New pharmacological treatments for heart failure with reduced ejection fraction (HFrEF)

A Bayesian network meta-analysis

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Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) has contributed to an increasing number of deaths and readmissions over the past few decades. Despite the appearance of standard treatments, including diuretics, β-receptor blockers and angiotensin-converting enzyme inhibitor (ACEI), there are still a large number of patients who have progressive deterioration of heart function and, inevitably, end-stage heart failure. In recent years, new medications for treating chronic heart failure have been clinically applied, but there is controversy surrounding drug selection and whether patients with HFrEF benefit from these medications. Therefore, we aimed to compare and rank different new pharmacological treatments in patients with HFrEF.

Methods: We performed a network meta-analysis to identify both direct and indirect evidence from relevant studies. We searched MEDLINE, EMBASE, and PsycINFO through the OVID database and CENTRAL through the Cochrane Library for clinical randomized controlled trials investigating new pharmacological treatments in patients with HFrEF published up to September 30, 2018. We included trials of ivabradine, levosimendan, omega-3, tolvaptan, recombinant human B-type natriuretic peptide (rhBNP), isosorbide dinitrate and hydralazine (ISDN/HYD) and angiotensin-neprilysin inhibition (LCZ696). We extracted the relevant information from these trials with a predefined data extraction sheet and assessed the risk of bias with the Cochrane risk of bias tool. Based on these items, more than half of the entries were judged as having an overall low to moderate risk of bias; the remaining studies had a high or unclear risk of bias. The outcomes investigated were left ventricle ejection fraction (LVEF %), heart rate (HR) and serum level of B-type natriuretic peptide (BNP). We performed a random-effects network meta-analysis within a Bayesian framework.

Results: We deemed 32 trials to be eligible that included 3810 patients and 32 treatments. Overall, 32 (94.1%) trials had a low to moderate risk of bias, while 2 (5.9%) trials had a high risk of bias. The quality of the included studies was rated as low in regard to allocation concealment and blinding and high in regard to other domains according to the Cochrane tools. As for increasing LVEF%, levosimendan was better than placebo (−3.77 (−4.96, −2.43)) and was the best intervention for improving ventricle contraction. As for controlling HR, n3-PUFA was better than placebo (4.01 (−0.44, 8.48)) and was the best choice for regulating HR. As for decreasing BNP, omega-3 was better than placebo (94.19 (−47.48, 1952.89)) and was the best therapy for improving ventricle wall tension.

Conclusions: Our study confirmed the effectiveness of the included new pharmacological treatments for optimizing the structural performance and improving the cardiac function in the management of patients with HFrEF and recommended several interventions for clinical practice.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ADDIS = aggregate data drug information system, ARB = angiotensin-receptor antagonists, BNP = B-type natriuretic peptide, HFrEF = heart failure with reduced ejection fraction, HR = heart rate, HYD = hydralazine, ISDN = isosorbide dinitrate, LVEF = left ventricular ejection fraction, MD = mean difference, NYHA = New York Heart Association, PSRF = potential scale reduction factor, RCTs = randomized controlled trials, rhBNP = recombinant human B-type natriuretic peptide.

Keywords: heart failure with reduced ejection fraction, network meta-analysis, pharmacological treatments
1. Introduction

For patients with chronic heart failure with reduced ejection fraction (HFrEF), multiple medication therapy that includes angiotensin converting enzyme inhibitors or angiotensin-receptor antagonists (ACEI/ARB), β-receptor blocker and spironolactone has been proven to decrease mortality and hospitalization rates in large randomized controlled trials (RCTs). The clinical benefits of these medical therapies have generally been applied in routine clinical practice. Therefore, these drugs form the cornerstone of contemporary evidence-based HFrEF care and are supported by class I indications in clinical treatment guidelines.

Despite their proven benefits and strong guideline recommendations, these traditional medications are restricted in application because of the complicated condition of patients and their many contraindications. With the high prevalence and mortality of patients with HFrEF each year, starting from the pathogenesis of the neural fluid mechanism of heart failure, a series of new clinical drugs that break through the limitations of traditional medicine have emerged. On this basis, several RCTs have been designed to evaluate the advantages and disadvantages of the new pharmacological therapy and traditional drugs using the cardiac function and structural optimization as the clinical outcomes. However, there is still a lack of direct comparisons between the efficacies of the new medications. To obtain high-quality evidence for making clinical decisions, we performed a Bayesian network meta-analysis to compare and rank different new pharmacological therapies for the management of patients with HFrEF.

2. Methods

This study was conducted in accordance with the Cochrane Handbook for the Systematic Review of Interventions (for details, see at http://training.cochrane.org/handbook) and the Preferred Reporting Items for Systematic Review and Meta-Analyses. The included studies were classified according to the types of pharmacological treatments.

2.1. Search strategy

For the network meta-analysis, we searched MEDLINE, EMBASE, and PsycINFO through the OVID database and searched CENTRAL through the Cochrane Library. We searched studies published from their inception to September 30, 2018, and compared different pharmacological treatments for clinical outcomes in patients with HFrEF (Appendix 1).

