Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis

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Aims: A network meta-analysis (NMA) of all recommended drug groups for the treatment of heart failure with reduced ejection fraction (HFrEF), including their combinations, was performed to assess the relative efficacy and incremental benefit.

Methods and Results: A search was made in biomedical databases for randomised controlled trials published between 1987 and 2017 on angiotensin-converting enzyme inhibitors (ACEI), beta-blockers (BB), angiotensin-II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRAs), ivabradine (IVA) or angiotensin receptor/neprilysin inhibitors (ARNI). A total of 58 relevant trials were identified. The relative efficacy of each treatment group (or combination) in terms of all-cause mortality, cardiovascular (CV) mortality, all-cause hospitalizations and hospitalizations for HF, per patient-year of follow-up, were combined in a random-effects Bayesian NMA. The pairwise comparison between each regimen and for each outcome was estimated.

The NMA was dominated by 15 large-scale trials with between 1984 and 18898 patient-years of follow-up. Combinations of drug groups showed incremental benefits on outcomes over single groups. The most effective combinations were ARNI+BB+MRA and ACEI+BB+MRA+IVA, showing reductions in all-cause mortality (versus placebo) of 62% and 59%, respectively; hazard ratios were 0.38 (Credible Interval [CrI]: 0.16–0.71) and 0.41 (CrI: 0.19–0.82); and in all-cause hospitalizations with reductions of 42% for both. These two combinations were also the most effective for the other outcomes studied.

Conclusion: Our analysis shows that the incremental use of combinations of disease-modifying therapies has resulted in the progressive improvement in mortality and hospitalization outcomes in HFrEF. Our findings support the current guideline recommendations.

Introduction

Despite recent therapeutic gains, heart failure (HF) remains a major cause of mortality and of hospitalizations worldwide. Its prevalence has been put at approximately 1–2% of the adult population in developed countries; more recent forecasts alarmingly predict more than doubling of this prevalence (1-3). The therapeutic management of chronic HF, particularly for patients with reduced ejection fraction (HFrEF), is built mainly around drug combinations including, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers (BBs), mineralocorticoid receptor antagonists (MRAs) and diuretics. Recently, the international guidelines in Europe (1) and in USA (4) for the treatment of HFrEF have been updated to include the use of sacubitril/valsartan (ARNI; for angiotensin receptor/neprilysin inhibitor) and ivabradine (IVA; a sinus node I_f channel inhibitor that reduces heart rate).

Over the last three decades, the implementation of guideline-recommended drug treatments for HFrEF has resulted in a decline of HF mortality (5), but early post-discharge mortality and hospital readmission rates have remained stable or may even be worsening due to the complexity of multiple comorbidities in ageing HF patients and to the lack of implementation of recommended medications or proper titration of these drugs (6;7).

Network meta-analysis and multiple treatment comparisons of randomized controlled trials (RCTs) facilitate the indirect comparisons of multiple interventions that have not been studied in head-to-head studies. These methods are attractive for clinical researchers because they seem to respond to their main concern: determining the best available intervention.

A recently published meta-analysis of drug treatment for HFrEF (8) has emphasized the benefits of certain drug combinations over the last 30 years. However by focusing only on all-cause mortality as an endpoint and not including all the recommended drug groups, the review does not fully reflect the burden of the disease and the options available. Thus, in order to provide a more comprehensive picture of the impact of therapy and in particular on the burden of hospitalizations, we reviewed all available evidence regarding the pharmacological treatment of chronic HFrEF including all guideline-recommended drug groups on the endpoints of all-cause mortality, cardio-vascular mortality, hospitalization for heart failure and all-cause hospitalization.

Methods

Identification and Selection of Studies

The databases PubMed, EMBASE, and Cochrane CENTRAL were searched using a strategy adapted from the above mentioned review (8), for the period January 2015 until May 2017. A search was made for the main drug groups for the treatment of HF (ACEIs, BBs, ARBs, MRAs) and the newer groups, including I_f channel blockers (namely, ivabradine; IVA) and angiotensin receptor/neprilysin inhibitors (ARNI; namely, valsartan/sacubitril or LCZ696). Studies were considered if they were RCTs and comparisons of drug efficacy within the same

drug group were excluded. The retrieved studies were added to the list of studies provided in reference 8; there was only one addition, the SHIFT trial of ivabradine (9).

The target studies were limited to those in adult outpatients (aged ≥18 years to 70 years) with chronic HFrEF (LVEF < 45%) of ischemic or idiopathic aetiology. The review focused on studies conducted principally in North America or Europe. Excluded, were studies where the entire population comprised patients with a concomitant diagnosis that was likely to have a major effect on endpoint attainment (e.g. acute heart failure, chronic obstructive pulmonary disease, diabetes mellitus, renal failure, coronary heart disease). The PRISMA diagram showing the search and selection of references is provided in the supplementary data, along with the list of references excluded on full text.

Information from the reports of the included studies was entered into a database (double entry with reconciliation). For each endpoint, the total number of events was extracted for each arm. The exposure time was the mean or median follow-up time if reported, or else the planned study duration. To account for concomitant therapy in the trials, treatments were categorized by drug group combination using a patient threshold of 50%; thus if >50% of the trial patients received concomitant drugs of interest (e.g. ACEI and BB), the treatment was described as a combination therapy (the study drug group + the concomitant drug group).

Network Meta-Analysis

Network meta-analysis (NMA) is a statistical method that combines direct (i.e. head-to-head) and indirect evidence (i.e. via one or more common comparator(s)) in a mixed treatment comparison (10). It therefore facilitates indirect comparisons of interventions that have not been studied in head-to-head studies. In such analyses, the treatments form a connected network, i.e. there is path from each treatment to every other treatment in the network. For consistency, we used same methodology as in the previous NMA in heart failure (8), with a modelling framework proposed by Dias et al (11). This comprises a random-effects model within a Bayesian framework using R software and Winbugs 1.4. The model input was arm-level data, using the numbers of patients with at least one event at the end of the trial, the total number of patients randomized, and the mean or median follow-up duration (of the overall trial). The log mean follow-up time was used to transform the probability of an event into a constant rate for each trial arm by assuming an underlying Poisson process. A complementary clog–log (cloglog) link was used to model the event rates. Non-informative priors were used. Outputs from the model are presented as hazard ratios (HRs) for each treatment versus placebo with 95% credible intervals (CrI) for the Bayesian probability that the treatment is better than placebo. Results were also computed for all pairwise comparisons.

