAF, who in turn estimated these probabilities on the basis of the Emperor-reduced trial. Table A4 also presents the inputs used for the probabilistic sensitivity analysis (i.e. standard deviations and statistical distributions). These inputs are available for the MEW probabilities only (TAF does not presents these data).

The two sets differ in a number of respects:

- MEW probabilities are based on the Total Symptom Score [TSS] while TAF probabilities are based on the Clinical Summary Score [CSS].
- MEW probabilities differ between month 0-4 and month 5+ while TAF probabilities differ between month 0-3, 4-8 and month 9+.
- In MEW, probabilities of moving to another quartile are much smaller than in TAF. This can be seen most easily by comparing the probabilities of remaining in the same quartile, which are much larger in MEW than in TAF.

**Table A4. Transition probabilities MEW**

| KCCQ-TSS [From, To] | Dapagliflozin + SoC | | | | SoC | | | |
|---|---|---|---|---|---|---|---|---|
| | Month 0 - 4 | | Month 5+ | | Month 0 – 4 | | Month 5+ | |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| **KCCQ[1,1]** | **0,86236** | **0,00015** | **0,94358** | **0,00007** | **0,88183** | **0,00015** | **0,94136** | **0,00007** |
| KCCQ[1,2] | 0,08042 | 0,00012 | 0,03682 | 0,00006 | 0,07071 | 0,00012 | 0,03876 | 0,00006 |
| KCCQ[1,3] | 0,03679 | 0,00008 | 0,01409 | 0,00004 | 0,03164 | 0,00008 | 0,01212 | 0,00003 |
| KCCQ[1,4] | 0,02043 | 0,00006 | 0,00551 | 0,00002 | 0,01582 | 0,00006 | 0,00776 | 0,00003 |
| KCCQ[2,1] | 0,03126 | 0,00007 | 0,02629 | 0,00004 | 0,0387 | 0,00008 | 0,0322 | 0,00005 |
| **KCCQ[2,2]** | **0,85793** | **0,00015** | **0,92198** | **0,00007** | **0,85301** | **0,00015** | **0,91553** | **0,00007** |
| KCCQ[2,3] | 0,07122 | 0,00011 | 0,03781 | 0,00005 | 0,06635 | 0,0001 | 0,03708 | 0,00005 |
| KCCQ[2,4] | 0,03959 | 0,00008 | 0,01392 | 0,00003 | 0,04194 | 0,00008 | 0,01519 | 0,00003 |
| KCCQ[3,1] | 0,00903 | 0,00004 | 0,0082 | 0,00002 | 0,01665 | 0,00006 | 0,00747 | 0,00002 |
| KCCQ[3,2] | 0,03829 | 0,00008 | 0,0275 | 0,00004 | 0,0491 | 0,00009 | 0,03459 | 0,00004 |
| **KCCQ[3,3]** | **0,86135** | **0,00015** | **0,92091** | **0,00006** | **0,85678** | **0,00015** | **0,91961** | **0,00006** |
| KCCQ[3,4] | 0,09133 | 0,00012 | 0,04339 | 0,00005 | 0,07747 | 0,00012 | 0,03833 | 0,00005 |
| KCCQ[4,1] | 0,00713 | 0,00004 | 0,00259 | 0,00001 | 0,00513 | 0,00003 | 0,00426 | 0,00002 |
| KCCQ[4,2] | 0,01519 | 0,00005 | 0,01024 | 0,00002 | 0,01676 | 0,00006 | 0,01359 | 0,00003 |
| KCCQ[4,3] | 0,04547 | 0,00009 | 0,033 | 0,00004 | 0,05305 | 0,0001 | 0,03852 | 0,00004 |
| **KCCQ[4,4]** | **0,93221** | **0,00011** | **0,95417** | **0,00004** | **0,92506** | **0,00012** | **0,94363** | **0,00005** |

Source: MEW

**Table A5. Transition probabilities TAF**

| KCCQ-CSS quartile | | Empagliflozin + SoC | | | SoC | | |
|---|---|---|---|---|---|---|---|
| **From** | **To** | **Month 0–3** | **Month 4–8** | **Month 9+** | **Month 0–3** | **Month 4–8** | **Month 9+** |
| Q1 | **Q1** | **0.797** | **0.91** | **0.918** | **0.835** | **0.904** | **0.929** |
| | Q2 | 0.155 | 0.077 | 0.065 | 0.133 | 0.082 | 0.056 |
| | Q3 | 0.025 | 0.005 | 0.013 | 0.014 | 0.009 | 0.013 |
| | Q4 | 0.023 | 0.008 | 0.004 | 0.018 | 0.005 | 0.002 |
| Q2 | Q1 | 0.066 | 0.068 | 0.051 | 0.069 | 0.058 | 0.051 |
| | **Q2** | **0.708** | **0.84** | **0.881** | **0.72** | **0.85** | **0.867** |
| | Q3 | 0.188 | 0.083 | 0.061 | 0.203 | 0.079 | 0.076 |
| | Q4 | 0.038 | 0.009 | 0.007 | 0.008 | 0.013 | 0.006 |
| Q3 | Q1 | 0.004 | 0.005 | 0.004 | 0.013 | 0.011 | 0.013 |
| | Q2 | 0.082 | 0.07 | 0.054 | 0.112 | 0.058 | 0.054 |
| | **Q3** | **0.772** | **0.848** | **0.868** | **0.743** | **0.859** | **0.871** |
| | Q4 | 0.142 | 0.077 | 0.074 | 0.132 | 0.072 | 0.062 |
| Q4 | Q1 | 0.006 | 0.004 | 0.003 | 0.006 | 0.004 | 0 |
| | Q2 | 0.016 | 0 | 0.006 | 0.009 | 0.008 | 0.005 |
| | Q3 | 0.074 | 0.063 | 0.044 | 0.096 | 0.058 | 0.049 |
| | **Q4** | **0.904** | **0.933** | **0.947** | **0.889** | **0.93** | **0.946** |

