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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 (941.99 (–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

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HL and YD contributed equally to this study.

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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).[1,2] The clinical benefits of these medical therapies have generally been applied in routine clinical practice.[3] Therefore, these drugs form the cornerstone of contemporary evidence-based HFrEF care and are supported by class I indications in clinical treatment guidelines.[1,2]

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.[4,5] 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.[6–9] 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.[10] 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 wk) 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 inconsistence model. When the *P* value of the node-splitting analysis was greater than .05, a consistency mode was selected.[11] 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.

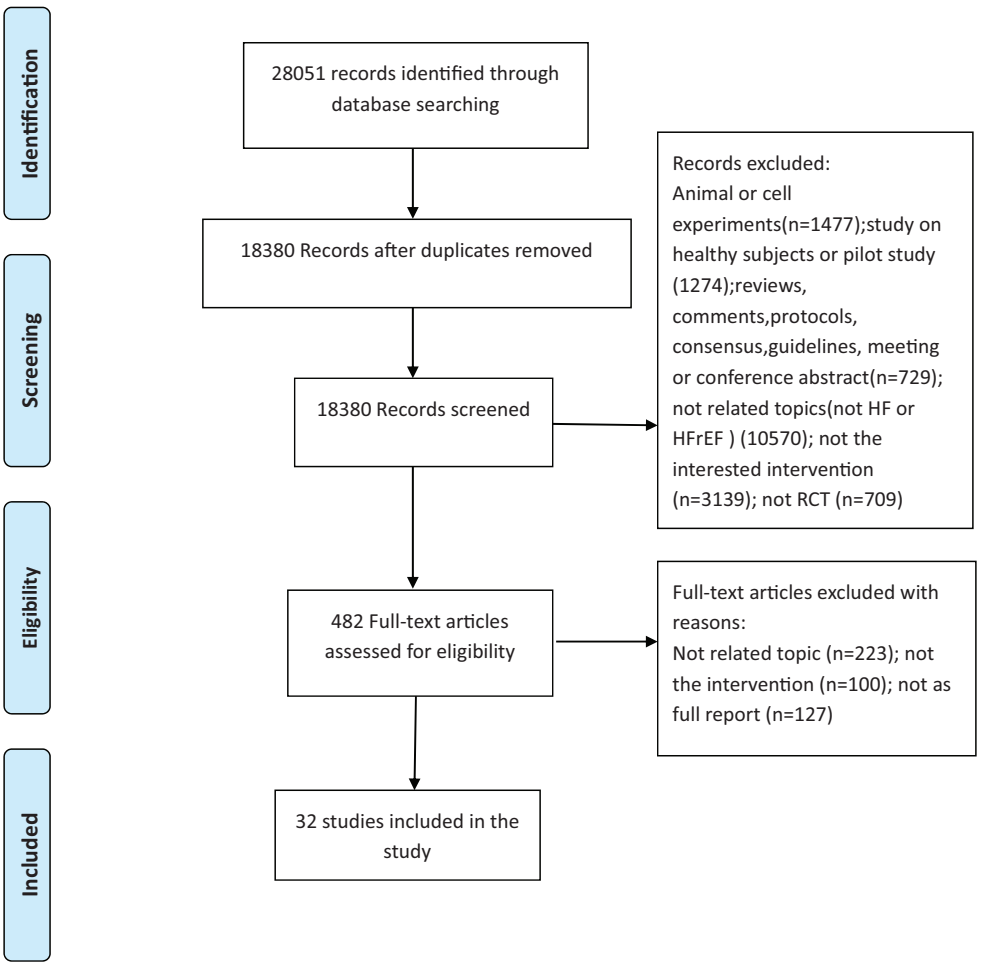


Figure 1. Study selection.

Table 2

The characteristics of the included studies.

