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CLINICAL RESEARCH

A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction

Jasper Tromp, MD, PhD,[a,b,c,*] Wouter Ouwerkerk, PhD,[b,d,*] Dirk J. van Veldhuisen, MD, PhD,[a] Hans L. Hillege, MD, PhD,[a] A. Mark Richards, MBChB, PhD,[e,f,g] Peter van der Meer, MD, PhD,[a] Inder S. Anand, MD,[h] Carolyn S.P. Lam, MBBS, PhD,[a,b,c] Adriaan A. Voors, MD, PhD[a]

ABSTRACT

OBJECTIVES This study sought to estimate and compare the aggregate treatment benefit of pharmacological therapy for heart failure (HF) with reduced ejection fraction.

BACKGROUND The estimated treatment effects of various combinations of contemporary HF medical therapies are not well characterized.

METHODS We performed a systematic network meta-analysis, using MEDLINE/EMBASE and the Cochrane Central Register of Controlled Trials for randomized controlled trials published between January 1987 and January 2020. We included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers (BB), mineralocorticoid receptor antagonists (MRAs), digoxin, hydralazine-isosorbide dinitrate, ivabradine, angiotensin receptor–neprilysin inhibitors (ARNi), sodium glucose cotransporter-2 inhibitors (SGLT2i), vericiguat, and omecamtiv-mecarbil. The primary outcome was all-cause death. We estimated the life-years gained in 2 HF populations (BIOSTAT-CHF [BIOlogy Study to TAilored Treatment in Chronic Heart Failure] and ASIAN-HF [Asian Sudden Cardiac Death in Heart Failure Registry]).

RESULTS We identified 75 relevant trials representing 95,444 participants. A combination of ARNi, BB, MRA, and SGLT2i was most effective in reducing all-cause death (HR: 0.39; 95% CI: 0.31-0.49); followed by ARNi, BB, MRA, and vericiguat (HR: 0.41; 95% CI: 0.32-0.53); and ARNi, BB, and MRA (HR: 0.44; 95% CI: 0.36-0.54). Results were similar for the composite outcome of cardiovascular death or first hospitalization for HF (HR: 0.36; 95% CI: 0.29-0.46 for ARNi, BB, MRA, and SGLT2i; HR: 0.44; 95% CI: 0.35-0.56 for ARNi, BB, MRA, and omecamtiv-mecarbil; and HR: 0.43; 95% CI: 0.34-0.55 for ARNi, BB, MRA, and vericiguat). The estimated additional number of life-years gained for a 70-year-old patient on ARNi, BB, MRA, and SGLT2i was 5.0 years (2.5-7.5 years) compared with no treatment in secondary analyses.

CONCLUSIONS In patients with HF with reduced ejection fraction, the estimated aggregate benefit is greatest for a combination of ARNi, BB, MRA, and SGLT2i. (J Am Coll Cardiol HF 2022;10:73–84)

From the [a]University Medical Centre Groningen, Department of Cardiology, University of Groningen, the Netherlands; [b]Saw Swee Hock School of Public Health and National University of Singapore and National University Health System, Singapore; [c]Duke-NUS Medical School Singapore, Singapore; [d]Department of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam Infection and Immunity Institute, Amsterdam, the Netherlands; [e]Cardiovascular Research Institute, Yong Loo-Lin School of Medicine, National University of Singapore, Singapore; [f]National University Heart Centre, Singapore; [g]Christchurch Heart Institute, University of Otago, Christchurch, New Zealand; and the [h]Veterans Affairs Medical Center, Minneapolis, Minnesota, USA.
*Drs Tromp and Ouwerkerk contributed equally to this work and are co-first authors.

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ABBREVIATIONS AND ACRONYMS

ACEi = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

ARNi = angiotensin receptor-neprilysin inhibitor

CV = cardiovascular

H-ISDN = hydralazine-isosorbide dinitrate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HHF = hospitalization for heart failure

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

NYHA = New York Heart Association

SGLT2i = sodium glucose cotransporter-2 inhibitors

Heart failure (HF) remains a major cause of mortality and hospitalization globally, despite advances in pharmacological treatment (1). Successes of early clinical trials established angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs) as the foundation for the pharmacological treatment of HF with reduced ejection fraction (HFrEF) (2,3). In the last decade, treatment options for HFrEF increased with the addition of sacubitril/valsartan (ARNi) and ivabradine (4,5). Results of trials published in the past year showed that treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) empagliflozin (6) and dapagliflozin (7–9), soluble guanylase cyclase stimulator vericiguat (10), and cardiac-specific myosin activator omecamtiv-mecarbil (11) can further improve outcomes in HFrEF.

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Continued success in treatment of HFrEF has led to important challenges for clinicians who are left with multiple effective treatment options for their patients (12,13). Earlier trials were performed largely sequentially—showing incremental benefit of novel pharmacological therapy on top of existing treatment—but recent trials were performed in parallel (6,8,10,11). Results of more recent trials cannot guide sequencing of therapy or determine the most beneficial combination of pharmacotherapy. Network-meta-analyses allow for comparisons between different combinations of therapies to compare differences in the aggregate treatment effects. Information on the optimal cumulative benefit of treatment can help physicians and patients in their shared decision for therapy. An underlying assumption is that therapies have an additive effect. This is plausible for ARNi, SGLT2i, vericiguat, and omecamtiv-mecarbil, because they potentially target different disease pathways. Therefore, we conducted a systematic review and network meta-analysis to estimate and compare the aggregate treatment benefit of pharmacological therapy for HFrEF.

METHODS

PROTOCOL. The protocol used for the current systematic review and network meta-analysis is included in the Supplemental Appendix.

STUDY DESIGN. A systematic review and network meta-analysis was performed with a frequentist statistical approach, based on a prespecified study protocol (Supplemental Appendix). Results of the present study are reported according to the PRISMA extension statement for network meta-analysis (14).

