Circulation: Heart Failure

ORIGINAL ARTICLE

Network Meta-Analysis of Quality of Life in Heart Failure With Reduced Ejection Fraction

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BACKGROUND: Although the effects of various combinations of treatments on mortality and morbidity outcomes in heart failure with reduced ejection fraction (HFrEF) have been evaluated, the impact on quality of life is unknown. This study evaluated and compared the composite impact of pharmacological therapies on quality of life in HFrEF using a frequentist network meta-analysis and systematic review methodology.

METHODS: We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for randomized controlled trials published between January 1, 2021 and August 10, 2024. We included all contemporary and efficacious HFrEF therapies used in adults. The primary outcome was change in quality of life measured through the Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure Questionnaire, expressed as mean difference (MD).

RESULTS: We identified 41 randomized controlled trials representing 41 145 patients (76.5% male). The trials had a median of 276 participants (105–464), a mean left ventricular ejection fraction of 28%, and a median follow-up time of 5 months (3–8). A combination of angiotensin receptor blocker/neprilysin inhibitors (ARNi)+β-blockers (BB)+sodium-glucose cotransporter 2 inhibitors (SGLT2i; MD, +5.3 [+0.4, +10.3]) was the most effective at improving quality of life followed by ARNi+BB+mineralocorticoid receptor antagonists (MRA)+SGLT2i (MD, +7.1 [−1.0 to +15.2]), ACE inhibitor+BB+MRA+SGLT2i (MD, +5.3 [−2.6, to +13.3]), and ACE inhibitor+BB+MRA+ivabradine (MD, +5.2 [−3.1 to +13.6]), which were not statistically significant. Individually, the most effective treatments for improving quality of life were SGLT2i (MD, +3.4 [+1.4 to +5.30]), ivabradine (MD, +3.3 [+0.1 to +6.4]), ARNi (MD, +2.6 [−3.2 to +8.5]), and MRA (MD, +1.8 [−4.8 to +8.4]).

CONCLUSIONS: A composite of ARNi+BB+SGLT2i or ARNi+BB+MRA+SGLT2i was the most effective at improving quality of life in patients with HFrEF.

Key Words: angiotensin-converting enzyme inhibitors ■ drug therapy ■ heart failure ■ ivabradine ■ quality of life

Heart failure (HF) affects >50 million people globally and is associated with frequent hospital and emergency department visits, reduced health-related quality of life (HRQoL), and high mortality rates.[1–5] There are a growing number of pharmacological treatments available for HF with reduced ejection fraction (HFrEF), such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), β-blockers (BB), mineralocorticoid receptor antagonists (MRAs), digoxin, hydralazine–isosorbide dinitrate (H-ISDN), ivabradine, angiotensin receptor–neprilysin inhibitors (ARNi), sodium-glucose cotransporter 2 inhibitors (SGLT2i), vericiguat, and omecamtiv mecarbil, allowing for differing combinations of medications. Individual medications have been tested additively, with each successive medication demonstrating a reduction in a primary end point (typically a decrease in the risk of mortality and hospitalization). Current guidelines recommend the initiation and uptitration of an ARNi or ACE inhibitor or ARB, together with a BB, MRA, and

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WHAT IS NEW?

- This network meta-analysis of 41 studies representing 41 145 patients affirmed that guideline-directed medical therapy consisting of angiotensin receptor blocker/neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors resulted in the greatest improvement in quality of life, with sodium-glucose cotransporter 2 inhibitors having the greatest individual impact on quality of life improvement.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Guideline-directed medical therapy should be provided to increase the quality of life of patients with heart failure with reduced ejection fraction. The impact of adding other medications such as ivabradine and vericiguat should be further explored on a patient-to-patient basis.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blockers
ARNi	angiotensin receptor blocker/neprilysin inhibitors
BB	β-blockers
EF	ejection fraction
GDMT	guideline-directed medical therapy
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
H-ISDN	hydralazine–isosorbide dinitrate
HRQoL	health-related quality of life
KCCQ	Kansas City Cardiomyopathy Questionnaire
MLHFQ	Minnesota Living With Heart Failure Questionnaire
MRA	mineralocorticoid receptor antagonists
RCT	randomized controlled trial
SGLT2i	sodium-glucose cotransporter 2 inhibitors

SGLT2i referred to as guideline-directed medical therapy (GDMT).[4,5]

Although several systematic reviews and meta-analyses have previously shown the individual effects of various classes of drugs used to treat HFrEF on HRQoL, there has not yet been an assessment that has compared available treatment combinations.[5–20] As a recent systematic review and network meta-analysis of pharmacological treatment effects on patient outcomes in HFrEF has shown evidence for the additive nature of these medications, evaluating the treatment effect of these combinations on HRQoL is feasible.[21] Because most patients with HFrEF are prescribed medications of various classes, understanding the effect of different combinations and determining the most effective treatment for improving HRQoL would support patients and physicians in achieving patient goals.[22] Accordingly, we conducted a systematic review and network meta-analysis to estimate and compare the impact of pharmacological therapies, individually and in combination, in patients with HFrEF.

METHODS

The detailed prespecified protocol for this study can be found in the Supplemental Material. This study is a meta-analysis and, as such, we are not required to seek approval from an institutional review board. The authors declare that all supporting data are available within the article and the Supplementary Material.

Study Design

We performed a systematic review and network meta-analysis using a frequentist framework. The study results are reported according to the PRISMA extension statement for systematic reviews incorporating network meta-analyses.

Search Strategy, Eligibility and Selection Criteria, and Data Collection

We systematically searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials published between January 1, 2021 and August 10, 2024. The full search terms and strategy details are outlined in the Supplemental Material.

