Original Article

Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction
A Network Meta-Analysis

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Background—Treatments that reduce mortality and morbidity in patients with heart failure with reduced ejection fraction, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers (BB), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor–neprilysin inhibitors (ARNI), have not been studied in a head-to-head fashion. This network meta-analysis aimed to compare the efficacy of these drugs and their combinations regarding all-cause mortality in patients with heart failure with reduced ejection fraction.

Methods and Results—A systematic literature review identified 57 randomized controlled trials published between 1987 and 2015, which were compared in terms of study and patient characteristics, baseline risk, outcome definitions, and the observed treatment effects. Despite differences identified in terms of study duration, New York Heart Association class, ejection fraction, and use of background digoxin, a network meta-analysis was considered feasible and all trials were analyzed simultaneously. The random-effects network meta-analysis suggested that the combination of ACEI+BB+MRA was associated with a 56% reduction in mortality versus placebo (hazard ratio 0.44, 95% credible interval 0.26–0.66); ARNI+BB+MRA was associated with the greatest reduction in all-cause mortality versus placebo (hazard ratio 0.37, 95% credible interval 0.19–0.65). A sensitivity analysis that did not account for background therapy suggested that ARNI monotherapy is more efficacious than ACEI or ARB monotherapy.

Conclusions—The network meta-analysis showed that treatment with ACEI, ARB, BB, MRA, and ARNI and their combinations were better than the treatment with placebo in reducing all-cause mortality, with the exception of ARB monotherapy and ARB plus ACEI. The combination of ARNI+BB+MRA resulted in the greatest mortality reduction. (*Circ Heart Fail*. 2017;10:e003529. DOI: 10.1161/CIRCHEARTFAILURE.116.003529.)

Key Words: drug combinations ■ drug therapy ■ heart failure ■ mortality ■ network meta-analysis

Mortality in patients with heart failure and reduced ejection fraction (HFrEF) has improved over time because of the step-wise introduction of a variety of pharmacological treatments. For years, recommended treatments for patients with HFrEF included the combination of an angiotensin-converting enzyme inhibitor (ACEI; or an angiotensin II receptor blocker [ARB] if an ACEI is not tolerated), a β-blocker (BB), and a mineralocorticoid receptor antagonist (MRA).[1] Despite these recommended treatments being evidence based, the mortality rate for patients with HFrEF remains high.[2–4]

Sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), was recommended as a new treatment option for patients with HFrEF in the 2016 European Society for Cardiology guidelines[5] and the 2016 American College of Cardiology/American Heart Association guidelines.[6] These recommendations were based on the results of

the PARADIGM-HF trial (Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure), which showed sacubitril/valsartan to be superior to enalapril in reducing the risks of cardiovascular and all-cause mortality when added to a BB (in most patients) and a MRA (in many), as well as a diuretic and digoxin.[7]

See Clinical Perspective

There are now 5 types (ACEI, ARB, BB, MRA, and ARNI) of life-saving pharmacological therapies available to treat patients with HFrEF. Given that most trials in HFrEF have compared newer agents to placebo, which has included alternative background treatments as recommendations have evolved, there is a need to understand how the efficacy of these individual treatments and various combinations compare in

terms of all-cause mortality. If all trials have at least one intervention in common with another, it is possible to develop a network of randomized controlled trials (RCTs), allowing for indirect comparisons of interventions not studied in a head-to-head fashion using network meta-analysis (NMA).[8] The validity of any NMA relies on whether there are systematic differences across RCTs in terms of patient or disease characteristics that are treatment effect modifiers.[8–11] Consequently, it is important to identify the relevant network of RCTs and to assess the feasibility of performing a valid NMA.

The objective of this study was to systematically identify RCTs evaluating recommended drug classes and combinations for HFrEF in terms of all-cause mortality and to perform a valid NMA assessing the comparative efficacy of these therapies.

Methods

Identification and Selection of Studies

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] Medline, EMBASE, and Cochrane CENTRAL were searched to identify studies published between January 1987 and April 28, 2015. Search terms included a combination of free text and Medical Subject Heading terms (see Data Supplement). Two reviewers (H. Burnett and A. Earley) independently screened citations against the following predefined selection criteria.

Population

Studies evaluating adults (aged ≥18 years) with chronic HFrEF (left ventricular ejection fraction <45%) and New York Heart Association class II–IV of varying etiology (ischemic and dilated cardiomyopathy) who were outpatients were included. Studies were excluded if the entire study population had one of the following characteristics, which are known to impact treatment response or all-cause

mortality: (1) acute heart failure, (2) hospitalized, (3) New York Heart Association class I, (4) clinical comorbidity (eg, chronic obstructive pulmonary disease, diabetes mellitus, or renal failure), (5) coronary heart disease, (6) post-myocardial infarction, (7) ischemia, (8) idiopathic dilated cardiomyopathy, (9) elderly (aged >70 years), or (10) from country outside of North America or Europe. Studies that included a proportion of patients with the characteristics described above were included.

Interventions

All guideline-recommended drug classes: ACEIs, BBs, ARBs, and MRAs and an ARNI, administered alone or in combination (see Table I in the Data Supplement for eligible drug molecules).

Comparators

Placebo or any intervention of interest of a different class; comparisons within the same class were excluded (eg, ACEI versus ACEI).

Outcomes

Death because of any cause reported as an efficacy or safety end point.

Study Design

Phase II or III RCTs published in English.

Data Extraction and Quality Assessment

For each included study, details were extracted on study design, patient characteristics, and interventions. The quality of the RCTs was assessed.[13] For all-cause mortality, the total number of events was extracted for each arm, and the exposure time for each trial was extracted for the planned study duration, if reported, or else the mean or median follow-up time.

Feasibility Assessment

The feasibility of conducting a valid NMA was assessed using the process described by Cope et al,[14] which involves an assessment of clinical heterogeneity in terms of the characteristics of the treatments, outcomes, study design, and patients and a comparison of
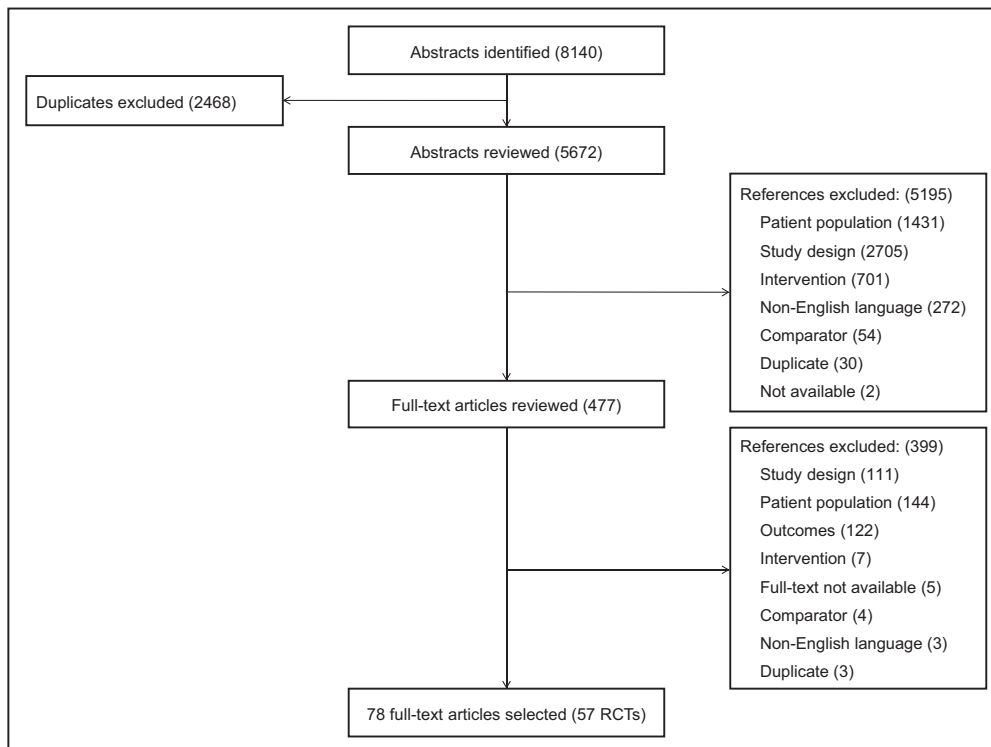
Figure 1. Flow diagram. RCT indicates randomized controlled trials.
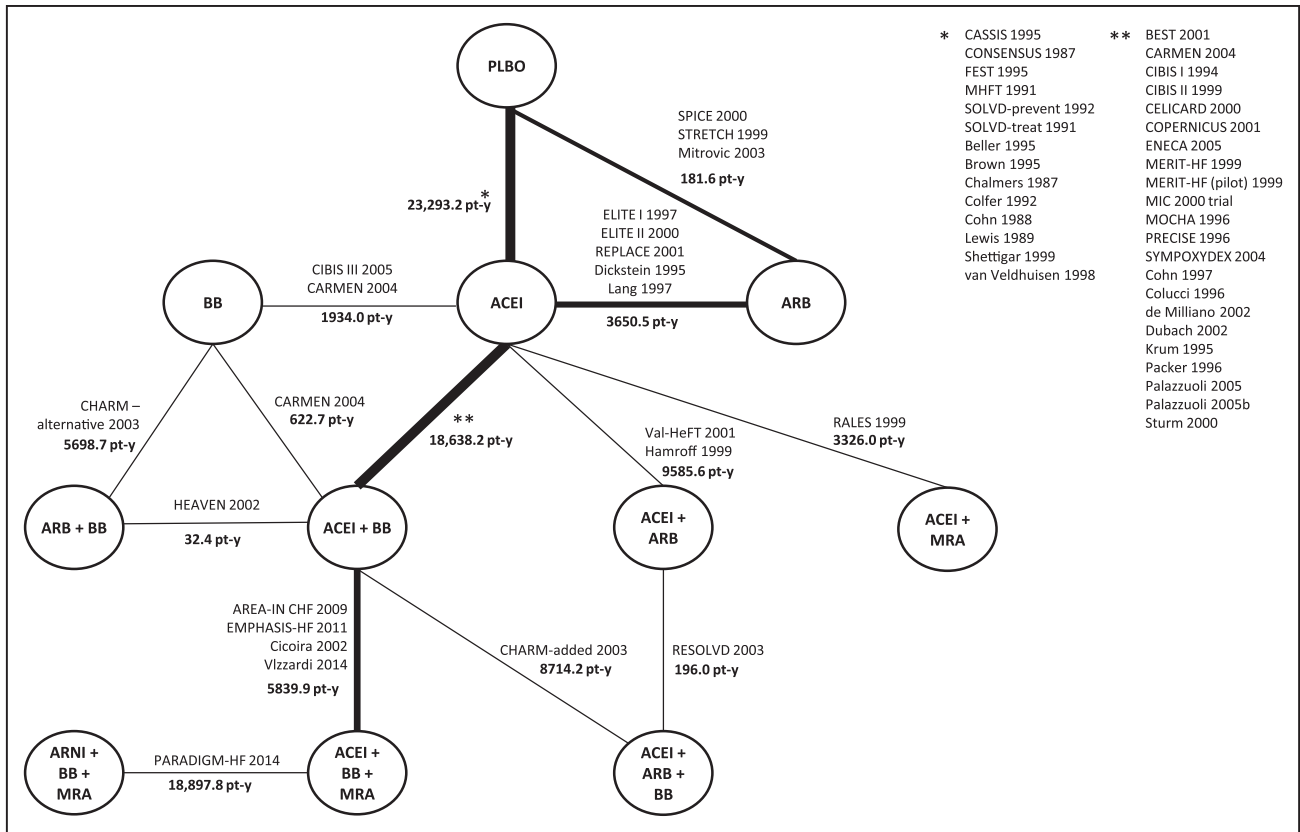
Figure 2. Network diagram of treatment classes and combinations reporting all-cause mortality. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; AREA-IN CHF, Anti-Remodelling Effect of Canrenone in Patients With Mild Chronic Heart Failure; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; BEST, Beta-Blocker Evaluation of Survival Trial; CARMEN, The Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; ELITE, Evaluation of Losartan in the Elderly Study; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENECA, Efficacy of Nebivolol in the Treatment of Elderly Patients With Chronic Heart Failure as Add-On Therapy to ACE Inhibitors or Angiotensin II Receptor Blockers, Diuretics, and/or Digitalis; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MHFT, Munich Mild Heart Failure Trial; MIC, Metoprolol in Patients With Mild to Moderate Heart Failure: Effects on Ventricular Function and Cardiopulmonary Exercise Testing; MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment; MRA, mineralocorticoid receptor antagonist; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PLBO, placebo; PRECISE, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RALES, Randomized Aldactone Evaluation Study; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure; SYMPOXYDEX, Sympathetic and Oxydative Stress Kredex Study; and Val-HeFT, Valsartan Heart Failure Trial.[7,21–77]

differences within and across treatments in terms of baseline risk and the observed treatment effects. The following factors were identified a priori as potential treatment effect modifiers: use of concomitant treatments (eg, digoxin), duration of follow-up, year of publication, severity of included patients (eg, New York Heart Association class and left ventricular ejection fraction), heart failure etiology (eg, ischemic versus nonischemic), and history of myocardial infarction.

Network Meta-Analysis

Bayesian NMA models were used to simultaneously synthesize the results of the included studies and to obtain relative treatment effects.[11,15–17] NMA within the Bayesian framework involves data, a hierarchical model or likelihood function with parameters, and prior distributions.[18] The model relates data from RCTs to parameters reflecting the (pooled) relative treatment effect of each intervention compared with the reference treatment (eg, placebo). Data sets for the model were based on the reported number of patients with an event at the end of the trial per

arm, the total number of patients randomized per arm, and the mean follow-up duration of the 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, and a complementary log–log (cloglog) link was used to model the event rates.[10] Outputs from the model were presented as hazard ratios (HRs) for each treatment versus placebo. Goodness of fit was assessed using the residual deviance and deviance information criterion.[19] Results of the random-effects model were presented unless the fixed-effect model resulted in a more parsimonious model. Noninformative prior distributions were used: a normal distribution for the difference measures (mean 0, var 10^4) and a uniform distribution for between-study standard deviation (range 0–5). The analysis was performed with published codes[10] using OpenBuGS software[20] (2 chains were used, including 100000 burn-in iterations followed by 200000 iterations).

