Systematic Review and Meta-Analysis

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Hemodynamic effects of inotropic drugs in heart failure

A network meta-analysis of clinical trials

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Abstract

Background: There is currently no consensus on the appropriate selection of inotropic therapy in ventricular dysfunction. The objective of the study was to detect the effects of different inotropes on the hemodynamics of patients who developed low cardiac output.

Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched (all updated December 31, 2017). The inclusion criteria were as follows: low cardiac index (CI < 2.5 L/min/m^2) or New York Heart Association class II–IV, and at least 1 group receiving an inotropic drug compared to another group receiving a different inotropic/placebo treatment. The exclusion criteria were studies published as an abstract only, crossover studies, and studies with a lack of data on the cardiac index.

Results: A total of 1402 patients from 37 trials were included in the study. Inotropic drugs were shown to increase the cardiac index (0.32, 95%CI:0.25, 0.38), heart rate (7.68, 95%CI:6.36, 9.01), and mean arterial pressure (3.17, 95%CI:1.96, 4.38) than the placebo. Overall, the pooled estimates showed no difference in terms of cardiac index, heart rate, mean arterial pressure, systemic vascular resistance, and mean pulmonary arterial pressure among the groups receiving different inotropes.

Conclusions: Our systematic review found that inotrope therapy is not associated with the amelioration of hemodynamics. An accurate evaluation of the benefits and risks, and selection of the correct inotropic agent is required in all clinical settings.

Abbreviations: CCTs = controlled clinical trials, CENTRAL = Cochrane Central Register of Controlled Trials, CI = cardiac index, HfrEF = heart failure and reduced ejection fraction, NYHA = New York Heart Association, PiCCO = pulse-indicated continuous cardiac output, SBP = systolic blood pressure.

Keywords: heart failure, hemodynamic, inotropic agent, network meta-analysis

1. Introduction

The worldwide increase in the incidence of heart decompensation is a major health concern, especially in adults over 65 years of age.[1,2] The late stages of heart failure are related to poor quality of life, with frequent hospitalizations and the need for inotrope support.[3] When the need for inotrope support in low cardiac output is identified, catecholamines, phosphodiesterase inhibitors, digitalis glycosides, and calcium sensitizers are commonly used. The inotropic agents can significantly improve the pump function and stabilize the patient's condition. Therefore, the 2013 American Heart Association/American College Cardiology Guidelines recommend short-term intravenous support for hospitalized patients with severe systolic dysfunction, hypotension, and depressed cardiac output in order to maintain systemic perfusion and preserve end-organ performance[4] and the latest guideline did not change this comment.[5] However, patients who received inotropic drugs had many side effects, including atrial fibrillation and sinus bradycardia. Some studies indicated that long-term treatment of end-stage chronic heart failure with intravenous inotropes increases mortality.[6–8]

The degree of ventricular dysfunction can be assessed by echocardiography, a pulmonary artery catheter, or pulse-indicated continuous cardiac output (PiCCO). Although many studies compared the effects of different inotropic drugs in patients with low cardiac output, there was no consensus on the appropriate selection of inotropic therapy in ventricular dysfunction; this was dependent on the physician evaluating the hemodynamic status of the patients with heart failure. The aim of the current study was to investigate the effects of different inotropic drugs on the hemodynamics of patients who developed low cardiac output.

2. Methods

2.1. Search strategy selection criteria

We developed a search strategy that aimed to include any controlled clinical trials (CCTs) performed in patients with at

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Table 1

Pubmed search strategy for meta-analysis.