We evaluated randomized controlled trials that investigated the effects of GDMTs and other drugs in patients with HFrEF. Target studies were limited to adults (aged ≥18 years) with HFrEF, enrolled in the outpatient setting or after stabilization after hospitalization for HF who were assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) or the Minnesota Living With HF Questionnaire (MLHFQ) as these are reliable assessment tools which are most prevalent in contemporary clinical trials.[23–25] Details of the exclusion criteria, screening and data collection process used are outlined in the Supplemental Material. Our meta-analysis adhered to Cochrane Group best practices, including data imputation. As SDs of changes from baseline HRQoL were often absent, we imputed missing SDs from a matched study considering measurement scale, study duration, and sample size.

Outcomes

The primary outcome of interest was the change in health-related HRQoL, assessed as the KCCQ Overall Summary Score (OSS) and the MLHFQ overall score, as these are the most comprehensive and commonly recorded score domains. The quality of life scores from studies using the KCCQ or MLHFQ were converted to a common overall score on the KCCQ scale based on a relevant clinical improvement conversion regression formula (MLWHF change=KCCQ OSS change×[−0.74902]−2.92430).[26]

Results are presented as a mean difference (MD) with 95% CIs. In addition, we analyzed the likelihood of drug discontinuation due to any reason.[27]

Network Meta-Analysis

The network meta-analysis was completed using fixed and random effects models. The primary results are from the random effects model, and the results from the fixed effects model are presented in Figure S1. We assessed the change in HRQoL scores for the individual components of the network compared with placebo and used an additive component network meta-analysis model to evaluate the influence of individual treatment components, as many treatments were combinations of several common components. This model assumes that the effect of treatment combinations is the sum of the effects of its components, which is an assumption of similar published, network meta-analyses evaluating HFrEF therapies that is supported by there being little evidence of interaction between medications of different classes and current physiological understandings of medications of different classes interacting with separate biochemical pathways. Therefore, this network meta-analysis compared different combinations of treatments based on the treatment given and the background therapy within a trial. Treatment combinations that are not included in the network cannot be compared, and a connected network is important for accurate results. For a given trial, we considered patients as receiving a background therapy if ≥50% of patients in both arms were on that therapy at baseline. Given the mixed use of ARNi, ACE inhibitor, and ARBs in recent clinical trials, we considered these trials against a background of ARNi if more than 40% of the patients using ACE inhibitor/ARNi/ARB in either arm were on ARNi, if <40% were taking an ARNi, then the background therapy was considered to be an ACE inhibitor.[28–37] Treatments were ranked using the *P* score, the frequentist equivalent of the surface under the cumulative ranking curve, which shows the proportion of treatments that are worse than the treatment in question.[38]

We assessed the internal validity and bias of individual trials using the August 2019 version of the Cochrane Risk of Bias Assessment Tool, version 2.[39] The risk of bias was classified as low risk, having some concerns, or high risk (major concerns) of bias in each domain using a combination of signaling questions and tool algorithms to inform a within-study risk of bias judgment (Table S1). We included all studies regardless of their Cochrane Risk of Bias Assessment Tool, version 2 classification to determine the confidence in individual comparisons using the Grading of Recommendations, Assessment, Development, and Evaluations framework and the Confidence in Network Meta-Analysis tool. Confidence in Network Meta-Analysis considers 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Cochrane Risk of Bias Assessment Tool, version 2 scores informed the within-study bias assessment (Table S2).[40–42] Reporting bias was formally tested via the Egger test funnel plot symmetry; a nonsignificant result indicated low risk. Indirectness, representing transitivity in the network, was deemed low per published guidelines. Imprecision compared 95% CIs with a range of equivalence based on a clinically important effect threshold of 5 points. For heterogeneity, we calculated I^2 values, which reflect the inconsistency within the network using the χ^2 statistic and its df.[42] Incoherence, which occurs when direct and indirect evidence disagree (violating transitivity), was assessed visually and via a global test using a random effects design-by-treatment interaction model; a nonsignificant *P* value indicated no incoherence.[41] As a sensitivity analysis, we assessed the validity of KCCQ and MLHFQ overall score standardization by separately analyzing trials using the MLHFQ through a comparison of results with converted and raw scores. We performed the fixed and random effects network meta-analysis using the *netmeta* package in R (R Foundation), with $P<0.05$ considered statistically significant. Additional model assumptions are in the Supplemental Material.

RESULTS

After a search of databases and the initial removal of duplicates, we identified 1131 studies. After title and abstract screening, 1058 studies were excluded (Figure 1). The full text of 73 studies was screened, and 41 were included in the analysis.[28–37,43–73] These studies had a median of 276 (interquartile range, 105–464) participants and together analyzed 41 145 patients who were mostly male (76.5%) with a mean left ventricular ejection fraction of 28% and a median follow-up time of 5 months (interquartile range, 3–8). Of the 41 included studies, 36 were multicenter, 16 were multinational, 20 used the MLHFQ, and 21 used the KCCQ. Details of the therapeutic agents assessed are available in the Table.

Risk of Bias and Certainty of Evidence

Two studies had major concerns of bias, as defined by the Cochrane Risk of Bias Assessment Tool, version 2 tool, due to an imbalance in the number of missing patients between treatment groups without reported evidence that the outcomes of the missing participants were accounted for with an appropriate method.[43,44] However, as one of the studies did not report the OSS change of their treatment groups, this study was not included in the main analysis.[44] The other study with major concerns of bias, Willenheimer et al,[43] was included in the main analysis, but sensitivity analyses showed that its removal did not significantly impact the main results (Figure S2). There was no evidence of funnel plot asymmetry or small study effects for the outcomes of change in HRQoL (Egger test $P=0.818$) or discontinuation (Egger test $P=0.429$; Figure S3).