Results of the NMA reflect the posterior distributions of the model parameters. In addition to point estimates of the HRs, 95% credible intervals (CrI), reflecting the range of true underlying effects with
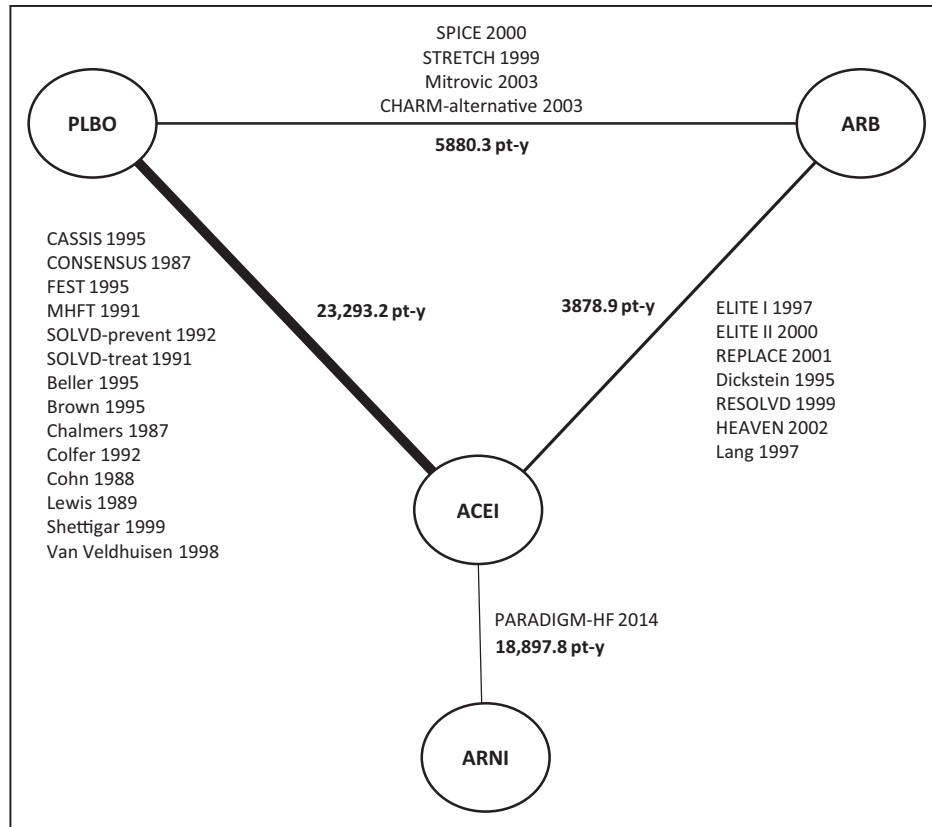
Figure 3. Sensitivity analysis evidence network of ARNI, ACEI, ARB and placebo for all-cause mortality ignoring background treatments. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; ELITE, Evaluation of Losartan in the Elderly Study; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; MHFT, Munich Mild Heart Failure Trial; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PLBO, placebo; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; and STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure.[7,21–45]

95% probability, are presented. The rank probabilities and expected rank for all treatments are presented, as well as the probability that one treatment is better than a specific comparator.[11] Means, standard deviations, and ranges were summarized for study and patient characteristics where possible.

Results

Study Selection

Fifty-seven RCTs were included (Figure 1) and are described in Table II in the Data Supplement.[7,21–77] The majority were multicenter, double-blind, placebo-controlled trials, including between 28 and 8399 patients with a mean follow-up duration ranging from 8 weeks to 4 years. The treatment classes assessed included ACEI, BB, ARB, MRA, and ARNI. Patients were generally allowed concomitant therapies, such as diuretics, digoxin, and nitrates, as well as other permitted concomitant treatment classes.

Network of Evidence

In the network of connected RCTs (Figure 2), the thickness of the lines corresponds to the number of trials included per treatment comparison. The evidence was centralized around placebo and ACEI, with most RCTs informing the comparison of ACEI+BB versus ACEI. The treatment combination with ARNI was informed by a single RCT.

Differences Within or Between Direct Treatment Comparisons That May Modify Treatment Effect

Treatment Definitions

There was a wide range in the types of individual and concomitant treatments (Table III in the Data Supplement). In fact, few trials included a true placebo arm because study patients were often permitted to receive or continue to receive the standard of care in addition to study drugs. An increase in the use of combination therapies was observed over the years, with the earliest trials being focused on ACEIs versus placebo, followed by the addition of BB (ACEI+BB versus ACEI studies), and then ARB and MRA containing therapies around the same time after their introduction. The combination ACEI+BB+MRA was first evaluated in 2002 compared with ACEI+BB. To take into account concomitant drug classes of interest and more accurately define placebo in the analysis, treatments were categorized to include the concomitant drug when the majority of

patients in the study were receiving it at baseline. Specifically, if >50% of the trial patients received a concomitant drug of interest in the systematic review (eg, BB), the treatment was described as a combination therapy (the study drug class+the concomitant drug class(es), eg, ACEI+BB versus BB) in the analysis. The threshold to define concomitant therapy was

based on expert opinion and involved an evaluation of different thresholds ranging from 50% to 60%.[78]

When the permitted concomitant drug was ACEI or ARB and the publication failed to report the distribution of patients receiving each class, it was assumed that patients were taking ACEI (Table IV in the Data Supplement). A sensitivity
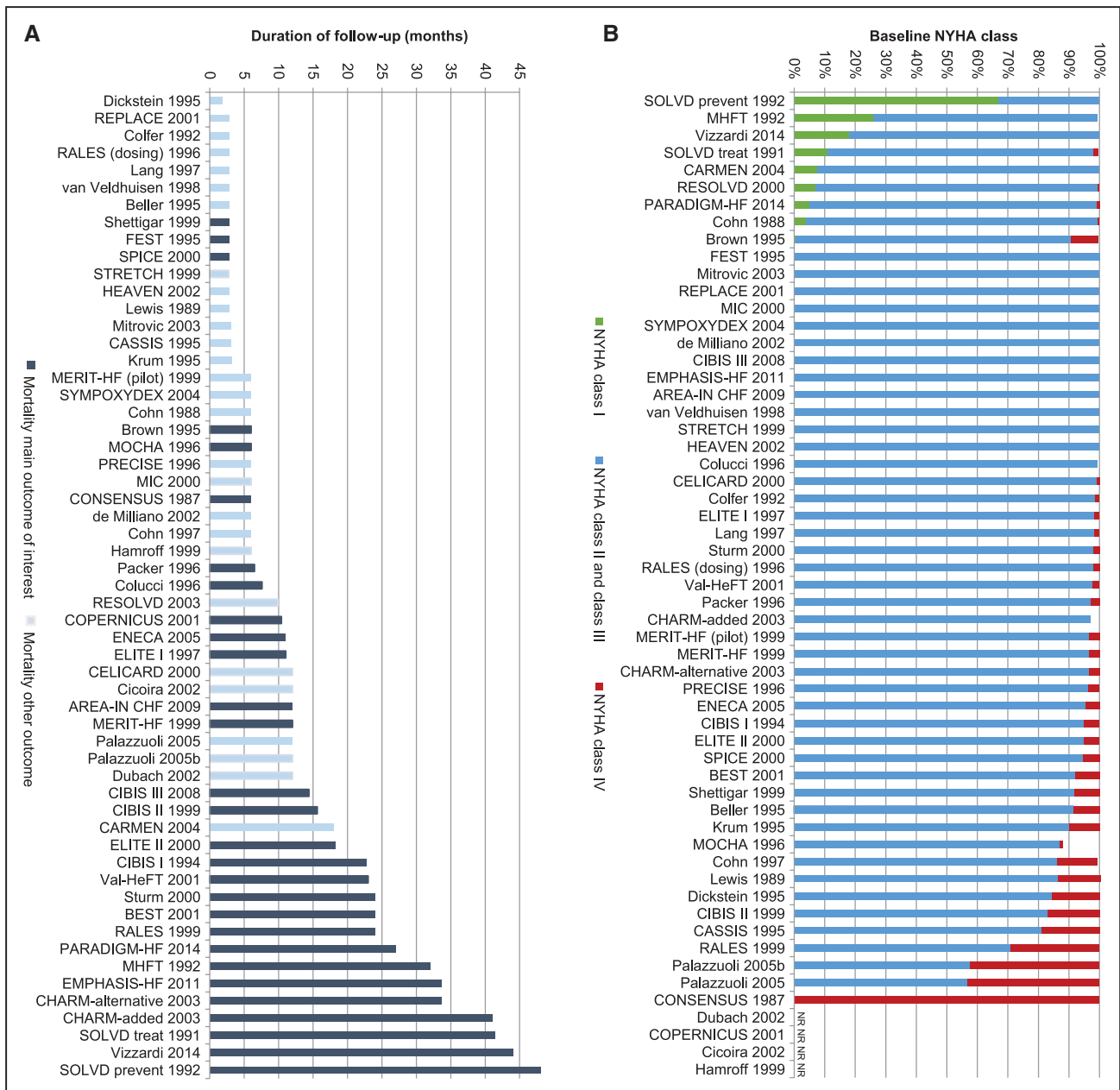
Figure 4. Distribution of potential treatment effect modifiers: **A**, Duration of follow-up[7,21–77]; **B**, NYHA class at baseline[7,21–77]; **C**, LVEF at baseline.[7,21–77] AREA-IN CHF indicates Anti-Remodelling Effect of Canrenone in Patients With Mild Chronic Heart Failure; BEST, Beta-Blocker Evaluation of Survival Trial; CARMEN, The Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; ELITE, Evaluation of Losartan in the Elderly Study; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENECA, Efficacy of Nebivolol in the Treatment of Elderly Patients With Chronic Heart Failure as Add-On Therapy to ACE Inhibitors or Angiotensin II Receptor Blockers, Diuretics, and/or Digitalis; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; LVEF, left ventricular ejection fraction; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MHFT, Munich Mild Heart Failure Trial; MIC, Metoprolol in Patients With Mild to Moderate Heart Failure: Effects on Ventricular Function and Cardiopulmonary Exercise Testing; MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment; NR, not reported; NYHA, New York Heart Association; PARADIGM-HF, Prospective (Continued)

C

Baseline LVEF

AREA-IN CHF 2009
STRETCH 1999
Lewis 1989
Vizzardi 2014
MHFT 1991
van Veldhuisen 1998
Cicoira 2002
Palazzuoli 2005
Palazzuoli 2005b
ELITE II 2000
ELITE I 1997
CARMEN 2004
CHARM-alternative...
PARADIGM-HF 2014
CIBIS III 2005
RESOLVD 2000
CHARM-added 2003
MIC 2000
SOLVD prevent 1992
MERIT-HF 1999
CASSIS 1995
Mitrovic 2003
Beller 1995
CIBIS II 1999
MERIT-HF (pilot)...
SPICE 2000
Val-HeFT 2001
FEST 1995
REPLACE 2001
Hamroff 1999
EMPHASIS-HF 2011
CELICARD 2000
ENECA 2005
SYMPOXYDEX 2004
Dubach 2002
Lang 1997
RALES 1999
de Milliano 2002
Colfer 1992
Brown 1995
SOLVD treat 1991
Cohn 1988
Shettigar 1999
Dickstein 1995
Colucci 1996
BEST 2001
MOCHA 1996
Packer 1996
PRECISE 1996
Cohn 1997
COPERNICUS 2001
CIBIS I 1994
Sturm 2000
Krum 1995
CONSENSUS 1987   NR
Chalmers 1987   NR
HEAVEN 2002   NR

Figure 4 Continued. Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PRECISE, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RALES, Randomized Aldactone Evaluation Study; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure; SYMPOXYDEX, Sympathetic and Oxydative Stress Kredex Study; and Val-HeFT, Valsartan Heart Failure Trial.

analysis was also performed that ignored concomitant therapies and evaluated how ARNI monotherapy was compared with ACEI and ARB monotherapies (Figure 3).[7,21–45]

Despite some variation in individual treatment doses and schedules (Table V in the Data Supplement), all analyses assumed that treatments within a given class were comparable in terms of their ability to prevent death. All trials were included, even though some variation was also observed in the proportion of patients receiving concomitant digoxin.

Outcome Definition

All-cause mortality is an objective end point and is usually reported as a primary or secondary outcome, although the NMA also included 28 trials that reported mortality as an adverse event or a reason for study withdrawal (Figure 4A). Because the quality of these 28 studies did not differ greatly from that of the other included trials, the broadest evidence base was included.

Study and Patient Characteristics

The RCTs were broadly comparable in terms of study design, despite a wide range in publication year (1987–2014). There were some differences in study quality, although overall the risk of bias was low (Figure I in the Data Supplement). Given the differences in the duration of follow-up across trials (Figure 4A), patient exposure was accounted for in the analysis.

Enrolled patients were predominantly male (mean 76%, range 49%–90%) and between the ages of 52 and 73 years (mean 62 years; Table II in the Data Supplement). Most patients were classified as New York Heart Association class II–III (mean 86%), although 8 (14%) trials included a proportion of patients in class I and 36 (63%) trials included patients in class IV (Figure 4B). Baseline left ventricular ejection fraction ranged between 15% and 40% (mean 27%; Figure 4C). In terms of heart failure etiology, 57% of the included patients had ischemic heart disease (range 10%–83%). It was not possible to consistently assess differences in the duration of heart failure, the use of pacemakers or implantable devices, or the history of myocardial infarction because of inconsistent reporting.

Baseline Risk and Observed Treatment Effects

Given variation in publication year across trials, differences attributable to changes in clinical practice over time may result in differences in baseline risk that could influence the treatment effect. However, the network of evidence does not provide a well-connected common comparator (placebo or standard of care), partly because of the treatment categorization based on concomitant therapy used to account for differences in placebo. Figure II in the Data Supplement reports the rates of death per patient year for all treatment arms and RCTs by publication year. Although the rates varied across included RCTs, it was unclear whether these differences were driven by changes in practice over time or acted as a treatment effect modifier.

Network Meta-Analysis Results

All identified RCTs were included in the NMA and provided comparative evidence on all-cause mortality in patients with HFrEF.