Source: TAF

### 3.2. Modelling progression when transition probabilities are unknown

Transition probabilities between KCCQ quartiles from MEW and TAF are valid under SoC and SoC + dapaglifozin or empaglifozin. Hence, these probabilities cannot directly be used for the treatment combinations in the present study.[5] In order to address this problem, two extrapolation methods have been used. These methods are described in the following two subsections.

### 3.3. Extrapolation of transition probabilities

This extrapolation method starts from the assumption that drug combinations that result in lower CV-mortality also result in slower progression, and vice versa. This assumption was found to be reasonable by a panel of 4 Dutch cardiologists. This assumption may be summarized in a mathematical formula as follows:

$$\mathrm{dPT_{ij}} = \mathrm{f}\big(\mathrm{dRRR_{ij}}\big), \qquad \mathrm{f}(0) = 0, \qquad \mathrm{f}(.)' < 0 \tag{2}$$

$\mathrm{dPT_{ij}}$ = difference in transition probability between treatment combinations i and j

$\mathrm{dRRR_{ij}}$ = difference in relative risk reduction (RRR) of cv mortality between treatment combinations i and j

$\mathrm{dPT_{ij}}$ and $\mathrm{dRRR_{ij}}$ take on different values for each KCCQ-quartile and each time period (month) since randomization; this is not shown in eq. 2 in order to keep the notation simple. In equation (2) f(.) denotes a (continuously differentiable) functional relationship and f'(.) its first derivative; f(.)'<0 reflects the assumption that a larger relative risk reduction (RRR) results in a lower probability of progressing to a worse KCCQ-quartile, while f(0) = 0 signifies the restriction that two treatment combinations with equal RRRs also generate equal transition probabilities.

For each KCCQ-quartile, one datapoint is available on $\mathrm{dRRR_{ij}}$.[6] If f(.) is linear, one datapoint coupled with f(0) = 0 is sufficient to compute $\mathrm{dPT_{ij}}$ from a given $\mathrm{dRRR_{ij}}$. This can be seen as follows. In the linear case with f(0) = 0 ,eq. 2 becomes:

$$\mathrm{dPT_{ij}} = \mathrm{C} \cdot \mathrm{dRRR_{ij}} \tag{3}$$

where C is a constant. C can be computed from one datapoint. E.g., using the datapoint from the DAPA-HF trial as reported by MEW we have:

$$\mathrm{C} \; = \; {(\mathrm{PT_{SoC+DAPA}} - \mathrm{PT_{SoC}})}\Big/{(\mathrm{RRR_{SoC+DAPA}} - \mathrm{RRR_{SoC}})} \tag{4}$$

[5] Also, the characteristics of the study populations in MEW and TAF differ from the characteristics of the population in this study in terms of age, gender, comorbidities, etc. However, MEW and TAF do not to differentiate transition probabilities in subgroup analyses (possibly for reasons of limited data availability).

[6] As pointed out above, we have two sets of transition probabilities, from MEW and TAF, but these refer to different subcategories of KKCQ-scores and also to different time periods after the start of treatment. Within each of these time horizons, we still have only one datapoint.

Where:

| | |
|---|---|
| $\mathrm{PT_{SoC+DAPA}}$ | = the transition probability in the SoC+DAPA arm |
| $\mathrm{PT_{SoC}}$ | = the transition probability in the SoC arm |
| $\mathrm{RRR_{SoC+DAPA}}$ | = relative risk reduction of SoC+DAPA compared to placebo |
| $\mathrm{RRR_{SoC}}$ | = relative risk reduction of SoC compared to placebo |