#1	((((Heart Failure[mh]) OR Cardiac Failure[tiab]) OR Heart Decompensation[tiab]) OR Myocardial Failure[tiab]) OR Congestive Heart Failure[tiab]
#2	(((((((Cardiotonic Agents[mh]) OR Cardiac Stimulants[tiab]) OR Inotropic Agents[tiab]) OR Positive Cardiac[tiab]) OR Cardiotonic Drugs[tiab]) OR Cardiotonics[tiab]) OR Myocardial Stimulants[tiab]) OR Cardioprotective Agents[tiab]
#3	((((Catecholamines[mh]) OR Dobutamine[tiab]) OR Dopamine[tiab]) OR Epinephrine[tiab]) OR Isoproterenol[tiab]
#4	((((Phosphodiesterase inhibitor[mh]) OR Amrinone[tiab]) OR Enoximone[tiab]) OR Milrinone[tiab]
#5	((((Levosimendan[mh]) OR Dextrosimendan[mh]) OR Dextrosimendan[tiab]) OR Levosimendan[tiab]
#6	((((((Digitalis Glycosides[mh]) OR Acetyldigitoxins[tiab]) OR Acetyldigoxins[tiab]) OR Cardiac Glycosides[tiab]) OR Deslanoside[tiab]) OR Digitoxin[tiab]) OR Digoxin[tiab]
#7	humans[mh] AND animals[mh]
#8	animals[mh] OR #7
#9	#2 OR #3 OR #4 OR #5 OR #6
#10	(#1 AND #9) NOT #8

least 1 group treated with an inotropic drug in any clinical setting. The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and Embase databases were searched up to December 2017 for relevant studies in English. We included published and ongoing trials and used a systematic search strategy in collaboration with two investigators. We specifically implemented the PubMed search strategy using the terms listed in Table 1.

Two authors independently screened all studies for relevance using the search strategy at the title, abstract, and full-text levels. Disagreements were resolved by a third author. Studies evaluated patients with a low cardiac index ($CI < 2.5\,L/min/m^2$) or New York Heart Association class II–IV. The exclusion criteria were as follows: studies published as an abstract only, crossover studies, studies with a lack of data on the cardiac index, and non-English articles.

2.2. Data extraction and assessment for risk bias

Two authors independently extracted data via a standardized form, including data on the fundamental characteristics of the studies and their outcomes. The fundamental characteristics included the name of the first author, publication year, study design, size of study population, mean age of the patients, study drugs, male percentage, and class of New York Heart Association (NYHA). The primary endpoint was the cardiac index, and the secondary outcomes were the heart rate, mean arterial pressure, systemic vascular resistance, and mean pulmonary arterial pressure. The data collected from each study were evaluated using the Cochrane collaboration's tool (Review Manager version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen) for assessing the risk of bias.[9]

2.3. Data synthesis and analysis

The primary aim of our network meta-analysis was to estimate the cardiac effects of inotropic drugs. Computations were performed with WinBUGS (version 1.4, MRC Biostatistics Unit, Cambridge, UK) and Stata (Stata Statistical Software: release 15, StataCorp LP, College Station, TX).

We used an extension of the multivariable Bayesian hierarchical random effects models for mixed multiple treatment comparisons with minimally informative prior distributions. First, we conducted a conventional pair-wise meta-analysis by synthesizing studies that compared the same interventions with a random-effects model.[10,11] Second, for head-to-head comparisons, we used an extension of the multivariable Bayesian hierarchical random-effects models for mixed multiple treatment comparisons with minimally informative prior distributions.[12,13] The relative ranking of different drug treatments was presented as the probabilities. A node-splitting method was used to evaluate the consistency of the network meta-analysis. To assess heterogeneity across the studies, we used the I^2 statistic, where either $I^2 > 50\%$ or $P < .10$ suggested a high level of heterogeneity. Convergence of Markov chains was deemed to be achieved if plots of the Gelman–Rubin statistics indicated that the widths of pooled runs and individual runs stabilized around the same value and their ratio around one. Accordingly, all analyses are based on 50,000 iterations, of which the first 20,000 were discarded as the burn-in period. A symmetrical and concentrated distribution of dots indicates no obvious deviation. The study was conducted in accordance with the PRISMA checklist, and ethical approval was not required.

2.4. Role of the funding source

This work had no supporting foundation. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

3. Results

We identified 10,071 studies that fitted our search strategy, 37 of which fulfilled the inclusion criteria and were included in our analysis[14–50] (Fig. 1 and Table 2). The results of this assessment are given in the "risk of bias summary" in Figure 2. These studies included 1402 subjects who were given different intropic agents and were included in the multiple-treatment meta-analysis to evaluate the hemodynamic effects. Figure 3 shows the network of eligible comparisons for the multiple-treatment meta-analysis.