2.2. Study selection

2.2.1. Types of studies. All RCTs with a sample size >10 per arm.

2.2.2. Types of participants. The inclusion criteria were as follows: diagnosis of HFrEF according to the report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Heart failure patients with preserved ejection fraction, acute or chronic infectious or inflammatory diseases and recent myocardial infarction (<8 weeks) or active ischemia were excluded. The details of eligibility criteria PICOS are shown in Table 1.

2.2.3. Types of interventions. Ivabradine, levosimendan, omega-3, tolvaptan, recombinant human B-type natriuretic peptide (rhBNP), isosorbide dinitrate and hydralazine (ISDN/HYD) and angiotensin-neprilysin inhibitor (LCZ696) were included. However, the data form the LCZ696 clinical trials did not satisfy the requirements of the network meta-analysis. In the control group, any of the above seven pharmacological treatments (positive control), placebo and usual care (blank control) were included.

2.2.4. Types of outcome measures. The primary outcomes were LVEF, heart rate (HR) and the serum level of the B-type natriuretic peptide (BNP), which were also analyzed by network meta-analysis.

2.3. Data extraction and quality assessment

Two investigators (HL, YTD) independently selected the studies. The review of the main reports and supplementary materials, the extraction of the relevant information from the included trials with a predetermined data extraction sheet, and the assessment of the risk of bias with the Cochrane risk of bias tool were independently performed by 3 investigators (BFC, YZ, JMW). Any disagreements were resolved through discussion. When the investigators did not reach a consensus, the final decision regarding each question was made by other investigators within the review team (SW, WSH, and LML).

We evaluated the quality of the included studies with the Cochrane Collaboration Recommendations assessment tool. The tool for assessing 7 domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding (or masking) of outcome assessors, incomplete outcome data, selective reporting and other biases, is described in the Cochrane Handbook for Systematic Reviews of Interventions (see details at http://training.cochrane.org/handbook). Based on these items, more than half of the entries had an overall low to moderate risk of bias, and the remaining entries had a high or unclear risk of bias.

| Table 1 | Eligibility criteria PICOS. |
|---------|-----------------------------|
| **Inclusion criteria** | **Exclusion criteria** |
| Participants | Meet the diagnosis heart failure with reduced ejection fraction (HFrEF) of a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines | Heart failure with preserved ejection fraction; acute or chronic infectious or inflammatory diseases; recent myocardial infarction (<8 weeks) or active ischemia |
| Interventions | Ivabradine, levosimendan, omega-3, tolvaptan, recombinant human B-type natriuretic peptide (rhBNP), isosorbide dinitrate and hydralazine (ISDN/HYD) and Angiotensin-neprilysin inhibition (LCZ696) | |
| Comparisons | Any of above 7 pharmacological treatment (positive control); placebo; usual care (blank control) | |
| Outcomes | LVEF, heart rate, serum level of B-type natriuretic peptide | |
| Study design | Randomized controlled trials; sample size >10/arm | |
2.4. Statistical analysis

A network meta-analysis with a Bayesian framework with Aggregate Data Drug Information System (ADDIS, version 1.16.8) was conducted to assess the clinical outcomes of pharmacological interventions. This software is based on the Bayesian framework and the Markov chain Monte Carlo method, which can evaluate a priori and process research data. We used a random-effects model to analyze the effect sizes in this study. The effect sizes for continuous outcomes were the mean difference (MD). Consistency and inconsistency were the 2 models used to estimate the effect size in ADDIS. A consistency assessment drew conclusions on the effect sizes of the included interventions and estimated the ranking probabilities for all the interventions. The consistency test results were judged by node-splitting analysis and an inconsistency model. When the P value of the node-splitting analysis was greater than .05, a consistency mode was selected. Otherwise, an inconsistency model was used. The potential scale reduction factor (PSRF) was used to evaluate the convergence of the model. The closer the PSRF value was to 1, the better the convergence. The convergence of the model was still acceptable if the PSRF value was less than 1.2. For each intervention, we estimated the ranking probabilities for each treatment at each possible rank.

3. Results

3.1. Study identification and selection

In total, 28,051 citations published between 1981 and September 30, 2018, were identified by the search. After removing duplicates and unrelated articles, 32 articles describing 32 RCTs including 3495 patients were eligible for further quantitative analyses. The flow chart of the specific screening procedures is shown in Figure 1.