Year	First author	Study design	Principle health problem	Patients	Age (I:C)	Sample size (I:C)	Male: Female (I:C)	Intervention (I)	Control (C)	Main outcomes	Motality/ NYHA	Follow up
2007	Sophie Mavrogeni[32]	RCT, open-label	Advanced HF ischemic/dilated/ valvular	NYHA III or IV; treatment with ACEIs, β-blockers, aldosterone; LV ejection fraction of <30%; cardiac index <2.5 L/min/m^2	62±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%	6 m
2010	Osman Can Yontar[33]	RCT	Ischemic HF	NYHA IV	66±11; 67±7	58 (36:22)	39:19	Levosimenda + conventional treatment 0.1 μg/kg/ minute for 50 min to 0.2 μg/kg/min for an additional 23 h (3–6 μg/kg)	Dobutamine+conventional treatment 2.5 μg/kg to 5 μg/kg up to a 24-hour	HR (beats/min); LVEF %; LVEDD mm; LVESD (mm)		24 h
2015	Ender Oner[34]	RCT, open-label	Severe LV systolic dysfunction	NYHA III or IV; LVEF < 35%	60±11; 64±9	61 (40:21)	32:8; 18:3	Levosimendan 0.1 mg/kg/ for 50 min to 0.2 mg/kg/ if tolerate	Dobutamine 5 mg/ kg/min to the dobutamine dose was left for the physician for 24 h	SBP [mm Hg]; DBP [mm Hg]; E [cm/s]; E/A; A [cm/s]; LVEF %; LVEDd [cm]; LVESd [cm]	3.6±0.5 before 2.2±0.7 after < 0.001; 3.7±0.5 3.1±0.7 0.003	5 d
2009	Mehmet Birhan Yilmaz[35]	RCT, open-label	Severe low-output systolic HF	NYHA III 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-h period initially 5 μg/kg/minute for at least 6 h then freely decide	LVEF %; PAP mmHg; Creatinine (mg/dl)		24 h
2009	Hamza Duygu[36]	RCT, open-label	HF	NYHA III or IV; LV ejection <40%	62±9; 58±6	46 (21:25)	14:7; 18:7	Levosimendan 24-hour 0.1 μg/kg/min 6–12 μg/kg	Dobutamine 24-hour infusion of 5 μg/kg/min gradually doubled up to 20 μg/kg/min	LVEF %; E (cm/s); A (cm/s); E/A ratio; Em (cm/s) tissue Doppler; PAP (mmHg);		24 h
2012	Michael J. Bonios[37]	RCT, open-label	End stage HF	NYHA IV; refractory to standard therapy; PCWP > 15 mmHg	55±12; 53±13	42 (21:21)	20:1; 20:1	Levosimendan 0.3 μg/kg/ min	Dobutamine 10 μg/kg/min	LVEF %; HR; SBP mmHg; Mean right atrial Pressures mmHg; Mean pulmonary arterial Pressures, mmHg; Pulmonary capillary wedge Pressures	19%: 38% (6m) 4±0 before 2.8±1.0 after 0.016 4±0 2.7±0.8 0.026 (3m)	3 m 6 m
2011	Deddo Moertl[38]	RCT, double-blind	Severe CHF of nonischemic origin	NYHA III-IV; LVEF < 35%	61.9±9.6; 58.6±7.0; 55.1±12.7	45 (13:16:16)	13:0; 14:2; 25:4	n3-PUFA 4 g/d n3-PUFA 1 g/d	placebo	LVEF (%)		3 m
2011	Maurizio Volterrani[39]	prospective, randomised, open, blinded endpoint (PROBE) study	HF	NYHA II-III; clinically stable for the 3 wk before selection or discharged; 6-min walking test 100–400 m; heart rates ≥50 bpm	67±10: 67±10	79 (41:38)	28:13; 26:12	Ivabradine up to 7.5 mg bid	Carvedilol up to 25 mg bid	SBP, mm Hg; DBP, mm Hg; Resting HR; Distance on 6-min walking test, m		12 wk
2016	Francisco J. Hidalgo[40]	RCT, open-label	Acute HF, either de novo or decompensated	LVEF <40%; HR >70 bpm; sinus rhythm	66±15; 68±12	71 (33:38)	24:9; 26:12	Ivabradine 5 mg/12 h combined with low-dose beta-blockers	low-dose beta-blockers	LVEF %; BNP levels (pg/ml); HR		4 m
2011	C. Ceconi[41]	RCT, double-blind	CHF (Previous MI)	NYHA I-III; LVEF ≤35%; sinus rhythm HR ≥70; stable for ≥4 wk;	60±11; 59±11	611 (304:307)	244:60; 252:55	Ivabradine 5 mg bid increased to 7.5 mg bid	Placebo	LVEF %; LVESVI; LVEDVI		12 m
2013	J. Kojuri[42]	RCT, double-blind	CHF	NYHA II or III; sinus rhythm; LVEF < 40%;	56; 58	70 (38:32)	22:16; 20:12	omega-3 2 g/d	Placebo	Plasma BNP (pg/mL); 6-min walk test (m); LVEF %; Sm: systolic velocity.(cm/s);		6 m
2007	John T. Parissis, Ioanna Andreadou[43]	RCT	Advanced HF (both Ischemic/dilated)	NYHA III-IV; LVEF < 35%	65±8; 61±14	39 (26:13)	24:2; 9:4	Levosimendan 24 h infusion, at a rate of 0.1 μg/kg/ min without a loading dose.	Placebo	BNP (pg/ml); Systolic blood pressure (mmHg);HR; LVEF (%);E/E′	3.6±0.3 2.8±0.4; 3.1±0.4 3.2±0.5 NYHA	Not clear

(*continued*)

Table 2

(continued).