SEARCH STRATEGY, SELECTION CRITERIA, AND DATA EXTRACTION. We performed a systematic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials published between 1987 and January 1, 2021. The systematic search strategy and search terms are documented in the Supplemental Appendix.

We considered randomized clinical trials investigating the effects of the main drug groups recommended for HFrEF or those that have recently shown to improve clinical outcomes in HFrEF. Pharmacological agents considered included digoxin, isosorbide dinitrate and hydralazine (H-ISDN), ACEi, ARB, BB, MRA, ivabradine, ARNi, SGLT2i, vericiguat, and omecamtiv-mecarbil. Target studies were limited to adult populations (aged ≥18 years) with HFrEF, enrolled in the outpatient setting or after stabilization following hospitalization for HF. Studies were excluded when the entire population included patients with a concomitant diagnosis that likely had a major effect on outcome (eg, patients with left ventricular dysfunction postmyocardial infarction, or trials only including patients with diabetes). Studies for treating patients in the acute phase of HF or comparing drugs within the same drug group were excluded.

Two investigators (J.T. and W.O.) screened titles and abstracts of retrieved citations independently to identify eligible trials. Full texts of retained citations were then independently screened by the same 2 investigators. Discrepancies were resolved by consensus at each step. Data from the final list of retained citations after full text review were extracted by the same 2 authors, who double-checked each other's work for inconsistencies.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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OUTCOMES. We focused on all-cause death as the primary outcome of interest, because older trials report this outcome more often, and this outcome has the least missing data. In addition, we analyzed a composite outcome of cardiovascular (CV) death and hospitalization for heart failure (HHF), CV death alone, and the likelihood of drug discontinuation because of any reason.

NETWORK META-ANALYSIS. We constructed network meta-analysis models using a frequentist framework. The statistical approach is derived from graph theoretical methods developed for electrical networks (15-18). Using this framework, we generated fixed and random effects models. We assessed the reduction in all-cause mortality and chances of discontinuation for the individual components of the network compared with placebo. Leveraging the fact that some treatments are combinations of common components, an additive component network meta-analysis model can be used to evaluate the influence of individual components. This model assumes that the effect of treatment combinations is the sum of the effects of its components (19,20). Therefore, in a network-meta-analysis we can compare different combinations of treatment based on the background therapy within a trial. Treatment combinations that are not included in the network cannot be compared. To perform a network meta-analysis, we need a connected network to make comparisons between different treatment combinations. Many of the early trials did not include a composite endpoint of CV death or HF hospitalizations. One of the earliest trials including such an outcome was Cardiac Insufficiency Bisoprolol Study (CIBIS) III, which was used as a reference for the analysis of the composite endpoint. We considered patients on background therapy if 50% of patients were on therapy. Given the low (<50%) use of ARNi in recent clinical trials, we considered these trials (6,8,10,11) in 2 scenarios as sensitivity analyses: 1) against a background of ARNi; and 2) against a background of ACEi. The primary results are presented against a background of ARNi; results against a background of ACEi are presented as sensitivity analyses and in the Supplemental Appendix. For the results, we report the HR for time to event analyses and OR for treatment discontinuation. Treatments were ranked using the surface under the cumulative ranking curve (SUCRA) score, also known as the P-Score (21). We used the confidence in Network Meta-Analysis (CINeMA) framework to evaluate confidence in the results (22). Briefly, the CINeMA framework considers 6 domains to assess confidence: 1) within-study bias; 2) reporting bias; 3) indirectness; 4) imprecision; 5) heterogeneity; and 6) incoherence. To assess within-study bias, we used the Cochrane tool classifying as "low," "medium," and "high" across 6 domains, including missing data, selective reporting, imbalanced dropout, similar groups at baseline, treatment allocation blinding, and allocation concealment and randomization (23). We used the average of all 6 domains to assess overall within-study bias—if more than 3 domains were considered high risk, the study was considered high risk, otherwise it was considered low risk. Reporting bias was formally tested using the Egger test, which assesses the symmetry of funnel plots (24). When this was found nonsignificant, we considered risk of reporting bias as "low." Indirectness, which captures transitivity in the network, was assessed as low based on published guidelines (25). Imprecision compares the treatment effects included in the 95% CI with the range of equivalence using clinically important effects as OR of 2.0. To assess heterogeneity, we calculated I^2 values. I^2 values are calculated using the chi-square statistic and its *df* and represent the amount of inconsistency in the network (26). The model used was determined by the degree of heterogeneity, with random effects favored in the presence of heterogeneity (I^2 >30%). Incoherence captures transitivity, which stipulates that 2 treatments can be compared indirectly via an intermediate treatment node. If estimates from direct and indirect evidence disagree, transitivity does not hold and there is incoherence within the network. Incoherence was assessed using a global test based on a random-effects design-by-treatment interaction model. In sensitivity analyses, we excluded hydralazine/nitrates and digoxin because of their low use and performed separate analyses restricting to studies with a minimum of 100 events. A nonsignificant *P* value means that there is no incoherence. The fixed effects network meta-analysis was performed using the *netmeta* package in R (R Foundation); P values < 0.05 were considered statistically significant.

ESTIMATION OF LIFE-YEARS GAINED. In secondary analyses, we estimated the absolute risk reduction and potential number of life-years gained in 2 HF populations with different treatment combinations: BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study and the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry. The designs of the BIOSTAT-CHF study and ASIAN-HF registry were published previously (27-29). In brief, BIOSTAT-CHF enrolled 2,516 adult patients with HF, of whom 2,100 had HFrEF (left ventricular ejection fraction [LVEF] ≤40%), across 69 participating centers in 11 European countries. The ASIAN-HF

registry was a multinational registry including 5,276 adult patients with HFrEF (LVEF ≤40%) from 46 sites across 11 regions in Asia. Inclusion criteria were comparable between studies: all patients had symptoms and signs of HF, had objective evidence of reduced LVEF, and were followed up for clinical outcomes of death and hospitalization. Ethics approvals were obtained from the local institutional review committee of each participating center, and all participating subjects gave informed consent.