Results

Study Selection

A total of 58 RCTs were included, constituting the diagram presented in **Figure 1**. This network forms a quasi-chronological progression of therapeutic advance starting from the top. Although many later studies compared their investigational treatment with standard of care, the analysis here is designed to calculate the treatment effect as compared with placebo (i.e. the absence of any of the studied drug groups).

The included trials were mostly multicentre, double-blind, placebo-controlled trials, although they varied considerably in terms of size and follow-up duration. Nine of the studies included less than 100 patients, whereas eleven included more than 2000. Follow-up durations ranged from 8 weeks, with 16 studies lasting 3 months or less, to 4 years, with 18 studies that were over 1 year. The severity of HF in the included patients ranged from mild in SOLVD-prevent (with 66% NYHA class I and 34% class II) to severe in CONSENSUS (with 100% class IV). The full list of studies is presented in the supplementary data section. The network was dominated by a few large-scale studies and these are listed in **Table 1**. These tended to be the more recent ones, reflecting the need to have larger studies to demonstrate the incremental benefit of added treatments.

When the study data are viewed in terms of patient-years of follow-up for the investigational arms of the included treatments (**Figure 2A**), the weight of evidence provided by the larger study programs is clear. It might also be noted that the heart failure indication for each of ARNI and ivabradine was informed by a single RCT. When the patient follow-up by drug group in this indication is considered (**Figure 2B**), it can be seen that the evidence is dominated by the studies of ARBs, beta-blockers, ARNI and ivabradine.

As might be expected given the variety in the included studies in terms of inclusion criteria, design and endpoint adjudication (all-cause mortality excepted), there is a significant amount of heterogeneity in the network for each endpoint, resulting in some uncertainty in comparative estimates. For example the heterogeneity parameter for all-cause mortality was between-study variability=0.17 (95% CrI 0.05 – 0.35); for all-cause hospitalizations this measure was slightly lower, but for other endpoints it was higher (supplementary data). The main results of the NMA for each drug group, or combination of groups, versus placebo for each endpoint, are summarized in **Table 2.** The results for each endpoint are also illustrated in forest plots (**Figures 3 – 6**), which show the hazard ratio for each treatment with its 95% credible interval. The full results of the NMA are presented in the supplementary data section with a separate matrix for each endpoint. It should be noted that the comparisons are presented versus placebo and do not necessarily emanate from an RCT; the network meta-analysis provides this placebo-comparison in an indirect manner.

All treatment groups or combinations were associated with some reduction in risk. The most efficacious treatment combinations versus placebo are found at the top of the figures with the point estimates relatively far (to the left) from the null-effect indicator of 1.0.

In the forest plot for all-cause mortality (**Figure 3)** it can be seen that all of the combination therapies as well as BB monotherapy have 95% CrI's and the point estimate shows superiority of the combination over placebo. The best combinations are ARNI+BB+MRA and ACEI+BB+MRA+IVA with a relative risk reduction of 62% and 59% respectively. Of the triple therapies, the combination ACEI+BB+MRA results in a somewhat better result than ACEI+ARB+BB.

In the forest plot for CV mortality **(Figure 4)**, the trend in HR estimates is quite similar to those already described for all-cause mortality, with the exception of BB monotherapy, which did not appear to perform so well on this endpoint. The credible intervals are wider for this comparison than all-cause mortality because fewer studies reported this endpoint (n = 41).

The data for all-cause hospitalization are presented in **Figure 5**. The best performing combinations appear once again to be ARNI+BB+MRA and ACEI+BB+MRA+IVA (relative risk reduction of 42% for both) although other combinations, such as ACEI+ BB+MRA (35% reduction), are close behind. A total of 21 studies reported this endpoint.

In the forest plot for hospitalizations due to worsening HF (**Figure 6)**, all treatment groups or combinations were associated with some reduction in risk. The best performing combinations were ACEI+BB+MRA+IVA, ACEI+ARB and ARNI+BB+MRA. However the credible intervals are wider here, indicating a lower precision in the estimates. A total of 28 studies reported this endpoint.

The pairwise comparisons of all treatments (and treatment combinations), for each endpoint, are provided in Appendix Table 1. The matrices indicate the estimated treatment effect (and CrI) for each treatment pair along with the Bayesian probability that one is better than the other. The hierarchy of treatment combinations versus single treatment group comparators was very similar to the comparisons versus placebo. For each endpoint, there was little difference in efficacy between the most effective combinations: for all-cause death, hazard ratios for ACEI+BB+MRA+IVA versus ARNI+BB+MRA and ACEI+BB+MRA were 1.08 (CrI: 0.61;0.91) and 0.91 (0.6;1.36) respectively; for hospitalization due to worsening HF, the hazard ratios for ACEI+BB+MRA+IVA versus ARNI+BB+MRA and ACEI+BB+MRA were 0.93 (CrI: 0.24;3.61) and 0.75 (CrI: 0.29;1.96) respectively

Discussion

Our results, based on the analysis of relevant clinical trials conducted between 1987 and 2017, show that the combination of disease modifying medications, i.e. ACEI, ARB, BB, MRA ivabradine and ARNI, resulted in the progressive improvement over the last 30 years in mortality and hospitalization outcomes in HFrEF. This improvement may be visualized, for each of the endpoints studied, by the leftward progression of the point estimates, with intensifying combinations of drug groups. Overall, our network analysis validates the recommendations made by international guidelines.