We performed a direct comparison between inotropic drugs and placebo, and demonstrated that inotropic drugs can increase the cardiac index (0.32, 95%CI:0.25, 0.38), heart rate (7.68, 95%CI:6.36, 9.01), mean arterial pressure (3.17, 95%CI:1.96, 4.38) more than placebo. Moreover, no difference in mean pulmonary arterial pressure between inotropic drugs and placebo was found (−0.25, 95%CI:−1.06, 0.57). Overall, the heterogeneity was moderate, although for most comparisons the 95%CI included values that showed no heterogeneity, reflecting the small number of included studies for each pair-wise comparison. In the meta-analysis of direct comparisons, we found I^2 values higher than 75% for the comparisons about relating to cardiac index ($I^2 = 95.8\%$), heart rate ($I^2 = 82.3\%$), mean arterial pressure ($I^2 = 98.4\%$), and mean pulmonary arterial pressure ($I^2 = 85.4\%$).

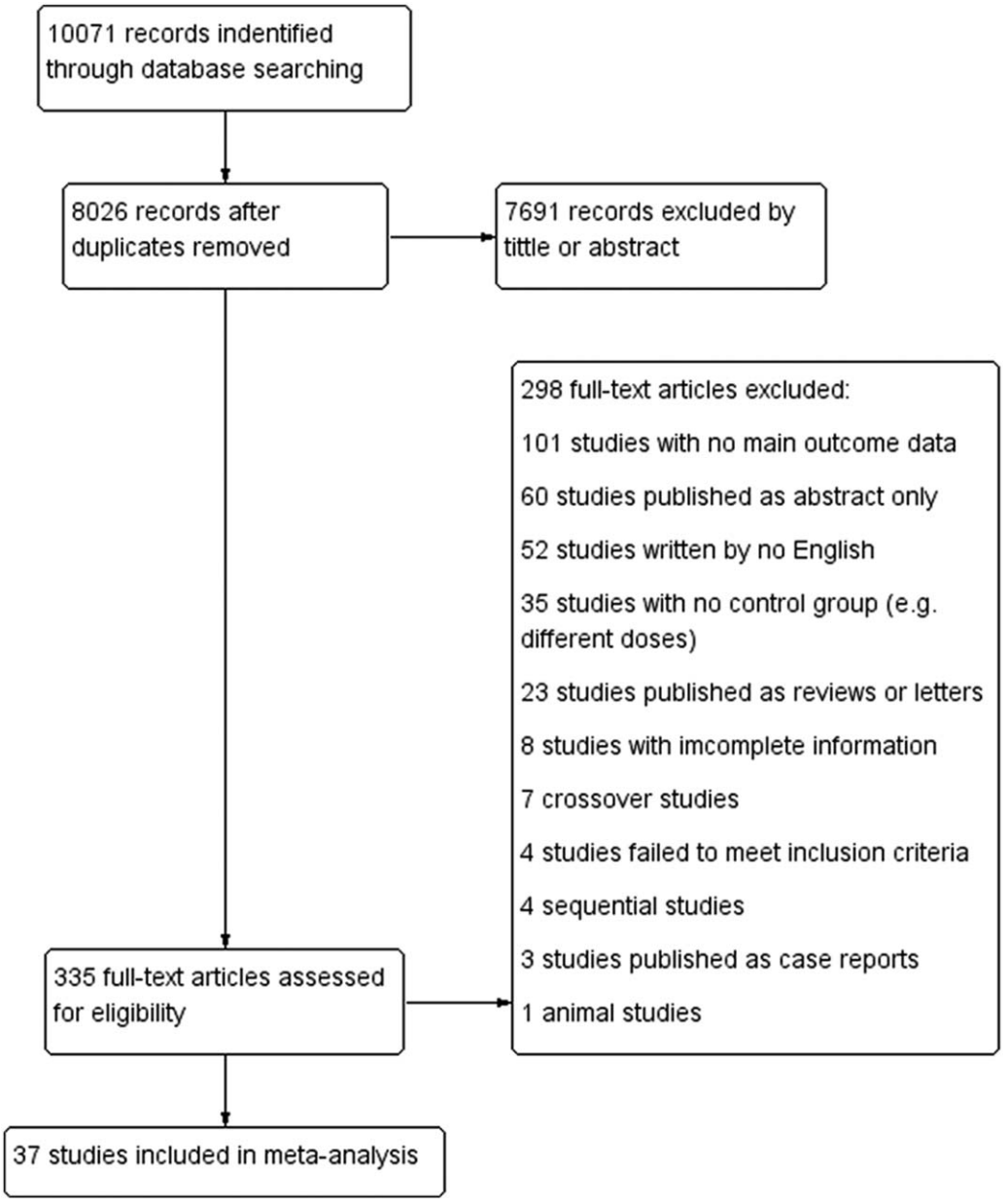

Figure 1. Flowchart of articles retrieved from the search of databases and reasons for exclusions.

Figures 4 and 5 summarize the results of the multiple-treatment meta-analysis. In the network meta-analysis for the hemodynamic effects, no significant difference was found between any pairs of the follow: cardiac index, heart rate, mean arterial pressure, systemic vascular resistance, and mean pulmonary arterial pressure. However compared to a placebo, a calcium sensitizer can improve the cardiac