To estimate the number of life-years free of death, we applied previously used actuarial (age-based) models (30). This method uses age as the time to event variable. We calculated nonparametric Kaplan-Meier estimates for overall life expectancy at every year of age using a life-table approach based on the area under the curve. Because none of the study medications showed a significant interaction with age, differences in survival curves are reflective of predicted event-free survival and residual survival (4,6,8,31). We accounted for differences in background therapy by estimating the treatment benefit for each treatment combination based on actual background therapy. For example, if a patient was on ACEi and BBs, the number of life-years for that patient estimated for ARNi, BB, MRA, and SGLT2i was determined against ACEi and BB. Second, we estimated the number of life-years gained on a patient level by estimating the additional benefit of different treatment combinations in the hypothetical scenario that the patient was on no treatment (placebo). All analyses were done using R, version 4.0.2.

ROLE OF THE FUNDING SOURCE. There was no funding source for the systematic review and network meta-analysis.

RESULTS

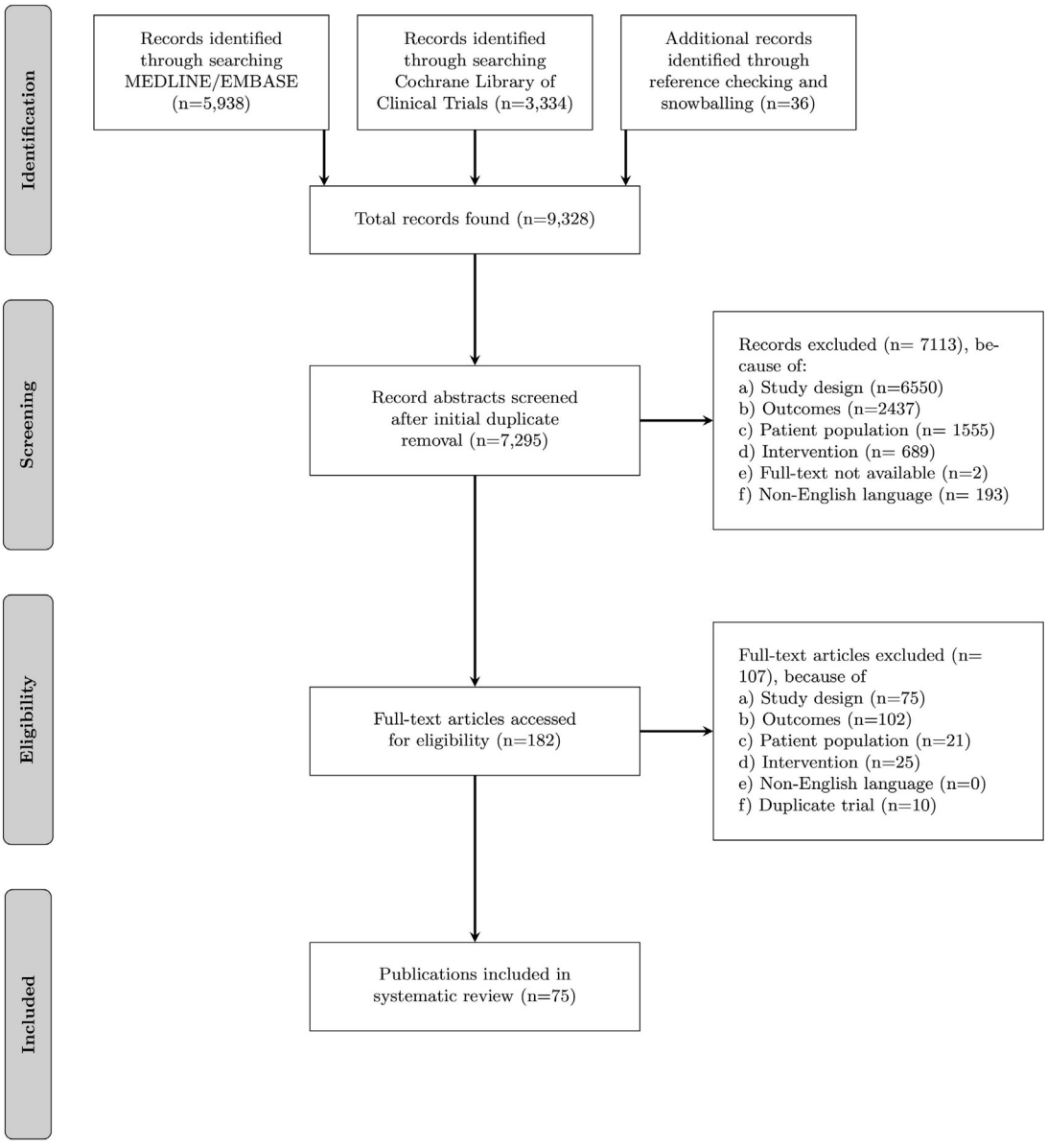
STUDY SELECTION. A systematic search identified a total of 9,328 records after exclusion of duplicates. After screening, 75 full-text papers were included. In total, these studies included 95,444 patients (23% women), and 199,978 participant years of follow-up (**Figure 1,** Supplemental Figure 1). Eleven studies included fewer than 100 patients, and 23 studies included more than 1,000 patients. The median follow-up duration was 11 months (25th-75th percentile 6-22 months). Age and LVEF were comparable among studies (Supplemental Figures 2 and 3). The majority of patients were in New York Heart Association (NYHA) functional class II across studies, except for patients in 3 studies who were predominantly in NYHA functional class III and IV (Supplemental Figure 4).