Among the different possible combinations, those including the most recently developed drugs, ivabradine and sacubitril/valsartan are among the most efficacious: ARNI+BB+MRA and ACEI+BB+MRA+IVA tended to be the combinations associated with the lowest point estimates of HR versus placebo for the mortality endpoints and for hospitalizations. There was a relative risk reduction of 62% and 59%, respectively on all-cause death, 64% and 59% on CV deaths, 42% and 42% on all-cause hospitalizations, and 73% and 75% on hospitalizations for worsening HF. However, none of these estimates can be taken as strong evidence of superiority over other combinations and it is clear that the options need to be carefully weighed given the characteristics of the individual patient. Numerous factors including rhythm (sinus or atrial fibrillation), heart rate at baseline, low systolic blood pressure, severe kidney disease can influence the choice of ARNI or ivabradine as third line therapy in HFrEF based on the respective indication and contra indication of each drug. However this combination of the two drugs is recommended by ESC guidelines if the patient's profile fits.

While individual RCTs are not always easy to compare given the differences in the entry criteria, recent analyses have concluded that the proportion of deaths adjudicated as cardiovascular has decreased over the last 30 years (12;13). The noteworthy effect of the combinations of disease modifying therapies observed in the clinical trials included in this analysis may however not fully translate to the real-life situations due to the inherent selection bias of patients enrolled in randomized trials whereas observational studies show that HF patients usually have a constellation of comorbidities and are generally older than those studied in clinical trials (14). However, it has been shown that adherence to guideline recommended therapies is associated with improved outcomes in observational studies (14). The results of the meta-analysis should therefore encourage physicians to apply the most efficacious combinations of HF medications.

The recent guidelines of the European Society of Cardiology (2016) emphasize the need to reduce the burden of hospitalizations and rehospitalizations as one of the major goals of the management of HFrEF (1) and the importance of this goal has been recently highlighted in a position paper regarding the conduct of future heart failure trials (15). Therefore, our analysis included not only mortality data but also all cause hospitalizations and HF hospitalizations together with the totality of available drugs tested in randomized controlled trials. It therefore extends the results of a previous meta-analysis to hospitalizations and finds a similar stepwise improvement of all cause death and of HF hospitalizations by modern combinations.

The review has a number of limitations. The start date for the literature search (January 1987) was arbitrary and chosen to capture a 30-year time span. This choice resulted in the omission of a few potentially relevant studies, notably some earlier captopril trails. Some important trials in high-risk CV patients were excluded because of the decision to focus on patients with established HF. Thus the trials, SAVE (16), AIRE (17) and HOPE (18), which were important in establishing ACE inhibitors as standard of care in patients at high CV risk or post-myocardial infarction were not included in the analysis. A large number of small short-term studies (often designed to investigate drug effects on biomarkers or exercise tolerance) were included in the review, which may have introduced spurious information since the mean

mortality rates were relatively higher in these than in the longer term trials (e.g. 0.16 deaths per patient-year in 3-month trials versus 0.07 deaths per patient-year in trials lasting >30 months). The review included treatments which do not have an indication in HF, namely: benazepril, imidapril, spirapril, telmisartan, celiprolol, bucindolol, atenolol, and canrenone, since the focus was on the drug groups only. Prescription of drugs with certain groups and not dosage used was considered for this analysis. This approach may have diluted the treatment effect of drugs with the indication. Our meta-analysis was based on the recommended add-on or substitution strategy and did not address other potential strategies such as ACEI + MRA + IVA, ARNI + IVA or ARNI + BB + digoxin, which might only be validated by properly designed clinical trials. It should also be noted that the patients enrolled in RCTs may not represent the real life situation by being relatively younger and having fewer comorbidities. Finally since 30 years separates the oldest and the most recent trials included in our analysis, it is possible that the profile and the environment of patients enrolled in these trials has changed significantly over time. The statistical analysis of the retrieved data indicates a fairly large amount of uncertainty for several of the comparisons, reflecting the limitations already mentioned.

In conclusion, our analysis of relevant clinical trials published between 1987 and 2017, shows that the incremental use of combinations of disease modifying therapies, i.e. ACEIs, ARBs, BBs, MRAs, ivabradine and ARNI, has resulted in the progressive improvement over the last 30 years in mortality and hospitalization outcomes in HFrEF. Our findings, illustrating the success of disease-modifying combinations, support the guideline recommendations.

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11. Figure Legends (296 words)

Figure 1: The evidence network of studies reporting all-cause mortality. The thickness of the connecting lines corresponds to the number of patient-years of evidence (5 indicative thicknesses) for each drug group/combination comparison. The contributing studies are indicated in the adjoining panels with the number of randomized patients that contributed to the analysis in parenthesis and the cumulative total of patient-years of evidence. The supplementary data includes networks for the other endpoints investigated in this review.

Figure 2A: Patient-years of evidence for the investigational arms of the included treatments (thus more than one study might contribute to evidence total). **B**: Patient-years of evidence for the investigational arms of the included treatment groups. Note: The evidence from the SOLVD Prevent study is not represented in these figures.

Figure 3: Forest plot of hazard ratios and their 95% CrIs for all-cause mortality for treatment versus placebo (random-effects model without adjustment). Hazard ratio < 1 favours treatment. The size of the square is proportional to the number of patients in the comparison.

Figure 4: Forest plot of hazard ratios for CV mortality (random-effects model without adjustment). The point estimates with a value less than one signify a relative superiority of the active treatment and the whiskers mark the limits of the 95% credible interval.

Figure 5: Forest plot of hazard ratios for all-cause hospitalization (random-effects model without adjustment). The point estimates with a value less than one signify a relative superiority of the active treatment and whiskers mark the limits of the 95% credible interval.

Figure 6: Forest plot of hazard ratios for hospitalization due to worsening HF (random-effects model without adjustment). The point estimates with a value less than one signify a relative superiority of the active treatment and the whiskers mark the limits of the 95% credible interval.