A total of 3495 participants were included, with sample sizes that ranged from 25 to 341. Participants’ mean age in the included studies ranged from 53 to 74, and the intervention duration was in the range of 24 hours to 12 months. All of the studies were parallel, randomized, and controlled, among which 2 studies (6.3%) were single-blinded, 9 studies (28.1%) were double-blinded, 13 studies (40.6%) were open-label and the remaining studies had 2 designs. Among the included studies, levosimendan (65.6%) was the main therapy in the treatment group, 6 studies (18.8%) employed ivabradine as the treatment group, while the other 4 drugs (omega-3, tolvaptan, rhBNP, ISDN/HYD) were used as treatments in the remaining studies. Outcome measures such as LVEF%, HR, and the serum level of BNP were used to evaluate the cardiac function. Eleven studies (34.4%) also treated New York Heart Association (NYHA) heart function and mortality as observation outcomes. All the characteristics of the included studies are shown in Table 2.
Table 2

The characteristics of the included studies.

| Year | First author | Study design | Principle health problem | Patients | Sample size (I:C) | Male: Female (I:C) | Intervention (I) | Control (C) | Main outcomes | Mortality/ NYHA (Follow up) |
|------|--------------|--------------|--------------------------|----------|------------------|--------------------|-----------------|--------------|----------------|-----------------------------|
| 2007 | Sophie Mayrov- gen[3][I] | RCT, open-label | Advanced HF (ischemic/idiopathic valvular) | NYHA II or IV; treatment with ACEIs, β-blockers, aldosterone LV ejection fraction of <30%; cardiac index <2.5L/min/m² | 6m:20, 61:19 | 50 (25:25) | 20:5:20:5 | Levosimendan 0.1 μg/kg/min to 0.2 μg/kg/min (10-minute intravenous bolus of 6 μg/kg) | None | Mean HR: LVEF (%): 8%: 32% | 6m |
| 2010 | Osam Can Yon- tur[3][I] | RCT | Ischemic HF | NYHA IV | 66:11, 67:7 | 58 (36:22) | 39:19 | Levosimendan + conventional treatment 0.1 μg/kg/min for 50 min to 0.2 μg/kg/min for an additional 23 h (0-6 μg/kg) | Dobutamine + conventional treatment 2.5 μg/kg to 5 μg/kg up to a 24-hour infusion for at least 6 h then gradually doubled up to 20 μg/kg/min | Dobutamine 5 μg/kg/min to the dabutamine dose was left for the physician for 24 h | HR (beats/min); LVEF; % LVESD (mm); LVEDD (mm); SBP (mm Hg); E (cm/s); E/A; A (cm/s); Sm (cm); LV ejection fraction | 24 h |
| 2015 | Ender Onel[3][I] | RCT, open-label | Severe LV systolic dysfunction | NYHA II or IV; LVEF <35% | 6m:11, 64:9 | 60 (40:21) | 32:8:18:3 | Levosimendan 0.1 mg/kg/5 min to 0.2 mg/kg if tolerate | Levosimendan 24 h, initially at a rate of 0.1 μg/kg/min to 0.2 μg/kg/min for at least 6 h then gradually doubled up to 20 μg/kg/min | Dobutamine 10 μg/kg/min | LVEF %; PAP mmHg; Crea-tinine (mg/dl) | 5d |
| 2009 | Mehmet İbahun Yil- maz[3][I] | RCT, open-label | Severe low-output systolic HF | NYHA II or IV; left ventricular (LV) ejection fraction (EF) of <35%; RV fractional area change of ≤24% | 65:9, 65:10 | 40 (27:13) | 21:6:9:4 | Levosimendan 24 h, initially at a rate of 0.1 μg/kg/min to 0.2 μg/kg/min | Dobutamine 24-hour infusion of 5 μg/kg/min for at least 6 h then gradually doubled up to 20 μg/kg/min | Dobutamine 24-h hour infusion of 5 μg/kg/min for at least 6 h then slowly doubled up to 20 μg/kg/min | LVEF %; PAP mmHg; Cre-a-tinine (mg/dl) | 24 h |
| 2009 | Hanaa Duye[3][I] | RCT, open-label | HF | NYHA II or IV; LVEF <40% | 62:9, 58:6 | 46 (21:25) | 14:7:18:7 | Levosimendan 24-hour 0.1 μg/kg/min to 0.2 μg/kg/min | Dobutamine 10 μg/kg/min | Dobutamine 24-h hour infusion of 5 μg/kg/min for at least 6 h then gradually doubled up to 20 μg/kg/min | LVEF %; PAP mmHg; Creatinine (mg/dl) | 24 h |
| 2012 | Michael J. Boni[3][I] | RCT, open-label | End stage HF | NYHA IV; refractory to standard therapy; PCWP > 15 mm Hg | 55:12, 53:13 | 42 (21:21) | 20:1:20:1 | Levosimendan 0.3 μg/kg/min | Levosimendan 24 h, initially at a rate of 0.1 μg/kg/min to 0.2 μg/kg/min | Dobutamine 24-h hour infusion of 5 μg/kg/min for at least 6 h then gradually doubled up to 20 μg/kg/min | LVEF %; HR; SBP mmHg; Mean right atrial pressures mmHg; Mean pulmonary arterial pressures mmHg; Pulmonary capillary wedge pressures | 19%: 38%: 42%: 0.016: 0.026: 0.006 (3m) |
| 2011 | Deddé Ibnbiod[3][I] | RCT, double-blind | Severe CHF of nonischemic origin | NYHA II IV; LVEF <35% | 61.9±9.6, 56.6±7.0, 55.1±12.7 | 45 (13:16:16) | 13:0:14:2:25:4 | Levasimendan 4 g/day | Levasimendan 4 g/day | Levasimendan 4 g/day | LVEF (%) | 3m |
| 2011 | Mauricio Vehren- rani[3][I] | prospective, random- mized, open- blinded endpoint (PROBE) study | HF | NYHA I-II; clinically stable for the 3 wk before selection or discharged; 6 min walking test 100-400 m; heart rate ≥50 bpm; SBP <100 mm Hg; LV EF <40%; HR <70 bpm, sinus rhythm | 67±10, 67±10 | 79 (41:38) | 28:38:26:12 | Levasimendan up to 7.5 mg bid | Levasimendan up to 7.5 mg bid | Levasimendan up to 7.5 mg bid | LVEF (%) | 3m |
| 2016 | Francisac J. Hidalgo[3][I] | RCT, open-label | Acute HF, either de novo or decompensated (PROBE) study | NYHA I-II; LVEF <35%; sinus rhythm HR <70; stable for ≥2 wk; sinus rhythm HR ≥70, stable for ≥2 wk; sinus rhythm; LVEF >40% | 66±15, 66±12 | 71 (33:38) | 24:9:26:12 | Levasimendan 5 mg/12 h combined with low-dose beta-blockers | Levasimendan 5 mg/12 h combined with low-dose beta-blockers | Levasimendan 5 mg/12 h combined with low-dose beta-blockers | LVEF %; NYHA; LVESDI; LVEDVI | 4m |
| 2011 | C. Gocan[3][I] | RCT, double-blind | CHF (Previous MI) | NYHA III IV; LVEF <35%; sinus rhythm HR ≥70; stable for ≥2 wk; sinus rhythm HR ≥70; stable for ≥2 wk; sinus rhythm; LVEF >40%; | 60±11, 59±11 | 611 (304:307) | 244:60:252:55 | Levasimendan 5 mg/12 h combined with low-dose beta-blockers | Levasimendan 5 mg/12 h combined with low-dose beta-blockers | Levasimendan 5 mg/12 h combined with low-dose beta-blockers | LVEF %; NYHA; LVESDI; LVEDVI | 12m |
| 2013 | J. Kojuri[3][I] | RCT, double-blind | CHF | NYHA II or III; sinus rhythm; LVEF <40%, | 56, 58 | 70 (38:32) | 22:12:9:20:12 | omega-3 2 g/day | omega-3 2 g/day | omega-3 2 g/day | LVEF %; NYHA; LVESDI; LVEDVI | 6m |
| 2007 | John T. Parissi- sio[3][I] | RCT | Advanced HF (both ischemic/idiopathic) | NYHA II IV; LVEF <35% | 65±8, 61±14 | 39 (26:13) | 24:2:9:4 | Levasimendan 24 h infusion, at a rate of 0.1 μg/kg/min without a loading dose. | Levasimendan 24 h infusion, at a rate of 0.1 μg/kg/min without a loading dose. | Levasimendan 24 h infusion, at a rate of 0.1 μg/kg/min without a loading dose. | LVEF %; NYHA; LVESDI; LVEDVI | 3.6±0.3: 2.6±0.4: 3.1±0.4: 3.2±0.5 NYHA | Not clear | 6m |