As the exclusion and inclusion criteria were selective, indirectness was judged as low/very low. The minimally important clinical difference represents the minimum change that represents a noticeable improvement for a patient. In the KCCQ scale, a small clinical benefit has been defined as a change of 5 units. Consequently, the effect size to evaluate the imprecision and heterogeneity in the study was defined as 5 units of score change in our study.[45] Because of the high variability in HRQoL scores observed across all the studies, there was a high level of imprecision

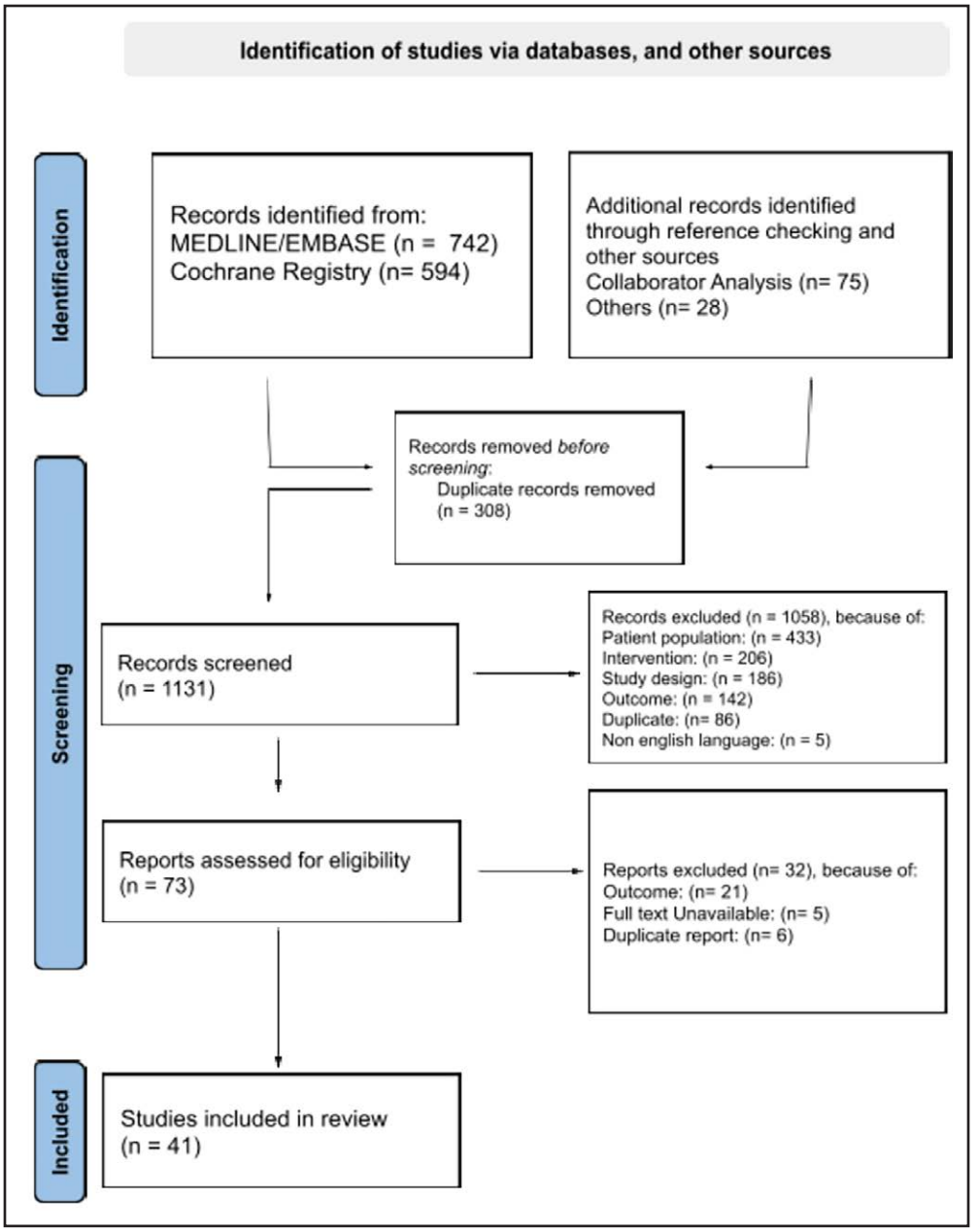

Figure 1. PRISMA flowchart.

in many treatment comparisons. Overall heterogeneity for the additive network meta-analysis model was high (I^2=61.9%); therefore, the results from the random effects model were considered the primary results. Incoherence was not significant, and the confidence rating was high or moderate for all clinically relevant treatment comparisons. The confidence in the results of comparisons between treatments was generally lower for many of the comparisons which relied on indirect evidence from a large trial and a smaller trial, such as ACE inhibitor compared with ARNi+BB+MRA+SGLT2i or ARB+BB compared with SGLT2i, and those that included data from the Willenheimer et al trial (Figure S2).[43]

Component Analysis

Out of the 41 studies included in the NMA, only 35 reported either the KCCQ OSS or the MLHFQ score.[6,28–37,43,45–73] These studies were included in the main analysis of change in HRQoL measured through the change in OSS and converted MLHFQ scores (Figure 2). It was not possible to analyze the other domains of the KCCQ as there were not enough studies to build an adequate network. The main analysis indicated that the therapy with the largest effect on HRQoL was H-ISDN (MD, +3.9 [−0.7 to +8.5]); however, this effect was not statistically significant. The treatment with the next largest effect was SGLT2i (MD, +3.4 [+1.4 to