Year	First author	Study design	Principle health problem	Patients	Age (I:C)	Sample size (I:C)	Male: Female (I:C)	Intervention (I)	Control (C)	Main outcomes	Motality/ NYHA	Follow up
2004	John T. Parissis,[44]	RCT	Decompensated HF (ischemic or dilated)	NYHA III-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 bolus6 μg/kg followed by continuous infusion 0.1–0.4 μg/kg	Placebo	LVEF (%); Systolic blood pressure (mm Hg); Diastolic blood pressure (mm Hg); LV end-diastolic diameter (cm); LV end-systolic diameter (cm); TNF-α (pg/ml); IL-6 (pg/ml)		Not clear
2007	Ignatios Ikonomidis[45]	RCT	Advanced HF Ischemic/dilated	NYHA III-IV; LVEF < 35%	63±8; 63±12	42 (21:21)	19:2; 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/s); Sm (cm/s)		24 h
2008	John T. Parissis[46]	RCT	Advanced CHF Ischemic/dilated	NYHA 2.6±0.3; LVEF < 35%	62±10; 62±11	26 (17:9)	16:1; 15:2	Levosimendan 0.1 μg/kg/min 24 h	Placebo	BNP (pg/ml); IL-6 (pg/ml); sICAM-1 (pg/ml); sVCAM-1 (pg/ml)		48 h
2008	Hamza Duygu[47]	RCT, open-label	Acute decompensated HF with ischemic cardiomyopathy	NYHA III or IV; LVEF < 40%; sinus rhythm; not receiving digoxin, other parenteral positive inotropics, or β-blockers	64±10; 65±8	60 (30:30)	19:11; 16:14	Levosimendan 10 min intravenous bolus infusion 6–12 μg/kg continuous 24 h 0.1 μg/kg/min	Dobutamine a continuous 24 h infusion of 5 μg/kg/min	LVEF (%);E (cm/s); A (cm/s); E/A ratio; Em (cm/s); PAP (mm Hg);		Not clear
2005	John T. Parissis[48]	RCT, open-label	Advanced HF ischemic/dilatated	NYHA III/IV (17/4;17/4) impaired LV systolic function	66±5; 68±5	34 (17:17)	16:1; 15:2	Levosimendan 10-minute intravenous bolus infusion 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)	NYHA III/IV: 17 /4 vs. 5/0, $p < 0.05$; NYHA III/IV: 17 /4 vs. 9/2, $p < 0.05$	24 h
2007	John T. Parissis[49]	RCT, single-blind	Advanced CHF dilated/ischemic	NYHA III–IV; LVEF <30%;	65±8; 66±8	63 (42:21)	35:7; 17:4	Levosimendan 24 h levosimendan infusion of 0.1 μg/kg/min	Placebo	LV end-diastolic diameter mm; LV end-systolic diameter mm; LVEF (%); E (m/s); A (m/s); E/A;	3.3±0.7 2.1±0.7; 3.4±0.6 3.0±0.5	Not clear
2006	John T. Parissis[50]	RCT, open-label	Advanced HF ischemic/dilated	NYHA III or IV; LVEF <35%	63±8; 63±12	54 (36:18)	34:2; 16:2	Levosimendan 24-hour infusion 0.1 μg/kg/min-0.2 μg/kg/min	Placebo	LVEF (%);Systolic pulmonary arterial pressure (mm); E (cm/s); A (cm/s); E/A; BNP (pg/ml); Interleukin-6 (pg/ml)	3.5±0.6 2.4±0.7; 3.5±0.5 3.6±0.6	Not clear
2009	YT Zhao[51]	RCT, single-blind	CHF ischemic or idiopathic dilated cardiomyopathy	NYHA II – III	74±6; 71±10	75 (38:37)	27:11; 28:9	2 g n-3 PUFA 180 mg eicosapentaenoic acid + 120 mg docosahexaenoic acid	Placebo	LVEF (%);LVEDD (mm); LVESD (mm); NT-proBNP (pg/ml); TNF-α (pg/ml); IL-6 (pg/ml); ICAM-1 (ng/ml)		3 m
2011	Savina Nodari[52]	RCT, double-blind	CHF due to nonischemic dilated cardiomyopathy	NYHA I-II; LVEF ≤45%; at least 3 mo on evidence-based medical treatment	61±11; 64±9	133 (67:66)	64:3; 56:10	n-3 PUFAs 1.0 g gelatin capsules containing 850 to 882 mg of EPA and DHA ethyl esters in	Placebo	LVEDD, mm; LVESD, mm; LVEDV, ml; LVEF%; E, cm/s; A, cm/s; E/A	1.83±0.38 2.14±0.65; 1.88±0.33 1.61±0.49	12 m
2011	Jean-Claude Tardif[53]	RCT, double-blind	CHF and systolic dysfunction	NYHA II – IV; LVEF ≤35%; sinus rhythm; HR ≥ 70 (bpm)	60±11; 59±11	611 (304:307)	244:60; 252:55	Ivabradine 5 mg bid	Placebo	LVEDV (mL); LVEF (%)		8 m
2006	J T Parissis[54]	RCT, open-label	decompensated CHF ischemic/dilated	NYHA III or IV; LVEF ≤ 30%; currently taking ACEIs and diuretics	67±6; 70±8	25 (17:8)	16:1; 7:1	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	Gabriella Malfatto[55]	RCT, open-label	CHF ischemic/non-ischemic etiology	LVEF ≤ 35%	71±7; 69±8	33 (22:11)	16:6; 8:3	Levosimendan Intermittent Infusions 0.1 to 0.4 μg/kg/min	Furosemide 2 mg/hour to 10 mg/hour maximal dose of 250 mg	Cardiac Index; BNP (pg/mL); Serum Na+ (mEq/L); Serum K+ (mEq/L); LVEF (%); LVEDV (mL)	3.07±0.36 2.55±0.33; 3.16±0.39 3.09±0.54	4 w

(*continued*)

Table 2

(continued).

