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RESEARCH ARTICLE

# Pharmacotherapy for heart failure with reduced ejection fraction and health-related quality of life: a systematic review and meta-analysis

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**Aims** The aim of this study was to synthesize the evidence on the effect of heart failure with reduced ejection fraction (HFrEF) pharmacotherapy on health-related quality of life (HRQoL).

**Methods and results** We searched MEDLINE, Embase, CENTRAL, CINAHL, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform in June 2020. Randomized placebo-controlled trials evaluating contemporary HFrEF pharmacotherapy and reporting HRQoL as an outcome were included. Two reviewers independently assessed studies for eligibility, extracted data, and assessed risk of bias and GRADE certainty of evidence. The primary outcome was HRQoL at last available follow-up analysed using a random-effects model. We included 37 studies from 5770 identified articles. Risk of bias was low in 10 trials and high/unclear in 27 trials. High certainty evidence from meta-analyses demonstrated improved HRQoL over placebo with sodium–glucose co-transporter 2 (SGLT2) inhibitors [standardized mean difference (SMD) 0.16, 95% confidence interval (CI) 0.08–0.23] and intravenous iron (SMD 0.52, 95% CI 0.04–1.00). Furthermore, high certainty evidence from ≥1 landmark trial further supported improved HRQoL with angiotensin receptor blockers (ARBs) (SMD 0.09, 95% CI 0.02–0.17), ivabradine (SMD 0.14, 95% CI 0.04–0.23), hydralazine–nitrate (SMD 0.24, 95% CI 0.04–0.44) vs. placebo, and for angiotensin receptor–neprilysin inhibitor (ARNI) compared with an angiotensin-converting enzyme (ACE) inhibitor (SMD 0.09, 95% CI 0.02–0.17). Findings were inconclusive for ACE inhibitors, beta-blockers, digoxin, and oral iron based on low-to-moderate certainty evidence.

**Conclusion** ARBs, ARNIs, SGLT2 inhibitors, ivabradine, hydralazine–nitrate, and intravenous iron improved HRQoL in patients with HFrEF. These findings can be incorporated into discussions with patients to enable shared decision-making.

**Keywords** Guideline-directed medical therapy • Heart failure • Medications • Quality of life

## Introduction

Heart failure with reduced ejection fraction (HFrEF) increases the risk of death and hospitalization, and impairs function and health-related quality of life (HRQoL).[1–3] The current approach to pharmacological management of HFrEF focuses on the sequential addition and titration of medications demonstrated to reduce the risk of death and hospitalization in randomized controlled trials (RCTs).[1–4] Less is known about the effect of these interventions on HRQoL, though several validated tools are now available to

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evaluate HRQoL in patients with heart failure.[5,6] Although some HFrEF pharmacotherapeutic options both prolong survival and improve HRQoL,[7] others may prolong survival with uncertain effect on HRQoL,[8] or even improve HRQoL with uncertain mortality benefit.[9]

Patients with HFrEF often have strong preferences for either improving HRQoL or prolonging survival as their dominant goal of therapy.[10–14] Therefore, it is important for patients and their clinicians to understand the potential impact of HFrEF pharmacotherapy on HRQoL in order to make decisions that are consistent with patient-specific goals. We aimed to perform a comprehensive systematic review and meta-analysis of RCTs evaluating the impact of contemporary pharmacotherapy for HFrEF on HRQoL.

# Methods

We reported this systematic review with meta-analysis according to the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement[15] and prospectively registered our protocol on PROSPERO (CRD42019135383).

## Search strategy

We performed a librarian-assisted search of the Cochrane Controlled Register of Trials (CENTRAL), Embase, MEDLINE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from database inception to 2 June 2020. The MEDLINE search query is presented in online supplementary Appendix. We adapted search terms according to the syntax of each database, restricted to studies reported in English. For grey literature, we searched trial registered on www.ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), and trial registries of relevant manufacturers (e.g. GlaxoSmithKline Study Register for trials of carvedilol: www.gsk-studyregister.com); and manually searched bibliographies of included trials, guidelines and other reviews.

## Eligibility criteria

We included parallel, placebo-controlled RCTs that enrolled patients with HFrEF, evaluated an intervention that consisted of ≥1 agent recommended for the chronic management of HFrEF in contemporary heart failure guidelines,[1–4] and reported HRQoL as an outcome. We defined HFrEF based on an ejection fraction threshold ≤40%; however, we also included trials using alternate thresholds (e.g. <35% or <50%). We considered the following interventions: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNI), beta-blockers (with a focus on the guideline-recommended beta-blockers bisoprolol, carvedilol and metoprolol succinate), mineralocorticoid receptor antagonists (MRA), sodium–glucose co-transporter 2 (SGLT2) inhibitors, the combination of hydralazine plus a nitrate, cardiac glycosides (including digoxin), ivabradine, diuretics, and iron replacement. The comparator group received a placebo matching the therapy in the intervention group, along with either active control or standard of care.

## Outcomes

The primary outcome was the standardized mean difference (SMD) between groups in HRQoL, defined using a validated heart failure-specific HRQoL instrument, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) or the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[5,6] or generic HRQoL instruments (e.g. Short Form-36, Sickness Impact Profile). When several HRQoL instruments were reported, we preferentially reported data for the KCCQ or MLHFQ, as these instruments have the best overall performance across several metrics, including validity, reliability, responsiveness, feasibility and interpretability, as determined in two independent systematic reviews.[5,6] The KCCQ is available as a 12-item and 23-item questionnaire that quantifies several domains (physical limitations; symptom burden, frequency and stability; social limitations; quality of life; and self-efficacy) on a scale of 0 (worst) to 100 (best).[5] When several KCCQ subscales were reported, we preferentially extracted data for the most inclusive (i.e. overall summary score, followed by the clinical summary score, and total symptom score). The MLHFQ is a 21-item questionnaire that quantifies physical, socioeconomic and psychological impairment on a scale of 0 (best) to 105 (worst).[5] For studies that reported outcomes at multiple timepoints, we used the longest period of follow-up in analyses.