Table 1. Results of Random Effect Network Meta-Analysis for All-Cause Mortality Rates: Difference in Intervention Versus the Comparator, 95% Credible Intervals (CrI), and Probability That the Intervention Is Better Than the Comparator [*P*(better)]

Intervention	Comparator				
	PLBO	ACEI	ARB	BB	ACEI+BB
PLBO					
Estimate (95% CrI)	1 (1,1)	1.203 (0.989–1.512)	1.132 (0.793–1.65)	1.752 (1.067–3.041)	1.758 (1.382–2.424)
P(better)	NA	0.03	0.23	0.01	0.00
ACEI					
Estimate (95% CrI)	0.831 (0.661–1.011)	1 (1–1)	0.941 (0.679–1.292)	1.454 (0.92–2.38)	1.462 (1.255–1.783)
P(better)	0.97	NA	0.66	0.05	0.00
ARB					
Estimate (95% CrI)	0.883 (0.606–1.261)	1.063 (0.774–1.473)	1 (1–1)	1.548 (0.886–2.8)	1.552 (1.103–2.31)
P(better)	0.77	0.34	NA	0.06	0.01
BB					
Estimate (95% CrI)	0.571 (0.329–0.937)	0.688 (0.42–1.087)	0.646 (0.357–1.129)	1 (1–1)	1.008 (0.615–1.633)
P(better)	0.99	0.95	0.94	NA	0.49
ACEI+BB					
Estimate (95% CrI)	0.569 (0.413–0.724)	0.684 (0.561–0.797)	0.644 (0.433–0.906)	0.992 (0.612–1.626)	1 (1–1)
P(better)	1.0	1.0	0.99	0.51	NA
ACEI+ARB					
Estimate (95% CrI)	0.827 (0.505–1.243)	0.994 (0.658–1.448)	0.935 (0.548–1.514)	1.441 (0.789–2.672)	1.448 (0.964–2.232)
P(better)	0.84	0.52	0.62	0.11	0.03
ARB+BB					
Estimate (95% CrI)	0.472 (0.23–0.855)	0.567 (0.293–1.002)	0.534 (0.254–1.021)	0.828 (0.518–1.215)	0.831 (0.435–1.493)
P(better)	0.99	0.97	0.97	0.85	0.74
ACEI+MRA					
Estimate (95% CrI)	0.574 (0.348–0.908)	0.69 (0.448–1.058)	0.648 (0.378–1.103)	1.003 (0.54–1.935)	1.004 (0.653–1.649)
P(better)	0.99	0.96	0.95	0.50	0.49
ACEI+ARB+BB					
Estimate (95% CrI)	0.518 (0.308–0.795)	0.623 (0.397–0.926)	0.586 (0.334–0.97)	0.903 (0.486–1.68)	0.908 (0.614–1.358)
P(better)	1.0	0.99	0.98	0.64	0.72
ACEI+BB+MRA					
Estimate (95% CrI)	0.44 (0.264–0.661)	0.53 (0.342–0.762)	0.498 (0.286–0.804)	0.767 (0.417–1.397)	0.773 (0.535–1.091)
P(better)	1.0	1.0	1.0	0.81	0.94
ARNI+BB+MRA					
Estimate (95% CrI)	0.372 (0.189–0.647)	0.448 (0.24–0.758)	0.421 (0.206–0.774)	0.648 (0.308–1.329)	0.652 (0.371–1.11)
P(better)	1.0	1.0	0.99	0.89	0.95

(*Continued*)

Table 1 presents the results of the random effect NMA for all head-to-head comparisons and illustrates the HRs, the 95% CrIs, and the probability of a treatment being better than the comparator. We found significant between-study heterogeneity in the network of evidence (SD 0.18, 95% CrI 0.06–0.35; Table 1), which was expected given the differences observed in the included studies.

Figure 5 illustrates the HRs for each treatment class versus placebo for all-cause mortality. The combination of ACEI+BB+MRA was associated with a 56% reduction in

mortality versus placebo (HR 0.44, 95% CrI 0.26–0.66), while ARNI+BB+MRA was associated with the greatest reduction in all-cause mortality versus placebo (HR 0.37, 95% CrI 0.19–0.65). Figure III in the Data Supplement summarizes the rank probabilities for all interventions.

Table 2 presents the results from the sensitivity analysis that ignored concomitant therapies and evaluated how ARNI monotherapy was compared with ACEI and ARB monotherapies. The random-effects model suggests that all active treatments are

Table 1. Continued

Intervention	Comparator					
	ACEI+ARB	ARB+BB	ACEI+MRA	ACEI+ARB+BB	ACEI+BB+MRA	ARNI+BB+MRA
PLBO						
Estimate (95% CrI)	1.21 (0.804–1.979)	2.121 (1.169–4.354)	1.744 (1.101–2.874)	1.929 (1.258–3.244)	2.272 (1.513–3.791)	2.689 (1.545–5.303)
P(better)	0.16	0.01	0.01	0.00	0.00	0.00
ACEI						
Estimate (95% CrI)	1.007 (0.691–1.521)	1.763 (0.998–3.415)	1.45 (0.945–2.232)	1.605 (1.08–2.518)	1.889 (1.312–2.925)	2.235 (1.319–4.166)
P(better)	0.48	0.03	0.04	0.01	0.00	0.00
ARB						
Estimate (95% CrI)	1.07 (0.66–1.824)	1.871 (0.98–3.945)	1.542 (0.907–2.645)	1.707 (1.031–2.997)	2.009 (1.243–3.501)	2.378 (1.291–4.847)
P(better)	0.38	0.03	0.05	0.02	0.00	0.01
BB						
Estimate (95% CrI)	0.694 (0.374–1.267)	1.207 (0.823–1.929)	0.997 (0.517–1.852)	1.107 (0.595–2.058)	1.304 (0.716–2.398)	1.543 (0.752–3.248)
P(better)	0.89	0.15	0.50	0.36	0.19	0.11
ACEI+BB						
Estimate (95% CrI)	0.691 (0.448–1.037)	1.203 (0.67–2.299)	0.996 (0.607–1.532)	1.102 (0.736–1.63)	1.294 (0.917–1.87)	1.533 (0.901–2.696)
P(better)	0.97	0.26	0.51	0.28	0.06	0.05
ACEI+ARB						
Estimate (95% CrI)	1 (1–1)	1.746 (0.883–3.743)	1.441 (0.787–2.537)	1.594 (0.944–2.734)	1.871 (1.111–3.326)	2.217 (1.148–4.567)
P(better)	NA	0.05	0.09	0.04	0.01	0.01
ARB+BB						
Estimate (95% CrI)	0.573 (0.267–1.132)	1 (1–1)	0.824 (0.368–1.655)	0.916 (0.427–1.838)	1.075 (0.517–2.146)	1.277 (0.551–2.847)
P(better)	0.95	NA	0.71	0.60	0.42	0.26
ACEI+MRA						
Estimate (95% CrI)	0.694 (0.394–1.27)	1.213 (0.604–2.715)	1 (1–1)	1.106 (0.621–2.083)	1.299 (0.755–2.439)	1.541 (0.784–3.311)
P(better)	0.91	0.29	NA	0.35	0.15	0.09
ACEI+ARB+BB						
Estimate (95% CrI)	0.627 (0.366–1.059)	1.092 (0.544–2.34)	0.904 (0.48–1.61)	1 (1–1)	1.174 (0.702–2.045)	1.392 (0.724–2.8)
P(better)	0.96	0.40	0.65	NA	0.25	0.13
ACEI+BB+MRA						
Estimate (95% CrI)	0.534 (0.301–0.9)	0.93 (0.466–1.935)	0.77 (0.41–1.325)	0.852 (0.489–1.425)	1 (1–1)	1.187 (0.784–1.799)
P(better)	0.99	0.58	0.85	0.75	NA	0.17
ARNI+BB+MRA						
Estimate (95% CrI)	0.451 (0.219–0.871)	0.783 (0.351–1.814)	0.649 (0.302–1.275)	0.718 (0.357–1.381)	0.843 (0.556–1.276)	1 (1–1)
P(better)	0.99	0.74	0.91	0.87	0.83	NA

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; and PLBO, placebo.

likely to be more efficacious than placebo, although with more uncertainty than the base case analysis. The sensitivity analysis showed that in comparison to placebo, ARNI was associated with a 29% reduction in mortality (HR 0.71, 95% CrI 0.39–1.17); ACEI, a 16% reduction (HR 0.84, 95% CrI 0.65–1.01); and ARB, a 12% reduction (HR 0.88, 95% CrI 0.65–1.17).

Discussion

New trials build on the evidence from previous trials and therefore, test new drugs in addition to existing ones; as a result, it becomes increasingly difficult for clinicians to maintain a perspective on the relative efficacy of the treatments they are advised to use or to fully appreciate the cumulative benefit of combining treatments. To provide this perspective, the relative efficacy of recommended drug classes and combinations in reducing mortality of HFrEF were estimated. This is the first NMA to consider the totality of RCT evidence for recommended treatment classes and combinations, including 57 trials conducted over the past 30 years in patients with HFrEF.

Figure 5. Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.

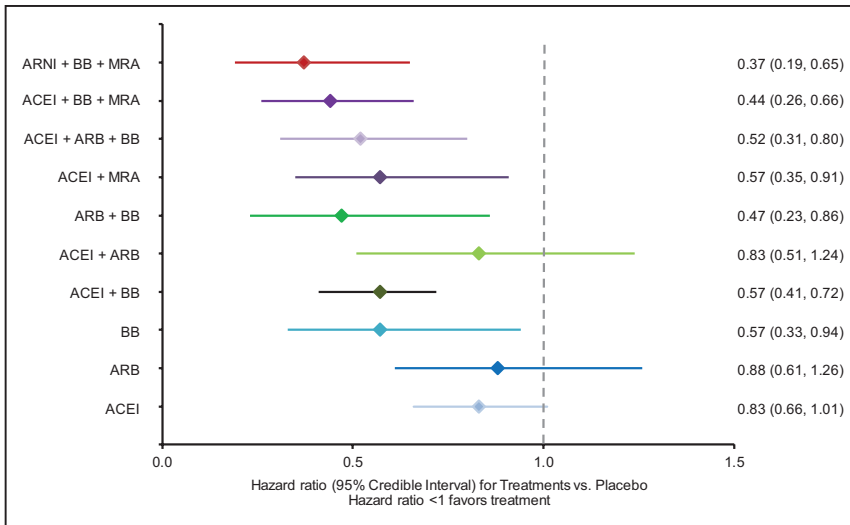Our results provide insight regarding the comparative efficacy of treatments for which no head-to-head trials exist and suggest that ARNI+BB+MRA and ACEI+BB+MRA are the most efficacious treatment combinations in terms of reducing all-cause mortality. These findings validate global guidelines, which recommend first-line treatment of HFrEF with ACEI+BB (ARB+BB for those unable to tolerate ACEI), followed by the addition of an MRA as second-line therapy and ARNI to replace ACEI in patients able to tolerate ACEI (or ARB) that remain symptomatic.[5,6]

Our findings also illustrate the step-wise reductions in mortality made possible by the incremental use of combinations of disease-modifying therapies. The NMA results suggest that ARNI+BB+MRA is the most efficacious therapy, reducing all-cause mortality by 63% compared with placebo. The magnitude of this benefit represents substantial progress in terms of treatments developed over the last 30 years (since the first report of an ACEI treatment). Although this finding depends on a single trial, PARADIGM-HF was the largest trial in the network, representing 18 898 patient-years of treatment exposure.[7] It is also important to note that although BB monotherapy is included in the network and, therefore, can be compared with other monotherapies using NMA, data to support this comparison are based on 2 small, short-duration trials (CIBIS III [Cardiac Insufficiency Bisoprolol Study III][46] and CARMEN trial [Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation][47]). The majority of available evidence regarding the efficacy of BB therapy is based on studies where patients were also receiving an ACEI (and MRA in more recent trials).

Our study is the result of a comprehensive and detailed NMA performed jointly by clinicians and methodologists. The

Table 2. Results of Random Effect Sensitivity Analysis Network Meta-Analysis for All-Cause Mortality Rates: Difference in Intervention Versus the Comparator, 95% Credible Intervals (CrI), and Probability That the Intervention Is Better Than the Comparator [*P*(better)]

Intervention	Comparator			
	PLBO	ACEI	ARB	ARNI
PLBO				
Estimate (95% CrI)	1 (1–1)	1.191 (0.995–1.537)	1.131 (0.856–1.545)	1.410 (0.854–2.558)
P(better)	NA	0.03	0.15	0.06
ACEI				
Estimate (95% CrI)	0.840 (0.651–1.005)	1 (1–1)	0.947 (0.699–1.234)	1.188 (0.716–1.967)
P(better)	0.97	NA	0.69	0.15
ARB				
Estimate (95% CrI)	0.884 (0.647–1.169)	1.056 (0.810–1.430)	1 (1–1)	1.252 (0.719–2.279)
P(better)	0.85	0.31	NA	0.13
ARNI				
Estimate (95% CrI)	0.709 (0.391–1.170)	0.842 (0.508–1.396)	0.799 (0.439–1.390)	1 (1–1)
P(better)	0.94	0.85	0.87	NA

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor antagonist; ARNI, angiotensin receptor-neprilysin inhibitor; and PLBO, placebo.

available data and underlying assumptions have been clearly illustrated to allow other researchers and decision-makers to critically analyze each choice and to update the analysis using a different approach. The way this study categorized the recommended drug combinations and concomitant drugs (eg, ACEIs, ARBs, BBs, and MRAs) reflects a methodological development necessary to assess the comparative efficacy of these treatment combinations. The threshold approach allowed for differences in placebo to be defined and yielded clinically meaningful results, with monotherapies being less effective than combination therapies and regimens, including 3 treatment classes likely to be most efficacious. The importance of this approach is highlighted by results of the sensitivity analysis where concomitant therapies were ignored: ARNI was associated with a 29% reduction in mortality compared with placebo, whereas the base case illustrated a 63% reduction with the combination of ARNI+BB+MRA. The difference relates to definition of placebo (as well as ACEI and ARB arms) in the sensitivity analysis, which included a wide range of concomitant drugs (eg, in CHARM-alternative trial [Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative],[43] an ARB versus placebo trial, 55% of patients were receiving a BB), which were ignored or in some cases pooled with true placebo studies. In the base case analysis, placebo more closely represents the baseline risk of the patient population of interest because treatments were categorized based on the study drugs and concomitant drugs of interest.

Overall, findings were generally consistent with other published (network) meta-analyses evaluating all-cause mortality that compared monotherapies within a single class to placebo in addition to standard of care.[79–85] A recent putative placebo analysis by McMurray et al[86] found that ARNI was associated with a 28% reduction in all-cause mortality, which was similar to the sensitivity analysis performed that ignored background therapy (ie, 29% reduction in all-cause mortality).

Direct comparisons of results from other published studies are limited by differences in included studies and the classification of concomitant drugs, which were often ignored or led to the exclusion of several trials. Therefore, the attempt in the current study to classify trials based on the background therapies may provide more valid insight regarding treatment classes used in combination in clinical practice.

Limitations

One limitation was the identification of concomitant therapy, which was based on data reported at baseline, which may have differed from treatments used during follow-up and certainly varied across the included trials. In addition, we assumed a class-effect, that is, all drugs in the same pharmacological class had similar efficacy, which may not be true. The same consideration applies to the dose of treatments used.

Most notably, differences were identified in terms of study duration, which may imply differences in the study purpose or type of mortality analysis. The length of follow-up in each trial was accounted for in the analysis assuming a proportional hazards model, which allowed for an assessment of the broadest evidence base. A comparison of alternative scales and statistical models may be of interest to explore alternative

underlying assumptions and the consistency of direct and indirect evidence.

Despite differences identified, no inconsistencies were identified, and adjustment for patient characteristics did not have substantial impact on the results. However, it should be recognized that there is a risk of ecological bias as study-level data were used to estimate the treatment effects. Individual patient data would be required to better explore differences in treatment effect modifiers.[9,11,87] In addition, some information was not consistently reported across the trials, limiting either the assessment of potential differences or the potential to adjust for differences (ie, duration of heart failure, etiology, use of devices, or history of myocardial infarction).

To our knowledge, this review includes the broadest evidence base. However, generalizability may be limited by including only English language studies and by excluding studies enrolling patients exclusively outside of North America and Europe. Based on the available data, it was not possible to assess some comparisons, such as MRA versus placebo, as well as the combination of a BB and MRA versus placebo. Although this study provides insight regarding all-cause mortality for patients with HFrEF, other important efficacy and safety outcomes should also be considered by decision-makers, including death because of cardiovascular causes and heart failure, hospitalizations, and health-related quality of life.