Year	First author	Study design	Principle health problem	Patients	Age (I:C)	Sample size (I:C)	Male: Female (I:C)	Intervention (I)	Control (C)	Main outcomes	Motality/ NYHA	Follow up
2007	Jay N. Cohn[56]	RCT	CHF	NYHA II-IV; LVEF ≤ 35%; >35 but <45% transverse diameter of LV in diastole of ≥2.9 cm/m^2 body surface	57±13; 57±13	678 (337:341)	182:155; 225:116	ISDN 20 mg and HYD 37.5 mg	Placebo	wave reflections, LV remodeling, 6MW distance, NT-pro-BNP, and quality of life		6 m
2007	Rudolf Berger[57]	RCT, open-label	Advanced CHF	NYHA IIIb or IV; LVEF<35%, pulmonary capillary wedge pressure >15 mm; cardiac index <2.5 l/min/m	57±10; 54±10	75 (39:36)	32:7; 29:7	Levosimendan 12 μg/kg for 10 min 0.1 μg/kg/min for 24 h	PGE1 fixed low dose of 2.5 ng/kg/min	Systolic BP, mm Hg; Diastolic BP, mm Hg; HR; BNP, pg/ml; LVEF %;	3.5±0.5 2.5±0.6 (3 monhs) 2.1±0.8 (1 year); 3.6±0.5 2.6±0.7 (3 monhs) 2.1±0.7 (1 year)	1 yr
2008	Hamza Duygu[58]	RCT, open-label	CHF	NYHA III to IV; LVEF <40%	62±10; 64±8	40 (20:20)	11:9; 10:10	Levosimendan 10-min intravenous bolus infusion at 6–12 μg/ 24 h infusion at 0.1 μg/kg/min	Dobutamine 5 μg/kg/min for 10 min to 10, 15, and 20 μg/kg/min at 10-min intervals	SBP (mm Hg); DBP (mm Hg); HR; LVEF (%);Sm (cm/s); E/A ratio	NYHA class II/III/IV, n 0/8/12 14/6/0; 0/9/11 4/12/4	>30 d
2011	Mikko Jalanko[59]	RCT, double-blind	Congestive CHF	NYHA class IIIB–IV;LVEF <30%	63±12; 63±13	29 (18:11)	16:2; 11:0	Levosimendan 1 mg;	Placebo	PCWP (mmHg); HR (bpm); SBP (mmHg); LVEDD (mm); LVEDV (ml); LVEF (%);Sm (cm/s)		180 d
2010	Ibrahim Halil Kurt[60]	RCT, open-label	Decompensated CHF	NYHA III–IV	63±12; 64±10	59 (30:29)	13:17; 12:17	Levosimendan 12 μg/kg for 10 min intravenous (i.v.) 0.1 μg/kg/min i.v. i	Standard treatment furosemide, ACEIs, spironolactone, and β-blockers	SBP (mmHg); DBP (mmHg); HR; BNP (pg/ml); Cr (mg/dl); K (mEq/l)		Not clear
2005	Deddo Moertl[61]	RCT, open-label	Decompensated CHF. ischemic/ non-ischemic	NYHA IIIb/IV; cardiac index <2.5 L/min/m^2; pulmonary capillary wedge pressure (PCWP) >15 mmHg	57±2; 54±2	73 (38:35)	31:7; 28:7	Levosimendan 0.1 μg/kg/min for 24 h	Prostaglandin E1 2.5 ng/kg/min for 7 days	CO (L/min); PCWP (mmHg); PAP		48 h
2003	Mihai Gheorghiade[62]	RCT, double-blind	CHF	NYHA I-IV	70±11; 67±13	127 (64:63)	40:24; 46:17	Tolvaptan 30 mg/d	Placebo	HR; Systolic blood pressure, mm Hg; Diastolic blood pressure, mm Hg; Serum K; Serum Na; Serum creatinine, mg/dL		25 d
2016	Hiroyuki Tsutsui[63]	RCT, double-blind	CHF	NYHA II – IV; LVEF ≤35%; age ≥20 years; resting HR ≥ 75 beats/min in sinus rhythm,	58±13; 60±14; 59±13	126 (42:42:42)	37:5; 37:5; 34:8	2.5 mg Ivabradine BID; 5 mg Ivabradine BID	Placebo	LVEF (%);BNP (pg/ml); NT-proBNP (pg/ml);		14 d

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

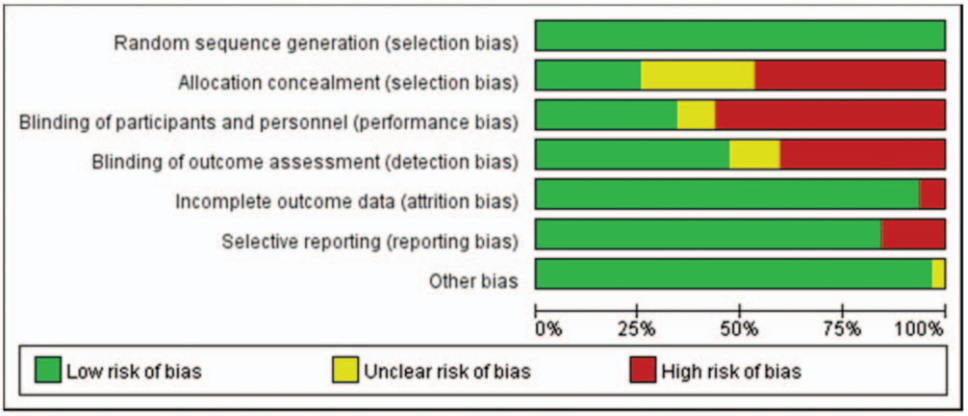


Figure 2. Risk of bias of included studies.