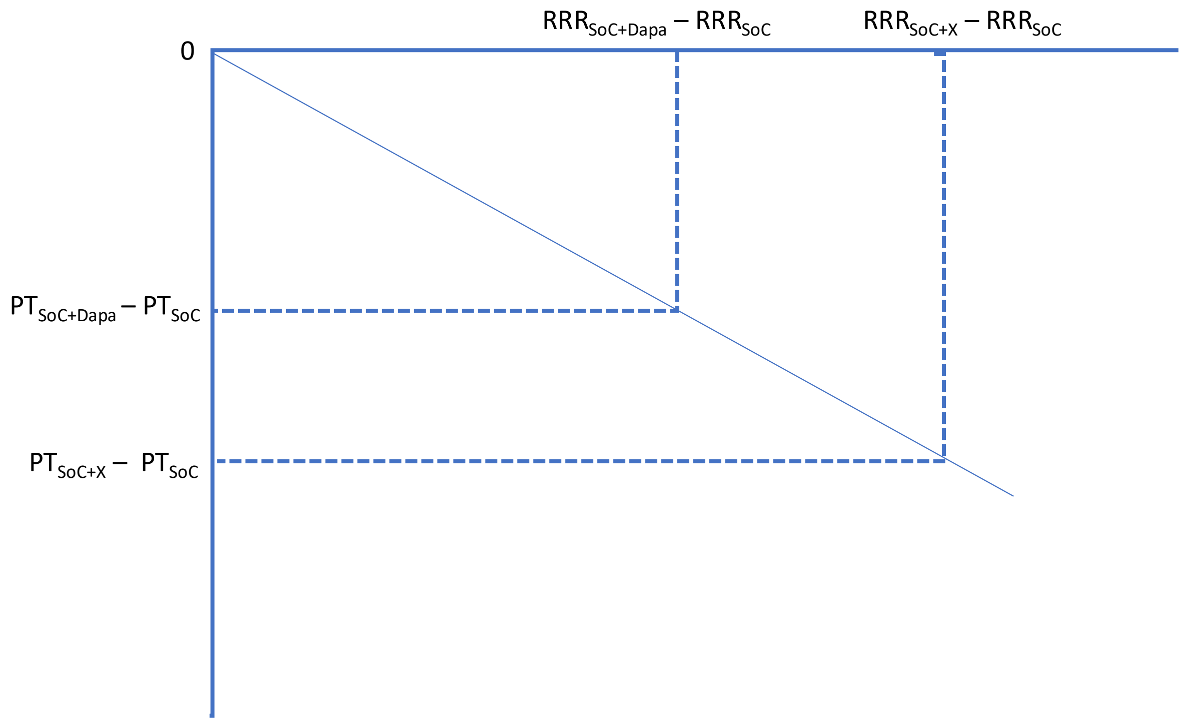
As indicated above, $\mathrm{dPT_{ij}}$ and $\mathrm{dRRR_{ij}}$ take on different values for each KCCQ-quartile and each time period (month) since randomization. This also results in different values of C for each KCCQ-quartile and each time period (month) since randomization. Again, this is not shown in eq. 4 in order to keep the notation simple. Note that f(.) < 0 implies C < 0: a higher relative risk reduction is associated with slower progression.

Using the value for C computed using (4), transition probabilities for treatment combination X can be computed using the RRR for treatment combination X:

$$\mathrm{PT_x} - \mathrm{PT_{SoC}} = \mathrm{C} \cdot (\mathrm{RRR_x} - \mathrm{RRR_{SoC}}) \qquad (5)$$

The steps in this derivation are illustrated in figure A5. The horizontal axis plots differences in RRS compared tot SoC, while the vertical axis plots differences in transition probabilities. Data on RRRs are available for all treatment combination, but data on transition probabilities are available only for SoC+DAPA (or SoC+EMPA, not shown in the figure). The datapoints on SoC+DAPA can be used to draw a straight line as shown in figure A6. Next, $\mathrm{PT_x} - \mathrm{PT_{SoC}}$ can be determined by starting on the horizontal axis at the point $\mathrm{RRR_x} - \mathrm{RRR_{SoC}}$ and then reading off the corresponding value for $\mathrm{PT_x} - \mathrm{PT_{SoC}}$ on the vertical axis.

**Figure A6.** **Extrapolating transition probabilities**




In order to use this method, data are needed on $RRR_x$ and $RRR_{SoC}$. Data on $RRR_x$ (= 1-$RR_x$) are available from the meta-analysis of Tromp et al. (2022); $RRR_{SoC}$( = 1-$RR_{SoC}$) was derived in section 1.2.

A potential problem with this method is that negative probabilities cannot be ruled out. To see this, rewrite eq. 5 as:

$$PT_x = C \cdot (RRR_x - RRR_{SoC}) + PT_{SoC} \tag{6}$$

Since C < 0, the first term on the right-hand side will be negative if $RRR_x > RRR_{SoC}$, i.e. if treatment combination X results in a larger reduction in relative mortality risk than SoC in MEW and/or TAF. If in addition $PT_{SoC}$, the transition probability under SoC in MEW or TAF, is small, the result may be $PT_x$ < 0. Actual calculations show that this occurs 3 times (out of 64) with the transition probabilities of MEW, and that the absolute size of these negative probabilities is very small (<.0001 in absolute value). In these cases, the transition probability was set to zero and the probability of remaining in the same KCCQ quartile was lowered by the same absolute amount in order to ensure that probabilities continue to sum to 1.