Conclusions

This report provides a comprehensive analysis of the comparative efficacy of the individual drug classes and combinations known to reduce mortality in patients with HFrEF. It was possible to pool and indirectly compare evidence from RCTs published over the last 34 years using NMA, providing insight into treatment comparisons in the absence of head-to-head trials. The threshold approach used to account for concomitant therapy provides a more accurate representation of the treatment comparisons evaluated in RCTs, often reflecting standard of care at the time. Our results show that the most efficacious combinations for reducing all-cause mortality are in line with the most recent guideline recommendations.

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CLINICAL PERSPECTIVE

Over the past 30 years, much progress has been made regarding the treatment of patients with heart failure and reduced ejection fraction. Mortality has reduced over time, and there are now 5 main classes of life-saving pharmacological therapies recommended for the treatment of patients with heart failure and reduced ejection fraction, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, mineralocorticoid receptor antagonists, and the angiotensin receptor–neprilysin inhibitor, sacubitril/valsartan. Given that new trials build on evidence from previous trials, and the fact that new drugs have mainly been tested on top of existing ones, it becomes increasingly difficult for clinicians to maintain a perspective on the relative efficacy of the separate treatments and their combinations. This study systematically identified 57 trials conducted over the past 34 years evaluating recommended treatment classes and combinations in patients with heart failure and reduced ejection fraction. Results from the systematic review were used to estimate the relative efficacy of these therapies with regards to survival, by means of network meta-analysis, providing insight into treatment comparisons in the absence of head-to-head trials. The network meta-analysis showed that all available treatment classes and combinations were more efficacious than placebo, with the exception of angiotensin II receptor blockers monotherapy and angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors. The combination of an angiotensin receptor–neprilysin inhibitor+β-blockers+mineralocorticoid receptor antagonists resulted in the greatest mortality reduction. Overall, these findings help illustrate the step-wise reductions in mortality made possible by the incremental use of combinations of disease-modifying therapies and validate the most recent global guideline recommendations.

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SUPPLEMENTAL MATERIAL

Expanded Methods & Results

Search Strategy

Databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid

                        MEDLINE(R))

Date of search: April 28, 2015

1.   exp Heart Failure/

2.   Cardiomyopathy, Dilated/

3.   (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$).tw.

4.   ((cardi$ or myocard$) adj2 (failure$ or insufficien$)).tw.

5.   OR/1-4

6.   (LCZ696 or LCZ 696 or LCZ-696).af

7.   exp dipeptidyl carboxypeptidase inhibitor/ OR exp Angiotensin-Converting Enzyme Inhibitors/

8.   (angiotensin converting enzyme inhibitor OR ACEI OR ACEI OR antagonist$ OR inhibitor$ benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril OR alacepril OR cilazapril OR spirapril OR delapril).mp.

9.   exp beta adrenergic receptor blocking agent/ OR exp Adrenergic beta-Antagonists/

10.   (beta blocker$ OR BB OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR carvedilol OR labetalol OR metoprolol OR nadolol OR nebivolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol).mp.

11.   exp aldosterone antagonist/

12. (aldosterone antagonist$ OR mineralocorticoid-receptor antagonist OR MRA OR eplerenone OR spironolactone).mp.

13. exp angiotensin receptor antagonist/

14. (angiotensin receptor blocker$ OR angiotensin receptor antagonist$ OR ARB OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan).mp.

15. OR/6-14

16. "randomized controlled trial".pt.

17. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

18. (retraction of publication or retracted publication).pt.

19. OR/18-20

20. (animals not humans).sh.

21. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.

22. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.

23. 20 OR 21 OR 22

24. 19 NOT 23

25. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

26. RETRACTED ARTICLE/

27. OR/25-26

28. (animal$ not human$).sh,hw.

29. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/

30. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/

31. OR/28-30

32. 27 NOT 31

33. 24 OR 32

34. 5 AND 19 AND 33

35. limit 34 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]

36. limit 35 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]

37. limit 36 to human

38. limit 37 to yr="1987 –July 2014"

Database: Cochrane Library of Clinical Trials

Date of search: April 28, 2015

#1 MeSH descriptor: [Heart Failure] explode all trees

#2 MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees

#3 (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$):ti,ab,kw

(Word variations have been searched)

#4 #1 or #2 or #3

#5 (LCZ696 or LCZ 696 or LCZ-696) :ti,ab,kw

#6 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees

#7 (angiotensin converting enzyme inhibitor or ACEI or ACEI or antagonist$ or inhibitor$ benazepril or captopril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or zofenopril or alacepril or cilazapril or spirapril or delapril):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees

#9 (beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or timolol):ti,ab,kw (Word variations have been searched)

#10 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees

#11 (aldosterone antagonist$ or mineralocorticoid-receptor antagonist or MRA or eplerenone or spironolactone):ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees

#13 (angiotensin receptor blocker$ or angiotensin receptor antagonist$ or ARB or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan):ti,ab,kw (Word variations have been searched)

#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #4 and #14

#16 human not animal

#17 #15 and #16

#18 #17 in trials

#17 #18 (limit from 1987)

Supplementary Table 1: Drug classes of interest

Class	Generic name	Trade Name
ARNI	LCZ696	Entresto
	valsartan/ sacubitril	
ACEI	benazepril	Lotensin
	captopril	Capoten, Lopril
	enalapril	Vasotec, Renitec
	fosinopril	Monopril
	imidapril	Tanatril
	lisinopril	Prinivil, Zestril, Tensopril, Hipril, Lisodur, Novatec
	moexipril	Univasc, Perdix
	perindopril	Aceon, Coversyl
	quinapril	Accupril
	ramipril	Altace, Tritace, Ramace, Ramiwin, Prilace, Ramipro
	trandolapril	Mavik
	zofenopril	Bifril, Teoula, Zofepril, Zopranol
	alacepril	Alacepul, Alaceril, Aprocorl, Asemipearl, Cenapride, Cetabavil, Cetapril, Cevozyl, Homerat, Iceden, Kananomin, Seplinok
	cilazapril	Cazaprol, Cilan, Cilazabace, Cilazil, Dynorm, Dynorm Plus, Inhibace Plus, Inhibace, Initiss, Inocar, Justor, Prilazid, Vascace, Zobox, Cilazapril-Teva, CO Cilazapril, Gen-Cilazapril, Inhirock, Inibace Plus, Initiss Plus, Inocar Plus
	spirapril	Quadropril, Renormax, Renpress, Setrilan
	delapril	Beniod, Delaket, Delapride, Dinapres, Trinordiol, Adecut, Araplit, Cupressin, Defolder, Virace
BB	acebutolol	Sectral, Prent
	atenolol	Tenormin, Senormin
	betaxolol	Kerlone, Betoptic, Lokren
	bisoprolol	Zebeta
	carvedilol	Coreg, Carvil, Dilatrend, Eucardic, Carloc

Class	Generic name	Trade Name
	labetalol	Trandate, Normodyne
	metoprolol	Lopressor, Toprol, Selokeen, Minax, Metrol, Betaloc, Bloxan, Neobloc, Presolol, Corvitol, Metxl, Metolar, Starpress
	nadolol	Corgard, Anabet, Solgol, Corzide, Alti-Nadolol, Apo-Nadol, Novo-Nadolol
	nebivolol	Bystolic, Nebilet, Nebilong, Nebicard, Nubeta, Nodon, Lobivon
	penbutolol	Levatol, Levatolol, Lobeta, Paginol, Hostabloc, Betapressin
	pindolol	Visken, Betapindol, Blockin L, Calvisken, Cardilate, Decreten, Durapindol, Glauco-Visken, Pectobloc, Pinbetol, Prindolol, Pynastin
	propranolol	Inderal, InnoPran, Avlocardyl, Deralin, Dociton, Inderalici, Sumial, Anaprilinum, Bedranol
	sotalol	Betapace, Sotalex, Sotacor
	timolol	Blocadren, Timoptic
MRA	eplerenone	Inspra
	spironolactone	Aldactone, Novo-Spiroton, Aldactazide, Spiractin, Spirotone, Verospiron, Berlactone
ARB	azilsartan	Edarbi
	candesartan	Atacand, Blopress, Amias, Ratacand
	eprosartan	Teveten, Eprozar
	irbesartan	Avapro, Karvea, Aprovel
	losartan	Cozaar
	olmesartan	Benicar, Olmetec
	telmisartan	Micardis, Targit, Temax, Telmore
	valsartan	Diovan, Angiotan, Valtan, Valzaar, Tareg

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NR = not reported; PLBO = placebo

Supplementary Table 2: Study design and baseline patient characteristics of included RCTs

Trial/ Author year	Study design	# centers/ location	Study duration	N	Interventions	LVEF inclusion criteria	mean LVEF (%)	% male	mean age	NYHA class 1 (%)	NYHA class 2 (%)	NYHA class 3 (%)	NYHA class 4 (%)	duration of HF (months)	Ischaemic HF (%)	Prior MI (%)
CASSIS 1995[1]	DB, MC, PC	18/ Czech and Slovak Rep	104 weeks	152 48 48	Spirapril Enalapril Placebo	≤40%	28%	83%	58	0%	25%	56%	19%	NR	70%	46%
CONSENSUS 1987[2]	DB, MC, PC	35/ Finland, Norway, Sweden	52 weeks	126 127	Enalapril Placebo	Reduced	NR	71%	70	0%	0%	0%	100%	NR	NR	48%
FEST 1995[3]	DB, MC, PC	42/ EU (8 countries)	12 weeks	155 153	Fosinopril Placebo	≤35%	26%	75%	63	0%	65%	36%	0%	NR	71%	NR
MHFT 1991[4]	DB, SC, PC	1/ Germany	2.7 years (median)	83 87	Captopril Placebo	≤35%	35%	78%	62	26%	50%	24%	0%	NR	58%	69%
SOLVD-prevent 1992[5]	DB, MC, PC	23/ US, Canada, Belgium	37.4 months (mean)	2111 2117	Enalapril Placebo	≤35%	28%	89%	59	0%	67%	33%	0%	NR	83%	80%
SOLVD-treat 1991[6]	DB, MC, PC	23/ US, Canada, Belgium	48 months	1285 1284	Enalapril Placebo	≤35%	25%	80%	61	11%	57%	30%	2%	NR	71%	66%
Beller 1995[7]	DB, MC, PC	12/ US	12 weeks	130 63	Lisinopril Placebo	<45%	28%	75%	60	0%	35%	56%	9%	36	NR	0%
Brown 1995[8]	DB, MC, PC	41/ US	24 weeks	116 125	Fosinopril Placebo	≤35%	25%	80%	62	0%	37%	54%	9%	NR	NR	NR
Chalmers 1987[9]	DB, MC, PC	13/ 10 countries	12 weeks	87 43	Lisinopril Placebo	<45%	NR	69%	58	0%	22%	65%	13%	45	NR	NR
Colfer 1992[10]	DB, MC, PC	22/ US	12 weeks	114 58	Benazepril Placebo	≤ 35%	25%	83%	62	0%	54%	45%	1%	48	56%	NR
Goldstein 1988 [11]	DB, SC, PC	NR/ NA	26 weeks	104 100	Captopril Placebo	≤ 40%	25%	82%	56	4%	85%	11%	1%	35	63%	NR

Study	Design	Sites/Countries	Duration	N	Treatment	EF	%	%		%	%	%	%		%	%
Lewis 1989[12]	DB, MC, PC	13/ AUS, EU, SA, NA, Africa (10 countries)	12 weeks	87 43	Lisinopril Placebo	NR	38%	NR	NR	0%	22%	64%	14%	48	NR	NR
Shettigar 1999[13]	DB, MC, PC	28/ US	12 weeks	102 104	Fosinopril Placebo	≤35%	24%	75%	62	0%	39%	52%	31%	NR	43%	34%
Veldhuisen 1999[14]	DB, MC, PC	25/ Ntherlnds, Germany, Belgium	12 weeks	182 62	Imidapril Placebo	<45%	34%	77%	61	0%	77%	23%	0%	35	63%	NR
SPICE 2000[15]	DB, MC, PC	270/ NA, EU	12 weeks	179 91	Candesartan Placebo	≤35%	27%	69%	66	0%	54%	41%	6%	NR	71%	62%
STRETCH 1999[16]	DB, MC, PC	86/ Germany, Czech Rep, Slovenia	12 weeks	633 211	Candesartan Placebo	30-45%	39%	69%	62	0%	81%	19%	0%	39	NR	NR
Mitrovic 2003[17]	DB, MC, PC	EU	12 weeks	174 44	Candesartan Placebo	≤40%	28%	85%	54	0%	61%	39%	0%	40	NR	NR
ELITE I 1997[18]	DB, MC	125/ US, SA, EU	48 weeks	352 370	Losartan Captopril	≤40%	30%	67%	73	0%	65%	34%	2%	NR	68%	50%
ELITE II 2000[19]	DB, MC	289/ NA, SA, EU	700 days	1578 1574	Losartan Captopril	≤40%	31%	70%	71	0%	52%	43%	5%	NR	79%	58%
REPLACE 2001[20]	DB, MC	NR/ EU, Israel	12 weeks	301 77	Telmisartan Enalapril	<40%	26%	89%	64	0%	64%	36%	0%	NR	NR	69%
Dickstein 1995[21]	DB, MC	19/ Denmark, Finland, Norway, Sweden	8 weeks	108 58	Losartan Enalapril	≤35%	23%	78%	64	0%	0%	84%	16%	46	69%	63%
Lang 1997[22]	DB, MC	16 / NA	12 weeks	78 38	Losartan Enalapril	≤45%	25%	78%	58	0%	47%	51%	2%	53	47%	NR
CIBIS III 2008[23]	OL, MC	128/ EU and AUS and Tunisia	30 months	505 505	Bisoprolol Enalapril	≤35%	29%	68%	72	0%	49%	51%	0%	19	NR	49%

Study	Design	Centers/Region	Duration	N	Intervention	EF										
CARMEN 2004[24]	DB, MC, PC	65/ EU	18 months	191 190 191	Carvedilol + Placebo Enalapril + Placebo Carvedilol + Enalapril	<40%	30%	81%	62	8%	65%	27%	0%	NR	67%	52%
CHARM-alternative 2003[25]	DB, MC, PC	618/ NA, EU	3.5 years	1013 1015	Candesartan Placebo	≤40%	30%	68%	67	0%	48%	49%	4%	NR	68%	61%
HEAVEN 2002[26]	DB, MC, PC	NR/ Sweden	12 weeks	70 71	Valsartan Enalapril	≤45%	NR	53%	67	0%	70%	30%	0%	47	43%	NR
RALES 1999[27]	DB, MC, PC	195/ 15 countries	24 months (mean)	822 841	Spironolactone Placebo	≤35%	25%	73%	65	0%	0%	70%	29%	NR	54%	NR
Val-HeFT 2001[28]	DB, MC, PC	302/ US, EU, Africa	23 months (mean)	2511 2499	Valsartan Placebo	<40%	27%	80%	63	0%	62%	36%	2%	NR	NR	NR
Hamroff 1999[29]	DB, MC	4/ NR	6 months	16 17	Losartan Placebo	Reduced	26%	49%	61	NR	NR	NR	NR	NR	30%	NR
BEST 2008[30]	DB, MC, PC	90/ US and Canada	3 years	1354 1354	Bucindolol Placebo	≤35%	23%	78%	60	0%	0%	92%	8%	37	42%	NR
CIBIS I 1994[31]	DB, MC, PC	NR/ EU	2 years	320 321	Bisoprolol Placebo	< 40%	17%	83%	60	0%	0%	95%	5%	38	54%	47%
CIBIS II 1999[32]	DB, MC, PC	47/ Western and Eastern EU	1.3 years (mean)	1327 1320	Bisoprolol Placebo	≤35%	28%	81%	61	0%	0%	83%	17%	43	50%	NR
CELICARD 2000[33]	DB, MC, PC	NR/ France, Poland	1 year	62 62	Celiprolol Placebo	<40%	26%	90%	57	0%	57%	43%	1%	NR	NR	40%
COPERNICUS 2001[34]	DB, MC, PC	334/ NA, EU, AUS	28.7 months	1156 1133	Carvedilol Placebo	<25%	20%	79%	63	0%	NR	NR	NR	NR	67%	NR
ENECA 2005[35]	DB, MC, PC	70/ NR	48 weeks	134 126	Nebivolol Placebo	≤35%	26%	73%	72	0%	49%	47%	5%	NR	NR	58%

