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
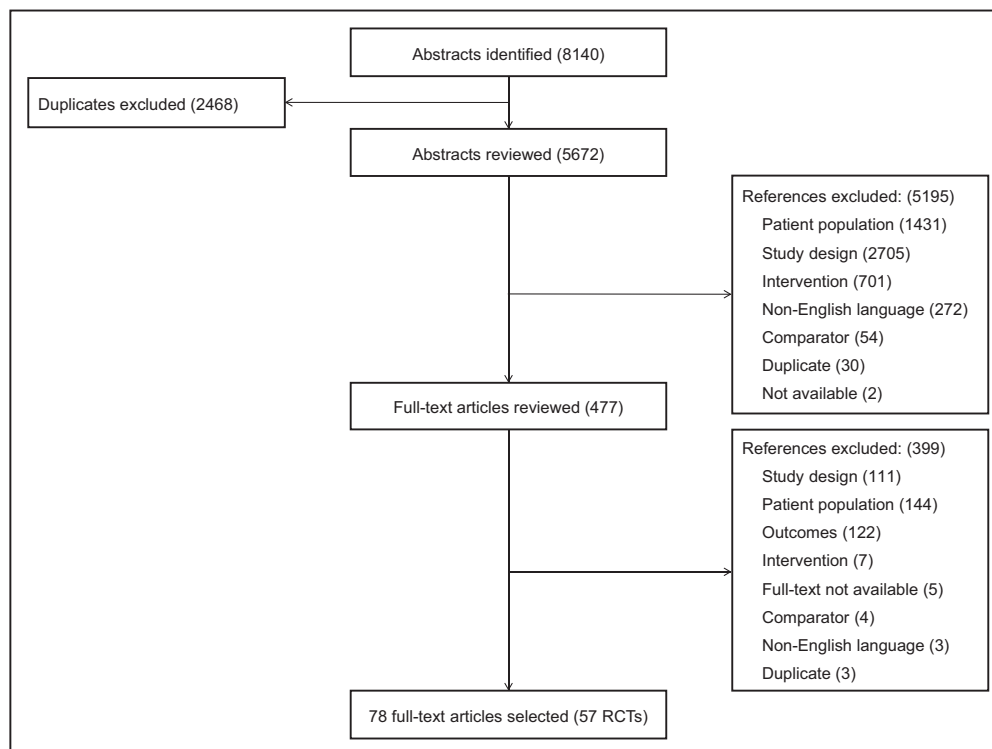

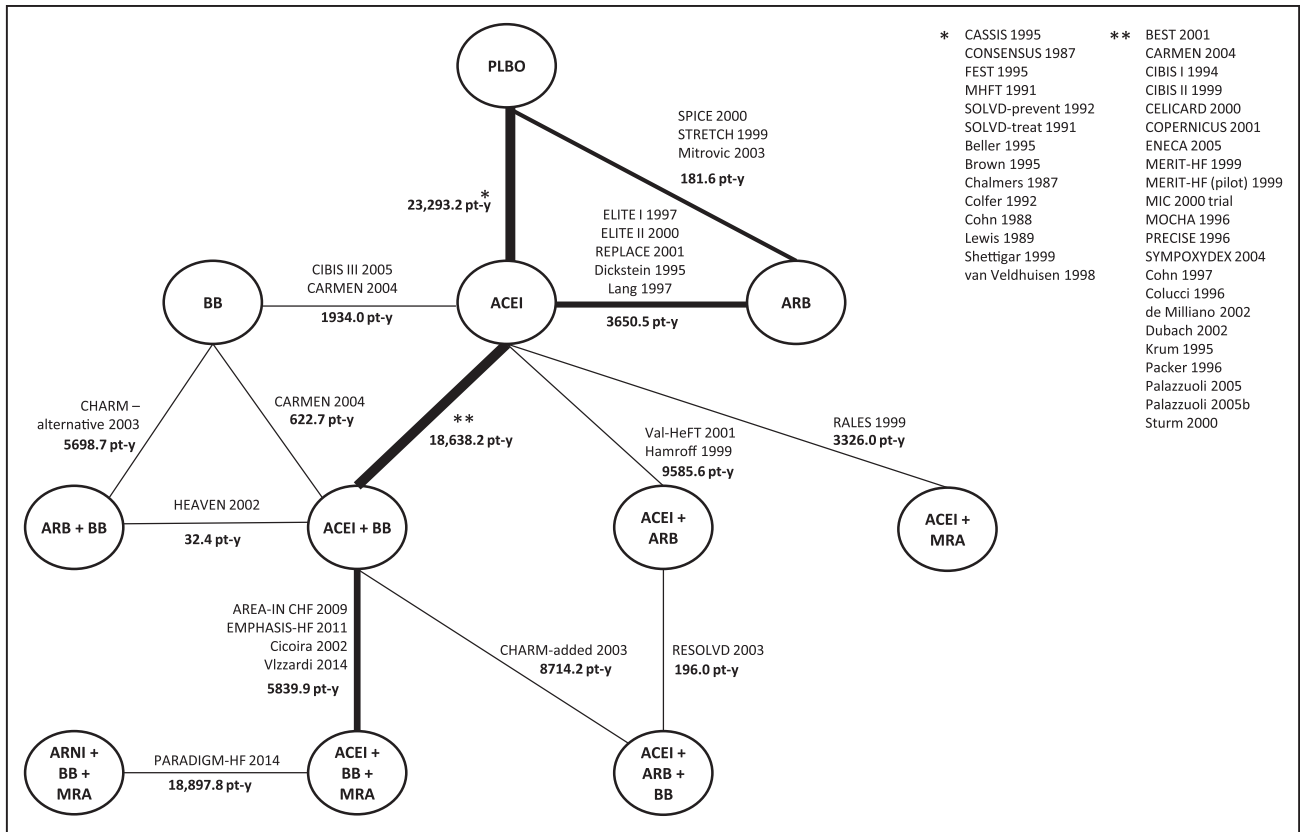**Figure 1.** Flow diagram. RCT indicates randomized controlled trials.

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; CAR-MEN, 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; CONSEN-SUS, 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 Inhibi-tors 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 Convert-ing 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, isch-emic versus nonischemic), and history of myocardial infarction.