index, whereas digitalis glucoside and catecholamines can increase the mean arterial pressure. However, in the probability ranking order, calcium sensitizers ranked the highest in terms of increasing the cardiac index (<***>*P*-score=.90), followed by catecholamines (*P*-score=.63), phosphodiesterase inhibitors (*P*-score=.51), placebo (*P*-score=.44), and finally, digitalis glycosides (*P*-score=.50). Compared to placebo, we found that calcium sensitizers were most likely to increase the heart rate (*P*-score=.62), followed by catecholamines (*P*-score=.47). Calcium sensitizers, phosphodiesterase inhibitors, and catecholamines may reduce the systemic vascular resistance. Furthermore, catecholamines, phosphodiesterase inhibitors, calcium sensitizers, and digitalis glycosides may lower the mean pulmonary arterial pressure.

4. Discussion

Heart failure is considered a leading cause of hospitalization in patients older than 65 years of age, and has a high in-hospital rate and 6-month mortality.[51,52] Patients who exhibit a severely impaired cardiac function with reduced systolic blood pressure have a fourfold greater risk of adverse cardiac events.[53] Thus, the main goals of treatment for patients with low cardiac index are the restoration of systolic blood pressure (SBP), improvement

Table 2

Baseline characteristics of the identified controlled trials of the different inotropic drugs in heart failure.