The secondary outcome was the proportion of patients who achieved a minimal important improvement in HRQoL, as originally defined in the study.

## Study selection, data extraction, and assessment of risk of bias and certainty of evidence

Two reviewers (RDT, ARB) independently screened article titles and abstracts, and reviewed full-text articles for inclusion. The same two reviewers independently extracted data, evaluated trials for risk of bias using the Cochrane risk of bias tool,[16] and graded certainty of evidence for the primary outcome using the Grading Recommendations Assessment, Development and Evaluation (GRADE) framework, which incorporates risk of bias, consistency, directness, precision, and other considerations.[17] We extracted the following data from each study using a standardized data collection form: lead author, publication year, sample size, inclusion criteria [ejection fraction, New York Heart Association (NYHA) class], baseline characteristics (age, sex, NYHA class, ischeamic cardiomyopathy, atrial fibrillation, ejection fraction, serum natriuretic peptide concentration), baseline use of HFrEF medications, intervention and comparator characteristics (agent, target dose and achieved dose), HRQoL outcome characteristics (instruments, timing of follow-up, proportion completing HRQoL assessment, values at baseline and last available follow-up, and change from baseline). When trial reports described insufficient data for meta-analysis, we contacted the corresponding trial authors for additional data, and obtained additional data for the DAPA-HF trial[7,18] from one of the authors (Jhund P.S., personal communication, 26 May 2020).

## Statistical analyses

We presented continuous data as SMD with 95% confidence intervals (CIs), as recommended by Cochrane for studies that report the same outcome using different scales.[19] To assist with clinical interpretation, we back-transformed statistically significant SMDs to mean differences on the KCCQ according to the method proposed by Cochrane, using data from the intervention group of the largest trial at lowest risk of bias for each comparison.[20] We presented dichotomous data as risk ratios (RR) with 95% CIs. For trials with multiple intervention arms of

medications within the same drug class, we combined groups using the methods proposed by Cochrane.[19]

We evaluated statistical heterogeneity with visual inspection of the forest plot and calculation of the $I^2$ statistic. For medication classes with ≥3 trials with methodological heterogeneity that did not preclude meta-analysis, we pooled studies using a random-effects model. When two or fewer trials were available, or pooling was judged to be inappropriate based on methodological heterogeneity, we narratively described results from individual trials. We aimed to perform subgroup analyses for sex, baseline NYHA class, heart failure aetiology and baseline atrial fibrillation; however, insufficient data were presented in the included studies for these analyses. We assessed for publication bias by visual inspection of funnel plot symmetry for comparisons with at least 10 studies. RDT had full access to all the data in the study and takes responsibility for its integrity and the data analysis. We considered $P < 0.05$ as statistically significant. We conducted all analyses using Review Manager version 5.4 (Cochrane, Copenhagen, Denmark).

# Results

## Study identification and characteristics

Of 5770 identified articles, we included 43 articles describing 37 studies that met our inclusion criteria, including one trial that was identified during our search and subsequently published (*Figure 1*). Details of 23 trials excluded at full-text review are provided in the online supplementary *Table S1*. *Table 1* summarizes key study and patient characteristics.[7–9,18,21–59] Median (minimum and maximum) study values were a sample size of 263 participants (20 to 8442), age 63 years (49 to 81), female 26% (9% to 52%), ejection fraction 28% (19% to 42%), and NYHA class II 53% (0% to 86%).

## Risk of bias and certainty of evidence

Ten trials had low risk of bias, 25 had unclear risk of bias (mostly due to insufficient reporting of sequence generation and allocation concealment in trials published in the 1990s and early 2000s), and two trials had high risk of bias in at least one domain (*Figure 2*). The comparison between beta-blockers and placebo had no evidence of publication bias (*Figure 3*). We did not assess funnel plot symmetry for other comparisons as they each had fewer than 10 trials. Based on GRADE methodology, certainty of evidence was high for ARBs, ARNIs, SGLT2 inhibitors, ivabradine, hydralazine–nitrate, and intravenous iron (*Table 2*). Certainty of evidence was downgraded to moderate for ACE inhibitors, beta-blockers, and oral iron due to serious imprecision, and downgraded to low for digoxin for serious imprecision and indirectness (*Table 2*).