3.2. Quality assessment of the included studies

We evaluated the quality of included studies with the Cochrane Collaboration Recommendations assessment tools.[12] 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 blank; 11 arms 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 rhBNP were better than that of the control group, suggesting that they were only used in specific circumstances.

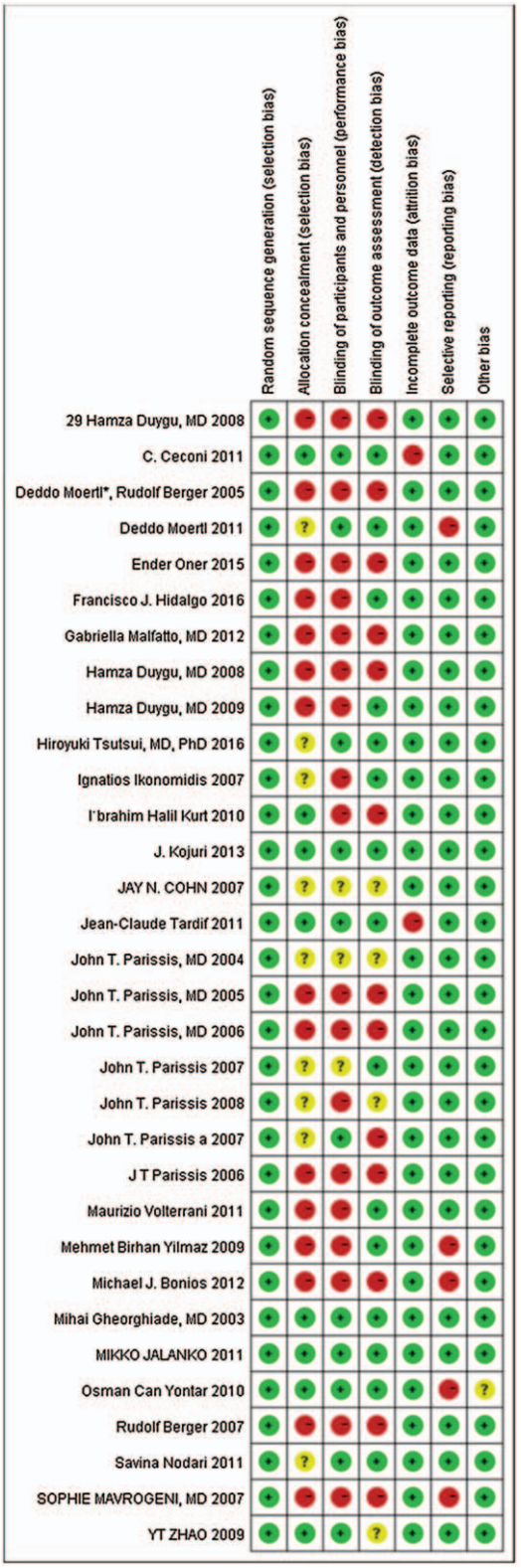


Figure 3. Risk of bias summary of included studies.

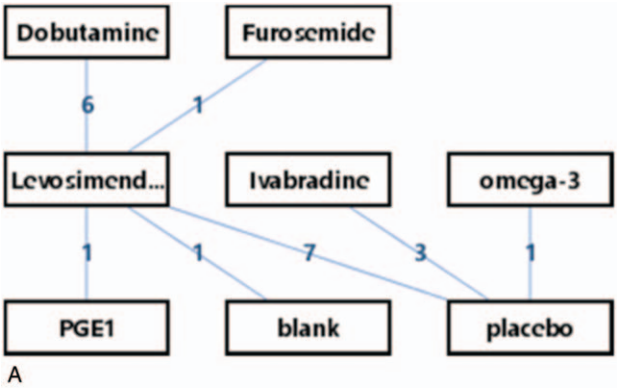


Figure 4. Rank probability of LVEF% in pharmacological treatments. LVEF = left ventricular ejection fraction, PGE1 = prostaglandin E1.

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.[13,14] 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.[15–19] 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.[20,21] 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.[22,23]