Author	Year	Design	Etiology	Number	Age	Male/female	NYHA Class	Study drug	Outcomes
Liang CS	1984	RCT	IDC, AC	15	53	13/2	III/IV = 7/8	Dobutamine, placeo	CI, HR, MAP, SVR, mPAP
Shah PK	1985	SCT	IDC, IHD	14	69	11/3	III/IV = 2/12	Dobutamine, enoximone	CI, HR, MAP, SVR, mPAP
Benotti JR	1985	SCT	IDC, RC	15	61	11/4	IV = 15	Dobutamine, dopamine, amrinone	CI, HR, MAP, SVR, mPAP
Uretsky BF	1986	SCT	IHD, IDC	9	Nuclear	Nuclear	III/IV	Dobutamine, enoximone	CI, HR, MAP, SVR, mPAP
Likoff MJ	1986	SCT	IHD, IDC	8	Nuclear	4/4	Nuclear	Dobutamine, enoximone	CI, HR, MAP, SVR, mPAP
Monrad ES	1986	SCT	CAD, IDC	10	Nuclear	Nuclear	III/IV	Dobutamine, milrinone	CI, HR, MAP, SVR, mPAP
Manzione NC	1986	CCT	CAD	11	58	11/0	III/IV = 6/5	Amrinone, milrinone	CI
Grose R	1986	SCT	CAD, IDC	11	60	9/2	III/IV	Dobutamine, milrinone	CI, HR, MAP, SVR
Biddle TL	1987	RCT	IHD, IDC	79	60	71/8	III/IV = 32/47	Dobutamine, milrinone	CI, HR, MAP, SVR, mPAP
Eichhorn EJ	1987	RCT	CAD, IDC	14	62	12/2	III/IV	Dobutamine, milrinone	CI, HR, MAP, SVR, mPAP
Murali S	1991	CCT	CAD, IDC	22	55	16/6	III/IV = 7/15	Dobutamine, enoximone	CI, HR, MAP, SVR, mPAP
Erlemeier HH	1992	RCT	CAD, CMP	20	57	18/2	Nuclear	Placebo, dobutamine	CI, HR, MAP, SVR, mPAP
Thuillez C	1993	SCT	IHD, IDC	8	60	7/1	III/IV = 3/5	Dobutamine, enoximone	CI, HR, SVR, mPAP
Casella G	1994	SCT	CAD, CMP	8	57	8/0	III/IV	Digoxin, enoximone	CI, HR, MAP, SVR, mPAP
Abraham WT	1994	SCT	IHD, IDC	13	59	10/3	III/IV = 11/2	Toborinone, dobutamine	CI, HR, MAP, SVR, mPAP
Rich MW	1995	RCT	IHD	14	80	5/9	IV = 14	Amrinone, dobutamine	CI, HR, MAP, SVR, mPAP
Nagata K	1995	RCT	IDC	20	56	17/3	II/III = 9/11	Dobutamine, MS-857	CI, HR, MAP, mPAP
Kanda H	1996	CCT	CAD, IDC	21	53	Nuclear	II/III	Toborinone, dobutamine	CI, HR, SVR
Karlsberg RP	1996	RCT	AMI	30	63	18/12	Nuclear	Milrinone, dobutamine	CI, HR, MAP, SVR, mPAP
Folláth F	1999	RCT	Nuclear	19	58	Nuclear	Nuclear	Levosimendan, dobutamine	CI, HR
Yamani MH	2001	CCT	IHD, IDC	329	61	249/80	IV = 329	Dobutamine, milrinone	CI, HR, SVR, mPAP
Lowes BD	2001	CCT	IDC, IHD, VHD	20	53	16/4	II/III/IV = 6/12/2	Milrinone, dobutamine	CI, HR, MAP, mPAP
Follath F	2002	RCT	IHD, other	203	59	176/27	Nuclear	Dobutamine, levosimendan	CI
De LL	2005	RCT	AMI	26	57	18/8	Nuclear	Levosimendan, placebo	CI, HR, SVR, mPAP
Adamopoulos S	2006	RCT	IHD, others	69	70	58/11	III/IV	Dobutamine, levosimendan, placebo	CI
Alvarez J	2006	RCT	Heart surgery	41	69	18/23	Nuclear	Dobutamine, levosimendan	CI, HR, MAP, SVR, mPAP
Alshawaf E	2006	RCT	CAD	30	59	27/3	Nuclear	Levosimendan, milrinone	CI, MAP, SVR
Heringlake M	2007	RCT	CAD	18	67	Nuclear	Nuclear	Adrenaline, milrinone	CI, HR, MAP, mPAP
Fuhrmann JT	2008	RCT	AMI	32	68	20/12	Nuclear	Levosimendan, enoximone	CI, HR, MAP
Carmona MJ	2010	RCT	Heart surgery	20	65	11/9	Nuclear	Dobutamine, milrinone	CI, HR, MAP
Bergh CH	2010	RCT	IHD, others	60	71	51/9	III/IV = 33/27	Levosimendan, dobutamine	CI, HR, SVR
Asaad OM	2011	RCT	Heart surgery	20	59	15/5	Nuclear	Levosimendan, placebo	CI, HR, MAP
Bonios MJ	2012	RCT	IHD, others	42	54	40/2	IV = 42	Dobutamine, levosimendan	CI, HR, mPAP
Bragadottir G	2013	RCT	Heart surgery	30	67	28/2	Nuclear	Placebo, levosimendan	CI, HR, MAP, SVR, mPAP
Ersoy O	2013	RCT	Heart surgery	20	47	8/12	Nuclear	Levosimendan, placebo	CI, SVR, mPAP
Fedele F	2014	RCT	Nuclear	21	74	18/3	Nuclear	Levosimendan, placebo	CI, mPAP
Sunny	2016	CCT	Heart surgery	60	37	31/29	III/IV = 54/6	Dobutamine, levosimendan, milrinone	CI, HR, MAP