Network Meta-Analysis
Bayesian NMA models were used to simultaneously synthesize the re-sults 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 refer-ence 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 complemen-tary log–log (cloglog) link was used to model the event rates.[10] Outputs from the model were presented as hazard ratios (HRs) for each treat-ment 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 100 000 burn-in iterations followed by 200 000 iterations).

Results of the NMA reflect the posterior distributions of the mod-el parameters. In addition to point estimates of the HRs, 95% credible intervals (CrI), reflecting the range of true underlying effects with
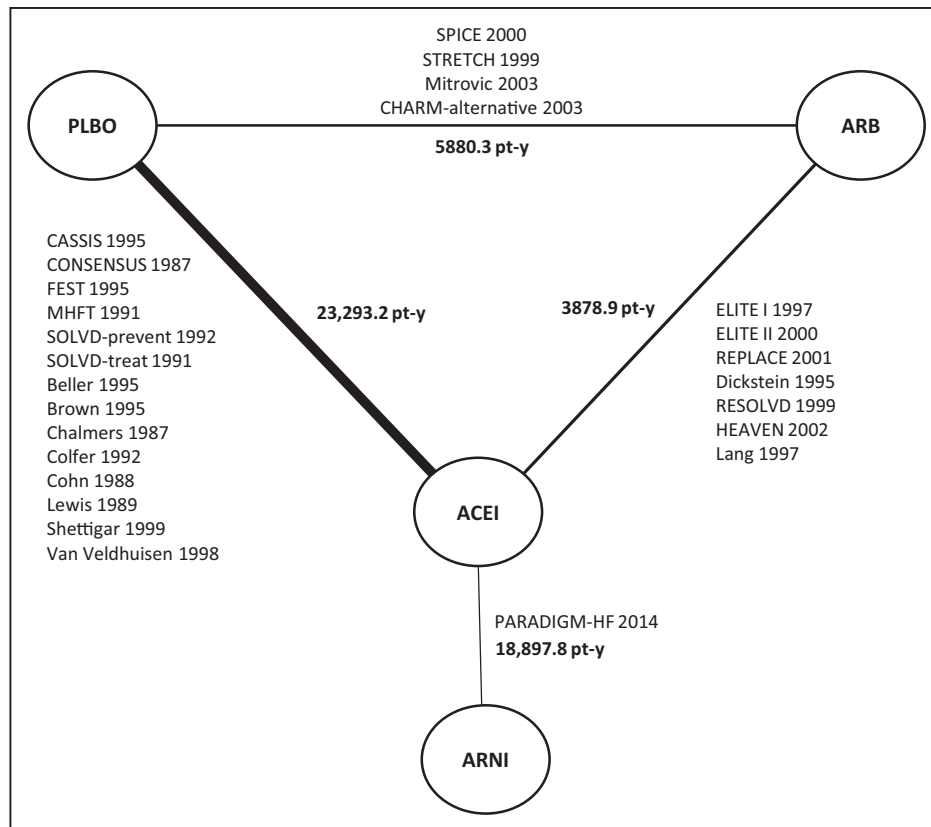
Figure 3. Sensitivity analysis evidence network of ARNI, ACEI, ARB and placebo for all-cause mortality ignoring background treatments. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CASSIS, Czech and Slovak 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
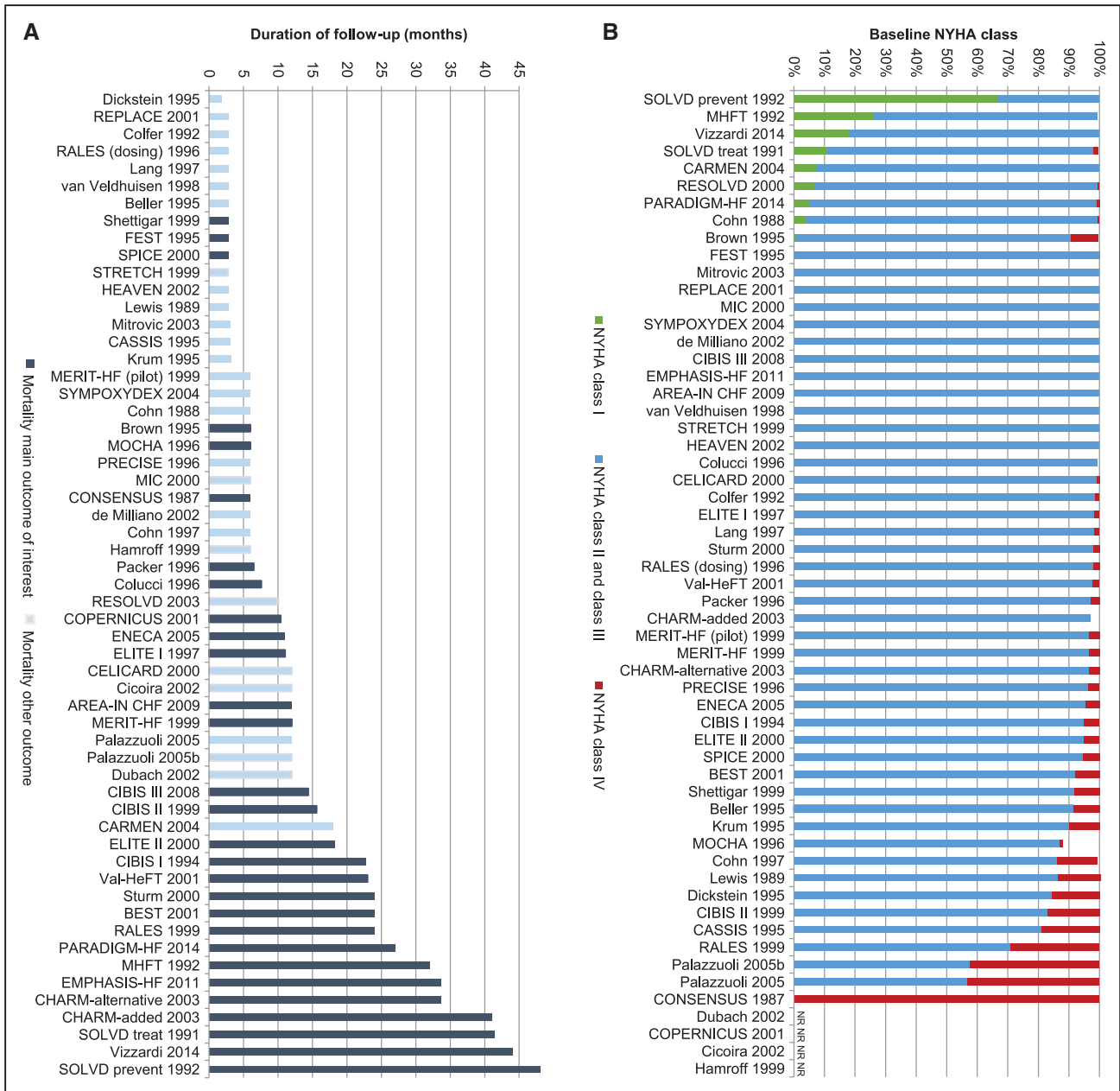

Figure 4. Distribution of potential treatment effect modifiers: **A**, Duration of follow-up[7,21–77]; **B**, NYHA class at baseline[7,21–77]; **C**, LVEF at baseline.