Study	Design	Sites/Location	Duration	N	Drug	EF	%	%	Age	%	%	%	%	Age	%	%
MERIT-HF 1999[36]	DB, MC, PC	14/ US, EU	18 months	1990 2001	Metroprolol Placebo	≤40%	28%	78%	64	0%	41%	55%	4%	NR	66%	49%
MERIT-HF (pilot) 1999[37]	DB, MC, PC	NR	6 months	42 19	Metroprolol Placebo	≤40%	27%	75%	NR	0%	56%	41%	3%	NR	NR	NR
MIC 2000[38]	DB, MC, PC	NR/ Germany, Sweden	6 months	26 26	Metroprolol Placebo	<40%	28%	71%	54	0%	58%	42%	0%	NR	NR	NR
MOCHA 1996[39]	DB, MC, PC	NR/ US	6 months	261 84	Carvedilol Placebo	≤ 35%	23%	76%	60	0%	53%	60%	2%	57	52%	NR
PRECISE 1996[40]	DB, MC, PC	31/ US	6 months	133 145	Carvedilol Placebo	≤35%	22%	73%	60	0%	40%	56%	4%	NR	52%	NR
SYMPOXYDEX 2004[41]	DB, MC, PC	NR/ France	6 months	28 22	Carvedilol Placebo	≤40%	26%	84%	59	0%	78%	22%	0%	NR	40%	NR
Cohn 1997[42]	DB, MC, PC	42 / US	6 months	70 35	Carvedilol Placebo	< 35%	22%	58%	60	0%	1%	86%	13%	49	45%	NR
Colucci 1996[43]	DB, MC, PC	NR/ US	12 months	232 134	Carvedilol Placebo	≤ 35%	23%	85%	54	0%	85%	14%	0%	48	41%	NR
de Milliano 2002[44]	DB, MC, PC	Netherlands	8 months	43 11	Metroprolol Placebo	<35%	25%	67%	65	0%	54%	46%	0%	NR	56%	NR
Dubach 2002[45]	DB, PC	NR	1 year	13 15	Bisoprolol Placebo	<40%	26%	NR	58	0%	NR	NR	0%	NR	57%	NR
Krum 1995[46]	DB, PC	NR/ US	14 weeks	33 16	Carvedilol Placebo	≤ 35%	16%	78%	55	0%	27%	63%	10%	NR	10%	NR
Packer 1996[47]	DB, MC, PC	NR/ US	6/12 months	696 398	Carvedilol Placebo	≤ 35%	23%	77%	58	0%	53%	44%	3%	NR	NR	NR
Palazzuoli 2005[48]	DB, PC	Italy	12 months	33 25	Carvedilol Placebo	<40%	32%	66%	71	0%	0%	57%	43%	NR	69%	NR

Study	Design	Country	Duration	N	Intervention	LVEF										
Palazzuoli 2005[49]	DB, PC	Italy	12 months	32 27	Carvedilol Placebo	<40%	32%	64%	71	0%	0%	58%	42%	NR	69%	NR
Sturm 2000[50]	DB, SC, PC	1/ Austria	2 years	51 49	Atenolol + Enalapril Placebo + Enalapril	≤25%	17%	88%	52	0%	78%	20%	2%	NR	28%	NR
RESOLVD 2000[51, 52]	DB, MC, PC	60/ NA, Italy	43 weeks	214 212	(Candesartan, Enalapril, or Candesartan + Enalapril) + Metroprolol (Candesartan, Enalapril, or Candesartan + Enalapril) + Placebo	<40%	28%	82%	61	7%	69%	23%	1%	NR	69%	64%
CHARM-added 2003[53]	DB, MC, PC	618/ NA, EU	3.5 years	1276 1272	Candesartan Placebo	≤40%	28%	79%	64	0%	24%	73%	0%	NR	62%	56%
AREA-IN CHF 2009[54]	DB, MC, PC	46/ Italy	12 months	231 236	Canrenone Placebo	≤45%	40%	84%	63	0%	100%	0%	0%	NR	52%	NR
EMPHASIS-HF 2011[55]	DB, MC, PC	278/ US, EU, AUS	3 years	1364 1373	Eplerenone Placebo	≤30%	26%	78%	69	0%	100%	0%	0%	58	69%	50%
Cicoira 2002[56]	OL	Italy	12 months	54 52	Spironolactone Placebo	≤45%	33%	87%	62	NR	NR	NR	NR	NR	64%	NR
Vizzardi 2014[57]	SB, SC, PC	1/Italy	44 months (mean)	65 65	Spironolactone Placebo	<40%	36%	NR	63	18%	82%	0%	0%	NR	NR	NR
PARADIGM-HF 2014[58]	DB, MC	1043/ 46 countries	27 months (median)	4187 4212	Valsartan/ sacubitril Enalapril	≤40%	29%	78%	64	5%	70%	24%	1%	NR	60%	43%

Abbreviations: AUS = Australia; d = day(s); DB = double-blind; EU = Europe; heart failure = heart failure; MC = multicentre; mos = months; MI = myocardial infarction; NA = North America; NYHA = New York heart association; LVEF = left ventricular ejection fraction; mo = month(s); NR = not reported; OL = open label; PC = placebo controlled; SB = single blind; SC = single centre; US = United States; yrs= years; wk = week(s); yr = year(s)

Supplementary Table 3: Characteristics of included interventions and concomitant therapies reported at baseline

Trial/Author year	Intervention class (>50%)	Main Intervention	ACEI %	ARB %	BB %	MRA %	Digoxin %	Diuretics %
CASSIS 1995	ACEI	Spirapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	ACEI	Spirapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	ACEI	Spirapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	ACEI	Enalapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	PLBO	Placebo	5%	NR	NR	NR	91%	96%
CONSENSUS 1987	ACEI	Enalapril	not allowed	NR	4%	NR	92%	100%
CONSENSUS 1987	PLBO	Placebo	not allowed	NR	2%	NR	94%	100%
FEST 1995	ACEI	Fosinopril	NR	NR	NR	NR	61%	100%
FEST 1995	PLBO	Placebo	NR	NR	NR	NR	62%	100%
MHFT 1991	ACEI	Captopril	NR	NR	23%	NR	59%	79%
MHFT 1991	PLBO	Placebo	NR	NR	23%	NR	59%	79%
SOLVD-prevent 1992	ACEI	Enalapril	not allowed	NR	NR	NR	12%	16%
SOLVD-prevent 1992	PLBO	Placebo	not allowed	NR	NR	NR	13%	17%
SOLVD-treat 1991	ACEI	Enalapril	not allowed	NR	8%	NR	66%	86%
SOLVD-treat 1991	PLBO	Placebo	not allowed	NR	7%	NR	68%	85%
Beller 1995	ACEI	Lisinopril	NR	NR	NR	NR	94%	99%
Beller 1995	PLBO	Placebo	NR	NR	NR	NR	86%	97%
Brown 1995	ACEI	Fosinopril	not allowed	NR	not allowed	NR	53%	100%
Brown 1995	PLBO	Placebo	not allowed	NR	not allowed	NR	54%	100%
Chalmers 1987	ACEI	Lisinopril	NR	NR	NR	10%	60%	55%
Chalmers 1987	PLBO	Placebo	NR	NR	NR	14%	72%	49%
Colfer 1992	ACEI	Benazepril	NR	NR	not allowed	NR	100%	100%
Colfer 1992	PLBO	Placebo	NR	NR	not allowed	NR	100%	100%
Goldstein 1988	ACEI	Captopril	NR	NR	NR	NR	60%	NR
Goldstein 1988	PLBO	Placebo	NR	NR	NR	NR	67%	NR
Lewis 1989	ACEI	Lisinopril	NR	NR	NR	NR	100%	100%
Lewis 1989	PLBO	Placebo	NR	NR	NR	NR	100%	100%

Shettigar 1999	ACEI	Fosinopril	not allowed	NR	not allowed	NR	42%	100%
Shettigar 1999	PLBO	Placebo	not allowed	NR	not allowed	NR	47%%	100%
Veldhuisen 1999	ACEI	Imidapril	NR	NR	not allowed	NR	23%	34%
Veldhuisen 1999	ACEI	Imidapril	NR	NR	not allowed	NR	26%	25%
Veldhuisen 1999	ACEI	Imidapril	NR	NR	not allowed	NR	24%	30%
Veldhuisen 1999	PLBO	Placebo	NR	NR	not allowed	NR	19%	25%
SPICE 2000	ARB	Candesartan	not allowed	not allowed	22%	NR	60%	NR
SPICE 2000	PLBO	Placebo	not allowed	not allowed	20%	NR	63%	NR
STRETCH 1999	ARB	Candesartan	not allowed	NR	1%	NR	40%	61%
STRETCH 1999	ARB	Candesartan	not allowed	NR	1%	NR	43%	63%
STRETCH 1999	ARB	Candesartan	not allowed	NR	0%	NR	42%	58%
STRETCH 1999	PLBO	Placebo	not allowed	NR	1%	NR	39%	58%
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	78%	NR
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	65%	NR
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	80%	NR
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	77%	NR
Mitrovic 2003	PLBO	Placebo	not allowed	not allowed	NR	NR	82%	NR
ELITE I 1997	ARB	Losartan	not allowed	not allowed	16%	NR	57%	74%
ELITE I 1997	ACEI	Captopril	not allowed	not allowed	17%	NR	56%	74%
ELITE II 2000	ARB	Losartan	not allowed	not allowed	23%	NR	50%	77%
ELITE II 2000	ACEI	Captopril	not allowed	not allowed	21%	NR	50%	79%
REPLACE 2001	ACEI	Enalapril	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
Dickstein 1995	ARB	Losartan	NR	NR	19%	NR	58%	NR
Dickstein 1995	ARB	Losartan	NR	NR	11%	NR	73%	NR
Dickstein 1995	ACEI	Enalapril	NR	NR	7%	NR	59%	NR
Lang 1997	ARB	Losartan	not allowed	NR	11%	NR	82%	100%
Lang 1997	ARB	Losartan	not allowed	NR	3%	NR	85%	100%
Lang 1997	ACEI	Enalapril	not allowed	NR	8%	NR	87%	97%

CIBIS III 2008	BB	Bisoprolol then Enalapril	not allowed	NR	not allowed	14%	33%	NR
CIBIS III 2008	ACEI	Enalapril then Bisoprolol	not allowed	NR	not allowed	12%	31%	NR
CARMEN 2004	BB	Carvedilol + placebo	not allowed	NR	not allowed	15%	44%	67%
CARMEN 2004	ACEI	Enalapril + placebo	not allowed	NR	not allowed	13%	44%	74%
CARMEN 2004	ACEI + BB	Carvedilol + enalapril	not allowed	NR	not allowed	12%	47%	73%
RALES 1999	ACEI + MRA	Spironolactone	95%	NR	11%	not allowed	75%	95%
RALES 1999	ACEI	Placebo	94%	NR	10%	not allowed	72%	94%
Val-HeFT 2001	ACEI + ARB	Valsartan	93%	not allowed	35%	NR	67%	NR
Val-HeFT 2001	ACEI	Placebo	93%	not allowed	35%	NR	68%	NR
Hamroff 1999	ACEI + ARB	Losartan	100%	NR	6%	NR	100%	100%
Hamroff 1999	ACEI	Placebo	100%	NR	6%	NR	94%	100%
BEST 2001	ACEI + BB	Bucindolol	91%	6%	not allowed	3%	93%	NR
BEST 2001	ACEI	Placebo	91%	7%	not allowed	4%	92%	NR
CELICARD 2000	ACEI + BB	Celiprolol	80%	NR	not allowed	NR	51%	NR
CELICARD 2000	ACEI	Placebo	90%	NR	not allowed	NR	66%	NR
CIBIS I 1994	ACEI + BB	Bisoprolol	89%	NR	NR	NR	57%	100%
CIBIS I 1994	ACEI	Placebo	91%	NR	NR	NR	56%	100%
CIBIS II 1999	ACEI + BB	Bisoprolol	96%	NR	NR	NR	53%	98%
CIBIS II 1999	ACEI	Placebo	96%	NR	NR	NR	51%	99%
COPERNICUS 2001	ACEI + BB	Carvedilol	97%*	97%*	not allowed	19%	67%	NR
COPERNICUS 2001	ACEI	Placebo	97%*	97%*	not allowed	20%	65%	NR
ENECA 2005	ACEI + BB	Nebivolol	91%	5%	not allowed	NR	60%	NR
ENECA 2005	ACEI	Placebo	92%	7%	not allowed	NR	53%	NR
MERIT-heart failure 1999	ACEI + BB	Metoprolol	89%	7%	not allowed	7%	63%	91%
MERIT-heart failure 1999	ACEI	Placebo	90%	6%	not allowed	8%	64%	90%
MERIT-heart failure (pilot) 1999	ACEI + BB	Metoprolol	95%	NR	NR	NR	91%	NR
MERIT-heart failure (pilot) 1999	ACEI	Placebo	89%	NR	NR	NR	90%	NR
MIC 2000	ACEI + BB	Metoprolol	92%	NR	not allowed	NR	51%	NR
MIC 2000	ACEI	Placebo	91%	NR	not allowed	NR	52%	NR
MOCHA 1996	ACEI + BB	Carvedilol (low-dose)	93%	NR	not allowed	NR	99%	98%
MOCHA 1996	ACEI + BB	Carvedilol (medium-dose)	99%	NR	not allowed	NR	88%	96%