All-cause Deaths

SOLVD-prevent (n=4228)
SOLVD-treat (n=2569)
FEST (n=308)
CONSENSUS (n=253)
Brown 1995 (n=241)
Shettigar 1999 (n=206)
Goldstein 1988 (n=204)
Beller 1995 (n=193)
Colfer HT, 1992 (n=172)
MHFT (n=170)
CASSIS (n=147) *
Lewis 1989 (n=130)
Chalmers 1987 (n=130)
van Veldhuisen 1998 (n=122) *

Placebo

181 patient-years

STRETCH (n=424) *
SPICE (n=270)
Mitrovic 2003 (n=88)

ARB

5527 patient-years

ELITE II (n=3152)
ELITE I (n=722)
REPLACE (n=154)*
Dickstein 1995 (n=114)*
Lang 1997 (n=78)

23223 patient-years

3326 patient-years

RALES (n=1663)

1077 patient-years

CIBIS-III (n=1010)
CARMEN (n=381)

BB

ACEI

ACEI + MRA

9619 patient-years

Val HeFT (n=5010)
Hamroff 1999 (n=33)

CARMEN (n=382)

287 patient-years

ACEI + ARB

81 patient-years

RESOLVD (n=175)*

CHARM Alt (n=2028)

5695 patient-years

BB + ARB

ACEI + BB

8706 patient-years

CHARM-Added (n=2548)

ACEI +BB + ARB

MERIT-HF (n=3991)
BEST (n=2708)
CIBIS-II (n=2647)
COPERNICUS (n=2289)
Packer (n=1094)
CIBIS (n=641)
CARMEN (n=381)
Colucci 1996 (n=366)
PRECISE (n=278)
ENECA (n=260)
MOCHA (n=173) *
CELICARD 2000 (n=132)
Cohn 1997 (n=105)
Sturm 2000 (n=100)
MERIT-HF-pilot (n=61)
Palazzuoli 2005b (n=59)
Palazzuoli 2005 (n=58)
De Milliano 2002 (n=54)
MIC (n=52)
SYMPOXYDEX (n=50)
Krum 1995 (n=49)
Dubach 2002 (n=28)

HEAVEN (n=141)

33 patient-years

18552 patient-years

EMPHASIS-HF (n=2737)
AREA IN-CHF (n=467)
Vizzardi 2014 (n=130)
Cicoira 2002 (n=106)

5839 patient-years

ACEI + BB + MRA

SHIFT (n=6558)

12515 patient-years

PARADIGM-HF (n=8399)