RISK OF BIAS AND PUBLICATION BIAS. Of the 75 studies included, overall risk of bias was low (Supplemental Figure 5): The majority of studies were multicenter, double-blind, placebo-controlled trials. The highest risk of bias was seen in 4 studies that were not double-blind (Supplemental Table 1). There was no evidence of systematic reporting bias for any of the outcomes (Supplemental Figure 6), ie, mortality (Egger test $P = 0.122$), the composite of CV mortality and HF hospitalization (Egger test $P = 0.267$), and CV death alone (Egger test $P = 0.283$). Indirectness was judged as low. The majority of comparisons did not show concerns of imprecision. Comparisons that showed major concerns of imprecision largely involved 2 single phase II studies investigating vericiguat (SOCRATES-Reduced [The Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study]) and omecamtiv-mecarbil (COSMIC-HF [Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure]) (Supplemental Table 2). Overall heterogeneity (I^2) among studies was 9.1% (range 0.0%-26.9%; $P = 0.55$) for all-cause death, 29.6% (range from 0.0%-68.6%; $P = 0.19$) for the composite of CV death or HHF, and 11% (range from 0.0%-41.0%; $P = 0.28$) for CV death. There was no evidence for incoherence found for any of the outcomes ($P > 0.10$ for all). The confidence rating of the majority of comparisons was considered high or moderate. Those comparisons with low confidence commonly involved results from the SOCRATES-Reduced and COSMIC-HF trials.

OUTCOMES. All-cause mortality was reported in 75 studies that enrolled 95,444 patients incurring a combined total of 17,684 events (Supplemental Table 3). **Figure 2A** shows that ARNi (HR: 0.75; 95% CI: 0.66-0.85) and MRA (HR: 0.76; 95% CI: 0.67-0.85) was associated with the largest reduction in all-cause death, followed by BB (HR: 0.78; 95% CI: 0.72-0.84), ACEi (HR: 0.89; 95% CI: 0.82-0.96), SGLT2i (HR: 0.88; 95% CI: 0.78-0.99), and ARB (HR: 0.95; 95% CI: 0.88-1.02). Vericiguat (HR: 0.94; 95% CI: 0.79-1.11) and omecamtiv-mecarbil (HR: 1.0; 95% CI: 0.92-1.09) did reduce the risk of all-cause death. **Figure 2B** shows that MRA (HR: 0.62; 95% CI: 0.54-0.72) was associated with the largest reduction in the composite outcome, followed by SGLT2i (HR: 0.70; 95% CI: 0.63-0.77).

Central Illustration A shows that the combination of ARNi, BB, MRA, and SGLT2i (HR: 0.39; 95% CI: 0.31-0.49) was most effective in reducing all-cause death relative to placebo. Supplemental Table 4 shows the ranking of different treatment combinations according to surface under the cumulative ranking curve P values. Supplemental Table 5 shows no significant

FIGURE 1 **Overview of Study Selection**

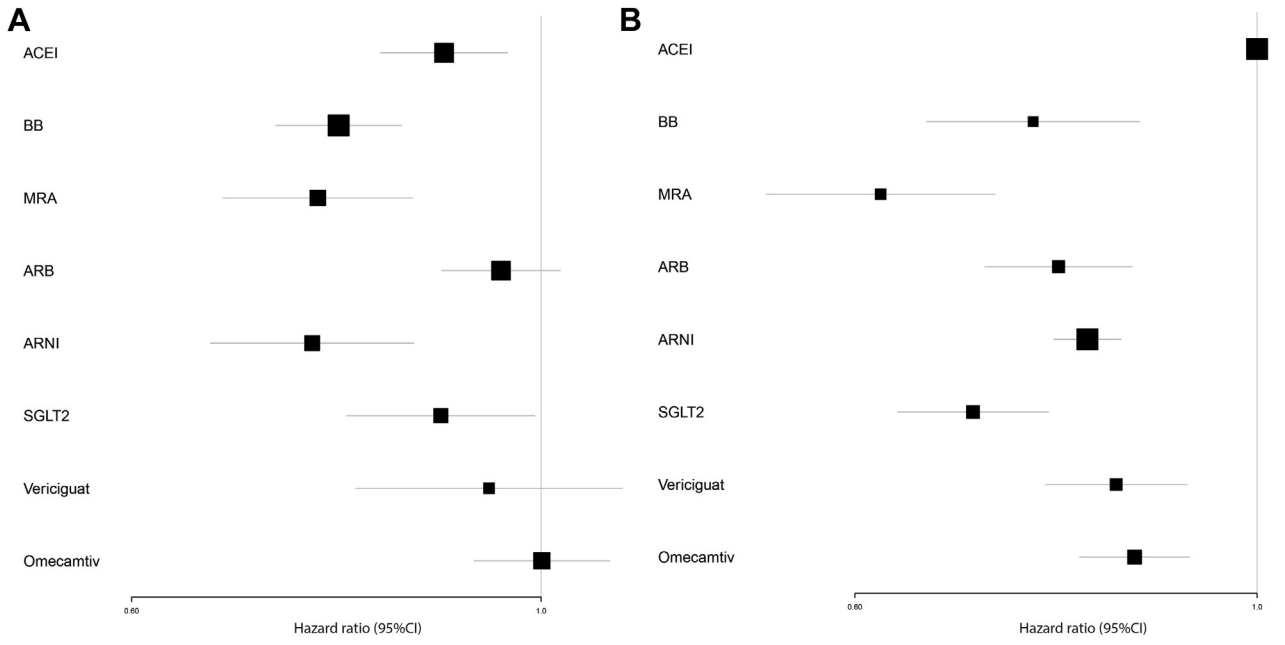


Schematic overview of study selection.

difference in the reduction of all-cause death among a combination of ARNi, BB, MRA, and SGLT2i; ARNi, BB, MRA, and vericiguat ($P = 0.562$); or ARNi, BB, MRA, and omecamtiv-mecarbil ($P = 0.088$). ARNi, BB, MRA, and SGLT2i was significantly more effective in reducing all-cause death than ARNi, BB, and MRA (HR: 0.88; 95% CI: 0.78-0.99; $P = 0.037$).