## Impact of heart failure with reduced ejection fraction pharmacotherapy on health-related quality of life: overview

A summary of findings is provided in *Table 2*. Ten trials that reported mean differences in HRQoL at multiple time-points generally demonstrated consistent or greater effect

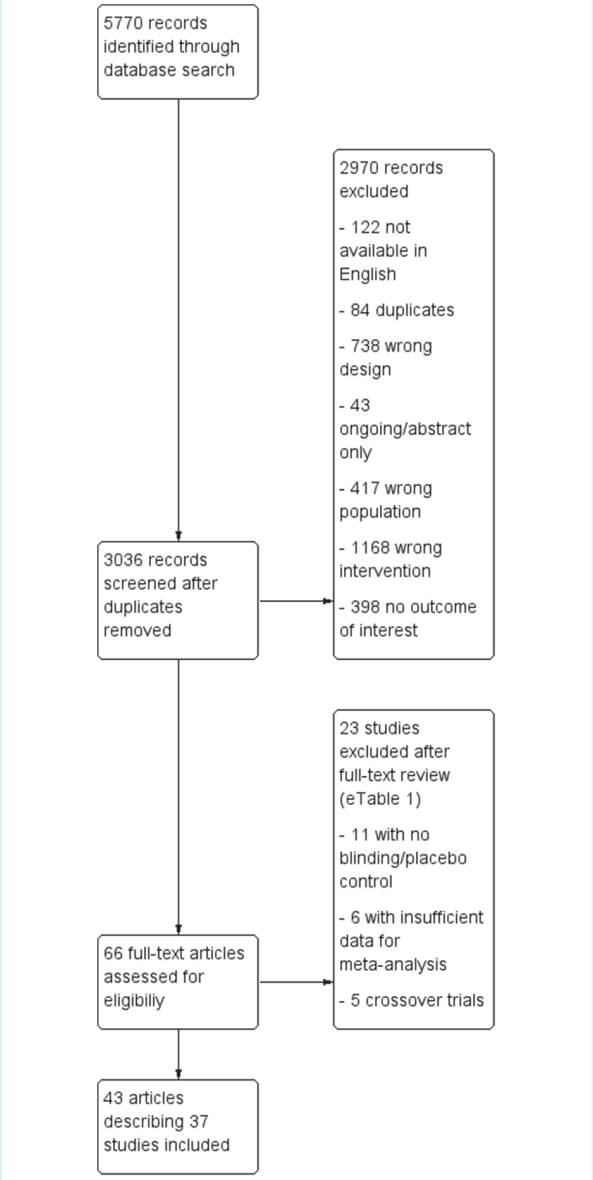


**Figure 1** Study flow diagram.

on HRQoL over time (online supplementary *Table S2*). Trials of four classes of medications (ACE inhibitors, beta-blockers, SGLT2 inhibitors and intravenous iron) were appropriate to meta-analyse (*Figure 4*), whereas the remainder were not pooled and are described narratively. Six classes of medications produced statistically significant improvements in HRQoL: ARBs, ARNIs, SGLT2 inhibitors, hydralazine–nitrate, ivabradine, and intravenous iron. We identified no placebo-controlled trials evaluating HRQoL with diuretics or MRAs. Few trials reported the secondary outcome (proportion of patients with minimal important improvement). All included studies defined a minimal important improvement as an improvement ≥5 for either the KCCQ or MLHFQ, consistent with previous definitions.[5]