18898 patient-years

BB + MRA + ARNI

ACEI + BB + MRA + IVA

**Contributing studies
ordered by decreasing size**

* Highest dose considered
# Total for considered comparison

	HR (95% Credible Interval)
ARNI+BB+MRA vs Placebo	0.38 (0.2;0.65)
ACEI+BB+MRA+IVA vs Placebo	0.41 (0.21;0.7)
ACEI+BB+MRA vs Placebo	0.44 (0.27;0.67)
ARB+BB vs Placebo	0.48 (0.24;0.86)
ACEI+ARB+BB vs Placebo	0.52 (0.32;0.8)
BB vs Placebo	0.58 (0.34;0.95)
ACEI+MRA vs Placebo	0.58 (0.36;0.9)
ACEI+BB vs Placebo	0.58 (0.42;0.73)
ACEI+ARB vs Placebo	0.83 (0.52;1.23)
ACEI vs Placebo	0.84 (0.67;1.01)
ARB vs Placebo	0.89 (0.61;1.27)
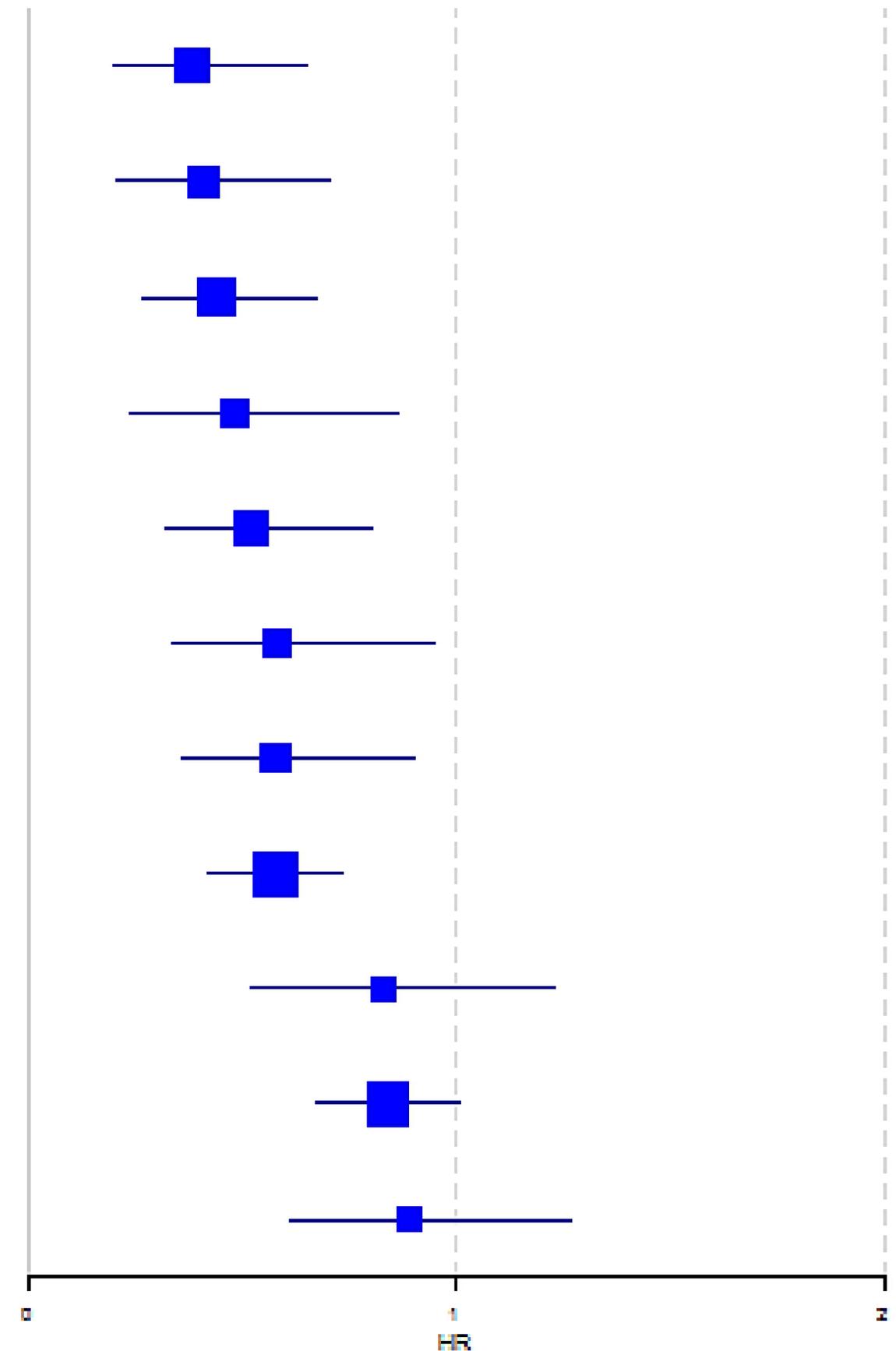
	HR (95% Credible Interval)
ARNI+BB+MRA vs Placebo	0.36 (0.16;0.71)
ACEI+BB+MRA+IVA vs Placebo	0.41 (0.19;0.82)
ACEI+BB+MRA vs Placebo	0.45 (0.25;0.75)
ACEI+ARB+BB vs Placebo	0.47 (0.24;0.82)
ARB+BB vs Placebo	0.5 (0.19;1.12)
ACEI+MRA vs Placebo	0.56 (0.31;0.95)
ACEI+BB vs Placebo	0.56 (0.37;0.75)
BB vs Placebo	0.62 (0.27;1.32)
ACEI+ARB vs Placebo	0.8 (0.43;1.33)
ACEI vs Placebo	0.81 (0.6;1.04)
ARB vs Placebo	0.85 (0.51;1.28)
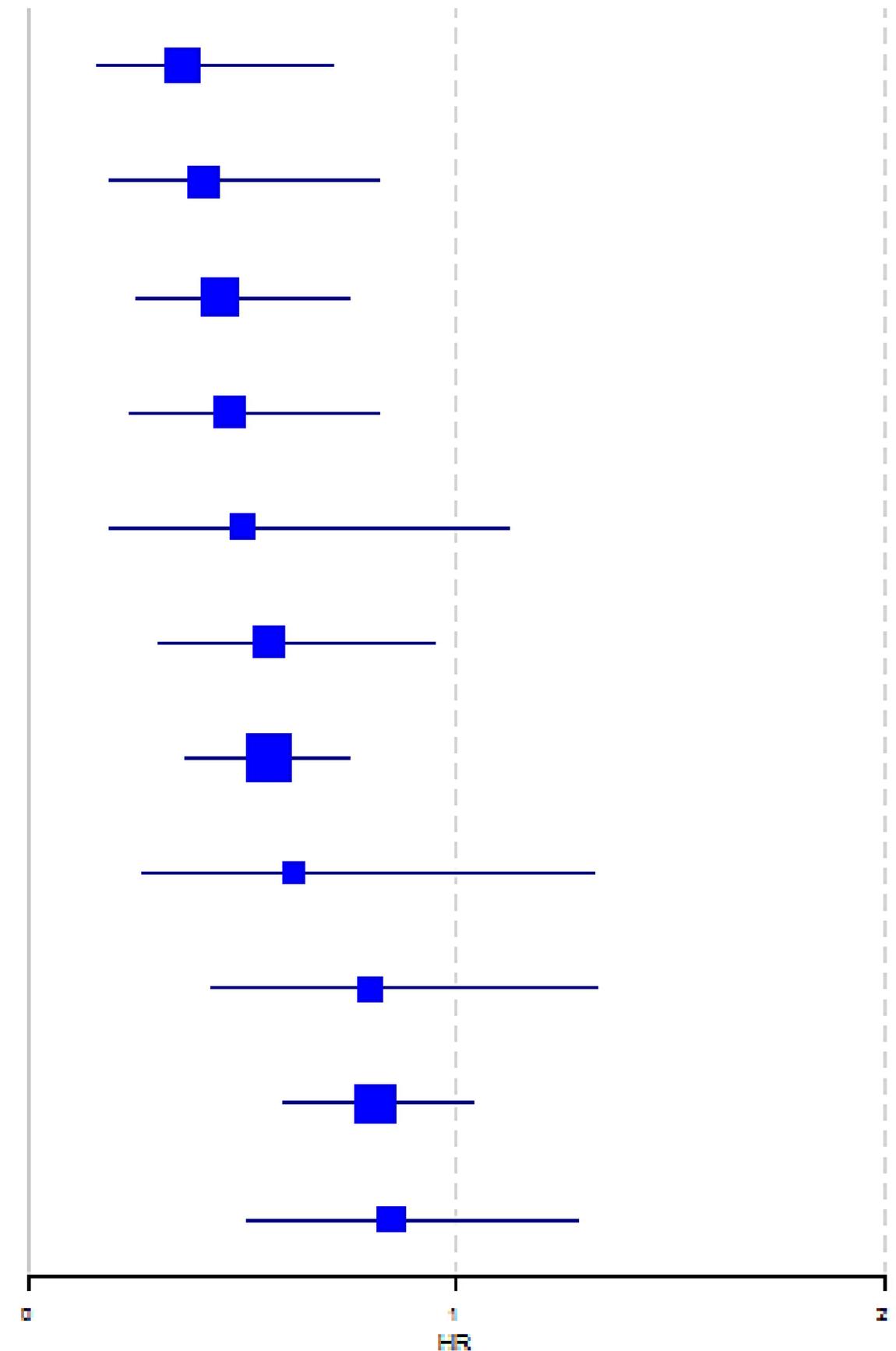
	HR (95% Credible Interval)
ACEI+BB+MRA+IVA vs Placebo	0.58 (0.36;0.92)
ARNI+BB+MRA vs Placebo	0.58 (0.36;0.92)
ACEI+BB+MRA vs Placebo	0.65 (0.45;0.93)
ACEI+MRA vs Placebo	0.69 (0.45;0.96)
ACEI+ARB+BB vs Placebo	0.74 (0.46;1.04)
ACEI+BB vs Placebo	0.75 (0.54;0.92)
ARB+BB vs Placebo	0.79 (0.47;1.21)
ARB vs Placebo	0.81 (0.56;1.01)
BB vs Placebo	0.86 (0.59;1.18)
ACEI vs Placebo	0.89 (0.71;1.05)