A total of 16 and 43 studies, respectively, reported a composite outcome of CV death and HHF or CV death alone. Supplemental Figures 7 and 8 show the networks of these secondary outcomes. A combination of ARNi, BB, MRA, and SGLT2i was most effective in reducing the composite outcome compared with ACEi alone (HR: 0.36; 95% CI: 0.29-0.46) (**Central Illustration B**), and compared with the second-best combination of ARNi, BB, MRA, and vericiguat (HR: 0.82; 95% CI: 0.66-0.1.01; $P = 0.061$) (Supplemental Table 6), and ARNi, BB, MRA and omecamtiv-mecarbil (HR: 0.81; 95% CI: 0.66-0.1.00; $P = 0.049$). There was no significant difference between the

FIGURE 2 Forest Plots Showing the Relative Risk Reduction Against Placebo



Forest plots showing the relative risk reduction for all-cause mortality **(A)**, and CV death or hospitalization for HF vs ACEi **(B)**. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium glucose cotransporter-2.

combination of ARNi, BB, MRA, and vericiguat and ARNi, BB, MRA, and omecamtiv-mecarbil in reducing the composite outcome.

Central Illustration C shows that the combination of ARNi, BB, MRA, and SGLT2i was most effective in reducing CV death (HR: 0.33; 95% CI: 0.26-0.43), followed by ARNi, BB, MRA, and vericiguat (HR: 0.35; 95% CI: 0.26-0.47) and ARNi, BB, MRA, and omecamtiv-mecarbil (HR: 0.36; 95% CI: 0.27-0.46), without a significant difference between the 3 combinations ($P > 0.10$ for both, Supplemental Table 7).

DRUG DISCONTINUATION. Drug discontinuation was reported in 58 studies. Supplemental Figure 9 shows the network. There was considerable heterogeneity in the network (60.7%; range 47.0%-70.9%; $P < 0.001$); therefore, a random effects model was used. There was no evidence for publication bias (Eggers test $P = 0.726$). In total, 9,451 patients discontinued pharmacotherapy. Compared with placebo, the risk of discontinuation was lower for ACEi (OR: 0.89; 95% CI: 0.82-0.96) and ARNi (OR: 0.77; 95% CI: 0.67-0.93), but higher for ARB (OR: 1.2; 95% CI: 1.07-1.36). There were no differences between the remaining drug classes compared with placebo ($P > 0.05$ for all), Supplemental Figure 10).

SENSITIVITY ANALYSES. In sensitivity analyses considering SGLT2i, vericiguat, and omecamtiv-mecarbil against a background of ACEi instead of ARNi, results were comparable. ACEi, BB, MRA, and SGLT2i was numerically more effective in reducing all-cause death (HR: 0.44; 95% CI: 0.37-0.54), than ACEi, BB, MRA, and vericiguat (HR: 0.49; 95% CI: 0.39-0.62) and ACEi, BB, MRA, and omecamtiv-mecarbil (HR: 0.52; 95% CI: 0.43-0.63) (Supplemental Figure 11). Results remained similar when excluding hydralazine/nitrates and digoxin (Supplemental Figure 12). When restricting our analyses to trials with a minimum of 100 events, results remained similar (Supplemental Figure 13).

ESTIMATED LIFE-YEARS GAINED. We estimated survival in 7,376 patients with HFrEF in the BIOSTAT-CHF and ASIAN-HF study who were treated with ACEi and BB. Median age was 63 years (IQR: 54-72 years), 1,664 (23%) were women, 2,904 (43%) were NYHA functional class III/IV. Over a median follow-up of 22 months (IQR: 12-25 months), 1,287 (19%) participants died. A more detailed description of the characteristics and event rates of the separate studies can be found in Supplemental Table 8).

At baseline, 5,691 (77%) patients were on ACEi/ARB, 6,018 (82%) on BB, and 4,093 (55%) on MRA.

Compared with actual care, the estimated life-years gained at age 50 years when all patients were treated with ARNi, BB, MRA, and SGLT2i was 4.9 years (95% CI: 1.4-8.4 years), and 3.3 years (95% CI: 0.7-5.8 years) in a 70-year-old patient (**Figure 3,** Supplemental Table 9). Compared with estimated placebo (no treatment), the aggregate treatment effect of ARNi, BB, MRA, and SGLT2i was 7.9 life-years (95% CI: 4.7-11.2 life-years) gained for a 50-year-old and 5.0 life-years (95% CI: 2.5-7.5 life-years) gained for a 70-year-old (Supplemental Table 10). Life-years gained of other combinations are described in **Figure 3**. The difference between no treatment and comprehensive treatment for all ages was similar between ASIAN-HF and BIOSTAT-CHF.