(continued)
| Year   | First author      | Study design | Principle health problem                  | Patients     | Age (C) | Sample size (C) | Male: Female (C) | Intervention (I) | Control (C) | Main outcomes | Morality / NYHA Follow up |
|--------|-------------------|--------------|-------------------------------------------|--------------|---------|----------------|-----------------|------------------|-------------|---------------|-------------------------|
| 2004   | John T. Parisis   | RCT          | Decompensated HF (ischemic or dilated)    | NYHA II–IV, currently on treatment with angiotensin-converting enzyme inhibitors, diuretic; LVEF < 30% | 72±2; 69±3 | 27 (13:14) | Not clear | Levosimendan 10-minute intravenous bolus/kg followed by continuous infusion 0.1–0.4 μg/kg | Placebo | LVEF (%); Systolic blood pressure (mm Hg); LV end-diastolic diameter (cm); LV end-systolic diameter (cm); TnF-α (pg/ml); L-6 (μg/ml) | Not clear |
| 2007   | Ignatios Ikonami- | RCT          | Advanced HF ischemic/dilated              | NYHA II–IV; LVEF < 30% | 63±8; 63±12 | 42 (21:21) | 19:2 | Levosimendan 24-hour infusion 0.1 μg/kg/min, with no a loading dose | Placebo | HR; LVEF (%); LV End-diastolic volume (mm3); LV End-systolic volume (mm3); BNP (pg/ml); Em (cm); Sm (cm) | 24 h |
| 2008   | John T. Parisis   | RCT          | Advanced CHF ischemic/dilated             | NYHA II–IV; LVEF < 30% | 62±10; 62±11 | 26 (17:9) | 16:1 | Levosimendan 0.1 μg/kg/min | Placebo | BNP (pg/ml); L-6 (μg/ml); sICAM-1 (pg/ml); sVCAM-1 (pg/ml) | 48 h |
| 2008   | Hamza Diagou     | RCT, open-label | Acute decompen-sated HF with ischemic cardiomyopathy | NYHA II–IV; LVEF < 40%; sinus rhythm, not receiving digoxin, other parenteral positive inotropes, or β-blockers | 64±10; 65±8 | 60 (30:30) | 19:11 | Dobutamine a continuous 24 h infusion of 5 μg/kg/min | Placebo | LVEF (%); E (cm/s); A (cm/s); sPAP (mm Hg) | Not clear |
| 2005   | John T. Parisis   | RCT, open-label | Advanced HF ischemic/dilated              | NYHA III (74/174) | 66±5; 65±5 | 34 (17:17) | 16:1 | Levosimendan 10-minute intravenous bolus at 6 μg/kg, 0.1 to 0.4 μg/kg/min | Placebo | LV end-diastolic diameter (mm); LV end-systolic diameter (mm); BNP (pg/ml); Interleukin-6 (pg/ml) | 24 h |
| 2007   | John T. Parisis   | RCT, single-blind | Advanced CHF dilated/ischemic              | NYHA II–IV; LVEF < 30% | 65±8; 66±5 | 63 (42:21) | 35:7 | Levosimendan 24 h; levosimendan infusion 0.1 μg/kg/min | Placebo | LV end-diastolic diameter (mm); LV end-systolic diameter (mm); LVEF (%) | 3.3±0.7 |
| 2006   | John T. Parisis   | RCT, open-label | Advanced HF ischemic/dilated              | NYHA II–IV; LVEF < 35% | 63±8; 63±12 | 54 (36:18) | 34:2 | Levosimendan 24-hour infusion 0.1 μg/kg/min | Placebo | LVEF (%); Pulmonary arterial pressure (mmHg); E (cm/s); A (cm/s); BNP (pg/ml); Interleukin-6 (pg/ml) | Not clear |
| 2009   | YT Zhang         | RCT, single-blind | CHF ischemic or idiopathic dilated cardiomyopathy | NYHA II–III | 74±6; 71±10 | 75 (56:37) | 27:11 | 2 g n-3 PUFA 180 mg eicosapentaenoic acid + 120 mg docosahexaenoic acid | Placebo | LVEF (%); LVEDD (mm); LVEDV (mm); NT-proBNP (pg/ml); TnF-α (pg/ml); L-6 (μg/ml); ICM-1 (ng/ml) | 3 m |
| 2011   | Savina Nodari    | RCT, double-blind | CHF due to non-ischemic dilated cardiomyopathy | NYHA IV; LVEF ≤ 45%; at least 3 mo on evidence-based medical treatment | 61±11; 64±9 | 133 (67:66) | 64:3 | n-3 PUFA 1.0 g gelatin capsules containing 850 to 900 mg of EPA and DHA ethyl esters | Placebo | LVEDV (mL); LVEF (%) | 1.83±0.38 |
| 2011   | Jean-Claude Tar- | RCT, double-blind | CHF and systolic dysfunction               | NYHA I–II; LVEF ≤ 35%; sinus rhythm; HR ≥ 70 (bpm) | 60±11; 59±11 | 611 (304:307) | 244:60; 252:55 | Levosimendan intermittent infusions 0.1 to 0.4 μg/kg/min | Placebo | LVEDV (mL); LVEF (%) | 2.1±0.65 |
| 2006   | J T Parisis      | RCT, open-label | Decompensated HF ischemic/dilated         | NYHA II or IV; LVEF ≤ 30%, currently taking AZDs and diuretics | 67±6; 70±8 | 25 (17:8) | 16:1 | Levosimendan 10-min bolus intravenous injection of 6 mg/kg continuous 24 h 0.1 μg/kg/min | Placebo | HR; Systolic blood pressure (mm Hg); Diastolic blood pressure (mm Hg); LV end-diastolic diameter (mm); LV end-systolic diameter (mm); LVEF%; NT-proBNP (pg/ml) | 30 d |
| 2012   | Gabriela Mal-    | RCT, open-label | CHF ischemic/non-ischemic etiology         | LVEF < 35% | 71±7; 69±8 | 33 (22:11) | 16:6 | Levosimendan intermittent infusions 0.1 to 0.4 μg/kg/min | Placebo | Cardiac Index; BNP (pg/ml); Serum Na+ (mg/dL); Serum K+ (mEq/L); LVEF (%) | 3.07±0.36 |
|        | fattolo          |              |                                           |              |          |                      |                 |                  |             | (continued) |                                      |