**Table 1 Characteristics of included studies**

| Study | *n* | Age, mean, years | Women, *n* (%) | NYHA class II/III/IV, % | LVEF, mean, % | Intervention | HRQoL instrument | Duration of follow-up, Months | No. in intervention and control group (%) completing follow-up |
|---|---|---|---|---|---|---|---|---|---|
| **ACE inhibitor, ARB, ARNI** | | | | | | | | | |
| Bulpitt 1998[23] | 443 | 63 | 144 (36) | 62/36/1 | – | Captopril, cilazapril | SIP | 3 | 269/82 (96) |
| Gundersen 1995[24] | 223 | 64.4 | 63 (28) | 65/35/0 | 35 | Ramipril | QLQ-SHF | 3 | 100/89 (85) |
| Hutcheon 2002[25] | 73 | 81.3 | 33 (45) | 48/45/3 | – | Perindopril | MLHFQ | 2.5 | 31/35 (90) |
| Val-HeFT (Cohn 2001[26]; Majani 2005[27]) | 5010 | 62.4 | 1025 (20) | 62/36/2 | 27 | Valsartan | MLHFQ | mean 23 | 1504/1506 (60) |
| Houghton 2000[28] | 20 | 70 | 1 (10) | 60/40/0 | – | Losartan | Custom questionnaire range 30 to 210 (best) | 3 | 9/9 (90) |
| PARADIGM-HF (Lewis 2017)[29] | 8442 | 64 | 1632 (19) | 71/24/1 | 30 | Sacubitril-valsartan vs enalapril | KCCQ Overall Summary Score | 8 | 3460/3421 (82) |
| EVALUATE-HF (Desai 2019)[30] | 465 | 67.8 | 109 (23) | 66/22/0 | 34 | Sacubitril-valsartan vs enalapril | KCCQ-12 | 3 | 216/222 (94) |
| **Beta-blocker** | | | | | | | | | |
| MERIT-HF (Hjalmarson 2000)[8] | 3991 | 63.9 | 898 (23) | 41/56/3 | 28 | Metoprolol succinate | MLHFQ | Mean 12 | 331/339 (17) |
| MDC (Waagstein 1993[31]; Wiklund 1996[32]) | 383 | 49 | 105 (27) | 44/50/3 | 22 | Metoprolol tartrate | QLQ-SHF | 18 | 177/168 (90) |
| Goldstein 1999[33] | 60 | – | 15 (25) | 50/45/5 | 27 | Metoprolol succinate | MLHFQ | 6 | 38/15 (88) |
| de Milliano 2002[34] | 54 | 65 | 18 (33) | 56/44/0 | 25 | Metoprolol succinate | MLHFQ | 6 | 43/11 (100) |
| Beanlands 2000[35] | 40 | 63 | 7 (17) | – | 31 | Metoprolol tartrate | MLHFQ | 4.75 | 14/19 (83) |
| BEST (Tate 2007)[36] | 2708 | 60 | 593 (22) | 0/92/8 | 23 | Bucindolol | MLHFQ | 48 | 1354/1354 (100) |
| Pollock 1990[37] | 19 | 56 | 4 (21) | 0/83/17 | 19 | Bucindolol | MLHFQ | 3 | 12/5 (89) |
| US Carvedilol HF Study (Colucci 1996)[38] | 366 | 55 | 55 (15) | 86/13/0 | 23 | Carvedilol | MLHFQ | 6–12 | 167/98 (72) |
| MOCHA (Bristow 1996)[39] | 345 | 60 | 54 (16) | 53/47/0 | 23 | Carvedilol | MLHFQ | 6 | 78/72 (87) |
| PRECISE (Packer 1996)[40] | 278 | 59.3 | 74 (27) | 38/59/3 | 22 | Carvedilol | MLHFQ | 6 | 117/124 (87) |
| Carvedilol HF Study (Cohn 1997)[41] | 105 | 59.7 | 44 (42) | 1/87/11 | 22 | Carvedilol | MLHFQ | 6 | 36/20 (53) |
| ENECA (Edes 2005)[42] | 260 | 72 | 69 (27) | 52/46/2 | 25 | Nebivolol | MLHFQ | 10 | 134/126 (100) |
| Hawkins 2009[43] | 27 | 72.8 | 8 (30) | – | 28 | Bisoprolol | MLHFQ | 4 | 14/13 (100) |
| CIBIS-ELD (Düngen 2011)[44] | 883 | 72.9 | 329 (37) | 63/32/1 | 42 | Carvedilol vs. bisoprolol | SF-36 physical function subscale | 2.5–3 | 295/289 (66) |
| Metra 2000[45] | 150 | 58 | 14 (9) | 31/59/11 | 21 | Carvedilol vs. metoprolol tartrate | MLHFQ | 12 | 61/61 (81) |
| Sanderson 1999[46] | 51 | 60.4 | 11 (22) | 27/73/0 | 25.5 | Carvedilol vs. metoprolol tartrate | MLHFQ | 3 | 25/26 (100) |
| **SGLT2 inhibitor** | | | | | | | | | |
| DAPA-HF (McMurray 2019[7]; Kosiborod 2020[18]) | 4744 | 66.2 | 1109 (23) | 68/31/1 | 31 | Dapagliflozin | KCCQ Overall Summary Score | 8 | 1982/1935 (82.5) |
| DEFINE-HF (Nassif 2019)[47] | 263 | 62.2 | 70 (27) | 69/31/0 | 27 | Dapagliflozin | KCCQ Overall Summary Score | 3 | 119/119 (90) |
| EMPEROR-Reduced (Packer 2020[21]; Butler 2021[22]) | 3730 | 67.2 | 893 (24) | 75/24/1 | 28 | Empagliflozin | KCCQ Overall Summary Score | 12 | 1239/1218 (66) |

**Table 1 (Continued)**

| Study | *n* | Age, mean, years | Women, *n* (%) | NYHA class II/III/IV, % | LVEF, mean, % | Intervention | HRQoL instrument | Duration of follow-up, Months | No. in intervention and control group (%) completing follow-up |
|---|---|---|---|---|---|---|---|---|---|
| **Cardiac glycoside** | | | | | | | | | |
| DIG substudy (Lader 2003)[48] | 589 | 64.6 | 157 (27) | 55/31/2 | 35 | Digoxin | MLHFQ | 12 | 298/291 (100) |
| **Ivabradine** | | | | | | | | | |
| SHIFT substudy (Ekman 2011)[49] | 1944 | 60.9 | 466 (24) | 59/40/1 | 28 | Ivabradine | KCCQ Overall Summary Score | 12 | 842/839 (86) |
| Sarullo 2010[50] | 60 | 52.1 | 15 (25) | – | 30 | Ivabradine | MLHFQ | 3 | 30/30 (100) |
| Abdel-Salam 2015[51] | 43 | 49.1 | 20 (47) | 30/60/10 | 34 | Ivabradine | MLHFQ | 3 | 20/23 (100) |
| **Hydralazine–nitrate** | | | | | | | | | |
| A-HeFT (Taylor 2004[52]; Carson 2009[53]) | 1050 | 56.7 | 421 (40) | 0/97/3 | 24 | Hydralazine plus isosorbide dinitrate | MLHFQ | 3–18 | 198/184 (36) |
| **Iron** | | | | | | | | | |
| FAIR-HF (Anker 2009[54]; Comin-Colet 2013[55]) | 459 | 67.8 | 244 (53) | 17/83/0 | 32 | Intravenous ferric carboxymaltose | KCCQ Overall Summary Score | 6 | 286/145 (94) |
| CONFIRM-HF (Ponikoswki 2015)[9] | 304 | 68.8 | 141 (46) | 53/47/0 | 37 | Intravenous ferric carboxymaltose | KCCQ Overall Summary Score | 12 | 114/106 (72) |
| PRACTICE-ASIA-HF (Yeo 2018)[56] | 50 | 61.1 | 11 (22) | – | 39 | Intravenous ferric carboxymaltose | KCCQ Overall Summary Score | 3 | 17/21 (98) |
| Toblli 2007[57] | 40 | 76 | – | – | 31 | Intravenous iron sucrose | MLHFQ | 6 | 20/20 (100) |
| FERRIC-HF 2 (Charles-Edwards 2019)[58] | 40 | 70 | 11 (27) | 43/57/0 | 37 | Intravenous iron isomaltoside | KCCQ Overall Summary Score | 0.5 | 21/19 (95) |
| IRONOUT-HF (Lewis 2017)[59] | 225 | Median 63 | 80 (36) | 73/23/0 | 25 | Oral iron polysaccharide | KCCQ Overall Summary Score | 4 | 111/114 (100) |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-12, 12-item Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NR, not reported; NYHA, New York Heart Association; QLQ-SHF, Quality of Life Questionnaire for Severe Heart Failure; SF-36, 36-item Short Form survey; SIP, Sickness Impact Profile.