DISCUSSION

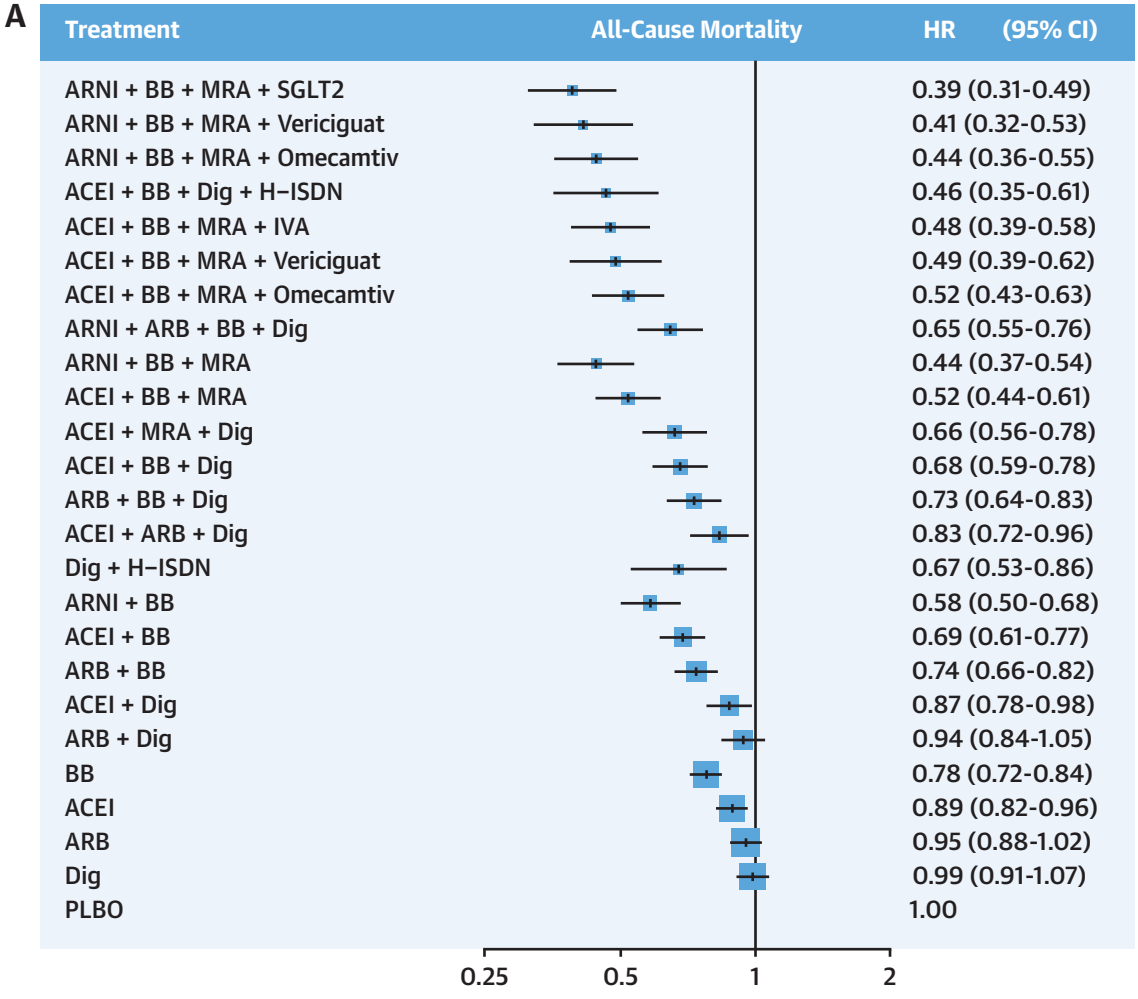
In the most comprehensive network-meta-analysis on pharmacotherapy for HFrEF to date, we found that the combination of ARNi, BB, MRA, and SGLT2i was most effective in improving outcomes among therapy combinations. In secondary analyses, the combination of ACEi, BB, MRA, and SGLT2i, when compared with no treatment, was estimated to extend the number of life-years for a 70-year-old by as much as 5.0 years in 2 independent cohorts. Results of this study support the concept of treating patients with a combination of ARNi, BB, MRA, and SGLT2i as first-choice therapy, and highlight its significant benefit.

Current guidelines for HF recommend starting with ACEi/ARB as first-line treatment (2,3). In our analyses, ARNi showed a smaller HR for all-cause mortality than ACEi/ARB and a lower risk for discontinuation compared with placebo. Therefore, our results support starting with ARNi as first-line therapy rather than ACEi or ARB (32). A combination of ARNi, BB, MRA, and SGLT2i demonstrated the greatest reduction in risk for all-cause death and composite of CV death or HHF compared with the same combination replacing SGLT2i by vericiguat or omecamtiv-mecarbil. The substantial combined survival benefit of comprehensive therapy for HFrEF compared with single pharmacological agents advocates for early initiation of comprehensive treatment over sequencing of single agents with titration to target dosages. There were no differences between the combination of ARNi, BB, MRA, and vericiguat or of ARNi, BB, MRA, and omecamtiv-mecarbil in reducing any of the outcomes. Notably, a combination of H-ISDN on top of ACEi and BB significantly reduced the risk of CV death and HHF in our analyses. H-ISDN can therefore be considered in symptomatic patients after treatment with ARNi, BB, MRA, and SGLT2i. However, these results were primarily based on a single trial enrolling self-identified Blacks (33). It is, therefore, difficult to assess how these findings translate to patients of other ethnicities.

Our analyses on patients from large multiethnic HF registries found that comprehensive pharmacological therapy (ARNi, BB, MRA, and SGLT2i) can collectively extend life-expectancy in HFrEF by 7.9 years in a 50-year-old and by 5.0 years in a 70-year-old patient compared with no treatment. This confirms results from a cross-trial analysis combining data from EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortalilty and morbidity in Heart Failure) trial, and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), which estimated 6.3 years of survival compared with ACEi/ARB and BB in a 55-year-old (34). The estimated treatment benefit of quadruple therapy in our study is also in line with an earlier study estimating that quadruple therapy in the United States can reduce the mortality risk by 73% (35). Importantly, we extend on these analyses by the following: 1) including more treatment combinations; 2) including estimates from more randomized controlled clinical trials; 3) estimating life-years gained in HFrEF populations with global representation; and 4) having consistent results in 2 independent cohorts.