Table. Study Characteristics and Outcomes by Treatment Arm

	Treatment	Follow-up, mo	N, randomized	Mean MLHFQ score change	Mean KCCQ OSS change	KCCQ SD	Mean KCCQ TSS change	Mean KCCQ CSS change	No. of participants discontinuing the drug in the group
Pollock et al[46]	DIG	3	7	−6.0	+4.1	15.6	NR	NR	4
	BB+DIG	3	12	−21.0	+24.1	15.6	NR	NR	2
Widimský et al[47]	DIG	3	48	−8.0	+6.8	15.6	NR	NR	6
	ACE inhibitor+DIG	3	48	−13.0	+13.5	15.6	NR	NR	4
	ACE inhibitor+DIG	3	53	−8.0	+6.8	15.6	NR	NR	2
	ACE inhibitor+DIG	3	51	−6.0	+4.1	15.6	NR	NR	4
	ACE inhibitor+DIG	3	48	−9.0	+8.1	15.6	NR	NR	6
Bristow et al[48]	ACE inhibitor+DIG	6	84	−7.3	+5.8	18.0	NR	NR	11
	ACE inhibitor+BB+DIG	6	83	−7.9	+6.6	18.0	NR	NR	3
	ACE inhibitor+BB+DIG	6	89	−7.3	+5.8	18.0	NR	NR	10
	ACE inhibitor+BB+DIG	6	89	−5.5	+3.4	18.0	NR	NR	5
Packer et al[49]	ACE inhibitor+DIG	6	145	−3.7	+1.0	18.0	NR	NR	30
	ACE inhibitor+BB+DIG	6	133	−5.5	+3.4	18.0	NR	NR	19
Colucci et al[50]	ACE inhibitor+DIG	12	134	−4.9	+2.6	17.3	NR	NR	14
	ACE inhibitor+BB+DIG	12	232	−2.4	−0.7	17.3	NR	NR	17
Cohn et al[51]	ACE inhibitor+DIG	3	35	−8.8	+7.8	15.6	NR	NR	4
	ACE inhibitor+BB+DIG	3	70	−11.6	+11.6	15.6	NR	NR	8
Goldstein et al[52]	ACE inhibitor+DIG	6	19	−4.8	+2.6	23.7	NR	NR	3
	ACE inhibitor+BB+DIG	6	42	−8.9	+7.9	27.2	NR	NR	9
Hjalmarson et al[53]	ACE inhibitor+DIG	1	339	+0.2	−4.2	17.3	NR	NR	NR
	ACE inhibitor+BB+DIG	12	331	−0.7	−3.0	17.3	NR	NR	NR
Granger et al[54]	DIG	3	91	−4.0	+1.4	15.6	NR	NR	12
	ARB+DIG	3	179	0	−3.9	15.6	NR	NR	31
Beanlands et al[55]	Placebo	3	21	+1.0	−5.2	15.6	NR	NR	1
	BB	3	19	+4.0	−9.2	15.6	NR	NR	1
de Milliano et al[56]	ACE inhibitor	6	11	−4.1	+1.6	18.0	NR	NR	1
	ACE inhibitor+BB	6	43	−6.8	+5.2	18.0	NR	NR	4
Hutcheon et al[57]	Placebo	2.5	37	−5.4	+3.3	15.6	NR	NR	2
	ACE inhibitor	2.5	36	−4.8	+2.5	15.6	NR	NR	5
Willenheimer et al[43]	ARB+BB	3	70	−0.7	−3.0	10.7	NR	NR	6
	ACE inhibitor+BB	3	71	−0.9	−2.7	10.8	NR	NR	14
Lader et al[58]	ACE inhibitor	12	291	−5.0	+2.8	17.3	NR	NR	NR
	ACE inhibitor+DIG	12	298	−1.0	−2.6	17.3	NR	NR	NR
Taylor et al[59]	ACE inhibitor+BB+DIG	10	532	−2.7	−0.3	24.4	NR	NR	NR
	ACE inhibitor+BB+DIG+H–ISDN	10	518	−5.6	+3.6	23.6	NR	NR	NR
Majani et al[60]	ACE inhibitor+DIG	23	1506	+2.4	−7.1	17.3	NR	NR	NR
	ACE inhibitor+ARB+DIG	23	1504	+0.4	−4.44	17.3	NR	NR	NR
Edes et al[61]	ACE inhibitor+DIG	12	126	−10.8	+10.5	15.2	NR	NR	0
	ACE inhibitor+BB+DIG	12	134	−9.2	+8.4	14.5	NR	NR	0
Chan et al[62]	ARB+BB	12	25	−11.0	+10.7	8.9	NR	NR	1
	ARB+BB+MRA	12	23	−12.3	+12.5	9.3	NR	NR	2
Ekman et al[63]	ACE inhibitor+BB+MRA	12	976	NR	+4.3	16.7	+3.6	+3.3	NR
	ACE inhibitor+BB+MRA+ivabradine	12	968	NR	+6.7	17.3	+4.6	+5.0	NR

(*Continued*)