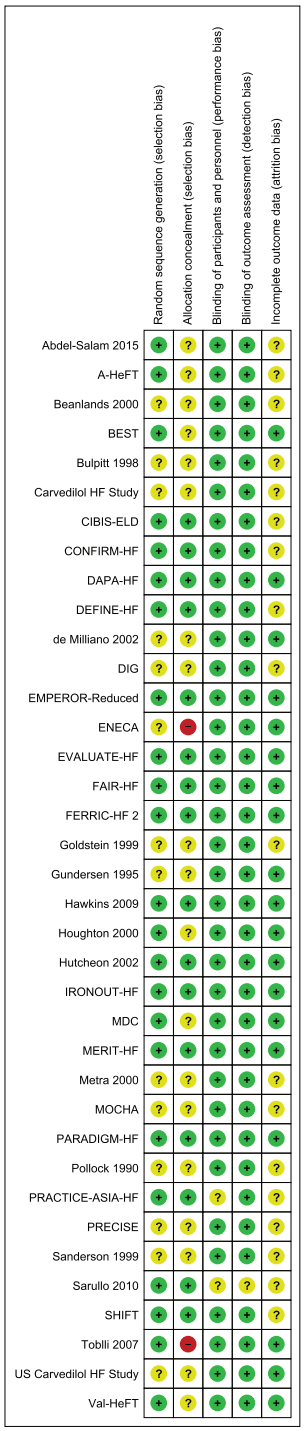


**Figure 2** Risk of bias assessment.

## Impact of ACE inhibitors, ARBs and ARNIs on health-related quality of life

Three trials analysing a total of 606 patients compared ACE inhibitors with placebo. In a random-effects meta-analysis of all three trials, the effect of ACE inhibitors vs. placebo on the primary outcome was inconclusive (SMD 0.03, 95% CI −0.15 to 0.20, $I^2 = 0\%$) (*Figure 4A*).

Two trials analysing a total of 3028 patients compared ARBs with placebo. Valsartan improved the primary outcome in Val-HeFT (SMD 0.09, 95% 0.02−0.17), whereas the smaller trial by Houghton *et al.* was inconclusive (SMD 0.86, 95% CI −0.12 to 1.83). In Val-HeFT, more patients had a minimal important improvement in HRQoL with valsartan than with placebo (20.4% vs. 18.2%; RR 1.12, 95% CI 1.00−1.25).

Two trials analysing a total of 7319 patients compared ARNIs to an ACE inhibitor. Key methodological differences in HRQoL analyses between these two trials (EVALUATE-HF and PARADIGM-HF) included numbers analyses (438 vs 6881) and timing (3 vs 8 months). Furthermore, PARADIGM-HF had an active run-in phase, whereas EVALUATE-HF did not. Both EVALUATE-HF (SMD 0.30, 95% CI 0.11−0.49) and PARADIGM-HF (SMD 0.09, 95% CI 0.02−0.17) showed improvements in HRQoL, translating to a mean KCCQ improvement of 4.5 at 3 months and 1.3 at 8 months, respectively. For the secondary outcome, differences were statistically significant in favour of ARNIs in EVALUATE-HF (53.9% vs. 40.8%, RR 1.32, 95% CI 1.09−1.61), but not in PARADIGM-HF (28.5% vs. 25.7%, RR 1.05, 95% CI 0.98−1.13).

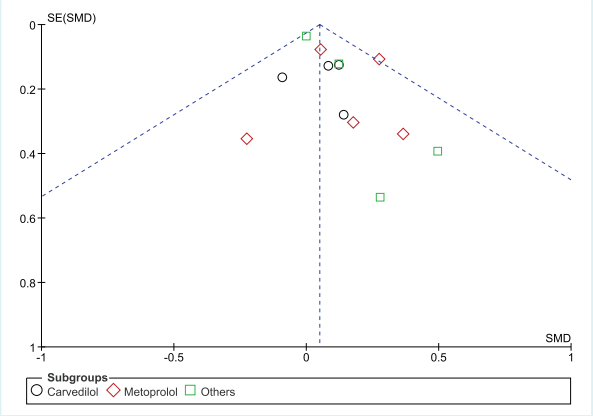


**Figure 3** Funnel plot for comparison of beta-blockers vs. placebo. SE, standard error; SMD, standardized mean difference.

## Impact of beta-blockers on health-related quality of life

Beta-blockers were the most studied drug class, including 13 trials comparing a beta-blocker with placebo ($n = 4650$) and three trials comparing carvedilol with an alternate beta-blocker ($n = 757$). In random-effects meta-analyses, differences were inconclusive for comparisons of beta-blockers vs. placebo (SMD 0.04, 95% CI −0.02 to 0.09, $I^2 = 0\%$; *Figure 4B*), including an analysis restricted to guideline-recommended beta-blockers (SMD 0.08, 95% CI −0.02 to 0.18, $I^2 = 0\%$), and for the comparison of carvedilol vs. other beta-blockers (SMD −0.06, 95% CI −0.20 to 0.08; three trials, $I^2 = 0\%$) for the primary outcome.