Three previous network meta-analyses evaluated pharmacotherapy in HFrEF (36-38). Two of these earlier studies were performed before the advent of SGLT2i, vericiguat, and omecamtiv-mecarbil, and did not include data on H-ISDN and digoxin (36,37). A recent network meta-analysis evaluated PARADIGM-HF, VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction), DAPA-HF, and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction)-Reduced (38). This study only included 6 trials, and did not include GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure). Our analyses extend these studies by the following: 1) including more comprehensive data on pharmacological treatment for HFrEF including H-ISDN, digoxin, SGLT2i, vericiguat, and omecamtiv-mecarbil; and 2) estimating the aggregate treatment effect in 2 large and well-phenotyped HF cohorts with global representation. Estimating the aggregate treatment benefit is important to guide shared decision-making for

CENTRAL ILLUSTRATION **Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure**



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Combination of treatment effect on all-cause mortality **(A)**, cardiovascular (CV) death or heart failure (HF) hospitalization **(B)**, or CV mortality **(C)**. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; Dig = digoxin; H-ISDN = hydralazine-isosorbide dinitrate; HF = heart failure; IVA = ivabradine; MRA = mineralocorticoid receptor antagonist; PLBO = placebo; SGLT2 = sodium glucose cotransporter-2 inhibitors.

Continued on the next page

patients and doctors, especially in the presence of polypharmacy.

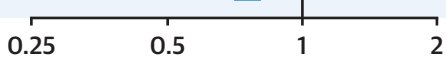
The increase in life-expectancy after comprehensive pharmacological treatment for HFrEF is substantial, especially compared with more expensive therapies for other diseases (34). For example, treatment with a PCSK9-inhibitor in a 51-year-old patient will extend life expectancy by an estimated 1.1 years, but would cost approximately 10 times the costs per quality-adjusted life year compared with the previously mentioned novel HF therapies (39,40). Together, these results highlight the substantial number of life-years saved with comprehensive medical therapy for HFrEF, at a cost which is likely lower per number of life-years saved compared with commonly used treatment for patients with diseases that carry a similarly worse prognosis.

STUDY STRENGTHS AND LIMITATIONS. Although the results of this study support treatment with a

CENTRAL ILLUSTRATION Continued

B

Treatment	CV Mortality or HF Hospitalization	HR (95% CI)
ARNI + BB + MRA + SGLT2		0.36 (0.29-0.46)
ARNI + BB + MRA + Vericiguat		0.43 (0.34-0.55)
ARNI + BB + MRA + Omecamtiv		0.44 (0.35-0.56)
ACEI + BB + MRA + IVA		0.49 (0.39-0.61)
ACEI + BB + MRA + Vericiguat		0.54 (0.43-0.67)
ACEI + ARB + BB + Dig		0.73 (0.62-0.85)
ARNI + BB + MRA		0.47 (0.38-0.58)
ACEI + BB + MRA		0.58 (0.47-0.71)
ARB + BB		0.65 (0.55-0.77)
ARNI + BB		0.68 (0.58-0.79)
ACEI + BB		0.84 (0.73-0.96)
ACEI + BB + Dig		0.84 (0.73-0.96)
ACEI + Dig		1.00
BB		0.75 (0.65-0.87)



C

Treatment	CV Mortality	HR (95% CI)
ARNI + BB + MRA + SGLT2		0.33 (0.26-0.43)
ARNI + BB + MRA + Vericiguat		0.35 (0.26-0.47)
ARNI + BB + MRA + Omecamtiv		0.36 (0.27-0.46)
ACEI + BB + MRA + IVA		0.43 (0.35-0.54)
ACEI + BB + MRA + Vericiguat		0.44 (0.33-0.57)
ACEI + BB + MRA + Omecamtiv		0.44 (0.35-0.56)
ACEI + BB + Dig + H–ISDN		0.57 (0.37-0.88)
ARNI + BB + MRA		0.38 (0.31-0.47)
ACEI + BB + MRA		0.47 (0.39-0.57)
ACEI + ARB + BB + Dig		0.57 (0.47-0.70)
ACEI + MRA + Dig		0.62 (0.52-0.74)
ACEI + BB + Dig		0.65 (0.56-0.76)
ACEI + BB		0.64 (0.56-0.73)
ARB + BB		0.68 (0.59-0.78)
ACEI + Dig		0.84 (0.75-0.96)
Dig + H–ISDN		0.88 (0.58-1.34)
ARB + Dig		0.89 (0.78-1.02)
BB		0.77 (0.70-0.85)
ACEI		0.83 (0.76-0.91)
ARB		0.88 (0.80-0.98)
PLBO		1.00
Dig		1.01 (0.93-1.10)