MOCHA 1996	ACEI + BB	Carvedilol (high-dose)	89%	NR	not allowed	NR	90%	93%
MOCHA 1996	ACEI	Placebo	94%	NR	not allowed	NR	93%	93%
PRECISE 1996	ACEI + BB	Carvedilol	96%	NR	not allowed	NR	91%	98%
PRECISE 1996	ACEI	Placebo	97%	NR	not allowed	NR	88%	99%
SYMPOXYDEX 2004	ACEI + BB	Carvedilol	96%	NR	not allowed	NR	NR	100%
SYMPOXYDEX 2004	ACEI	Placebo	96%	NR	not allowed	NR	NR	100%
Cohn 1997	ACEI + BB	Carvedilol	94%	NR	NR	NR	90%	97%
Cohn 1997	ACEI	Placebo	91%	NR	NR	NR	89%	100%
Colucci 1996	ACEI + BB	Carvedilol	98%	NR	not allowed	NR	89%	NR
Colucci 1996	ACEI	Placebo	98%	NR	not allowed	NR	89%	NR
de Milliano 2002	ACEI + BB	Metoprolol	93%	NR	not allowed	NR	28%	NR
de Milliano 2002	ACEI	Placebo	91%	NR	not allowed	NR	36%	NR
Dubach 2002	ACEI + BB	Bisoprolol	100%	NR	not allowed	NR	5%	NR
Dubach 2002	ACEI	Placebo	100%	NR	not allowed	NR	9%	NR
Krum 1995	ACEI + BB	Carvedilol	90%	NR	NR	NR	NR	NR
Krum 1995	ACEI	Placebo	90%	NR	NR	NR	NR	NR
Packer 1996	ACEI + BB	Carvedilol	95%	NR	not allowed	NR	91%	95%
Packer 1996	ACEI	Placebo	95%	NR	not allowed	NR	90%	95%
Palazzuoli 2005	ACEI + BB	Carvedilol	100%	NR	not allowed	NR	NR	NR
Palazzuoli 2005	ACEI	Placebo	100%	NR	not allowed	NR	NR	NR
Palazzuoli 2005	ACEI + BB	Carvedilol	100%	NR	not allowed	NR	NR	NR
Palazzuoli 2005	ACEI	Placebo	100%	NR	not allowed	NR	NR	NR
Sturm 2000	ACEI + BB	Atenolol + enalapril	100%	NR	not allowed	NR	51%	NR
Sturm 2000	ACEI	Placebo + enalapril	100%	NR	not allowed	NR	49%	NR
HEAVEN 2002	ARB + BB	Valsartan	not allowed	not allowed	52%	NR	26%	NR
HEAVEN 2002	ACEI + BB	Enalapril	not allowed	not allowed	56%	NR	32%	NR
CHARM-alternative 2003	ARB + BB	Candesartan	not allowed	not allowed	55%	25%	60%	NR
CHARM-alternative 2003	BB	Placebo	not allowed	not allowed	55%	23%	63%	NR
RESOLVD 2000	ACEI + ARB + BB	(Candesartan, enalapril, or candesartan + enalapril) + metoprolol	ACEI alone: 14% ACEI + ARB: 41%	ARB alone: 45%	not allowed	NR	65%	NR
RESOLVD 2000	ACEI + ARB	(Candesartan, enalapril, or candesartan + enalapril) + placebo	ACEI alone: 19%	ARB alone: 40%	not allowed	NR	69%	NR

			ACEI + ARB: 41%					
RESOLVD 2003	ARB + BB	(Candesartan or enalapril) + metoprolol	23%	77%	not allowed	NR	68%	82%
RESOLVD 2003	ACEI + ARB + BB	(Candesartan + enalapril) + metoprolol	not allowed	not allowed	not allowed	NR	62%	83%
RESOLVD 2003	ARB	(Candesartan or enalapril) + placebo	33%	67%	not allowed	NR	74%	85%
RESOLVD 2003	ACEI + ARB	(Candesartan + enalapril) + placebo	not allowed	not allowed	not allowed	NR	70%	83%
CHARM-added 2003	ACEI + ARB + BB	Candesartan	100%	not allowed	55%	17%	58%	NR
CHARM-added 2003	ACEI + BB	Placebo	100%	not allowed	56%	17%	59%	NR
AREA-IN CHF 2009	ACEI + BB + MRA	Canrenone	85%	12%	81%	not allowed	24%	NR
AREA-IN CHF 2009	ACEI + BB	Placebo	75%	24%	78%	not allowed	27%	NR
EMPHASIS-heart failure 2011	ACEI + BB + MRA	Eplerenone	78%	19%	87%	not allowed	27%	84%
EMPHASIS-heart failure 2011	ACEI + BB	Placebo	77%	19%	87%	not allowed	28%	86%
Cicoira 2002	ACEI + BB + MRA	Spironolactone	100%	NR	72%	not allowed	NR	NR
Cicoira 2002	ACEI + BB	Placebo	100%	NR	65%	not allowed	NR	NR
Vizzardi 2014	ACEI + BB + MRA	Spironolactone	100%*	100%*	97%	NR	NR	75%
Vizzardi 2014	ACEI + BB	Placebo	100%*	100%*	98%	NR	NR	86%
PARADIGM-heart failure 2014	ARNI + BB + MRA	Sacubitril/valsartan	not allowed	NR	93%	54%	29%	80%
PARADIGM-heart failure 2014	ACEI + BB + MRA	Enalapril	not allowed	NR	93%	57%	31%	80%

* data presented for ACEI/ARB

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NR = not reported; PLBO = placebo

Supplementary Table 4: Proportion of patients taking concomitant ACEI and ARB in RCTs that allow concomitant use of ACEI or ARB

Criteria for ACEI or ARB	n studies	% of studies
ACEI or ARB allowed	9	100%
≥90% patients taking ACEI	3/9	33%
≥75% patients taking ACEI	6/9	67%
Only present pooled % (ACEI or ARB)	2/9	22%
Treatment classification unclear*	1/9	11%

* RESOLVD trial [51,52]

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist

Supplementary Table 5: Treatment doses and schedules by molecule

Intervention class (>50%)	Trial/Author year	Main Intervention	Target dosage	Frequency	Target daily dosage	Treatment duration
ACEI	Colfer 1992	Benazepril	20mg	OD	20mg	12 weeks (titration first 8 weeks)
ACEI	MHFT 1991	Captopril	25mg	BID	40mg	Median: 2.7 years
ACEI	ELITE I 1997	Captopril	50mg	TID	150mg	48 weeks (uptitration every 7 days)
ACEI	ELITE II 2000	Captopril	50mg	TID	150mg	700 days
ACEI	Anonymous 1988	Captopril	50mg	TID	150mg	24 weeks (uptitrated from 25mg/day if tolerated)
ACEI	Dickstein 1995	Enalapril	10mg	BID	20mg	8 weeks
ACEI	REPLACE 2001	Enalapril	10mg	BID	20mg	12 weeks
ACEI	CARMEN 2004	Enalapril	10mg	BID	20mg	18 months (plus upward titration and downward titration, undefined lengths of time
ACEI	CASSIS 1995	Enalapril	10mg	OD	10mg	12 weeks
ACEI	SOLVD-treat 1991	Enalapril	10mg	BID	20mg	48 months
ACEI	SOLVD-prevent 1992	Enalapril	10mg	BID	20mg	37.4 months (mean)
ACEI	CIBIS III 2008	Enalapril	10mg	BID	20mg/10mg	6 months
ACEI	CONSENSUS 1987	Enalapril	10mg-20mg	BID	20mg-40mg	52 weeks
ACEI	Lang 1997	Enalapril	20mg	BID	40mg	12 weeks
ACEI	Sturm 2000	Enalapril	40mg	OD	40mg	2 years (includes titration)
ACEI	Brown 1995	Fosinopril	20mg	OD	20mg	24 weeks
ACEI	FEST 1995	Fosinopril	40mg	OD	40mg	12 weeks
ACEI	Shettigar 1999	Fosinopril	40mg	OD	40mg	12 weeks (uptitration over first 4-weeks)
ACEI	Veldhuisen 1999*	Imidapril	2.5mg	OD	2.5mg	12 weeks
ACEI	Veldhuisen 1999*	Imidapril	5mg	OD	5mg	12 weeks
ACEI	Veldhuisen 1999	Imidapril	10mg	OD	10mg	12 weeks
ACEI	Beller 1995	Lisinopril	5mg-20mg	OD	5mg-20mg	12 weeks
ACEI	Chalmers 1987	Lisinopril	5mg-20mg	OD	5mg-20mg	12 weeks

ACEI	Lewis 1989	Lisinopril	5-20mg	OD	5-20mg	12 weeks
ACEI	CASSIS 1995*	Spirapril	1.5mg	OD	1.5mg	12 weeks
ACEI	CASSIS 1995*	Spirapril	3mg	OD	3mg	12 weeks
ACEI	CASSIS 1995	Spirapril	6mg	OD	6mg	12 weeks
ACEI	MERIT-heart failure 1999	Placebo	NA	NA	NA	18 months (including 6-8 week titration)
ACEI	MOCHA 1996	Placebo	NA	NA	NA	6 months (plus 2-4 week titration)
ACEI	SYMPOXYDEX 2004	Placebo	NA	NA	NA	6 months (including 6 weeks titration)
ACEI	Cohn 1997	Placebo	NA	NA	NA	6 months (plus 4 week titration)
ACEI	Val-HeFT 2001	Placebo	NA	NA	NA	38 months (including 4 weeks titration)
ACEI	de Milliano 2002	Placebo	NA	NA	NA	6 months (plus 10 wks titration)
ACEI	Dubach 2002	Placebo	NA	NA	NA	12 months (titration first month)
ACEI	ENECA 2005	Placebo	NA	NA	NA	48 weeks (includes 6 week titration period)
ACEI	BEST 2001	Placebo	NA	NA	NA	42 months (titration first 6 weeks)
ACEI	MIC 2000	Placebo	NA	NA	NA	6 months (including 6 week titration)
ACEI	MERIT-heart failure (pilot) 1999	Placebo	NA	NA	NA	26 weeks (titration first 8 weeks)
ACEI	Hamroff 1999	Placebo	NA	NA	NA	6 months
ACEI	CIBIS I 1994	Placebo	NA	NA	NA	2 years (mean duration 1.9)
ACEI	CIBIS II 1999	Placebo	NA	NA	NA	mean duration: 1.3 years (titration weeks 1-5)
ACEI	PRECISE 1996	Placebo	NA	NA	NA	6 months
ACEI	Packer 1996	Placebo	NA	NA	NA	6 months (plus 2-10 week titration (mild heart failure protocol;12 months + titration)
ACEI	Colucci 1996	Placebo	NA	NA	NA	52 weeks (plus uptitration 2-6 weeks)
ACEI	Krum 1995	Placebo	NA	NA	NA	14 weeks (titration in first week)
ACEI	COPERNICUS 2001	Placebo	NA	NA	NA	28.7 months (includes approximately 8 week titration period)
ACEI	Palazzuoli 2005	Placebo	NA	NA	NA	12 months (titration first 7 weeks)
ACEI	Palazzuoli 2005	Placebo	NA	NA	NA	12 months (titration first 7 weeks)
ACEI	RALES 1999	Placebo	NA	NA	NA	24 months

ACEI	CELICARD 2000	Placebo	NA	NA	NA	1 year (including 1 month titration period)
BB	CIBIS III 2008	Bisoprolol	10mg	OD	10mg	26 weeks (including 10 week titration)
BB	CARMEN 2004	Carvedilol	25mg or 50mg if >85kg	BID	50mg or 100mg if >85kg	18 months (plus upward titration and downward titration, undefined lengths of time
BB	CHARM-alternative 2003	Placebo	NA	NA	NA	33.7 months (median follow-up, plus 6 weeks titration period)
ARB	SPICE 2000	Candesartan	16mg	OD	16mg	12 weeks (including 4 weeks titration)
ARB	STRETCH1999*	Candesartan	4mg	OD	4mg	12 weeks
ARB	STRETCH1999*	Candesartan	8mg	OD	8mg	12 weeks
ARB	STRETCH1999	Candesartan	16mg	OD	16mg	12 weeks
ARB	Lang 1997	Losartan*	25mg	OD	25mg	12 weeks
ARB	Lang 1997	Losartan	50mg	OD	50mg	12 weeks
ARB	Mitrovic 2003*	Candesartan	2mg	OD	2mg	12 weeks (titration first 3 weeks)
ARB	Mitrovic 2003*	Candesartan	4mg	OD	4mg	12 weeks (titration first 3 weeks)
ARB	Mitrovic 2003*	Candesartan	8mg	OD	8mg	12 weeks (titration first 3 weeks)
ARB	Mitrovic 2003	Candesartan	16mg	OD	16mg	12 weeks (titration first 3 weeks)
ARB	Dickstein 1995*	Losartan	25mg	OD	25mg	8 weeks
ARB	Dickstein 1995	Losartan	50mg	OD	50mg	8 weeks
ARB	ELITE I 1997	Losartan	50mg	OD	50mg	48 weeks (uptitration every 7 days)
ARB	ELITE II 2000	Losartan	50mg	OD	50mg	700 days
ARB	REPLACE 2001*	Telmisartan	10mg	OD	10mg	12 weeks
ARB	REPLACE 2001*	Telmisartan	20mg	OD	20mg	12 weeks
ARB	REPLACE 2001*	Telmisartan	40mg	OD	40mg	12 weeks
ARB	REPLACE 2001	Telmisartan	80mg	OD	80mg	12 weeks
ACEI + ARB	RESOLVD 2003	(Candesartan + enalapril) + placebo	NA	NA	NA	19 weeks without placebo (including mean titration 93 days), placebo received for 24weeks (43 weeks total)
ACEI + ARB	Hamroff 1999	Losartan	50mg	OD	50mg	6 months
ACEI + ARB	Val-HeFT 2001	Valsartan	160mg	BID	320mg	38 months (including 4 weeks titration)

ACEI + BB	Sturm 2000	Atenolol + enalapril	50mg-100mg/40mg	daily	50mg-100mg/40mg	2 years (includes titration)
ACEI + BB	Dubach 2002	Bisoprolol	10mg	daily	10mg	12 months (titration first month)
ACEI + BB	CIBIS I 1994	Bisoprolol	5mg	OD	5mg	2 years (mean duration 1.9)
ACEI + BB	CIBIS II 1999	Bisoprolol	2.5-10mg	OD	2.5-10mg	mean duration: 1.3 years (titration weeks 1-5)
ACEI + BB	BEST 2001	Bucindolol	50mg if <75kg; 100mg if >75kg	BID	100mg or 200mg	42 months (titration first 6 weeks)
ACEI + BB	SYMPOXYDEX 2004	Carvedilol	25mg	BID	50mg	6 months (including 6 weeks titration)
ACEI + BB	Cohn 1997	Carvedilol	25mg	BID	50mg	6 months (plus 4 week titration)
ACEI + BB	PRECISE 1996	Carvedilol	25mg	BID	50mg	6 months
ACEI + BB	Krum 1995	Carvedilol	25mg	BID	50mg	14 weeks (titration in first week)
ACEI + BB	Packer 1996	Carvedilol	25-50mg	BID	50mg-100mg	6 months (plus 2-10 week titration (mild heart failure protocol;12 months + titration)
ACEI + BB	Colucci 1996	Carvedilol	25-50mg	BID	50-100mg	52 weeks (plus uptitration 2-6 weeks)
ACEI + BB	COPERNICUS 2001	Carvedilol	25mg	BID	50mg	28.7 months (includes approximately 8 week titration period)
ACEI + BB	Palazzuoli 2005	Carvedilol	50mg	daily	50mg	12 months (titration first 7 weeks)
ACEI + BB	Palazzuoli 2005	Carvedilol	50mg	daily	50mg	12 months (titration first 7 weeks)
ACEI + BB	MOCHA 1996*	Carvedilol (low-dose)	6.25mg	BID	12.5mg	6 months (plus 2-4 week titration)
ACEI + BB	MOCHA 1996*	Carvedilol (medium-dose)	12.5mg	BID	25mg	6 months (plus 2-4 week titration)
ACEI + BB	MOCHA 1996	Carvedilol (high-dose)	25mg	BID	50mg	6 months (plus 2-4 week titration)
ACEI + BB	CARMEN 2004	Carvedilol + enalapril	25mg or 50mg if >85kg/10mg	BID	50mg or 100mg if >85kg/20mg	18 months (plus upward titration and downward titration, undefined lengths of time)
ACEI + BB	CELICARD 2000	Celiprolol	100mg	OD	100mg	1 year (including 1 month titration period)