AC = alcoholic cardiomyopathy, AMI = acute myocardial infarction, CAD = coronary artery disease, CCT = controlled clinical study, CI = cardiac index, CMP = cardiomyopathy, HR = heart rate, IDC = idiopathic dilated cardiomyopathy, IHD = Ischemic heart disease, MAP = mean arterial pressure, mPAP = mean pulmonary arterial pressure, RC = Rheumatic cardiomyopathy, RCT = randomized controlled study, SCT = self-controlled study, SVR = systemic vascular resistance, VDH = valvular heart disease.

of peripheral tissue oxygenation, protection of vital organs, alleviation of symptoms, and finally, the prevention of new exacerbations. In order to alleviate peripheral hypoperfusion and improve central hemodynamics, short-term inotropic support is needed for heart failure patients. The ideal inotropic agent would improve systolic and diastolic cardiac function and reduce systemic vascular resistance, and mean pulmonary arterial pressure, without increasing myocardial oxygen consumption and worsening cardiac metabolic status.

Common inotropic medications include catecholamines, phosphodiesterase inhibitors, calcium sensitizers, and digitalis glycosides. It is worth noting that although many studies have shown that these agents increase the cardiac index and mean arterial pressure, they also increase the risk of arrhythmias. The aim of this study was to summarize the current knowledge of the role of inotropes in the hemodynamic management of heart failure and propose evidence-based strategies for the rational use of these drugs. Our analysis was based on 37 studies including 1042 individuals randomly assigned to different inotropic drugs.

Catecholamines stimulate the alpha and beta adrenergic receptors; as a result, catecholamines can increase the contractility, heart rate, mean arterial pressure, and systemic vascular resistance. Adrenaline strongly stimulates both alpha and beta adrenergic receptor, and can improve the cardiac index by increasing the contractility and heart rate. Adrenaline can also increase pulmonary vascular resistance, and due to the strong effect on heart rate and contractility, adrenaline can also markedly increase the myocardial oxygen demand and elevate both lactate and blood glucose levels. Dopamine is also known to have a dose-dependent effect on various adrenergic receptors. At low doses, dopamine stimulates the D2 receptor, resulting in vasodilation of the splanchnic vascular beds. At medium doses, it stimulates the beta-2 adrenergic receptor and leads to an increase in contractility. At high doses, it stimulates the alpha adrenergic receptor, resulting in an increase in systemic vascular pressure.[54] Dobutamine stimulates both beta adrenergic receptors, and although dobutamine can improve cardiac contractility and cardiac index, hypotension can worsen through stimulation of