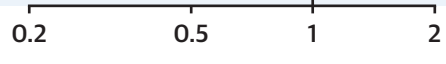
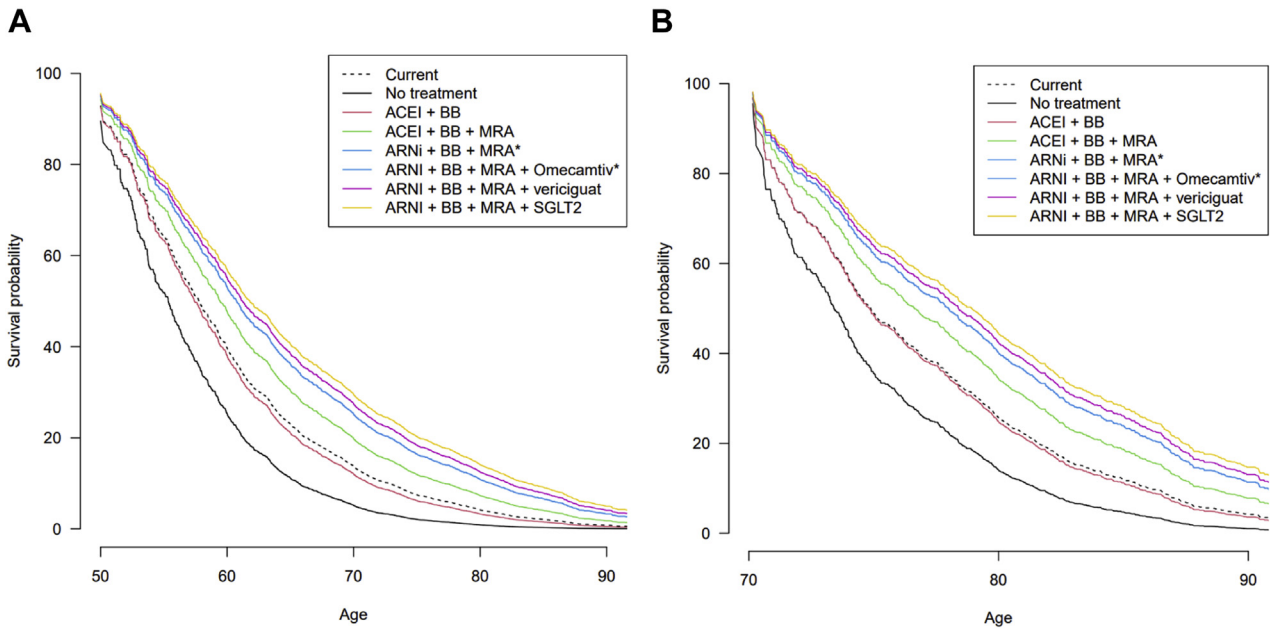


FIGURE 3 Estimated Average Lifetime Graphs



Estimated average lifetime benefit for selected treatment combinations in BIOSTAT-CHF and ASIAN-HF at age 50 years **(A)** and age 70 years **(B)**. Survival curves overlap for combinations with a *. Abbreviations as in Figure 2.

combination of ARNi, BB, MRA and SGLT2i, we were not able to assess the aggregate treatment effect of vericiguat or omecamtiv-mecarbil on top of SGLT2i. ARNi was used by fewer than 50% of the populations in the recent trials. We performed sensitivity analyses substituting ARNi by ACEi in the different treatment combinations, which showed similar results between combinations including SGLT2i, vericiguat, and omecamtiv-mecarbil. We did not account for differences in drug dosages in our NMA. The choice to estimate the aggregate treatment effect of SGLT2i, vericiguat, and omecamtiv-mecarbil on top of ARNi is further supported by the absence of significant interactions between treatment with ARNi and the study drug in the individual trials (9-11). Our estimated risk reduction with ARNI, BB, MRA, and SGLT2i compared with ACEi/BB and projected life years gained is similar to a previous report using patient level estimates (34). Importantly, ARNi, SGLT2i, vericiguat, and omecamtiv-mecarbil target different disease pathways (13). The analyses used to estimate the lifetime treatment benefit assume that adherence to treatment persists over time. Although estimations of the effects of some agents (eg, omecamtiv-mecarbil, vericiguat) were based on single large phase III trials, large confirmatory phase III follow-up trials for these agents are unlikely. Therefore, our analyses represent the best available estimates. The timespan over which different HF trials have been performed is substantial, which might have introduced bias. Yet, *P* values for heterogeneity for the primary and many secondary outcomes were nonsignificant, suggesting that this might not have meaningfully affected our results. The results for discontinuation showed considerable heterogeneity, despite the use of a random effects model. This might be caused by differences in definition of discontinuation. Therefore, these results should be interpreted with caution. Last, we did not take nonpharmacological device use into account, which can affect estimation of treatment benefit.

CONCLUSIONS

Together, results of this comprehensive network meta-analysis support treatment of patients with HFrEF with a combination of ARNi, BB, MRA, and SGLT2i. The expected number of life-years gained with this and other combinations is considerable.

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Dr Tromp is supported by the National University of Singapore Start-up Grant; and has received consultancy fees from Olink proteomics and Roche Diagnostics; and served as a scientific advisor and shareholder of Us2.ai. Dr Richards has received consultancy/advisory board/speaker fees, research grants, and/or support in kind from Roche Diagnostics, Abbott Laboratories, Thermo Fisher, AstraZeneca, Novartis, Medtronic, and Boston Scientific. Dr van der Meer has received consultancy and/or research grants from Vifor Pharma, AstraZeneca, Servier, Novartis, Pfizer, and Ionis. Dr Anand has received consultancy fees from Amgen, ARCA, AstraZeneca, Boehringer Ingelheim, Boston Scientific, LivaNova, Novartis, Rockwell Medical, and Zensun. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the advisory board/steering committee/executive committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research and Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd, and Corpus; and serves as cofounder and non-executive director of Us2.ai. Dr Voors has received consultancy fees and/or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novartis, Novo Nordisk, and Roche Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Carolyn S.P. Lam, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609. E-mail: Carolyn.lam@duke-nus.edu.sg. OR Dr Adriaan A. Voors, University Medical Centre Groningen, Department of Cardiology, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands. E-mail: A.A.Voors@umcg.nl. Twitter: @drjasper01, @AdriaanVoors, @lamcardio.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present network meta-analysis demonstrated that a combination of ARNi, BB, MRA and SGLT2i was most effective in reducing the risk of all-cause mortality and a combined outcome of CV death or hospitalization for HF in patients with HFrEF.

TRANSLATIONAL OUTLOOK: Treatment of patients with HFrEF with a combination of ARNi, BB, MRA, and SGLT2i can extend the number of life years of a 70-year-old by an average of 5 years. Therefore, every effort should be made to treat patients with comprehensive pharmacological therapy.

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KEY WORDS heart failure, network meta-analysis, pharmacotherapy

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.