With the transition probabilities of TAF, this problem occurred no less than 25 times, and sometimes the probabilities were quite large (larger than 1% in absolute value). Therefore, this extrapolation method has only been used with the MEW probabilities.[7]

## 3.4. Extrapolation of effects

Our second method for addressing unknown transition probabilities is based on extrapolation of *the effect* of different transition probabilities in the SoC+Dapa arm compared to the SoC arm in MEW, and the SoC+Empa arm compared to the SoC arm in TAF. This approach starts from the observation that in the models used by MEW and TAF, differences in the HF population between the SoC+Dapa/Empa-arm and the SoC-arm are due to two factors:

- Lower mortality rates *within* each of the KCCQ quartiles in the SoC+Dapa/Empa-arm.
- Different transition probabilities to other KCCQ-quartiles *between* the two arms.

Using the models of MEW and TAF, these two factors can be quantified separately using the following steps:

1. Run the model for the SoC arm.
2. Run the model for the SoC+Dapa/Empa arm.
3. Run the model again for the SoC+Dapa/Empa arm, but this time with the *transition probabilities of the SoC arm*.

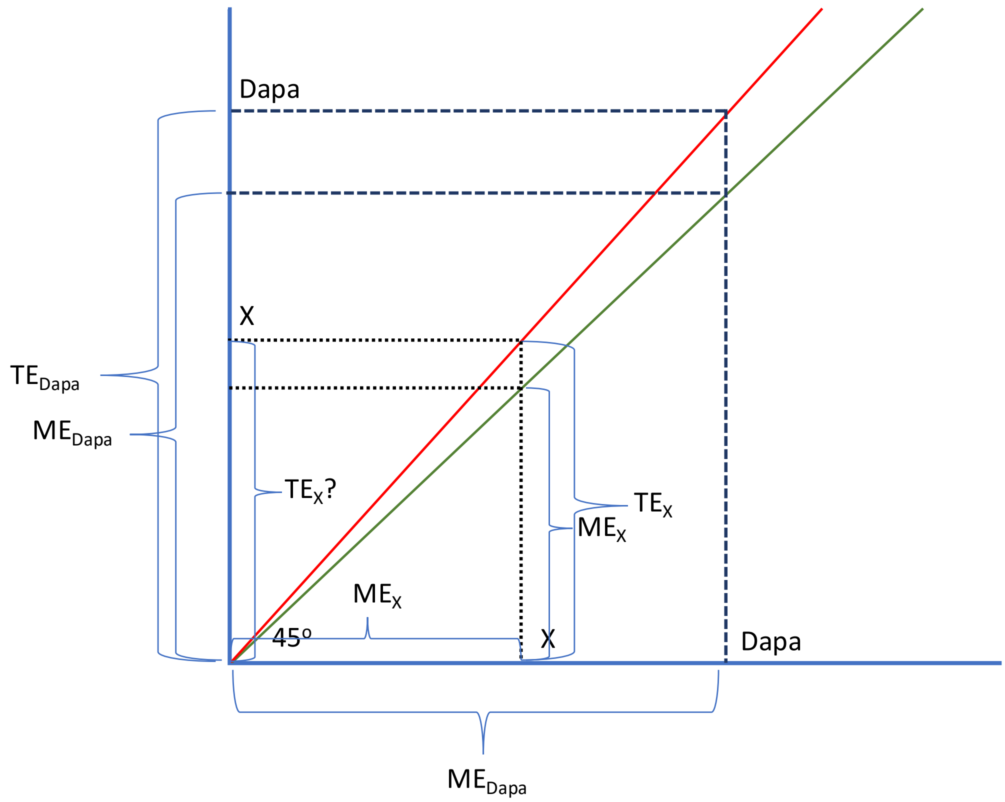
Each step results in a time series of the HF population for each KCCQ quartile. The differences between steps 1 and 2 equals the total effect (TE) of SoC+Dapa/Empa compared to SoC. The difference between step (3) and step (1) equals the partial effect of more favourable mortality probabilities (ME) in the SoC +Dapa/Empa arm compared to SoC. Thus, TE/ME is the ratio of the total effect to the effect of the more favourable mortality probabilities TE/ME. This ratio will differ between KCCQ-quartiles and over time.

For drug combinations with unknown transition probabilities, only step 3 can be carried out. This results in time series of ME for each KCCQ-quartile and for each drug combination. In order to translate these time series into time series for TE, it is assumed that TE/ME in each KCCQ-quartile and each month equals the ratio TE/ME calculated from the three steps above for SoC+Dapa/Empa.

Figure A7 illustrates this method for one period and one KCCQ-quartile. The figure takes as data $TE_{Dapa}$, $ME_{Dapa}$ and $ME_X$, computed following the steps above. In this example, $TE_{Dapa}$ is larger than $ME_{Dapa}$. As already indicated, $TE_X$, the total effect of treatment on the number of patients in each KCCQ quartile, cannot be computed in he usual way (by running a Markov model) since the transition probabilities for treatment combination X are unknown. However, *if* $TE_X / ME_X = TE_{Dapa} / ME_{Dapa}$, it follows that $TE_X = ME_X \times TE_{Dapa} / ME_{Dapa}$.