**Table 2 Summary of findings**

| Medication class | Primary outcome | | | Secondary outcome |
|---|---|---|---|---|
| | Certainty of evidence | SMD (95% CI), random-effects | Mean difference on KCCQ | Proportion with minimal important improvement |
| Improve HRQoL compared with placebo | | | | |
| ARB | High | 0.09 (0.02–0.17) | +1.8 at 23 months | +2.2% (NNT 46) |
| SGLT2 inhibitor | High | 0.16 (0.08–0.23) | +2.0 at 3–12 months | +3%–6.7% (NNT 15–34) at 8–12 months |
| Ivabradine | High | 0.14 (0.04–0.23) | +2.4 at 12 months | +3.6% (not significant) |
| Hydralazine–nitrate | High | 0.24 (0.04–0.44) | −4.5 at 3–18 months (on MLHFQ) | – |
| Intravenous iron | High | 0.52 (0.04–1.00) | +8.8 at ∼6 months | +9.9% (NNT 11) |
| Improve HRQoL compared with ACE inhibitor | | | | |
| ARNI | High | 0.30 (0.11–0.49) at 3 months, 0.09 (0.02–0.17) at 8 months | +4.5 at 3 months, +1.3 at 8 months | +13.1% (NNT 8) at 3 months, +2.8% (not significant) at 8 months |
| Uncertain effect on HRQoL | | | | |
| ACE inhibitor | Moderate[a] | 0.03 (−0.15 to 0.20) | – | – |
| Guideline-recommended beta-blocker | Moderate[a] | 0.04 (−0.02 to 0.18) | – | – |
| Digoxin | Low[a,b] | 0.06 (−0.10 to 0.23) | – | – |
| Oral iron | Moderate[a] | 0.08 (−0.18 to 0.34) | – | – |
| Carvedilol (vs. other beta-blocker) | Moderate[a] | −0.06 (−0.20 to 0.08) | – | – |
| No evidence identified for HRQoL | | | | |
| • Loop diuretics | | | | |
| • Mineralocorticoid receptor antagonists | | | | |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NNT, number needed to treat; SGLT2, sodium–glucose co-transporter 2; SMD, standardized mean difference.
[a]Graded down 1 level due to serious imprecision.
[b]Graded down 1 level due to serious indirectness.

## Impact of SGLT2 inhibitors on health-related quality of life

Three trials analysing a total of 6877 patients compared SGLT2 inhibitors with placebo. In a random-effects meta-analysis, SGLT2 inhibitors improved the primary outcome (SMD 0.16, 95% CI 0.08–0.23, $I^2$ = 47%) (*Figure 4C*), translating to a mean 2.0-point improvement in KCCQ at 3–12 months. The secondary outcome was reported in three trials, and was statistically significant in favour of SGLT2 inhibitors in DAPA-HF at 8 months (53.3% vs. 46.6%; RR 1.14, 95% CI 1.08–1.21) and EMPEROR-Reduced at 3, 8 and 12 months (50.8% vs. 47.8% at 12 months; RR 1.16, 95% CI 1.01–1.35), and inconclusive in DEFINE-HF at 3 months (41.2% vs. 31.1%; RR 1.33, 95% CI 0.96–1.84).

## Impact of ivabradine on health-related quality of life

Three trials analysing a total of 1784 patients compared ivabradine with placebo. These trials differed substantially in methodology, including numbers analysed, geographical location, and timing of HRQoL ascertainment, precluding meta-analysis. Despite this, the primary outcome was significantly better in all three trials, including the trials by Abdel-Salam (SMD 0.75, 95% CI 0.13–1.37) and Sarullo (SMD 1.08, 95% CI 0.54–1.63), as well as the large SHIFT trial (SMD 0.14, 95% CI 0.04–0.23). The effect of ivabradine vs. placebo on the secondary outcome in SHIFT was inconclusive, but directionally consistent with the primary outcome (51.4% vs. 47.8%, RR 1.08, 95% CI 0.98–1.18).

## Impact of iron replacement on health-related quality of life

Five trials analysing a total of 769 patients compared intravenous iron with placebo, and one trial of 225 patients compared oral iron with placebo. In random-effects meta-analyses, intravenous iron improved the primary outcome (SMD 0.52, 95% CI 0.04–1.00, $I^2$ = 86%) (*Figure 4D*), translating to a mean 8.8-point improvement in KCCQ at 6 months, whereas oral iron did not (SMD 0.08, 95% CI −0.18 to 0.34). In FAIR-HF, significantly more patients receiving intravenous iron had a minimal important improvement in HRQoL vs. placebo (60.9% vs. 51.0%; RR 1.19, 95% CI 1.00–1.43).