Table. Continued

	Treatment	Follow-up, mo	N, randomized	Mean MLHFQ score change	Mean KCCQ OSS change	KCCQ SD	Mean KCCQ TSS change	Mean KCCQ CSS change	No. of participants discontinuing the drug in the group
Abdel-Salam et al[64]	ACE inhibitor+BB+MRA	3	23	−8.6	+7.6	15.6	NR	NR	0
	ACE inhibitor+BB+MRA+ivabradine	3	20	−12.4	+12.7	15.6	NR	NR	0
Lewis et al[65]	ACE inhibitor+BB+MRA	8	3826	NR	−0.1	15.5	−0.6	−0.3	NR
	ARNi+BB+MRA	8	3797	NR	+1.1	15.4	+0.5	+0.6	NR
Nassif et al[36]	ACE inhibitor+BB+MRA	3	132	NR	+1.9	15.6	−0.5	+0.5	12
	ACE inhibitor+BB+MRA+SGLT2i	3	131	NR	+5.2	15.6	+4.5	+4.2	11
Desai et al[37]	ACE inhibitor+BB	3	233	NR	+4.2	15.6	NR	NR	17
	ARNi+BB	3	231	NR	+8.7	15.5	NR	NR	16
McMurray et al[66]	ACE inhibitor+BB+MRA	8	2371	NR	+4.0	15.6	+3.3	+3.0	249
	ACE inhibitor+BB+MRA+SGLT2i	8	2373	NR	+6.5	15.6	+6.1	+6.0	258
Jensen et al[35]	ACE inhibitor+BB+MRA	3	95	NR	+1.9	15.6	+1.1	+0.5	1
	ACE inhibitor+BB+MRA+SGLT2i	3	95	NR	+2.0	15.6	+3.2	+3.3	0
Felker et al[67]	ACE inhibitor+BB+MRA	5	149	NR	NR	0.0	+5.0	+4.1	4
	ACE inhibitor+BB+MRA+OM	5	149	NR	NR	0.0	+9.9	+7.0	12
	ACE inhibitor+BB+MRA+OM	5	150	NR	NR	0.0	+6.6	+6.3	5
Abraham et al[33]	ARNi+BB+MRA	3	156	NR	+6.4	14.7	+3.7	+4.8	13
	ARNi+BB+MRA+SGLT2i	3	156	NR	+9.7	14.7	+7.3	+8.2	15
Santos-Gallego et al[34]	ARNi+BB	6	42	NR	+1.9	15.0	NR	NR	2
	ARNi+BB+SGLT2i	6	42	NR	+21.0	18.0	NR	NR	2
Tsutsui et al[69]	ACE inhibitor+BB+MRA	6	113	NR	NR	0.0	NR	−3.5	13
	ARNi+BB+MRA	6	112	NR	NR	0.0	NR	−2.2	11
Khandwalla et al[70]	ACE inhibitor+BB+MRA	2	70	NR	+4.2	15.6	NR	NR	8
	ARNi+BB+MRA	2	70	NR	+2.9	15.6	NR	NR	5
Lee et al[45]	ACE inhibitor+BB+MRA	9	53	NR	NR	0.0	+4.2	NR	0
	ACE inhibitor+BB+MRA+SGLT2i	9	52	NR	NR	0.0	+0.7	NR	5
Teerlink et al[68]	ACE inhibitor+BB+MRA	6	3072	NR	NR	0.0	+6.3	NR	50
	ACE inhibitor+BB+MRA+OM	6	3076	NR	NR	0.0	+5.8	NR	41
Butler et al[32]	ACE inhibitor+BB+MRA	12	1867	NR	+5.0	17.3	+5.0	+4.0	335
	ACE inhibitor+BB+MRA+SGLT2i	12	1863	NR	+6.5	17.3	+6.8	+5.5	303
Halle et al[71]	ACE inhibitor+BB+MRA	3	98	NR	+5.8	14.5	+4.8	+4.9	7
	ARNi+BB+MRA	3	103	NR	+8.1	16.7	+8.3	+7.3	4
Mann et al[72]	ARB+BB+MRA	6	168	NR	+10.8	18.0	NR	NR	36
	ARNi+BB+MRA	6	167	NR	+11.8	18.0	NR	NR	49
Ye et al[73]	ACE inhibitor+BB+MRA	8	172	NR	+5.0	17.0	NR	+3.0	13
	ACE inhibitor+BB+MRA+ivabradine	8	170	NR	9.0	13.0	NR	+7.0	13
Palau et al[29]	ARNi+BB+MRA	3	45	−2.6	−0.4	15.6	NR	NR	0
	ARNi+BB+MRA+SGLT2i	3	45	−6.0	+4.1	15.6	NR	NR	0
Spertus et al[30]	Placebo	3	91	NR	+6.6	15.6	+4.2	+3.9	18
	SGLT2i	3	90	NR	+9.8	15.6	+9.1	+7.5	13

(*Continued*)

Table. Continued

	Treatment	Follow-up, mo	N, randomized	Mean MLHFQ score change	Mean KCCQ OSS change	KCCQ SD	Mean KCCQ TSS change	Mean KCCQ CSS change	No. of participants discontinuing the drug in the group
Butler et al[31]	ACE inhibitor+BB+MRA	4	2524	NR	+6.8	15.6	+7.3	+6.3	565
	ACE inhibitor+BB+MRA+vericiguat	4	2526	NR	+7.8	15.6	+6.3	+6.3	610
Lewis et al[28]	ARNi+BB+MRA	5	91	NR	NR	0.0	+1.8	NR	6
	ARNi+BB+MRA+OM	5	185	NR	NR	0.0	+0.3	NR	21
McMurray et al[44]	ACE inhibitor+BB+MRA	4	157	NR	NR	0.0	+3.1	NR	12
	ACE inhibitor+BB+MRA+SGLT2i	4	156	NR	NR	0.0	+6.2	NR	9

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BB, β-blocker; CSS, Clinical Summary Score; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living With Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NR, not recorded; OM, omecamtiv mecarbil; OSS, Overall Summary Score; SGLT2i, sodium-glucose cotransporter 2 inhibitors; and TSS, Total Symptom Score.