[7] The cause of this difference between the frequence with which this problem occurs with transition probabilities from MEW compared to TAF is that the latter probabilities are much larger. This may be due to differences in estimation techniques used.

**Figure A7. Extrapolation method 2.**




TE = total effect of treatment on population in KCCQ-quartile I at time t
ME= pure mortality effect of treatment on population in KCCQ-quartile I at time t (i.e. excluding the effect of treatment on transition probabilities.)

It is unlikely that in reality the proportionality assumption holds exactly. However, as argued above it is plausible (and confirmed by a panel of cardiologists) that a drug combination that results in low mortality within each KCCQ quartile also results in slower progression to worse quartiles (with higher mortality). Moreover, this method is only used in 1 sensitivity analysis, and the results are in line with the base case.

# 4. Hospitalization

## 4.1. Introduction

Hospitalization is the only adverse event, apart from mortality, that is included in the analysis in the present study. The studies by MEW and TAF, and also a Dutch cost-effectiveness study based on the MEW model, indicate that hospitalization is the only event that results in substantial HF-related treatment costs and disity. Hospitalization probabilities for the treatment combinations analysed in the present study are not available, but Tromp et al. (2022) presents relative risks for composite endpoint CV mortality or (first) hospitalization for various treatment combinations. This section describes how hospitalization probabilities were derived from these data, supplemented by data from other sources

## 4.2. Hospitalization probabilities in MEW and TAF

The risk equations for hospitalization in MEW and TAF form the starting point for modelling hospitalization (these equations are available in the online supplements of MEW and TAF). Relative risks calculated from these risk equations compared to KCCQ1 are reproduced in table A6. The RR of hospitalization of SoC+Dapa compared to SoC is almost the same between SoC+Empa compared to SoC (table A6), which was to be expected given the class similarity between the two drugs. However, the risk equations of TAF result in monthly probabilities of hospitalization that are much higher than the risk equations of MEW (see figure A7). Moreover, in MEW the probability of hospitalization depends on time since randomization (and increases over time) and on various patient characteristics, while in TAF these factors do not affect hospitalization (in TAF only KCCQ quartile and SoC vs SoC+ Empa affect the prob of hospitalization).

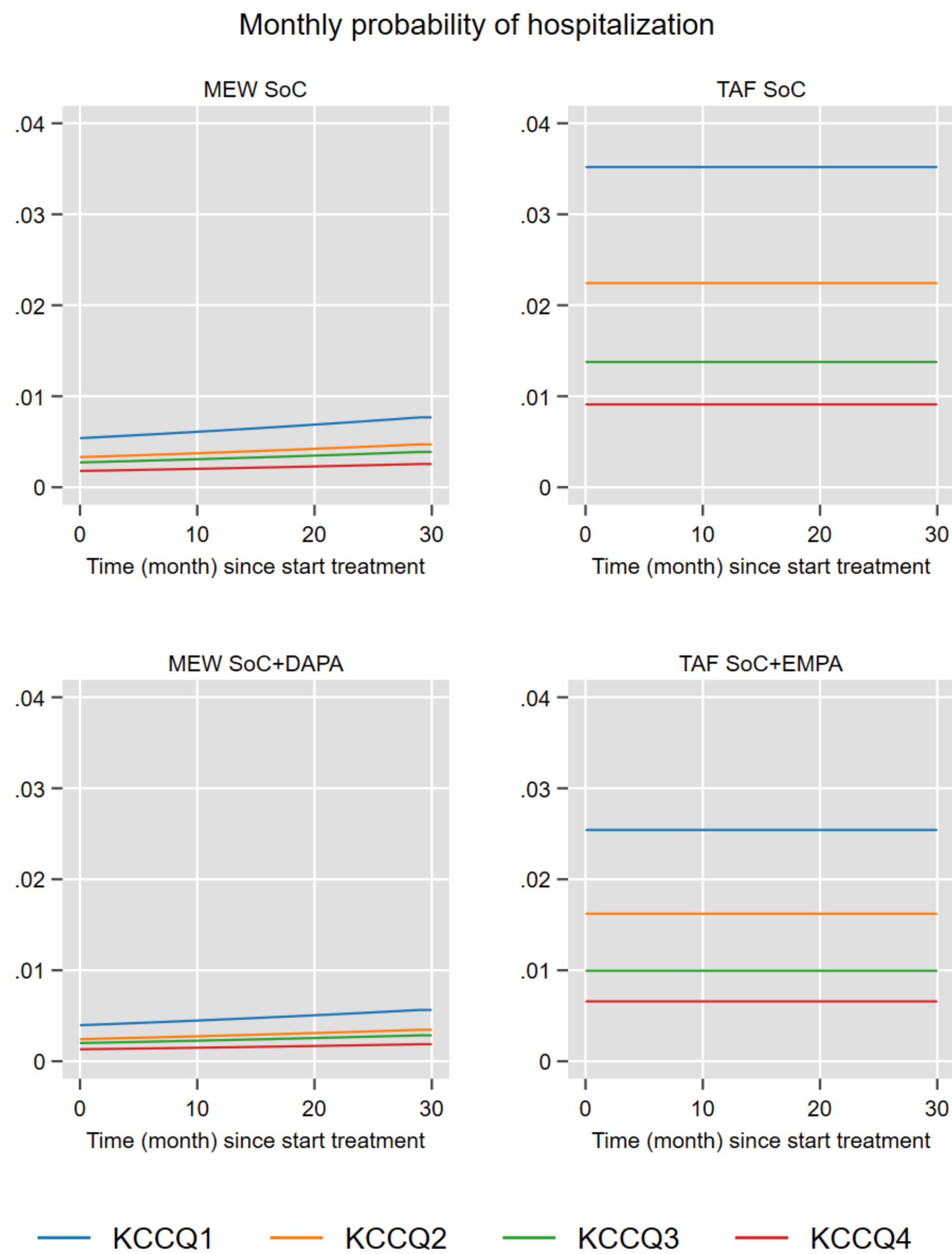
The probabilities based on the TAF risk equations are much closer to the values reported in the literature than the values based on the MEW-risk equations. For example, Srivastava et al. (2021) report a 12-months hospitalization probability of about 60% for patients in the CHAMP-HF registry. In a sensitivity analysis, the impact of using the MEW risk equations will be explored.