HR

	HR (95% Credible Interval)
ACEI+BB+MRA+IVA vs Placebo	0.25 (0.07;0.99)
ACEI+ARB vs Placebo	0.26 (0.08;0.57)
ARNI+BB+MRA vs Placebo	0.27 (0.07;1.07)
ARB+BB vs Placebo	0.31 (0.07;1.29)
ACEI+BB vs Placebo	0.34 (0.17;0.56)
ACEI+BB+MRA vs Placebo	0.34 (0.13;0.91)
ACEI+MRA vs Placebo	0.36 (0.12;0.96)
ACEI+ARB+BB vs Placebo	0.42 (0.16;1.23)
BB vs Placebo	0.45 (0.13;1.39)
ACEI vs Placebo	0.52 (0.32;0.76)
ARB vs Placebo	0.53 (0.26;1.03)
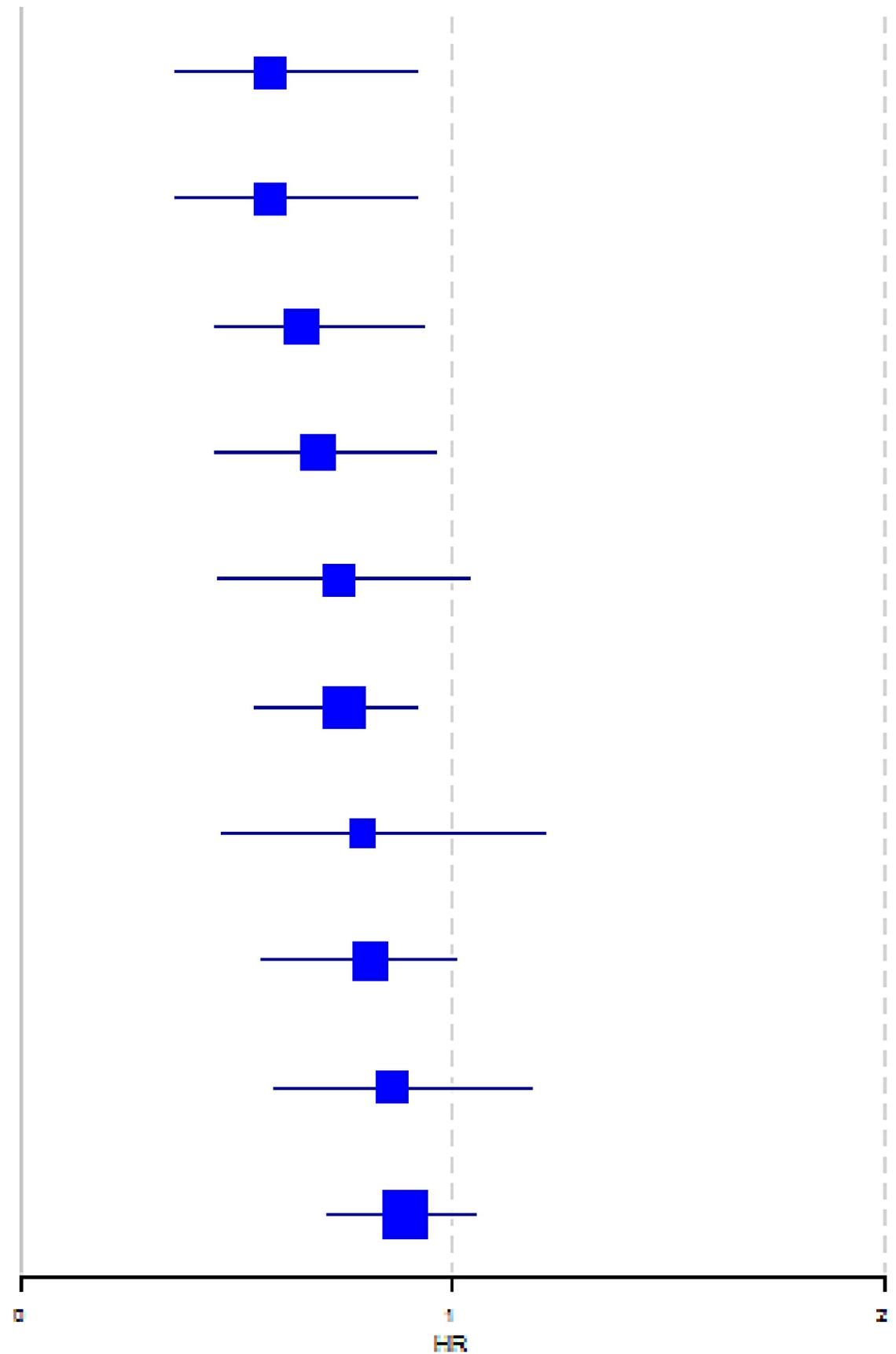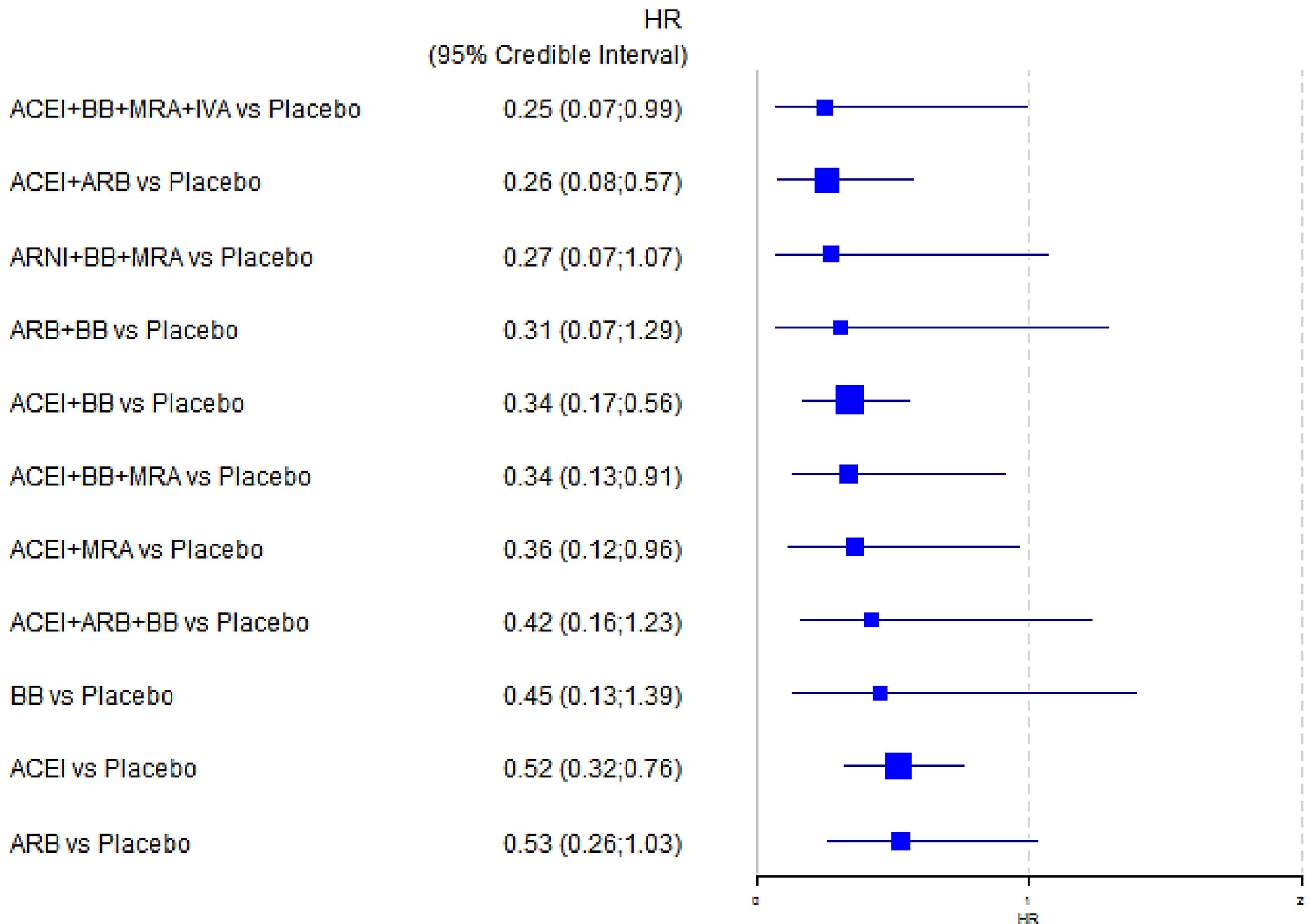
13. Tables