+5.3]), which led to the greatest statistically significant improvement in quality of life, followed by ivabradine (MD, +3.3 [+0.1 to +6.4]). The treatments which followed were ARNi (MD, +2.6 [−3.2 to +8.5]) and then vericiguat (MD, +1.0 [−3.2 to +5.2]), neither of which had a statistically significant effect. BB, ACE inhibitor, and ARB had a neutral impact on HRQoL, and digoxin significantly reduced HRQoL (MD, −5.3 [−10.3 to −0.4]; Figure 3).

Additive Network Analysis

A combination of ARNi+BB+MRA+SGLT2i (MD, +7.1 [−1.0 to +15.2]) had the largest effect on HRQoL, but this effect was not significant. The largest and only statistically significant impact on quality of life was observed with the combination of ARNi+BB+SGLT2i (MD, +5.3 [+0.4 to +10.3]). Other combinations, such as ACE inhibitor+BB+MRA+SGLT2i (MD, +5.3 [−2.6 to +13.3]) and ACE inhibitor+BB+MRA+ivabradine (MD, +5.2 [−3.1 to +13.6]) did not have a significant effect on quality of life (Figure 4). Other combinations of ACE inhibitor/ARB/ARNi with BB and MRA generally had an unclear impact on HRQoL, and most combinations involving digoxin had a negative impact on HRQoL compared with placebo, even when paired with ACE inhibitor/ARB or BB. The *P* score values given in Table S3 demonstrate a similar pattern of ranking. The combination of ARNi+BB+MRA+SGLT2i did not improve HRQoL significantly better than the combination of ACE inhibitor+BB+MRA+SGLT2i or the combination of ARNi+BB+SGLT2i, but was significantly more effective than a combination of ARNi+BB+MRA (MD, +3.3 [+1.5 to +5.1]; $P<0.001$; Table S4).

The discontinuation of study interventions was recorded in 35 studies comprising 2977 discontinuations, and there was low heterogeneity (I^2=19.2%) in the network.[28–37,43–49,51–55,59–61,64–73] Compared with placebo, participants were significantly more likely to discontinue the use of ACE inhibitor (hazard ratio, +2.6 [+1.3 to +5.1]), and ARNi (hazard ratio, +2.2 [+1.1 to +4.4]), but not any other interventions (Figure S4).

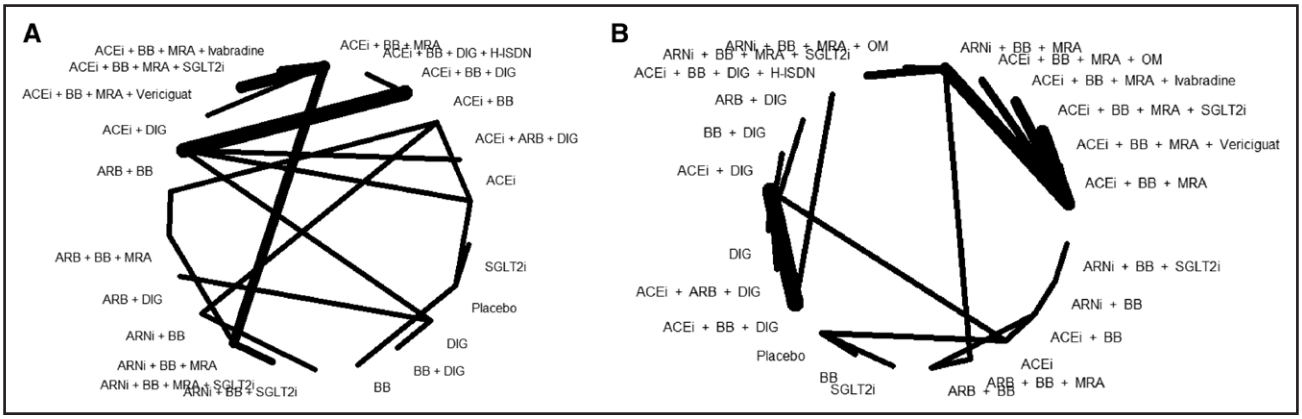

Figure 2. xxx.
Network connection diagram for change in quality of life (**A**) and discontinuation (**B**) outcomes. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BB, β-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

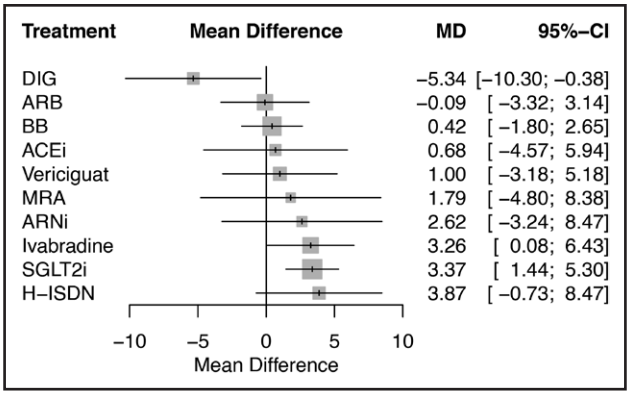

Figure 3. Forest plot showing the mean difference in health-related quality of life score change in individual treatments against placebo.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BB, β-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; OM, omecamtiv mecarbil; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Sensitivity Analysis