(continued)
| Year | First author | Study design | Principle health problem | Age (I:C) | Sample size (I:C) | Male: Female (I:C) | Intervention (I) | Control (C) | Main outcomes | Morbidity/ NYHA | Follow up |
|------|--------------|--------------|--------------------------|-----------|------------------|-------------------|-----------------|-------------|--------------|---------------|-----------|
| 2007 | Jay N. Cohn  | RCT          | CHF                      | 57±13: 57±13 | 678 (337:341)   | 182:155; 225:116 | ISDN 20 mg and HFD 37.5 mg | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | 3.5±0.5 | 2.5±0.6 | (3 months) |
| 2007 | Rudolf Berger | RCT, open-label | Advanced CHF              | 57±10: 54±10 | 75 (39:36)       | 32:29            | Levosimendan 12 μg/kg for 10 min, 0.1 μg/kg/min for 24 h | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | 2.5±0.6 | 2.1±0.8 | (0 year) |
| 2008 | Hamza Duygu  | RCT, open-label | CHF                      | 62±10: 64±8 | 40 (20:20)       | 11:10            | Levosimendan 10 min intravenous bolus infusion at 6–12 μg/kg, 12 μg/kg 24 h infusion at 0.1 μg/kg/min | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | 2.1±0.7 | 2.1±0.7 | (1 year) |
| 2011 | Mikko Jalanko | RCT, double-blind | Congestive CHF          | 63±12: 63±13 | 29 (18:11)       | 16:2             | Levosimendan 1 mg | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | Not clear | Not clear | (Not clear) |
| 2010 | Ibrahim Hall Kurt | RCT, open-label | Decompensated CHF       | 63±12: 64±10 | 59 (30:29)       | 13:17            | Levosimendan 12 μg/kg for 10 min intravenous bolus infusion at 0.1 μg/kg/min | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | 37:5 | 37:5 | (Not clear) |
| 2005 | Doddo Mort | RCT, open-label | CHF                       | 57±2: 54±2 | 73 (38:35)       | 31:27            | Levosimendan 0.1 μg/kg/min for 24 h | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | Not clear | Not clear | (Not clear) |
| 2003 | Mihai Ghiorghiu | RCT, double-blind | CHF                      | 70±11: 67±13 | 127 (64:63)      | 40:24            | Tolvaptan 30 mg/d | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | Not clear | Not clear | (Not clear) |
| 2016 | Hiroki Tsuchiya | RCT, double-blind | CHF                      | 59±13: 60±14: 59±13 | 126 (42:42:42) | 37:5 | 2.5 mg ivabradine 9D: 5 mg ivabradine 8D | Placebo | Plasma wave reflections, LV remodeling, 6MWT distance, NT-proBNP, and quality of life | Not clear | Not clear | (Not clear) |