ACEI + BB	MERIT-heart failure 1999	Metoprolol	200mg	daily	200mg	18 months (including 6-8 week titration)
ACEI + BB	MERIT-heart failure (pilot) 1999	Metoprolol	150mg	o.d.	150 mg	26 weeks (titration first 8 weeks)
ACEI + BB	de Milliano 2002	Metoprolol	50, 100 or 150mg	daily	50, 100 or 150mg	6 months (plus 10 wks titration)
ACEI + BB	MIC 2000	Metoprolol	NR	NR	135mg (mean)	6 months (including 6 week titration)
ACEI + BB	ENECA 2005	Nebivolol	10mg	daily	10mg	48 weeks (includes 6 week titration period)
ACEI + BB	HEAVEN 2002	Enalapril	10mg	BID	20mg	12 weeks (including titration)
ACEI + BB	AREA-IN CHF 2009	Placebo	NA	NA	NA	12 months
ACEI + BB	Cicoira 2002	Placebo	NA	NA	NA	12 months (includes titration)
ACEI + BB	Vizzardi 2014	Placebo	25mg	OD	25mg	44 months (mean)
ACEI + BB	CHARM-added 2003	Placebo	NA	NA	NA	41 months (median follow-up, plus 6 weeks titration period)
ACEI + BB	EMPHASIS-heart failure 2011	Placebo	NA	NA	NA	3 years
ARB + BB	HEAVEN 2002	Valsartan	160mg	OD	160mg	12 weeks (including titration)
ARB + BB	CHARM-alternative 2003	Candesartan	32mg	OD	32mg	33.7 months (median follow-up, plus 6 weeks titration period)
ACEI + MRA	RALES 1999	Spironolactone	25-50mg	OD	25-50mg (mean 30mg)	24 months
ACEI + ARB + BB	RESOLVD 2003	(Candesartan + enalapril) + metoprolol	200mg	daily	200mg	19 weeks without metoprolol (including mean titration 93 days), metoprolol received for 24weeks (43 weeks total)
ACEI + ARB + BB	CHARM-added 2003	Candesartan	32mg	OD	32mg	41 months (median follow-up, plus 6 weeks titration period)
ACEI + BB + MRA	AREA-IN CHF 2009	Canrenone	50mg	OD	50mg	12 months
ACEI + BB + MRA	EMPHASIS-heart failure 2011	Eplerenone	50mg	OD	50mg	3 years
ACEI + BB + MRA	PARADIGM-heart failure 2014	Enalapril	10mg	BID	20mg	27 months (median)
ACEI + BB + MRA	Cicoira 2002	Spironolactone	50mg	OD	50mg	12 months (includes titration)

ACEI + BB + MRA	Vizzardi 2014	Spironolactone	25mg-100mg	OD-QID	25mg-400mg	44 months (mean)
ARNI + BB + MRA	PARADIGM-heart failure 2014	Sacubitril/valsartan	200mg	BID	400mg	27 months (median)
PLBO	Beller 1995	Placebo	5mg-20mg	OD	5mg-20mg	12 weeks
PLBO	Brown 1995	Placebo	NA	NA	NA	24 weeks
PLBO	Chalmers 1987	Placebo	5mg-20mg	OD	5mg-20mg	12 weeks
PLBO	STRETCH 1999	Placebo	NA	NA	NA	12 weeks
PLBO	Anonymous 1988	Placebo	NA	NA	NA	24 weeks (uptitrated from 25mg/day if tolerated)
PLBO	Colfer 1992	Placebo	NA	NA	NA	12 weeks (titration first 8 weeks)
PLBO	FEST 1995	Placebo	NA	NA	NA	12 weeks
PLBO	SPICE 2000	Placebo	NA	NA	NA	12 weeks (including 4 weeks titration)
PLBO	MHFT 1991	Placebo	NA	NA	NA	Median: 2.7 years
PLBO	Lewis 1989	Placebo	NA	NA	NA	12 weeks
PLBO	Mitrovic 2003	Placebo	NA	NA	NA	12 weeks (titration first 3 weeks)
PLBO	Shettigar 1999	Placebo	NA	NA	NA	12 weeks (uptitration over first 4-weeks)
PLBO	CONSENSUS 1987	Placebo	NA	NA	NA	52 weeks
PLBO	Veldhuisen 1999	Placebo	NA	NA	NA	12 weeks
PLBO	CASSIS 1995	Placebo	NA	NA	NA	12 weeks
PLBO	SOLVD-treat 1991	Placebo	NA	NA	NA	48 months
PLBO	SOLVD-prevent 1992	Placebo	NA	NA	NA	37.4 months (mean)

* Arm excluded from analysis (more common dose available)

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; BID = twice daily; mg = milligrams; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NR = not reported; OD = once daily; PLBO = placebo; QID = four times daily; TID = three times daily

Supplementary Figure 1: Quality assessment results A) Summary by domain, B) Summary by RCT

A)
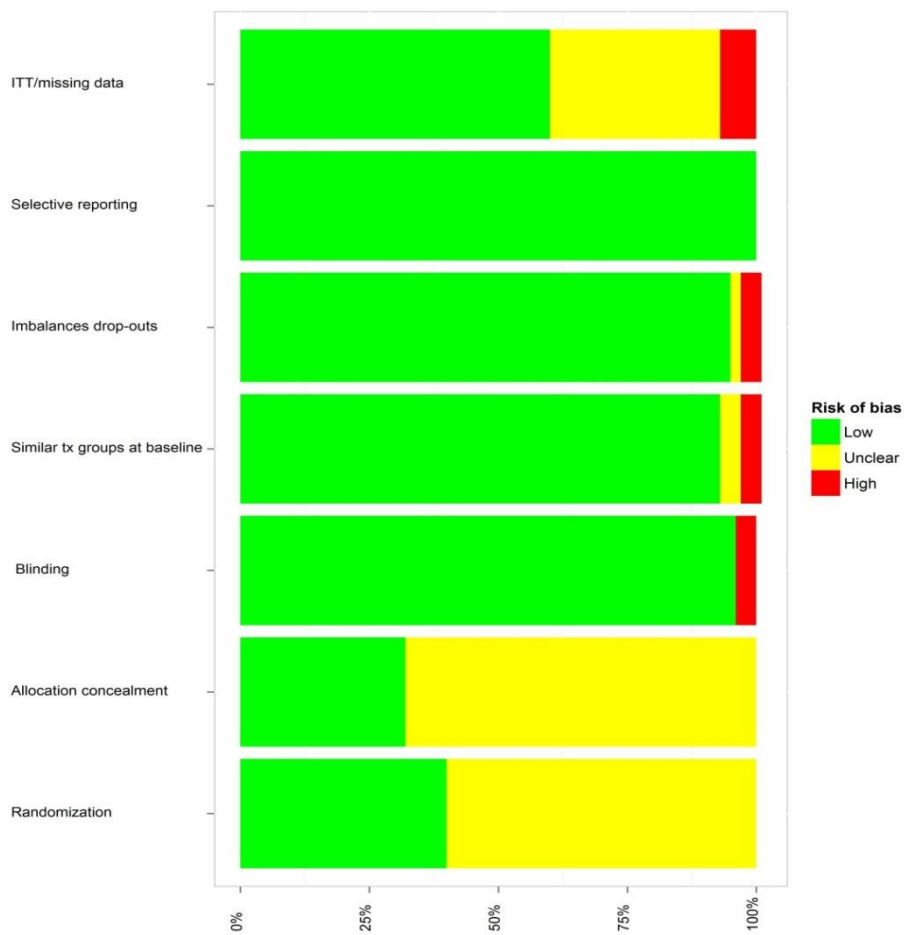
B)

Supplementary Figure 2: Rates per patient year sorted by publication year and presented by treatment arm for A) Placebo, B) ACEI, C) all other treatment arms

A)

Death per patient year in placebo arm

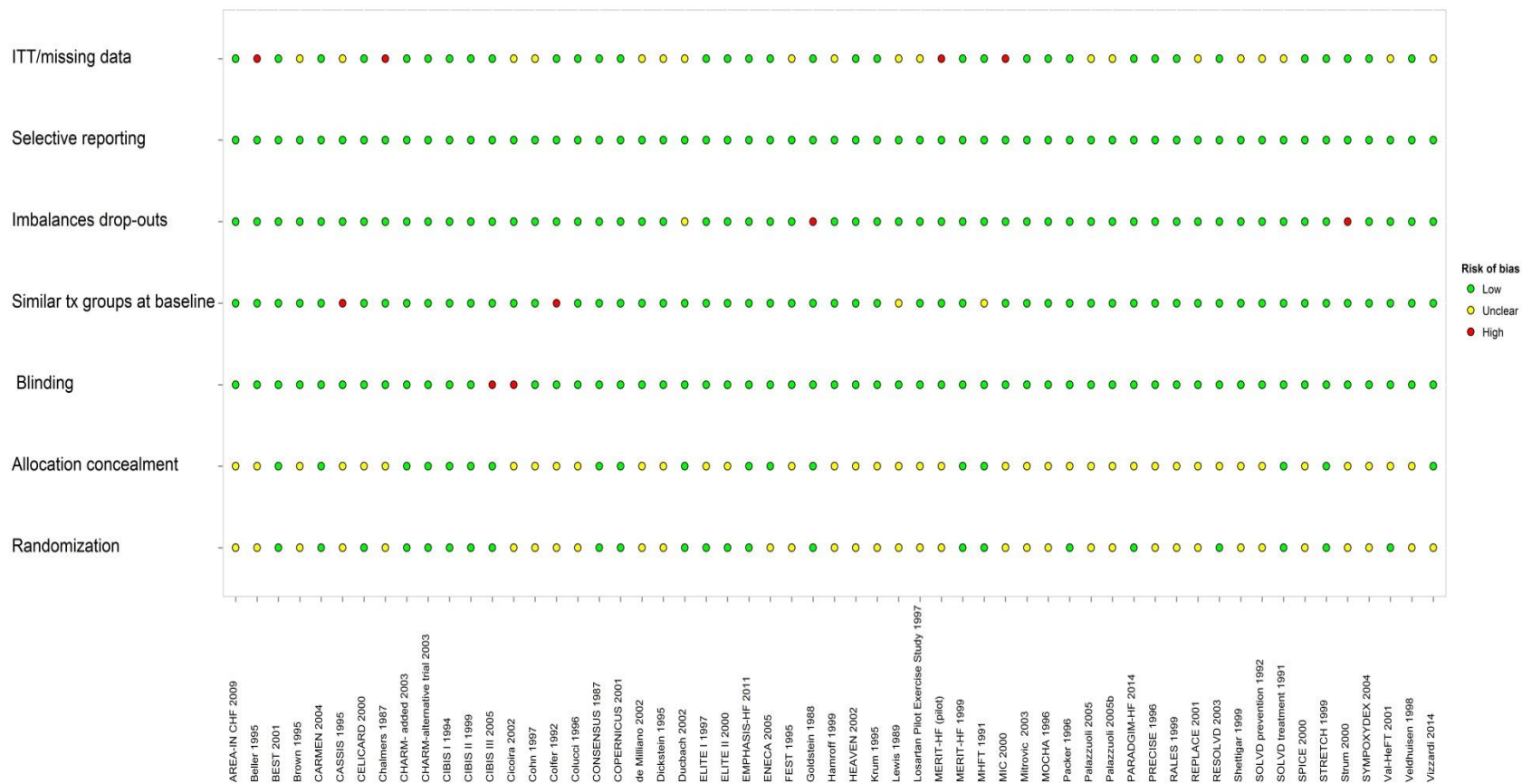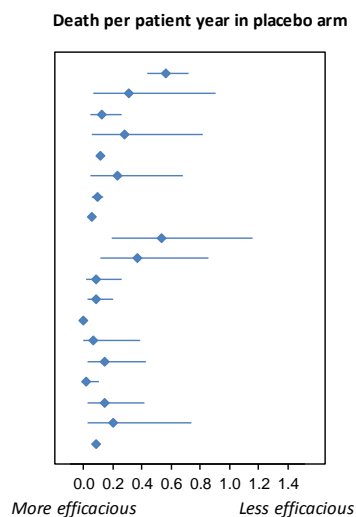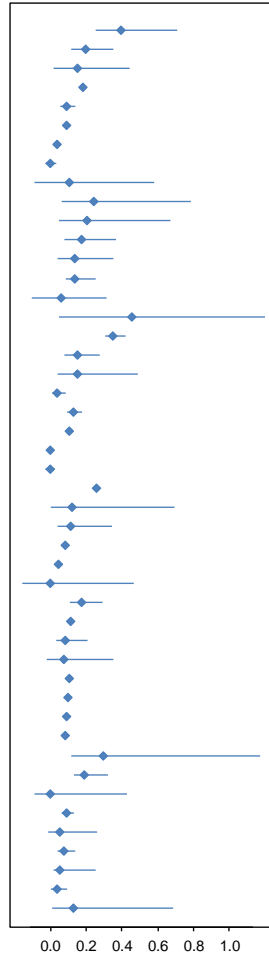| Tx class	Trial	Follow-up (months)	# randomized	# completers	Person years at risk	Deaths	Rate (per patient year)	95% CrI low	95% CrI high
PLBO	CONSENSUS 1987	12.0	126	108	117	66	0.56	0.72	0.44
PLBO	Chalmers 1987	3.0	43	35	10	3	0.31	0.90	0.06
PLBO	Goldstein 1988	6.0	100	100	50	6	0.12	0.26	0.04
PLBO	Lewis 1989	3.0	43	43	11	3	0.28	0.82	0.06
PLBO	SOLVD treat 1991	55.0	1284	752	4667	510	0.11	0.12	0.10
PLBO	Colfer 1992	3.0	58	45	13	3	0.23	0.68	0.05
PLBO	MHFT 1992	36.5	87	74	245	22	0.09	0.14	0.06
PLBO	SOLVD prevent 1992	48.0	2117	1164	6563	334	0.05	0.06	0.05
PLBO	CASSIS 1995	3.0	48	42	11	6	0.53	1.16	0.19
PLBO	Beller 1995	3.0	63	46	14	5	0.37	0.85	0.12
PLBO	FEST 1995	3.0	153	118	34	3	0.09	0.26	0.02
PLBO	Brown 1995	6.0	125	74	50	4	0.08	0.21	0.02
PLBO	RALES (dosing) 1996	3.0	40	40	10	0	0.00	0.00	0.00
PLBO	Veldhuisen 1998	3.0	62	54	15	1	0.07	0.38	0.00
PLBO	Shettigar 1999	3.0	104	60	21	3	0.15	0.43	0.03
PLBO	STRETCH 1999	3.0	211	211	53	1	0.02	0.11	0.00
PLBO	SPICE 2000	3.0	91	79	21	3	0.14	0.41	0.03
PLBO	Mitrovic 2003	3.0	44	34	10	2	0.21	0.74	0.02
PLBO	CHARM-alt 2003	42.0	1015	1015	3553	296	0.08	0.09	0.07