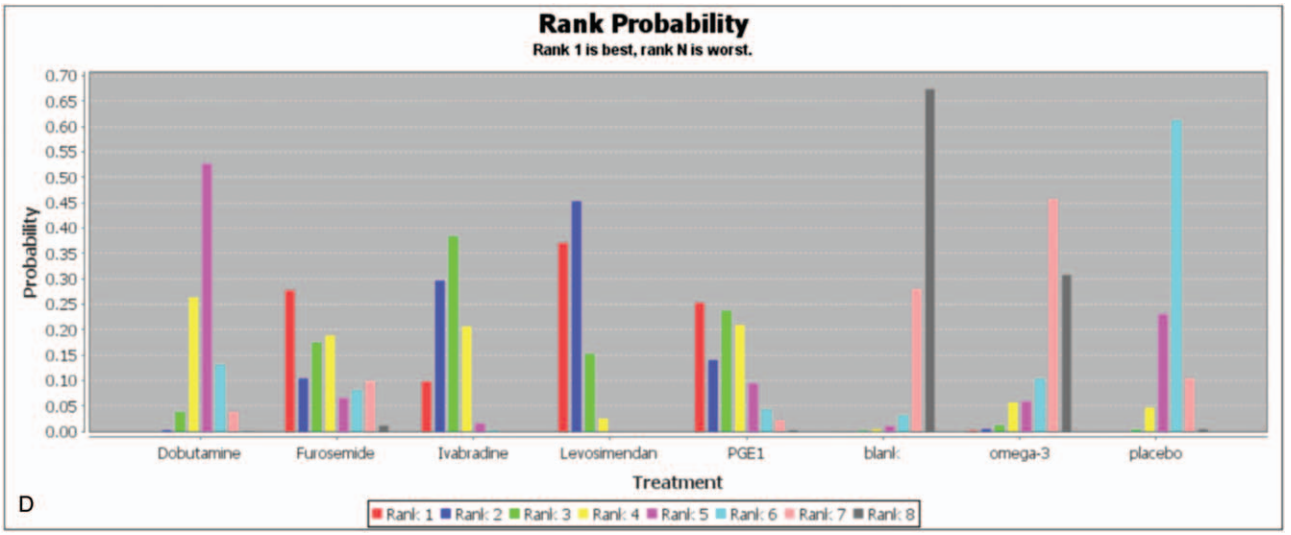
As a supplement to traditional diuretics, tolvaptan is mainly used by patients with heart failure with high volume of hyponatremia. EVEREST and other trials have shown that tolvaptan can only alleviate short-term symptoms and signs (sodium retention and dyspnea), but does not help decrease mortality.[24,25] 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.[26,27]

Dobutamine	1.81 (−3.41, 7.18)	2.02 (0.00, 4.43)	2.90 (1.60, 4.21)	1.80 (−1.81, 5.55)	−3.99 (−8.04, −0.57)	−2.76 (−7.94, 1.60)	−0.80 (−2.59, 0.99)
−1.81 (−7.18, 3.41)	Furosemide	0.25 (−5.21, 5.41)	1.17 (−4.05, 5.91)	0.38 (−6.89, 7.42)	−5.75 (−12.30, −0.01)	−4.55 (−11.15, 1.62)	−2.72 (−8.02, 2.17)
−2.02 (−4.43, −0.00)	−0.25 (−5.41, 5.21)	Ivabradine	0.85 (−1.12, 2.53)	−0.37 (−4.21, 3.69)	−6.22 (−10.14, −2.66)	−4.90 (−9.81, −0.82)	−2.92 (−4.41, −1.66)
−2.90 (−4.21, −1.60)	−1.17 (−5.91, 4.05)	−0.85 (−2.53, 1.12)	Levosimendan	−1.10 (−4.44, 2.55)	−7.06 (−10.43, −3.69)	−5.74 (−10.53, −1.56)	−3.77 (−4.96, −2.43)
−1.80 (−5.55, 1.81)	−0.38 (−7.42, 6.89)	0.37 (−3.69, 4.21)	1.10 (−2.55, 4.44)	PGE1	−6.12 (−11.00, −0.98)	−4.90 (−10.64, 0.74)	−2.65 (−6.43, 0.99)
3.99 (0.57, 8.04)	5.75 (0.01, 12.30)	6.22 (2.66, 10.14)	7.06 (3.69, 10.43)	6.12 (0.98, 11.00)	blank	1.34 (−4.61, 6.82)	3.25 (−0.18, 6.94)
2.76 (−1.60, 7.94)	4.55 (−1.62, 11.15)	4.90 (0.82, 9.81)	5.74 (1.56, 10.53)	4.90 (−0.74, 10.64)	−1.34 (−6.82, 4.61)	omega-3	2.02 (−1.91, 6.66)
0.80 (−0.99, 2.59)	2.72 (−2.17, 8.02)	2.92 (1.66, 4.41)	3.77 (2.43, 4.96)	2.65 (−0.99, 6.43)	−3.25 (−6.94, 0.18)	−2.02 (−6.66, 1.91)	placebo

B

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Dobutamine	0	0	0.04	0.26	0.53	0.13	0.04
Furosemide	0.28	0.1	0.17	0.19	0.07	0.08	0.1
Ivabradine	0.1	0.3	0.38	0.21	0.02	0	0
Levosimendan	0.37	0.45	0.15	0.03	0	0	0
PGE1	0.25	0.14	0.24	0.21	0.09	0.04	0.02
blank	0	0	0	0	0.01	0.03	0.28
omega-3	0	0	0.01	0.06	0.06	0.1	0.46

C



D

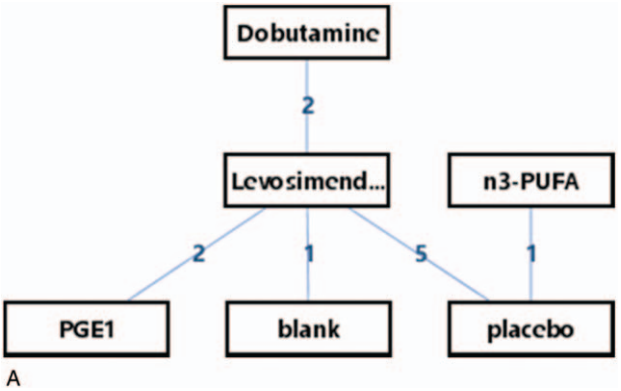
Figure 4. (Continued).