ACEI = angiotensin-converting enzyme inhibitor, BNP = B-type natriuretic peptide, CHF = congestive heart failure, DPP = diastolic blood pressure, HF = high frequency, HR = heart rate, HFD = hydralazine, ISDN = isosorbide dinitrate, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, PCWP = pulmonary capillary wedge pressure, SBP = systolic blood pressure.
3.2. Quality assessment of the included studies

We evaluated the quality of included studies with the Cochrane Collaboration Recommendations assessment tools. Among 32 trials, 32 studies (100%) described a random component in the sequence generation process, such as a computer-generated random number or a random number table. Allocation concealment was performed using an appropriately sealed method in 25% (8) of the studies, while 46.9% (15) either did not describe concrete methods or used an inappropriate allocation concealment method. In regard to performance bias, 34.4% (11) of the included trials reported the methods of blinding for both participants and personnel. In regard to detection bias, 53.1% (17) of the outcome assessors in the studies either could not be blinded or were unclear. In regard to attrition bias, 30 studies were deemed to have low-risk outcome data (ie, the reported dropout rates were within the range of the statistical estimations, provided detailed explanations of dropout rates or performed intention-to-treat analysis). Other risks were unclear due to insufficient information in 1 study. A detailed quality assessment is presented in Figures 2 and 3.

3.3. Bayesian network meta-analyses

3.3.1. Outcome 1: LVEF%. The network of eligible comparisons for efficacy consisted of 20 studies and 8 treatments (16 arms of levosimendan; 6 arms of dobutamine; 3 arms of ivabradine; 1 arm of PGE1, omega-3 and furosemide; 1 arm of placebo). The specific network is presented in Figure 4A.

Node-splitting analysis was used to assess consistency. All of the P values between the direct and indirect effects in node-splitting analysis were >.05 (Table 3). A PSRF value closer to 1 indicated convergence and stable results for the model. Therefore, the consistency model was selected for the subsequent network analysis.

The results of the network meta-analyses for LVEF% are presented as a league table in Figure 4B. In terms of efficacy, levosimendan was better than placebo (−3.77 (−4.96, −2.43)) and was the best intervention for improving ventricle contraction. The efficacies of ivabradine and PGE1 were also better than that of placebo (−2.92 (−4.41, −1.66)), −2.65 (−6.43, 0.99), respectively.