**Table A6. RR of hospitalization compared to KCCQ1 and SoC**

| | Dapa | Empa |
|---|---|---|
| **KCCQ2 compared to KCCQ1** | 0.61 | 0.64 |
| **KCCQ3 compared to KCCQ1** | 0.51 | 0.39 |
| **KCCQ4 compared to KCCQ1** | 0.33 | 0.26 |
| **dapaglifozin/empaglifozin+SoC compared to SoC (all KCCQ quartiles)** | 0.73 | 0.72 |

Source: MEW, TAF

**Figure A8: Monthly probabilities of hospitalization**




Source: calculated from risk equations in online appendices of MEW and TAF

## 4.3. Relative risks of hospitalization for the treatment combinations included

As indicated above, data on relative risks of hospitalization by KCCQ-quartile for other treatment combinations than those included in MEW and TAF are not available. However, Tromp et al. (2020) provide RRs for CV mortality as well as RRs of the composite outcome mortality or (often first) hospitalization for a number of treatment combinations. From these data RRs of (first) hospitalization can be derived. Denote the probability of the composite outcome mortality or (first) hospitalization *under placebo* by $P_{m|h}$ and the probability that both events occur by $P_{m\&h}$. All probabilities refer to an event occurring during one time unit, in this case a month. With this notation, the probability of the composite outcome equals:

$$P_{m|h} = P_h + P_m - P_{m\&h} \tag{7}$$

The final term in eq. 7 reflects the fact that the two events are probably not independent.[8] For some treatment combination X other than placebo, the corresponding equation is:

$$P'_{m|h} = P'_h + P'_m - P'_{m\&h} \tag{8}$$

The last term in both equations is unknown, but if the assumption is made that the extent to which mortality and hospitalization are not independent is equal for all treatment combinations, (7) and (8) may be rewritten as follows:[9]

$$P_{m|h} = (1 + \gamma)(P_h + P_m) \tag{7 *}$$

and

$$P'_{m|h} = (1 + \gamma)(P'_h + P'_m) \tag{8 *}$$

Where $\gamma = {P_{m\&h}}/{(P_h + P_m)} = {P'_{m\&h}}/{(P'_h + P'_m)}$.

Denote relative risks of hospitalization and mortality of X compared to placebo by $RR_h$ and $RR_m$. Then $P'_{m|h}$ can be written as follows:

$$P'_{m|h} = (1 + \gamma)(P'_h + P'_m) = (1 + \gamma)(P_h RR_h + P_m RR_m) \tag{9}$$

$RR_{m|h}$, the relative risk ratio of the composite outcome mortality or (often first) hospitalization of some treatment combination compared to placebo, then equals:

$$RR_{m|\mathrm{h}} = \frac{P'_{m|h}}{P_{m|h}} = \frac{P_h RR_h + P_m RR_m}{P_h + P_m} \tag{10}$$

[8] Eq. 7 follows from De Morgan's law but can also be derived by drawing a simple Venn diagram.
[9] In a Venn diagram, γ would equal the area of overlap of the two individual areas corresponding to the two events, divided by the sum of the two individual areas corresponding to the two events.

Since the unknown $1 + \gamma$ occurs as a multiplicative factor acting on both the numerator and the denominator of (10), it drops out of equation 10. Thus, $RR_{m|h}$ is a weighted average of $RR_h$ and $RR_m$ with $P_h$ and $P_m$ as weights. Solving eq. 10 for $RR_h$ results in:

$$RR_h = RR_{m|\mathrm{h}}(P_h + P_m)/P_h - RR_m(P_m/P_h) \tag{11}$$

Multiplying both sides by $P_h$ results in the expression for $P'_h$. Equation 10 makes intuitive sense: if $P_m = 0$, the relative risk of the composite outcome mortality or hospitalization equals the relative risk of hospitalization. Also, if $RR_{m/\mathrm{h}} = RR_m$, eq,. 11 implies that $RR_h = RR_m$: the relative risk of the composite outcome mortality *or* hospitalization can only equal the relative risk of mortality if the relative risk of hospitalization equals the relative risk of mortality.