[7,21–77] AREA-IN CHF indicates Anti-Remodelling Effect of Canrenone in Patients With Mild Chronic Heart Failure; BEST, Beta-Blocker Evaluation 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*)
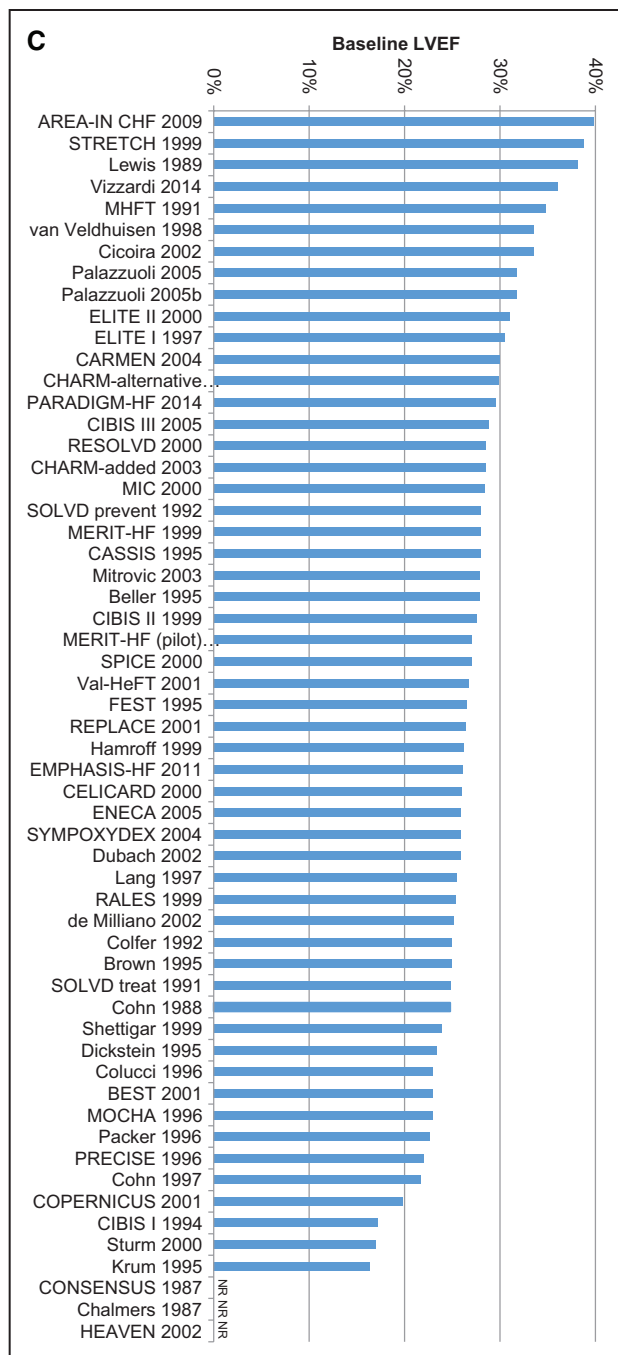
Figure 4 Continued. Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PRECISE, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RALES, Randomized 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.
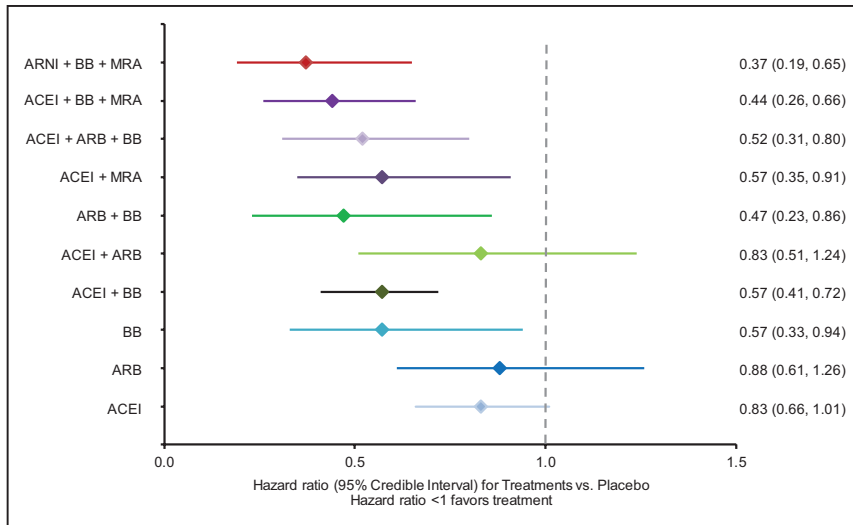
Figure 5. Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin 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.