Table 1: Contributing studies that have at least 1000 patient-years of evidence, ordered by year of publication

Name of study	Year Published	Drug entity	Patients (randomized)	Median duration	Patient-years of evidence
SOLVD Treat	1991	Enalapril	2569	3.5	8863.1
SOLVD Prevent	1992	Enalapril	4228	3.1	13177.3
CIBIS	1994	Bisoprolol	641	1,9	1217.9
CIBIS-II	1999	Bisoprolol	2647	1.3	3441.1
MERIT-HF	1999	Metoprolol	3991	1,0	3991.0
RALES	1999	Spironolactone	1663	2.0	3326.0
ELITE II	2000	Losartan	3152	1.5	4789.5
BEST	2001	Bucindolol	2708	2.0	5416.0
Val-HeFT	2001	Valsartan	5010	1.9	9602.5
CHARM Alternative	2003	Candesartan	2028	2.8	5695.3
CHARM Added	2003	Candesartan	2548	3.4	8705.7
COPERNICUS	2003	Carvedilol	2289	0.9	1983.8
SHIFT	2010	Ivabradine	6558	1.9	12514.9
EMPHASIS-HF	2011	Eplerenone	2737	1.8	4789.8
PARADIGM-HF	2014	Valsartan/sacubitril	8399	2.3	18897.8

Table 2: Summary results of treatment effect versus placebo for each drug group or combination of groups and for each endpoint.

Estimate (95% CrI)	All-cause mortality	CV mortality	All-cause Hospitalization	Hospitalization for HF
ARNI+BB+MRA	0.38 (0.20;0.65)	0.36 (0.16;0.71)	0.58 (0.36;0.92)	0.27 (0.07;1.07)
ACEI+BB+MRA+IVA	0.41 (0.21;0.70)	0.41 (0.19;0.82)	0.58 (0.36;0.92)	0.25 (0.07;0.99)
ACEI+BB+MRA	0.44 (0.27;0.67)	0.45 (0.25;0.75)	0.65 (0.45;0.93)	0.34 (0.13;0.91)
ARB+BB	0.48 (0.24;0.86)	0.50 (0.19;1.12)	0.79 (0.47;1.21)	0.31 (0.07;1.29)
ACEI+ARB+BB	0.52 (0.32;0.80)	0.47 (0.24;0.82)	0.74 (0.46;1.04)	0.42 (0.16;1.23)
ACEI+BB	0.58 (0.42;0.73)	0.56 (0.37;0.75)	0.75 (0.54;0.92)	0.34 (0.17;0.56)
ACEI+MRA	0.58 (0.36;0.90)	0.56 (0.31;0.95)	0.69 (0.45;0.96)	0.36 (0.12;0.96)
BB	0.58 (0.34;0.95)	0.62 (0.27;1.32)	0.86 (0.59;1.18)	0.45 (0.13;1.39)
ACEI+ARB	0.83 (0.52;1.23)	0.80 (0.43;1.33)	n.a.	0.26 (0.08;0.57)
ACEI	0.84 (0.67;1.01)	0.81 (0.60;1.04)	0.89 (0.71;1.05)	0.52 (0.32;0.76)
ARB	0.89 (0.61;1.27)	0.85 (0.51;1.28)	0.81 (0.56;1.01)	0.53 (0.26;1.03)

Results of the NMA: Hazard ratios and their 95% CrIs versus placebo; n.a. no available result.