In order to compute $P'_h$, the probability of hospitalization for some treatment combination other than placebo, we need data on $RR_{m|h}$, $RR_m$ (both relative risks compared to placebo), $P_m$ and $P_h$ (the mortality probability and the probability of hospitalization under placebo respectively). The following subsection describes the sources for these RRs, and estimation methods where these sources are lacking. The methodology for calculating mortality under placebo $P_m$ was already outlined in section 1.2. The method used to estimate $P_h$ is presented in subsection 4.5 below.

Since $P_m$ increases with time since randomization, $RR_{m|h}$ should also depend on time since randomization. However, the available data on $RR_{m|h}$ assume this is a constant. These two possibilities may be reconciled by the fact that the trial data on which estimates in the literature of $RR_{h|m}$ are based, cover only the first 1 – 1.5 years after randomization. Over such a brief time horizon $P_m$ is almost constant. This also implies that the above equations only hold for this time horizon.

## 4.4. Relative risks for the composite outcome mortality or (first) hospitalization

As indicated, data on RRs for the composite outcome of mortality or (first) hospitalization are available for a number of treatment combination from Tromp et al. (2022). Again, in cases where the required RRs were not available, RRs were computed by combining RRs (`dividing out') as indicated in the notes of table A7. The comparator in Tromp et al. (2022) for the composite outcome of mortality or (first) hospitalization is ACE+DIG, not placebo. These data are reproduced in the ACE+DIG column in table A7. As indicated in the previous subsection, RRs with placebo as the comparator are needed in order to use the method described in that subsection. In order to obtain these RRs from $RR_{m|h}$ in the ACE+DIG column, the estimates reported in Aronow (2016) were used. They report that "... an overview of 32 randomized clinical trials in patients with HFrEF demonstrated that compared with placebo, ACE inhibitors reduced mortality by 23% and mortality or hospitalization for HFrEF by 35%." This implies a RR of mortality or hospitalization .65 for ACEi vs. placebo. Thus, in translating the composite RRs in the ACEi+DIG column to placebo, these RRs were multiplied by .65. The result is shown in the final column of table A7.

**Table A7. RRs for the composite outcome mortality or (first) hospitalization**

| | $RR_{h\|m}$ with comparator: | | |
|---|---|---|---|
| **Treatment combination:** | ACE+DIG | Placebo | |
| **ARNi+BB+MRA+SGLT2i** | 0.36 | 0.23 | |
| **ACEi+BB+MRA+SGLT2i** | 0.45 | 0.29 | |
| **ARNi+BB+MRA** | 0.47 | 0.31 | |
| **ARNi+BB+SGLT2i** | 0.52 | 0.34 | * |
| **BB+MRA+SGLT2i** | 0.40 | 0.26 | ** |
| **ARNi+MRA+SGLT2i** | 0.48 | 0.31 | *** |
| **BB+ACEi+SGLT2i** | 0.64 | 0.42 | **** |
| **ACEi+BB+MRA** | 0.58 | 0.38 | |
| **ACEi+BB** | 0.84 | 0.55 | |

* ARNI , BB, MRA, and SGLT2i / MRA
** ARNI , BB, MRA, and SGLT2i / ARNI
*** ARNI , BB, MRA, and SGLT2i / BB
**** ACEi+BB x SGLT2i

Source: Col. 2, Tromp et al. (2022), Central Illustration; Multiplication factor for column 3: Aronow (2016)

## 4.5. Hospitalization under placebo

The risk equations in MEW and TAF can be used to compute hospitalization probabilities for each KCCQ quartile under SoC in the DAPA-HF and EMPEROR-reduced trials. In order to implement the method described above for computing $P_h$ for the treatment combinations included in the present report, hospitalization risks for each KCCQ quartile under *placebo* are needed instead. These are estimated using a method similar to the one used earlier to translate *mortality* probabilities under SoC to *mortality* probabilities under placebo. See table A8. The resulting $RR_h$ with placebo as comparator is almost identical for the treatment mix under SoC for DAPA-HF and EMPEROR-reduced (0.42 and 0.43 respectively).