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



A

B

Dobutamine	−5.57 (−9.43, −1.17)	−7.48 (−12.45, −1.56)	−2.51 (−10.85, 6.07)	−10.74 (−17.67, −3.17)	−6.71 (−12.02, −1.07)
5.57 (1.17, 9.43)	Levosimendan	−1.93 (−5.30, 1.92)	3.11 (−4.36, 10.50)	−5.07 (−10.94, 0.73)	−1.05 (−4.65, 2.40)
7.48 (1.56, 12.45)	1.93 (−1.92, 5.30)	PGE1	4.96 (−3.38, 13.02)	−3.06 (−10.20, 3.53)	0.85 (−4.48, 5.64)
2.51 (−6.07, 10.85)	−3.11 (−10.50, 4.36)	−4.96 (−13.02, 3.38)	blank	−8.09 (−17.44, 1.35)	−4.06 (−12.40, 4.16)
10.74 (3.17, 17.67)	5.07 (−0.73, 10.94)	3.06 (−3.53, 10.20)	8.09 (−1.35, 17.44)	n3-PUFA	4.01 (−0.44, 8.48)
6.71 (1.07, 12.02)	1.05 (−2.40, 4.65)	−0.85 (−5.64, 4.48)	4.06 (−4.16, 12.40)	−4.01 (−8.48, 0.44)	placebo

C

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Dobutamine	0.73	0.25	0.01	0.01	0	0
Levosimendan	0	0.12	0.6	0.24	0.03	0
PGE1	0	0.03	0.08	0.3	0.48	0.1
blank	0.26	0.52	0.07	0.07	0.06	0.03
n3-PUFA	0	0.01	0.01	0.03	0.09	0.86
placebo	0	0.07	0.23	0.36	0.32	0.01