Four sensitivity analyses were conducted. The first sensitivity analysis found that removing the studies that were deemed to have major concerns of bias from the primary analysis did not change the results (Figure S4). The sensitivity of the results to the conversion of the MLHFQ scores to the KCCQ score scale was evaluated through an analysis which compared a subnetwork with only trials that have converted scores to a subnetwork of only trials with the original MLHFQ scores, and the result was largely the same (Figure S5). Another sensitivity analysis evaluated the validity of the consideration of the trials against a background of ARNi if more than 40% of the patients using ACE inhibitor/ARNi/ARB in either arm were on ARNi, or a background of ACE inhibitor if <40% of patients were on ARNi. We evaluated all of the trials with mixed ACE inhibitor/ARNi/ARB use on a background of ACE inhibitor instead of ARNi, and the results remained largely the same (Figure S6). The fourth sensitivity analysis found that removing the studies that did not describe the background therapy did not change the results (Figure S7).

DISCUSSION

This study evaluated the impact of interventions efficacious in HFrEF on HRQoL. Our study has 2 major findings. First, evidence with high confidence showed that a combination of ARNi+BB+MRA+SGLT2i had the greatest impact on HRQoL, followed by combinations of ARNi+BB+SGLT2i or ACE inhibitor+BB+MRA+SGLT2i. This complements the findings of a prior NMA focused on other clinical outcomes, and supports the guideline statements surrounding the use of all 4 medication classes concurrently.[4,5,74] Second, the addition of SGLT2i and ivabradine to other treatment combinations improved HRQoL scores, while the addition of digoxin to the treatment improved HRQoL less than placebo. Clinicians should consider adding medications that improve HRQoL and discontinuing medications without strong evidence of benefit.

The current GDMT for HFrEF involves the initiation and uptitration of a combination of ARNi+BB+MRA+SGLT2i,

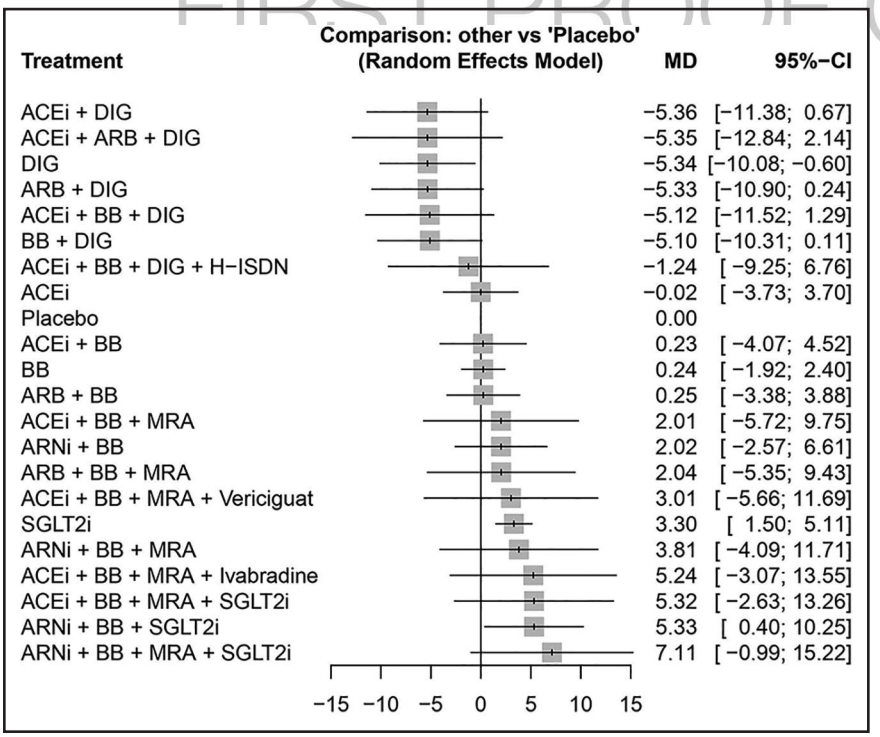

Figure 4. Forest plot showing the mean difference (MD) in quality of life score change in various treatment combinations against placebo.
ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BB, β-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

if possible, as it is likely the most effective for improving survival. This combination was numerically favored for improving HRQoL, but due to its evaluation in only 2 small studies, we could not statistically confirm that it was the most effective. Furthermore, we found no significant difference in HRQoL when SGLT2i was replaced with vericiguat or ivabradine in the ACE inhibitor/BB/MRA combination. To our knowledge this is the first study to build a network meta-analysis for the evaluation of the efficacy of HFrEF interventions in improving HRQoL; however, similar analyses evaluating these treatment combinations for their impact on patient mortality and hospitalization have found similar rankings of treatment combinations, but were often able to identify statistically significant treatment effects.[75–77] The current evidence, together with the results of similar studies, supports the immediate initiation and uptitration of a quadruple therapy consisting of ARNi+BB+MRA, and SGLT2i or a triple therapy of ARNi+BB+SGLT2i for the majority of patients with HFrEF. More evidence is needed to determine if vericiguat or ivabradine can or should be added to quadruple therapy or used in combination with some parts of GDMT to increase HRQoL for any subgroup of patients with HFrEF. The heterogeneity of the trials contributed to the lack of statistical significance in treatment effects through the use of a random effects model. One such quality with significant variability was trial length; the median trial length was 5 months (interquartile range, 3–8). It is not likely, however, that the shorter median duration had a significant impact on the estimated change in HRQoL with treatment; change in HRQoL over time in several included trials shows that the majority of HRQoL change occurs in the first months of the trial, with a flattening off in the following months.[30,32,60] Ultimately, longer trials will provide more accurate results, but practically, this is challenging due to cost-related constrictions.