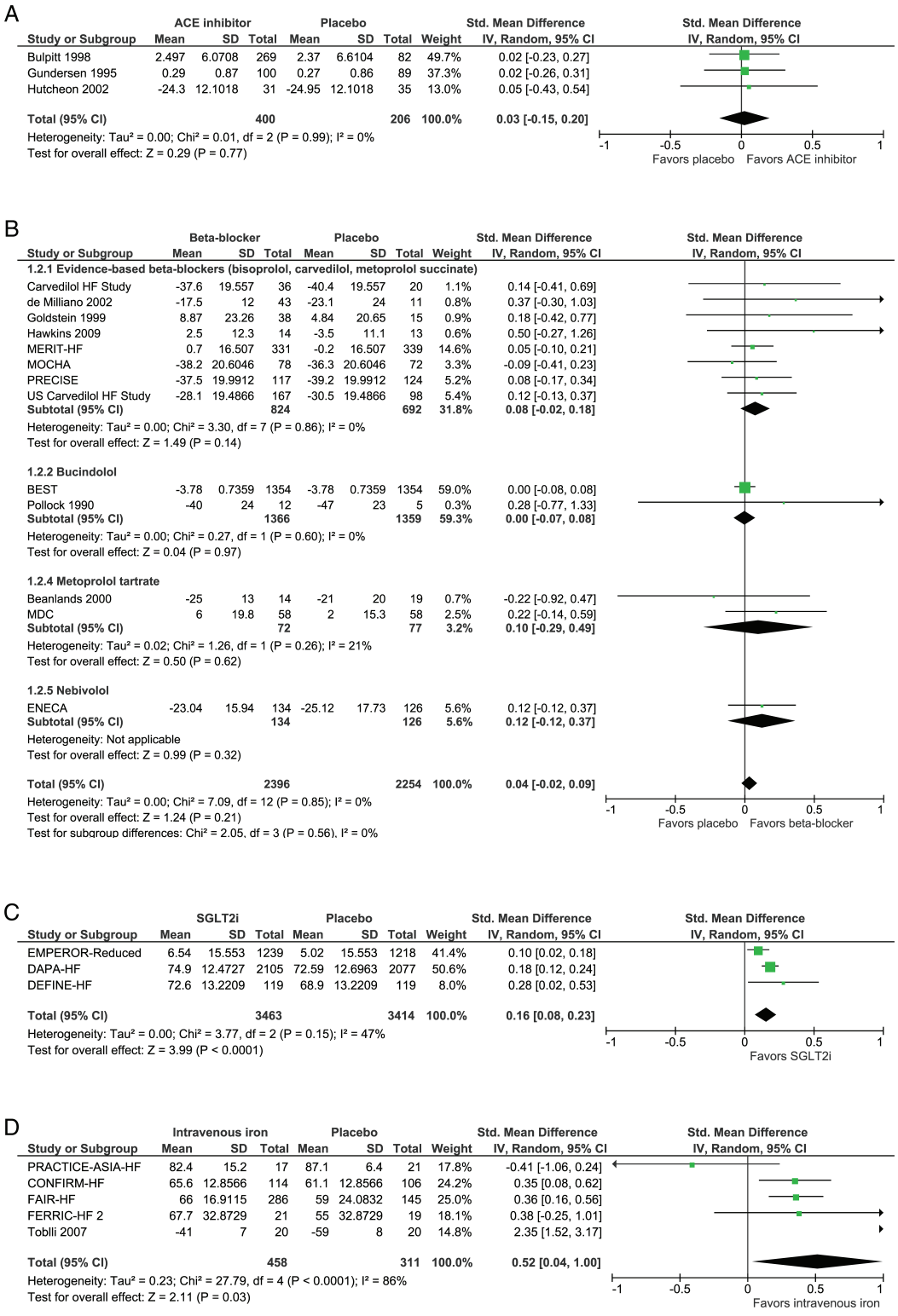


**Figure 4** Meta-analysis of the effect of (*A*) angiotensin-converting enzyme (ACE) inhibitors, (*B*) beta-blockers, (*C*) sodium–glucose co-transporter inhibitors (SGLT2i) and (*D*) intravenous iron vs. placebo on health-related quality of life in heart failure with reduced ejection fraction. CI, confidence interval; IV, inverse variance; SD, standard deviation.

### Impact of digoxin and hydralazine–nitrate on health-related quality of life

Digoxin and the fixed-dose combination of hydralazine–nitrate were each compared to placebo in a single trial evaluating HRQoL. In the DIG trial, the effect of digoxin vs. placebo on the primary outcome was inconclusive (SMD 0.06, 95% CI −0.10 to 0.23, $n = 589$). In A-HeFT, hydralazine–nitrate significantly improved the primary outcome (SMD 0.24, 95% CI 0.04–0.44, $n = 382$), translating to a mean MLHFQ improvement of 4.5.

## Discussion

### Principal findings

In this systematic review and meta-analysis of RCTs evaluating the impact of HFrEF pharmacotherapy, high-certainty evidence supported an improvement in HRQoL with ARBs, SGLT2 inhibitors, ivabradine, hydralazine–nitrate and intravenous iron compared with a matching placebo. Further high-certainty evidence supported the use of an ARNI improved HRQoL over an ACE inhibitor. The few studies that evaluated the secondary outcome – proportion of patients experiencing a minimal important improvement – found differences that were generally consistent with the primary outcome. The effect of ACE inhibitors, beta-blockers, digoxin, and oral iron were inconclusive, primarily due to imprecision. Finally, our search did not identify any published parallel, placebo-controlled RCTs evaluating the effect of MRAs or diuretics on HRQoL in patients with HFrEF.

### Comparison to other studies

This is the first systematic review with meta-analysis to broadly synthesize the data of the impact of HFrEF pharmacotherapy on HRQoL. Prior reviews have focused on describing issues in reporting of HRQoL in heart failure trials, including the large number of available instruments and lack of measurement and reporting standards.[60,61] One meta-analysis from 2007 concluded that beta-blockers did not significantly worsen HRQoL compared with placebo in patients with HFrEF.[62] A meta-analysis combining intravenous and oral iron formulations concluded that iron replacement improved HRQoL in patients with HFrEF and iron deficiency.[63] Our meta-analysis extends analyses beyond a single medication class, evaluates the impact of all contemporary HFrEF pharmacotherapy options, and also includes additional trials of beta-blocker and iron therapy that were not included in these prior meta-analyses.