Prisma flow diagram

Identification

Burnett list:
57 RCTs

Ivabradine HF
(pre 2015):
1 RCT

1447 records identified for
2015 - 2017:
263 Medline; 527 Embase;
657 Cochrane

1441 records excluded on
title/abstract

Mostly on patient population
or study design

Screening

6 records assessed for
eligibility on full-text

1 record retained for
further detailing the
Paradigm study

Eligibility

58 RCTs included in
analysis

CV Deaths

SOLVD-prevent (n=4228)
SOLVD-treat (n=2569)
FEST (n=308)
CONSENSUS (n=253)
Brown 1995 (n=241)
Shettigar 1999 (n=206)
Colfer HT, 1992 (n=172)
Lewis 1989 (n=130)
van Veldhuisen 1998 (n=122) *

STRETCH (n=424) *
Mitrovic 2003 (n=88)

Placebo

22553 patient-years

118 patient-years

ARB

ELITE II (n=3152)
ELITE I (n=722)
REPLACE (n=154)*
Lang 1997 (n=78)

CARMEN (n=381)#

572 patient-years

BB

ACEI

5510 patient-years

3326 patient-years

RALES (n=1663)

ACEI
+
MRA

9619 patient-years

Val HeFT (n=5010)
Hamroff 1999 (n=33)

CARMEN (n=382)#

287 patient-years

ACEI
+
ARB

CHARM Alt (n=2028)

5695 patient-years

BB
+
ARB

ACEI
+ BB

8706 patient-years

CHARM-Added (n=2548)

15214 patient-years

MERIT-HF (n=3991)
BEST (n=2708)
CIBIS-II (n=2647)
Packer (n=1094)
CIBIS (n=641)
CARMEN (n=381)
MOCHA (n=173) *
CELICARD 2000 (n=132)
Sturm 2000 (n=100)
MERIT-HF-pilot (n=61)
De Milliano 2002 (n=54)
MIC (n=52)
SYMPOXYDEX (n=50)
Dubach 2002 (n=28)

HEAVEN (n=141)

33 patient-years

ACEI
+BB
+ARB

EMPHASIS-HF (n=2737)
AREA IN-CHF (n=467)
Vizzardi 2014 (n=130)

5733 patient-years

ACEI
+ BB
+
MRA

PARADIGM-HF (n=8399)

18898 patient-years

12515 patient-years

SHIFT (n=6558)

Contributing studies
ordered by decreasing size

* Highest dose considered
# Total for considered comparison

BB +
MRA
+
ARNI

ACEI +
BB +
MRA +
IVA

All Hospitalisations

Placebo

83 patient-years — SPICE (n=270) / Mitrovic 2003 (n=88)

SOLVD-prevent (n=4228) / SOLVD-treat (n=2569) / CASSIS (n=147) * — 22074 patient-years

ARB

ELITE II (n=3152) / ELITE I (n=722)

CIBIS-III (n=1010) / CARMEN (n=381)# — 1077 patient-years

3326 patient-years — RALES (n=1663)

5456 patient-years

BB

ACEI

ACEI + MRA

ACEI + ARB

CARMEN (n=382)# — 287 patient-years

CHARM Alt (n=2028) — 5695 patient-years

BB + ARB

ACEI + BB

8706 patient-years — CHARM-Added (n=2548)

ACEI +BB + ARB

EMPHASIS-HF (n=2737) / AREA IN-CHF (n=467) — 5257 patient-years

9192 patient-years — BEST (n=2708) / CIBIS-II (n=2647) / MOCHA (n=173) * / ENECA (n=260)

ACEI + BB + MRA

PARADIGM-HF (n=8399) — 18898 patient-years

12515 patient-years — SHIFT (n=6558)

BB + MRA + ARNI

ACEI + BB + MRA + IVA

Contributing studies ordered by decreasing size

* Highest dose considered
# Total for considered comparison

HF Hospitalisations

Placebo

SPICE (n=270)

62 patient-years

SOLVD-prevent (n=4228)
SOLVD-treat (n=2569)
FEST (n=308)
CONSENSUS (n=253)
Brown 1995 (n=241)
Shettigar 1999 (n=206)
Goldstein 1988 (n=204)
Beller 1995 (n=193)

22602 patient-years

ARB

ELITE II (n=3152)
ELITE I (n=722)

CARMEN (n=381)#

572 patient-years

RALES (n=1663)

5456 patient-years

BB

ACEI

ACEI + MRA

3326 patient-years

CARMEN (n=382)#

287 patient-years

Val HeFT (n=5010)

9603 patient-years

ACEI + ARB

CHARM Alt (n=2028)

5695 patient-years

81 patient-years

RESOLVD (n=175)*

8706 patient-years

CHARM-Added (n=2548)

BB + ARB

ACEI + BB

ACEI +BB + ARB

BEST (n=2708)
CIBIS-II (n=2647)
CARMEN (n=381)#
Colucci 1996 (n=366)
MOCHA (n=173) *
Sturm 2000 (n=100)
MERIT-HF-pilot (n=61)

EMPHASIS-HF (n=2737)
AREA IN-CHF (n=467)

5257 patient-years

9388 patient-years

ACEI + BB + MRA

PARADIGM-HF (n=8399)

18898 patient-years

12515 patient-years

SHIFT (n=6558)

**Contributing studies
ordered by decreasing size**

* Highest dose considered
\# Total for considered comparison

BB + MRA + ARNI

ACEI + BB + MRA + IVA