The ranking probability of treatments is presented in Figure 4C and D. The results indicated that levosimendan was significantly more effective than the other treatments. The second and third most effective interventions were ivabradine and PGE1, respectively.

3.3.2. Outcome 2: HR. The network of eligible comparisons for efficacy consisted of 11 studies and 6 treatments (10 arms of levosimendan; 2 arms of dobutamine and PGE1; 1 arm of n3-PUFA; 1 arm of blank; 6 arms of placebo). The specific network is presented in Figure 5A.

The results of the network meta-analyses for HR are presented as a league table in Figure 5B. In terms of efficacy, n3-PUFA was better than placebo (4.01 (−0.44, 8.48)) and was the best intervention for regulating HR. The efficacies of PGE1 was also better than placebo (0.85 (−4.48, 5.64)).

The ranking probability of treatments is presented in Figure 5C and D. The results indicated that ivabradine was significantly more effective than the other treatments. The next most effective interventions were PGE1 respectively.

3.3.3. Outcome 3: BNP. The network of eligible comparisons for efficacy consisted of 10 studies and 6 treatments (8 arms of levosimendan; 1 arm of omega-3, ISDN/HYD, PGE1 and furosemide; 8 arms of placebo). The specific network is presented in Figure 6A.

The results of the network meta-analyses for BNP are presented as a league table in Figure 6B. In terms of efficacy, omega-3 was better than placebo (941.99 (−47.48, 1952.89)) and was the best therapy for improving ventricle wall tension. The efficacies of levosimendan and PGE1 were also better than that of placebo (365.88 (199.34, 550.01)), 306.39 (−159.12, 753.17), respectively.

The ranking probability of treatments is presented in Figure 6C and D. The results indicated that omega-3 was significantly more effective than the other treatments. The second and third most effective interventions were levosimendan and PGE1, respectively.

4. Discussion

4.1. Summary of results

This comprehensive network meta-analysis found that levosimendan was superior to the other therapeutic drugs in improving the ventricular systolic function and reducing ventricular wall tension. In the reduction of HR, n3-PUFA plays a critical role that is compatible with its pharmacological effect. The effects of omega-3 in reducing rBNP were better than that of the control group, suggesting that they were only used in specific circumstances.
4.2. Clinical implications

As a new medication designed for improving cardiac contractility, levosimendan can obtain improved myocardial contraction and blood oxygen supply without increasing the intracellular Ca2+ concentration and avoid adverse events, such as myocardial stunning and malignant arrhythmia. A series of clinical studies, including LIDO, RUSSLAN, CASINO, SURVICE, and REVIVE, have confirmed that levosimendan can improve the clinical outcome in patients with congestive heart failure caused by systolic dysfunction. In this study, it was found that levosimendan was superior to other drugs in regard to improving myocardial contraction (higher LVEF%, SMD = 3.77 (–4.96, –2.43)) and reducing ventricular wall tension (lower serum BNP level, SMD: 365.88 (199.34, 550.01)) mainly because of its unique biological effects in vivo. Levosimendan increases myocardial contraction and improves ventricular diastolic function during the cardiac cycle by pulsed binding to troponin C at low Ca2+ concentrations, which has been demonstrated in laboratory and clinical studies.

Given that the latest guidelines consider HR (frequency) control to be an important component of heart failure management, the use of ivabradine has increased. Unlike the negative muscle force and conduction induced by a β receptor blocker, ivabradine reduces both atrial rhythm and ventricular nonconduction by specifically inhibiting the cationic current If (funny current), which is activated by the hyperpolarization of the sinoatrial node. Studies such as SHIFT and BEAUTIFUL have shown that ivabradine can translate HR reduction into beneficial effects for improving the prognosis of heart failure.

As a third generation β receptor blocker, carvedilol regulates the adverse effects of catecholamines on the heart and kidneys via non-selective inhibition of the β receptor and selective inhibition of the α1 receptor, thereby improving the long-term prognosis of patients with HFrEF. Further clinical studies have also confirmed that patients with HFrEF taking carvedilol have improved survival compared to those taking a metoprolol succinate or tartrate formulation.

As a suplement to traditional diuretics, tolvaptan is mainly used by patients with heart failure with high volume of hyponatremia. EVEREST and other trials have shown that tolvaptan can only alleviate short-term symptoms and signs (sodium retention and dyspnea), but does not help decrease mortality. Similar to atorvastatin, exogenous rhBNP (nesiritide) supplementation may improve short-term hemodynamics and acute symptoms in patients with HFrEF, but is not helpful for improving the long-term prognosis.
Considered the antiarrhythmic, anti-inflammatory and antioxidant effects of omega-3 polyunsaturated fatty acids, GISSI-HF study from Tavazzi et al. further revealed that omega-3 supplementation may reduce heart failure-related hospitalizations and death in patients with HFrEF (56 patients needed to be treated for a median duration of 3.9 years to avoid one death or 44 to avoid one event like death or admission to hospital for cardiovascular reasons[28,29]). It was also found in this study that omega-3 polyunsaturated fatty acids supplements improved myocardial performance for patients with HFrEF. Therefore, we suggest that HFrEF patients may benefit from omega-3 supplementation to lower their risk of congestive heart failure-related hospitalizations and death.
Table 3
Direct and indirect effects between drugs.