### Implications of study results

Although several medications significantly improved HRQoL in HFrEF, the magnitude of effect differed by agent. Patients and clinicians may find it challenging to interpret the potential impact of these medications on their daily lives to come to a shared decision about their management. Several methods may help to conceptualize these results. First, we can use SMD values of 0.2, 0.5 and 0.8 as approximate thresholds for small, moderate, and large effects, respectively, as initially proposed by Cohen and used in trials of psychiatric and symptomatic therapies.[20] Based on this categorization, no individual HFrEF pharmacotherapeutic agent produced a large average improvement in HRQoL, though intravenous iron produced a moderate improvement, and ARBs, ARNIs, SGLT2 inhibitors, ivabradine and hydralazine–nitrate produced small improvements. However, these thresholds are arbitrary and not derived from preferences and values of patients with HFrEF. An alternate assessment of clinical significance involves comparing the measured effect size to an established minimal important difference. In our study, only intravenous iron produced an average HRQoL improvement that surpassed the typical 5-point threshold on the KCCQ to define the minimal important difference.[5] Using a lower threshold of 3.6 points as recently suggested by an analysis of the FAIR-HF trial,[64] hydralazine–nitrate and possible ARNI may provide an average improvement that is clinically meaningful. It should be noted that a mean improvement in HRQoL does not account for the distribution of effect among individual patients. Therefore, we can further compare the proportion of patients in the treatment and comparator group who experienced a minimal important improvement, the secondary outcome of our review. Using this measure, more patients experienced clinically meaningful improvements with ARBs, SGLT2 inhibitors, intravenous iron, and possibly ARNI and ivabradine; however, this outcome was reported in few of the included studies. Finally, it may also be useful to indirectly compare the mean HRQoL improvement from various interventions, including pharmacotherapy as demonstrated in our review, as well as other therapeutic options for HFrEF, such as exercise-based cardiac rehabilitation (mean 7.1-point improvement on the MLHFQ)[65] and cardiac resynchronization therapy (mean 6.6-point improvement on the MLHFQ).[66] Thus, the results of our primary and secondary outcomes provide complementary information that is practical in conveying to patients and clinicians the potential impact on HRQoL of various HFrEF pharmacotherapeutic options, in addition to the well-known effects on improving survival and reducing hospitalizations, when making therapy decisions.

With the availability of many pharmacotherapeutic options for HFrEF, there is now a greater opportunity to engage in shared decision-making with patients with HFrEF. Eliciting patient preferences is at the core of shared decision-making,[67] and previous studies have shown a strong bimodal preference by patients with HFrEF to either improve HRQoL or prolong survival.[10–14] As these preferences can change over the course of illness,[10–14] it is important to engage in these discussions at multiple timepoints, ideally with decision aids that incorporate the best available evidence on the benefits and harms of the various options. Moreover, several pharmacotherapeutic options simultaneously improve HRQoL, prolong survival, and reduce the risk of hospitalizations. A single endpoint that aggregates these outcomes, such as HRQoL-adjusted days alive and out of hospital similar to the 'patient journey' proposed by Ariti *et al.*,[68] could further facilitate communication of benefits.

## Limitations

This study has limitations stemming primarily from the included trials. First, HRQoL was measured and reported in relatively few of the RCTs of HFrEF pharmacotherapy, particularly for older trials. Many landmark trials were completed before the availability of validated HRQoL instruments and prioritization of HRQoL as an outcome of interest. As a result, the effect on HRQoL remains unclear for several mainstay HFrEF therapies, including ACE inhibitors, loop diuretics, and MRAs. Second, formal meta-analyses were only possible for 5 out of 11 comparisons due to small number of trials for each medication class. As a result, there was limited ability to perform trial-level subgroup and sensitivity analyses. Despite this, most individual trials in each comparison demonstrated point estimates that were directionally consistent with benefit from these interventions, and this was therefore insufficient to downgrade comparisons for inconsistency. Third, the availability of numerous HRQoL instruments complicates comparisons between therapies. Although the MLHFQ was the most widely used HRQoL instrument in trials conducted from 1990 to 2009, the KCCQ has been the main instrument used in more recent trials.[61] Most interventions found to significantly improve HRQoL in this review were evaluated using the KCCQ, which has demonstrated greater sensitivity to change than the MLHFQ.[69] Therefore, non-significant results – particularly among trials using the MLHFQ – do not provide definitive evidence for a lack of an effect on HRQoL, whereas the data from studies showing an improvement in HRQoL can readily be used for clinical decision-making. Finally, inadequate reporting of HRQoL precluded inclusion of several trials from our study. However, this study includes numerous high-quality RCTs and represents the most comprehensive and complete assessment of the HRQoL impact of HFrEF pharmacotherapy.

# Conclusions

In a systematic review and meta-analysis of randomized trials, ARBs, ARNIs, SGLT2 inhibitors, ivabradine, hydralazine–nitrate, and intravenous iron improved HRQoL in patients with HFrEF with high certainty of evidence. The effects of ACE inhibitors, beta-blockers, MRA, digoxin and oral iron on HRQoL were inconclusive. These findings can be incorporated into shared decision-making discussions with patients with HFrEF to select the medication regimen that best meets their goals and preferences.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Conflict of interest**: none declared.

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