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

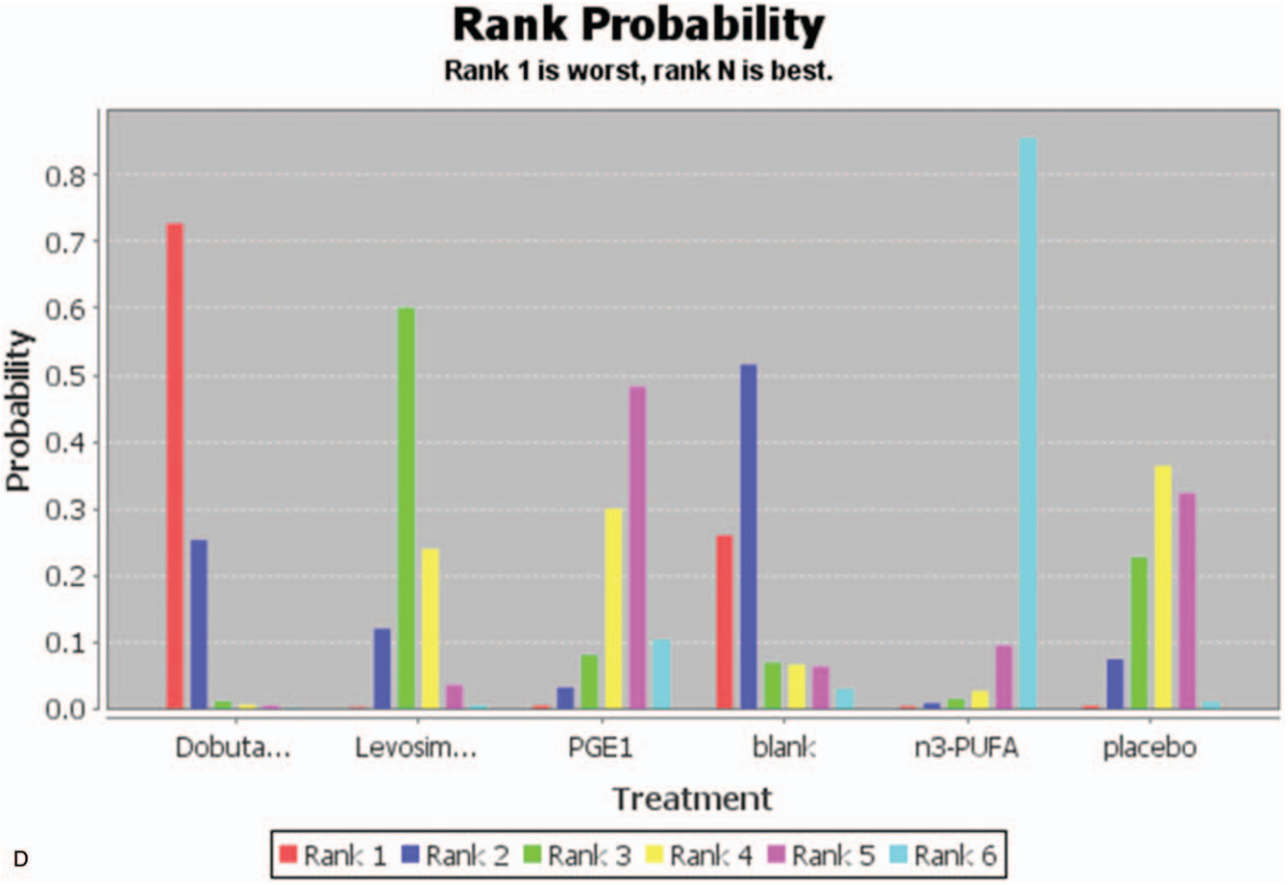


Figure 5. (Continued).

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]

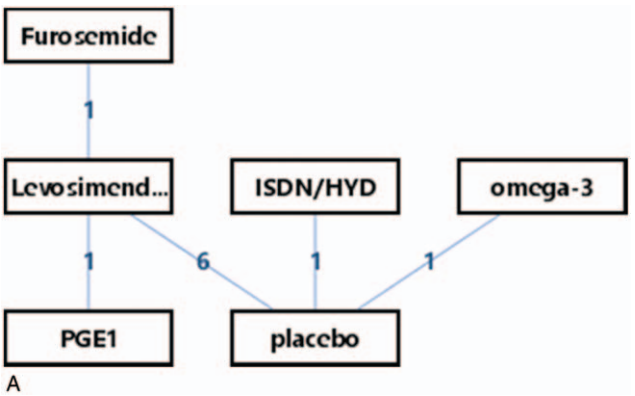


Figure 6. Rank probability of BNP in pharmacological treatments. BNP = brain natriuretic peptide, PGE1 = Prostaglandin E1, ISDN/HYD = isosorbide dinitrate and hydralazine.

B

Furosemide	-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)
258.86 (-467.88, 940.10)	ISDN/HYD	-282.31 (-650.51, 43.47)	-218.68 (-761.32, 318.41)	-864.91 (-1918.12, 182.82)	84.45 (-227.29, 371.56)
535.79 (-71.76, 1197.53)	282.31 (-43.47, 650.51)	Levosimendan	63.49 (-367.10, 495.60)	-584.05 (-1602.52, 450.31)	365.88 (199.34, 550.01)
467.43 (-282.73, 1215.60)	218.68 (-318.41, 761.32)	-63.49 (-495.60, 367.10)	PGE1	-633.45 (-1737.56, 465.47)	306.39 (-159.12, 753.17)
1108.37 (-110.05, 2272.31)	864.91 (-182.82, 1918.12)	584.05 (-450.31, 1602.52)	633.45 (-465.47, 1737.56)	omega-3	941.99 (-47.48, 1952.89)
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)	placebo

C

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	0.38	0.33	0.06
omega-3	0.01	0.02	0.02	0.05	0.05	0.85
placebo	0.23	0.58	0.17	0.02	0	0

D

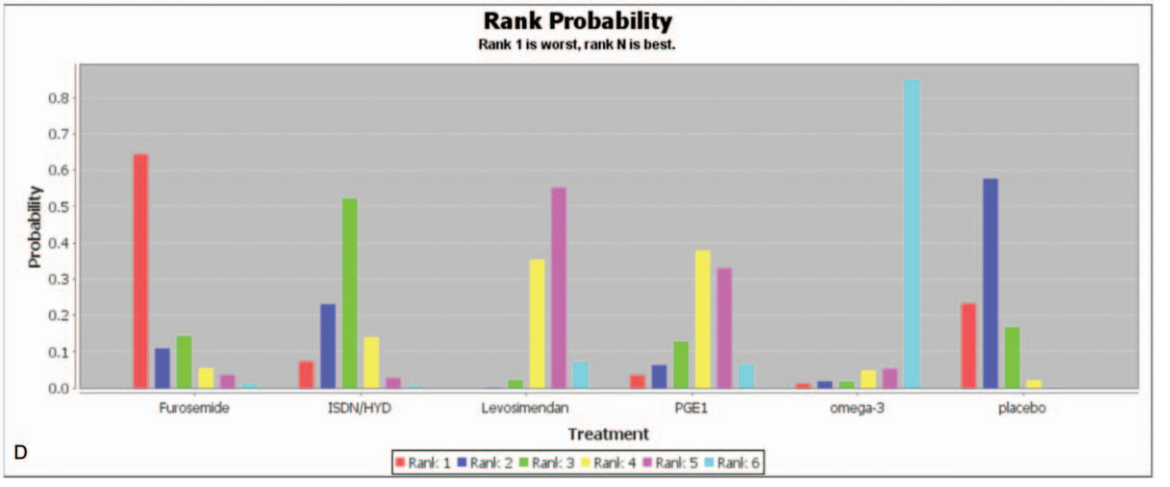


Figure 6. (Continued).

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 HFrEF 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.

Author contributions

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Resources: Yu Zhao.
Software: Yuting Duan.
Supervision: Liming Lu.
Validation: Weiping Su.
Writing – original draft: Heng Li, Yuting Duan.

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