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4

More efficacious   *Less efficacious*

B)

Death per patient year in ACEI arm

0.0 0.2 0.4 0.6 0.8 1.0

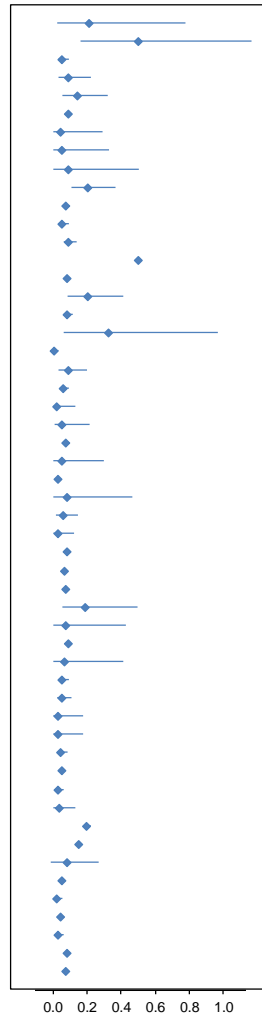*More efficacious*   *Less efficacious*

| Tx class	Trial	Follow-up (months)	# randomized	# completers	Person years at risk	Deaths	Rate (per patient year)	95% CrI low	95% CrI high
ACEI	CONSENSUS 1987	12.0	127	105	116	46	0.40	0.53	0.29
ACEI	Chalmers 1987	3.0	87	72	20	4	0.20	0.52	0.05
ACEI	Goldstein 1988	6.0	104	104	52	8	0.15	0.30	0.07
ACEI	Lewis 1989	3.0	87	87	22	4	0.18	0.47	0.05
ACEI	SOLVD treat 1991	55.0	1285	867	4933	452	0.09	0.10	0.08
ACEI	MHFT 1992	40.4	83	59	239	22	0.09	0.14	0.06
ACEI	SOLVD prevent 1992	48.0	2111	1942	8106	313	0.04	0.04	0.03
ACEI	Colfer 1992	3.0	114	98	27	0	0.00	0.00	0.00
ACEI	CIBIS I 1994	26.0	321	239	607	67	0.11	0.14	0.09
ACEI	CASSIS 1995	3.0	51	47	12	3	0.24	0.72	0.05
ACEI	Dickstein 1995	2.0	58	58	10	2	0.21	0.75	0.02
ACEI	CASSIS 1995	3.0	48	42	11	2	0.18	0.64	0.02
ACEI	FEST 1995	3.0	155	127	35	5	0.14	0.33	0.05
ACEI	Beller 1995	3.0	130	105	29	4	0.14	0.35	0.04
ACEI	Brown 1995	6.0	116	81	49	3	0.06	0.18	0.01
ACEI	Krum 1995	3.5	16	14	4	2	0.46	1.65	0.05
ACEI	MOCHA 1996	6.0	84	63	37	13	0.35	0.60	0.19
ACEI	Packer 1996	6.0	398	398	199	31	0.16	0.22	0.11
ACEI	PRECISE 1996	6.0	145	145	73	11	0.15	0.27	0.08
ACEI	Colucci 1996	12.0	134	134	134	5	0.04	0.09	0.01
ACEI	Cohn 1997	6.0	35	27	16	2	0.13	0.47	0.01
ACEI	ELITE I 1997	11.0	370	259	288	32	0.11	0.16	0.08
ACEI	Lang 1997	3.0	38	38	10	0	0.00	0.00	0.00
ACEI	Veldhuisen 1998	3.0	60	56	15	0	0.00	0.00	0.00
ACEI	RALES 1999	24.0	841	630	1471	386	0.26	0.29	0.24
ACEI	Hamroff 1999	6.0	17	13	8	1	0.13	0.70	0.00
ACEI	MERIT-HF 1999	12.0	2001	1691	1846	217	0.12	0.13	0.10
ACEI	Shettigar 1999	3.0	102	85	23	2	0.09	0.31	0.01
ACEI	CIBIS II 1999	46.0	1320	1320	5063	228	0.05	0.05	0.04
ACEI	Goldstein 1999	6.0	19	16	9	0	0.00	0.00	0.00
ACEI	MIC 2000	6.0	26	19	11	2	0.18	0.64	0.02
ACEI	Sturm 2000	24.0	49	20	69	8	0.12	0.23	0.05
ACEI	ELITE II 2000	24.0	1574	1353	2927	250	0.09	0.10	0.08
ACEI	CELICARD 2000	12.0	66	39	53	4	0.08	0.20	0.02
ACEI	REPLACE 2001	3.0	75	75	19	2	0.11	0.39	0.01
ACEI	COPERNICUS 2001	21.0	1133	953	1825	190	0.10	0.12	0.09
ACEI	BEST 2001	42.0	1354	1351	4734	449	0.09	0.10	0.09
ACEI	Val-HeFT 2001	27.0	2499	2499	5623	484	0.09	0.09	0.08
ACEI	HEAVEN 2002	3.0	71	62	17	5	0.30	0.70	0.10
ACEI	de Milliano 2002	6.0	11	10	5	1	0.19	1.06	0.00
ACEI	Dubach 2002	12.0	15	15	15	0	0.00	0.00	0.00
ACEI	SYMPOXYDEX 2004	6.0	22	21	11	1	0.09	0.52	0.00
ACEI	CARMEN 2004	18.0	190	133	242	14	0.06	0.10	0.03
ACEI	Palazzuoli 2005b	12.0	27	24	26	2	0.08	0.28	0.01
ACEI	ENECA 2005	11.0	126	112	119	7	0.06	0.12	0.02
ACEI	Palazzuoli 2005	12.0	25	22	24	1	0.04	0.24	0.00
ACEI	CIBIS III 2008	6.0	505	456	240	32	0.13	0.19	0.09

C)

Death per patient year in other arms

Tx class	Trial	Follow-up (months)	# randomized	# completers	Person years at risk	Deaths	Rate (per patient year)	95% CrI low	95% CrI high
ARB	Dickstein 1995	2.0	56	56	9	2	0.21	0.77	0.02
ARB	Lang 1997	3.0	40	40	10	5	0.50	1.17	0.16
ARB	ELITE I 1997	11.0	352	287	293	17	0.06	0.09	0.03
ARB	STRETCH 1999	3.0	213	213	53	5	0.09	0.22	0.03
ARB	SPICE 2000	3.0	179	148	41	6	0.15	0.32	0.05
ARB	ELITE II 2000	24.0	1578	1453	3031	280	0.09	0.10	0.08
ARB	REPLACE 2001	3.0	77	77	19	1	0.05	0.29	0.00
ARB	HEAVEN 2002	3.0	70	65	17	1	0.06	0.33	0.00
ARB	Mitrovic 2003	3.0	44	44	11	1	0.09	0.51	0.00
ARB	RESOLVD 2003	6.0	126	122	57	12	0.21	0.37	0.11
ARB	CHARM-alt 2003	42.0	1013	1013	3546	265	0.07	0.08	0.07
BB	CARMEN 2004	18.0	191	134	244	14	0.06	0.10	0.03
BB	CIBIS III 2008	6.0	505	470	244	23	0.09	0.14	0.06
ACEI + ARB	Hamroff 1999	6.0	16	13	7	5	0.50	0.00	0.00
ACEI + ARB	Val-HeFT 2001	27.0	2511	2511	5650	495	0.09	0.10	0.08
ACEI + ARB	RESOLVD 2003	6.0	86	82	39	8	0.21	0.41	0.09
ACEI + BB	CIBIS I 1994	26.0	320	245	612	53	0.09	0.11	0.06
ACEI + BB	Krum 1995	3.5	33	29	9	3	0.33	0.97	0.07
ACEI + BB	Colucci 1996	12.0	232	232	232	2	0.01	0.03	0.00
ACEI + BB	PRECISE 1996	6.0	133	133	67	6	0.09	0.20	0.03
ACEI + BB	Packer 1996	6.0	696	696	348	22	0.06	0.10	0.04
ACEI + BB	MOCHA 1996	6.0	89	82	43	1	0.02	0.13	0.00
ACEI + BB	Cohn 1997	6.0	70	66	34	2	0.06	0.21	0.01
ACEI + BB	MERIT-HF 1999	12.0	1990	1711	1851	145	0.08	0.09	0.07
ACEI + BB	Goldstein 1999	6.0	42	33	19	1	0.05	0.30	0.00
ACEI + BB	CIBIS II 1999	46.0	1327	1327	5090	156	0.03	0.04	0.03
ACEI + BB	MIC 2000	6.0	26	22	12	1	0.08	0.46	0.00
ACEI + BB	Sturm 2000	24.0	51	28	79	5	0.06	0.15	0.02
ACEI + BB	CELICARD 2000	12.0	66	48	57	2	0.04	0.13	0.00
ACEI + BB	BEST 2001	42.0	1354	1349	4730	411	0.09	0.10	0.08
ACEI + BB	COPERNICUS 2001	21.0	1156	1010	1896	130	0.07	0.08	0.06
ACEI + BB	Cicoira 2002	12.0	52	46	49	4	0.08	0.21	0.02
ACEI + BB	de Milliano 2002	6.0	43	39	21	4	0.20	0.50	0.05
ACEI + BB	Dubach 2002	12.0	13	13	13	1	0.08	0.43	0.00
ACEI + BB	CHARM-added 2003	42.0	1272	1272	4452	412	0.09	0.10	0.08
ACEI + BB	SYMPOXYDEX 2004	6.0	28	26	14	1	0.07	0.41	0.00
ACEI + BB	CARMEN 2004	18.0	191	132	242	14	0.06	0.10	0.03
ACEI + BB	ENECA 2005	12.0	134	124	129	7	0.05	0.11	0.02
ACEI + BB	Palazzuoli 2005b	12.0	32	30	31	1	0.03	0.18	0.00
ACEI + BB	Palazzuoli 2005	12.0	33	31	32	1	0.03	0.17	0.00
ACEI + BB	AREA-IN CHF 2009	12.0	236	236	236	12	0.05	0.09	0.03
ACEI + BB	EMPHASIS-HF 2011	36.0	1373	1145	3777	213	0.06	0.06	0.05
ACEI + BB	Vizzardi 2014	44.0	65	65	238	8	0.03	0.07	0.01
ARB + BB	RESOLVD 2003	6.0	125	108	53	2	0.04	0.13	0.00
ACEI + MRA	RALES 1999	24.0	822	600	1422	284	0.20	0.22	0.18
ACEI + ARB + BB	RESOLVD 2003	6.0	89	77	38	6	0.16	0.34	0.06
ACEI + ARB + BB	CHARM-added 2003	42.0	1276	1276	4466	377	0.08	0.09	0.08
ACEI + BB + MRA	Cicoira 2002	12.0	54	47	51	3	0.06	0.17	0.01
ACEI + BB + MRA	AREA-IN CHF 2009	12.0	231	231	231	6	0.03	0.06	0.01
ACEI + BB + MRA	EMPHASIS-HF 2011	36.0	1364	1142	3759	171	0.05	0.05	0.04
ACEI + BB + MRA	Vizzardi 2014	44.0	65	65	238	8	0.03	0.07	0.01
ACEI + BB + MRA	PARADIGM-HF 2014	27.0	4212	4203	9467	835	0.09	0.09	0.08
ARNI + BB + MRA	PARADIGM-HF 2014	27.0	4187	4176	9408	711	0.08	0.08	0.07

0.0 0.2 0.4 0.6 0.8 1.0

More efficacious   *Less efficacious*

Supplementary Figure 3: Results of random effect network meta-analysis probability rank for all-cause mortality
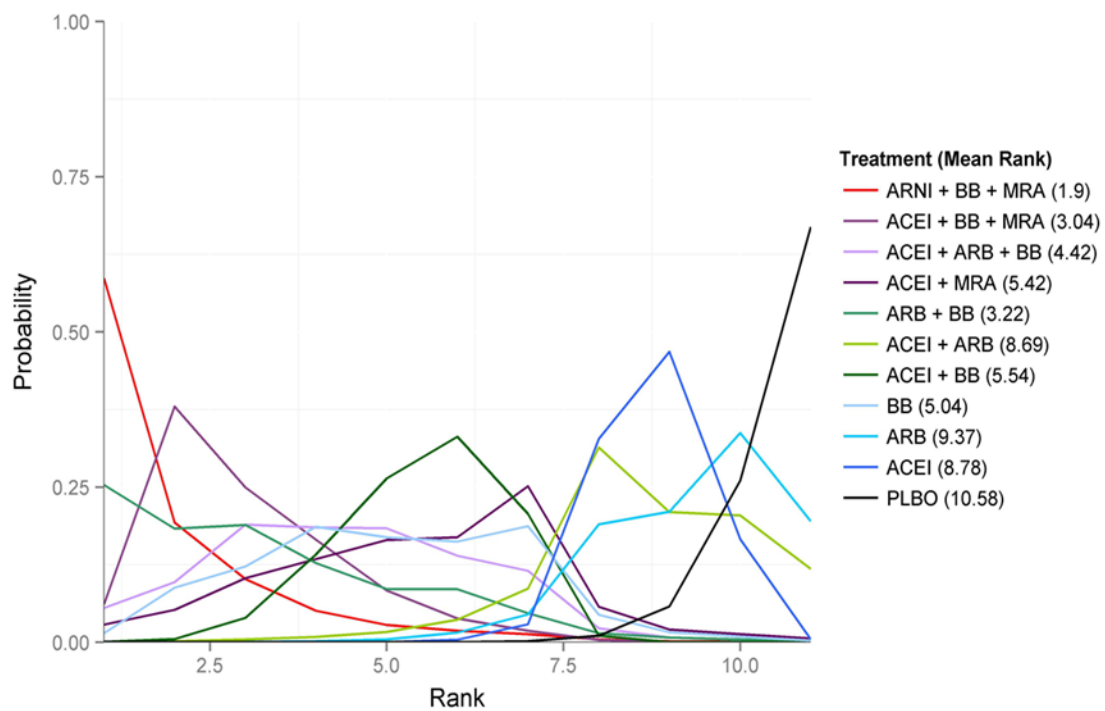
Supplemental References

(List of Studies Included in the Systematic Literature Review and Network Meta-Analysis)

1.   Widimsky J, Kremer HJ, Jerie P and Uhlir O. Czech and Slovak spirapril intervention study (CASSIS). A randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur. J. Clin. Pharmacol*. 1995;49:95-102.

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