**Table A8 Computing $RR_h$ SoC / Placebo**

| | **Share of patients using** | | | | | |
|---|---|---|---|---|---|---|
| | MEW/Dapa-HF | TAF/Emperor-reduced | $RR_h$ comparator Placebo | | Weighted $RR_h$ MEW | Weighted $RR_h$ TAF |
| **ACE or ARB** | NA | 69,7 | 0,71 | * | NA | 0,80 |
| **ACE** | 56,1 | NA | 0,71 | * | 0,84 | NA |
| **ARB** | 28,4 | NA | 0,71 | * | 0,92 | NA |
| **BB** | 96 | 94,7 | 0,75 | ** | 0,76 | 0,76 |
| **MRA** | 71,5 | 71,3 | 0,65 | *** | 0,75 | 0,75 |
| **ARNI** | 10,5 | 19,5 | 0,67 | **** | 0,97 | 0,94 |
| **Ivabradine** | NM | 7 | 0,92 | ***** | NA | 0,99 |
| ***RRh* SoC/Placebo** | | | | | 0,42 | 0,43 |

* Calculated from Yusuf et al. 1991, table 2; RRh ACE and ARB assumed equal. ** Calculated from Masrone et al. 2021; *** Pitt et al. 1999; **** Vaduganathan et al. 2020; ***** Pandey et al. 2019

## 4.6. Hospitalization probabilities used

The resulting monthly hospitalization probabilities, derived using the method outlined above, are shown in table A9. In most cases, the differences between treatment combinations are qualitatively in line with what would be expected, quadruple therapy resulting in the lowest probability of hospitalization. The pattern in table A9 was also judged to be plausible by a panel of 4 Dutch cardiologists. The exception is BB+MRA+SGLT2i, for which he methodology resulted in implausibly low probabilities of hospitalization compared to other therapies. After consulting the expert panel, it was decided to equate the hospitalization probabilities for BB+MRA+SGLT2i to those for BB+MRA+ACEi.

**Table A9. Monthly probabilities of 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 | 24.9 | 15.6 | 9.2 | 5.6 |
| ARNi+MRA+SGLT2i | 33.5 | 20.5 | 12.1 | 7.7 |
| BB+ACEi+MRA | 43.6 | 26.2 | 15.4 | 9.8 |
| B+ACEi | 68.3 | 39.9 | 23.0 | 14.5 |

Source: see text.

## 5. The insensitivity of the ICER to discontinuation

As shown in Appendix II, ICERs are hardly affected by even large changes in the rate of discontinuation compared to the base case. This seemingly puzzling finding is due to the fact that costs and QALYs are affected proportionally by changes in the rate of discontinuation. To make this explicit, note that both costs and QALYs are computed by multiplying the relevant populations in each KCCQ-quartile by costs and utilities per patient. Denote the per patient costs by $\alpha_i$ and the per patient QALYs by $\beta_i$, where the subscript i denotes the treatment combination. The cumulative difference in cost for the same treatment combinations but with different discontinuation rates will then be given by:

$$(\alpha_1 Pop_1 + \alpha_{1d} Pop_{1d}) - (\alpha_2 Pop_2 + \alpha_{2d} Pop_{2d}) \tag{12}$$

Where $Pop_i$ indicates the cumulative (discounted) number of patients under treatment combination i, and the additional subscript d indicates the cumulative (discounted) number of patients starting on treatment combination i who have discontinued treatment. A similar expression holds for the number of QALYs:

$$(\beta_1 Pop_1 + \beta_{1d} Pop_{1d}) - (\beta_2 Pop_2 + \beta_{2d} Pop_{2d}) \tag{13}$$

The ICER in this case is the ratio of (12) to (13). A sufficient condition for this ratio to be constant (and independent of $Pop_i \ and \ Pop_{id}$) is that $\beta_1 = \beta_{1d} = \beta_2 = \beta_{2d}$ and $\alpha_1 = \alpha_{1d} = \alpha_2 = \alpha_{2d}$. This turns out to be almost the case, because the *shares* of each KCCQ-quartile in $Pop_i$ and $Pop_{id}$ turn out to be hardly affected by differences in discontinuation rates. This implies $\beta_1 = \beta_{1d} = \beta_2 = \beta_{2d}$ and $\alpha_1 = \alpha_{1d} = \alpha_2 = \alpha_{2d}$, since all $\alpha$s and $\beta$s in (12) and (13) are weighted averages of the underlying costs and utilities in each KCCQ-quartile (irrespective of treatment combination), with the KCCQ-shares in each population as weights.

## Additional references


Aronow WS. Update of treatment of heart failure with reduction of left ventricular ejection fraction. Arch Med Sci Atheroscler Dis. 2016 Oct 17;1(1):e106-e116.

Masarone, D., Martucci, M. L., Errigo, V., & Pacileo, G. (2021). The use of β-blockers in heart failure with reduced ejection fraction. Journal of Cardiovascular Development and Disease, 8(9), 101.

McMurray, John JV, et al. "Angiotensin–neprilysin inhibition versus enalapril in heart failure [PARADIGM-HF]." New England Journal of Medicine 371.11 (2014): 993-1004.

Pandey, A., et al. A systematic review and meta-analysis of randomized controlled trials evaluating ivabradine in heart failure. Canadian Journal of Cardiology, 2019, 35.10: S180.

Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-717.

Srivastava, Pratyaksh K., et al. "Heart failure hospitalization and guideline-directed prescribing patterns among heart failure with reduced ejection fraction patients." Heart Failure 9.1 (2021): 28-38.

Vaduganathan M, Jhund PS, Claggett BL, Packer M, Widimský J, Seferovic P, Rizkala A, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction. Eur Heart J. 2020 Jul 1;41(25):2356-2362.

Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293-302. doi:10.1056/NEJM199108013250501.