An important assumption of this analysis is that the impact of medications used in combination is additive. The other major approach to this analysis would assume a synergistic effect where combinations of medications would have a unique greater or lesser effect unrelated to the effects of individual components. Assuming an additive effect of medication combinations is the more conservative assumption, and clinical reasoning supports this assumption; current physiological evidence shows that HF medications of different classes interact with unrelated biochemical pathways, and there is limited evidence suggesting contraindications between medications of different classes. The clinical implications of this assumption are that any medication can be added or subtracted to produce an expected clinical effect and that it is not necessary to evaluate each of these combinations on their own in individual randomized controlled trials to identify combinations with unique effects. Conversely, if this assumption is violated, it may be the case that a combination of medications, which may not be the largest number of medications, may be more effective than a larger number of medications which are not as synergistic.

Regarding the individual effect of each treatment component, our results largely align with previous non-network meta-analyses, supporting the efficacy of SGLT2i and ivabradine in improving HRQoL and the neutral impact of BB and ACE inhibitor on HRQoL.[18,19,66] However, our findings indicate that digoxin, despite previous suggestions of a neutral impact on HRQoL, may not offer greater HRQoL improvement than placebo.[6] Furthermore, ARNi, ARB, and H-ISDN, while previously suggested to significantly improve HRQoL, did not have a statistically significant impact on HRQoL in our study.[6–8] The impact of vericiguat and MRA on HRQoL, which have been evaluated in a limited capacity, in our study did not have a significant impact. The impact of vericiguat and MRA on HRQoL was not significant in our study, likely due to their limited evaluation. Furthermore, a lack of data precluded our assessment of omecamtiv mecarbil's efficacy. Our results suggest that ivabradine could be considered for addition after GDMT is optimized. However, more evidence is needed to determine the efficacy of vericiguat and H-ISDN in improving HRQoL before they are added to GDMT. This is particularly true for H-ISDN, as only one trial, involving solely self-identified Black patients, evaluated its impact.[59] Future trials should evaluate the additive effect on HRQoL of medications like ivabradine, MRA, vericiguat, and H-ISDN when administered in addition to GDMT. Digoxin, however, should not be considered for addition to GDMT as it may not improve HRQoL; our data suggests it may hinder it. The DIG trial (Digitalis Investigation Group), which was the only trial that evaluated digoxin directly in our study, found a lower HRQoL improvement for digoxin compared with placebo.[56,78] As digoxin may not reduce mortality in patients with HFrEF, the potential toxicity and risks of digoxin treatment may not be compensated in the way that other medications, such as ACE inhibitors and ARNi, are due to their beneficial effects on mortality.[21,78,79]

As the estimated MD of treatment combinations also describes the mean change in the KCCQ OSS, patients who are initiated on a combination of ARNi+BB+MRA+SGLT2i may, on average, experience a small to medium clinically meaningful HRQoL improvement, and for combinations of ARNi+BB+SGLT2i, ACE inhibitor+BB+MRA+SGLT2i, or ACE inhibitor+BB+MRA+ivabradine, a small clinically meaningful HRQoL improvement may be experienced on average. Due to the variable nature of HRQoL, mean change has been suggested to be an incomplete description of the change in HRQoL that a patient may experience. Patients are not likely to experience a mean improvement in HRQoL but rather a deterioration, no improvement or

an improvement in HRQoL which may be much larger than the predicted mean change; consequently, it is suggested to summarize the intervention's impact on HRQoL by considering and comparing the proportion of patients who experience a change of 5 units, 10 units, and 20 units in the KCCQ, which have been defined as small, medium and large clinical changes, respectively, in either direction in addition to the mean change in HRQoL.[80] Trials have not traditionally reported HRQoL changes in this way, so it was not possible to use this measurement for our study. However, it should be considered for future research evaluating the impact of HF treatments on HRQoL.

Strengths and Limitations

Several strengths and limitations should be considered. First, although this is the largest and only study to evaluate the impact of combinations of treatments for HFrEF on HRQoL using a network meta-analysis and systematic review methodology, it is reliant on studies conducted over 4 decades and may be susceptible to secular changes in care. Nevertheless, the inclusion of 41 placebo or active controlled, randomized, double blind trials, the majority of which are multicenter trials, represents the best available evidence for the impact of efficacious HFrEF treatments on patients' HRQoL. Second, the main analysis for the most clinically relevant treatment combinations largely relied on high-confidence evidence with little detected bias. Third, 2 different HRQoL instruments were used, and conversion can be challenging. Therefore, we conducted sensitivity analyses, which showed that the conversion of scores from one score scale to the other and the bias that was detected in some studies did not significantly influence the results of our study. Fourth, while the heterogeneity of the standard NMA model was low, the additive NMA model showed high heterogeneity, which was partially compensated for by using a random effects model. Fifth, due to the additive nature of medication prescription in heart failure, comparing the efficacy of medications that are frequently used together has not occurred. As a result, our study findings rely largely on indirect comparisons of treatments; however, while more direct data may strengthen our results, reliance on indirect comparisons of evidence from the best currently available subset of trials does not reduce the significance of the insights of this study. Finally, we were unable to account for the dosages of study treatments or the variability in the length of follow-up between studies.

Conclusions

The results of this study indicate the most effective treatment combinations and additional therapies for improving HRQoL. This provides clinically meaningful information that can help patients and clinicians achieve patient goals more effectively.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S4
Figures S1–S7
Search Terms
Protocol

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