| Name               | Direct effect     | Indirect effect    | Overall       | P value |
|--------------------|-------------------|--------------------|---------------|---------|
| Blank, ivabradine  | 1.08 (–3.47, 5.52)| 6.52 (1.56, 11.45) | N/A           | .11     |
| Blank, levosimendan| 7.02 (2.71, 11.19)| 1.58 (–3.46, 6.70) | N/A           | .10     |
| Ivabradine, placebo| –3.11 (–4.86, –1.38)| 2.15 (–4.05, 8.67) | N/A           | .11     |
| Levosimendan, placebo| –3.83 (–5.16, –2.23)| –9.52 (–15.29, –2.82) | N/A           | .09     |

Figure 5. Rank probability of HR in pharmacological treatments. HR = heart rates, n3-PUFA = n-3 polyunsaturated fatty acids, PGE1 = prostaglandin E1.
4.3. Limitations

There were several limitations in the current study. First, the quality of several of the included studies was not optimal. When evaluating these studies, we found that many lacked details on allocation concealment or blinding. Additionally, several studies had high dropout rates, inevitably due to the lengths of the trials. Second, although we evaluated the studies according to the tool, any evaluation of bias is subjective. There is no quantitative index that can evaluate only an artificial risk of bias. Third, because we used strict inclusion and exclusion criteria, the number of included studies was low, which may have influenced the strength of the evidence. For example, 2 RCTs on LCZ696 were not included in this study due to the lack of the main outcomes required for meta-analysis. Nonetheless, as a revolutionary drug that is most likely able to change the status of heart failure, LCZ696 has been shown to significantly reduce the risk of cardiovascular death and readmission due to heart failure by 20%, while the total mortality is reduced by approximately 20%.\[30,31\]
### Figure 6. (Continued)

| Drug          | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 |
|---------------|--------|--------|--------|--------|--------|--------|
| Furosemide    | 0.64   | 0.11   | 0.14   | 0.06   | 0.04   | 0.01   |
| ISDN/HYD      | 0.07   | 0.23   | 0.52   | 0.14   | 0.03   | 0.01   |
| Levosimendan  | 0      | 0      | 0.02   | 0.35   | 0.55   | 0.07   |
| PGE1          | 0.04   | 0.06   | 0.13   | 0.34   | 0.33   | 0.06   |
| Omega-3       | 0.01   | 0.02   | 0.02   | 0.05   | 0.05   | 0.05   |
| Placebo       | 0.23   | 0.59   | 0.17   | 0.02   | 0.0   | 0      |

#### Figure 6B

| Drug          | 258.86 (-940.10, 467.88) | -535.79 (-1197.53, 71.76) | -467.43 (-1215.60, 282.73) | -1108.37 (-2272.31, 110.05) | -169.71 (-830.61, 475.79) |
|---------------|----------------------------|-----------------------------|----------------------------|----------------------------|----------------------------|
| ISDN/HYD      | 258.86 (-467.88, 940.10)  | -282.31 (-650.51, 43.47)   | -218.68 (-761.32, 864.91)  | 318.41 (1918.12, 182.82)    | 84.45 (-227.29, 248.16)   |
| Levosimendan  | 535.79 (-71.76, 1197.53)  | 282.31 (-43.47, 650.51)    | 63.49 (-387.10, 495.60)    | -584.05 (-1602.52, 450.31)  | 365.88 (199.34, 550.01)   |
| PGE1          | 467.43 (-282.73, 1215.60) | 218.68 (-318.41, 761.32)   | -63.49 (-495.60, 367.10)   | -633.45 (-1737.56, 753.17)  | 506.39 (-159.12, 753.17)  |
| Omega-3       | 1108.37 (-110.05, 2272.31)| 864.91 (-182.82, 1918.12)  | 584.05 (-450.31, 1602.52)  | 633.45 (-465.47, 1737.56)   | 941.99 (-47.48, 1952.89)  |
| Placebo       | 169.71 (-475.79, 830.61)  | -84.45 (-371.56, 227.29)   | -365.88 (-550.01, -199.34) | -306.39 (-753.17, 159.12)   | -941.99 (-1952.89, 47.48) |
5. Conclusion

Our study confirmed the effectiveness of the included new pharmacological treatments for optimizing the structural performance and improving the cardiac function in the management of patients with HF/REF and recommended several interventions for clinical practice. No single clinical trial can answer all pertinent questions, nor can all trial results be perfectly replicated in clinical practice. Additional high-quality RCTs should be performed to provide more powerful evidence in a wider population of heart failure patients.

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