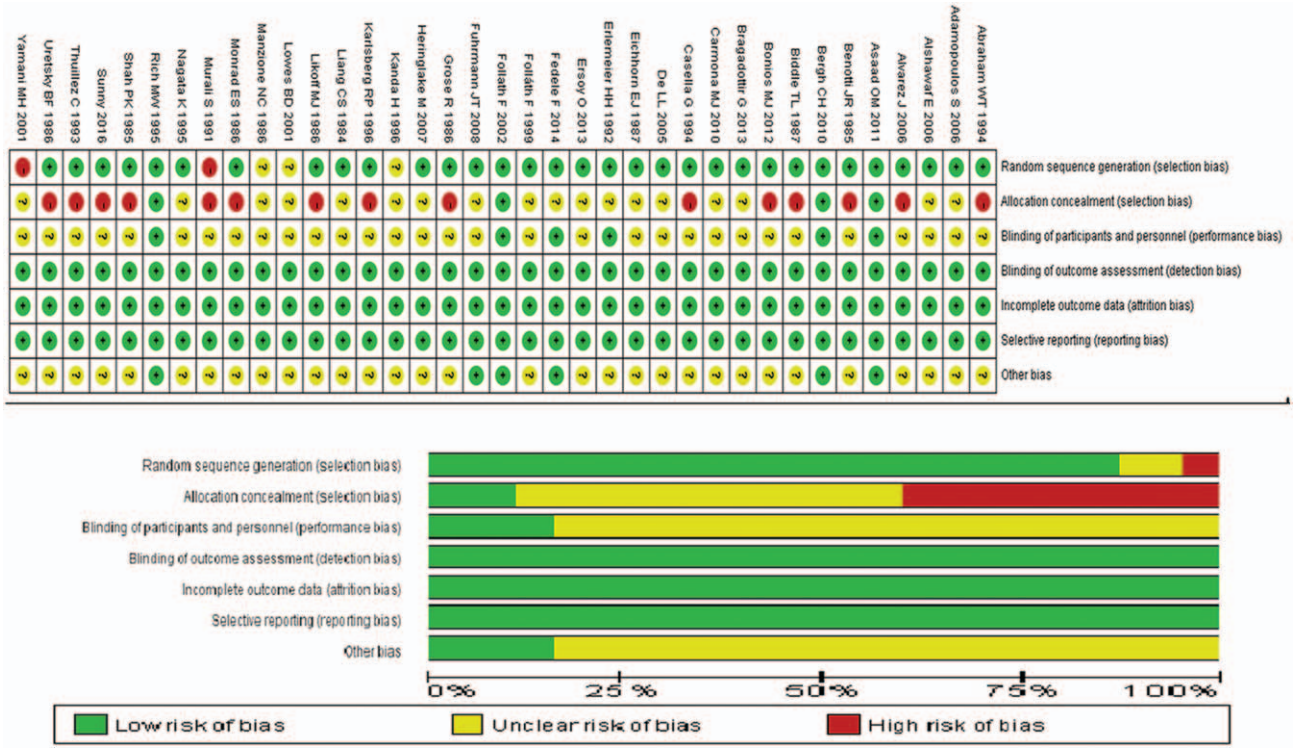

Figure 2. Details of quality assessment by the Cochrane collaboration's tool.

the beta-2 receptor.[55] Catecholamines have historically been the first-line medication of choice for patients with heart failure. However, recent literature has confirmed an increase in arrhythmogenic events in patients.[56,57] Our study shows that catecholamines are more efficacious than placebo in terms of mean arterial pressure, and there are no differences in the other aspects of hemodynamics compared to other inotropic agents.

Phosphodiesterase inhibitors can increase cyclic adenosine phosphate, leading to an increase in cardiac contractility without the significant increase in heart rate seen with other inotropic

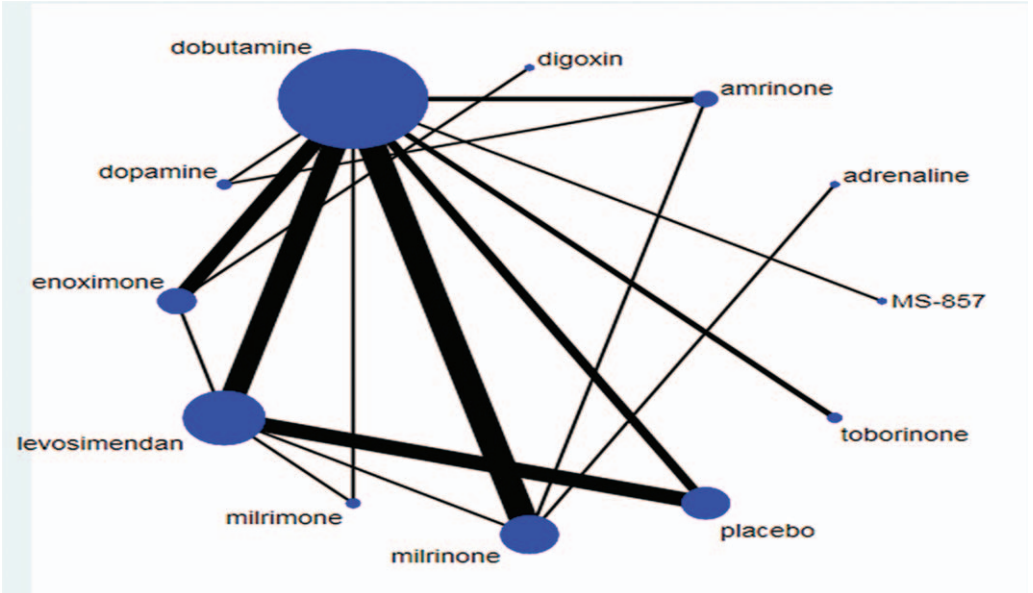

Figure 3. Network of eligible comparisons for the multiple-treatment meta-analysis for cardiac index. Note: The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size).

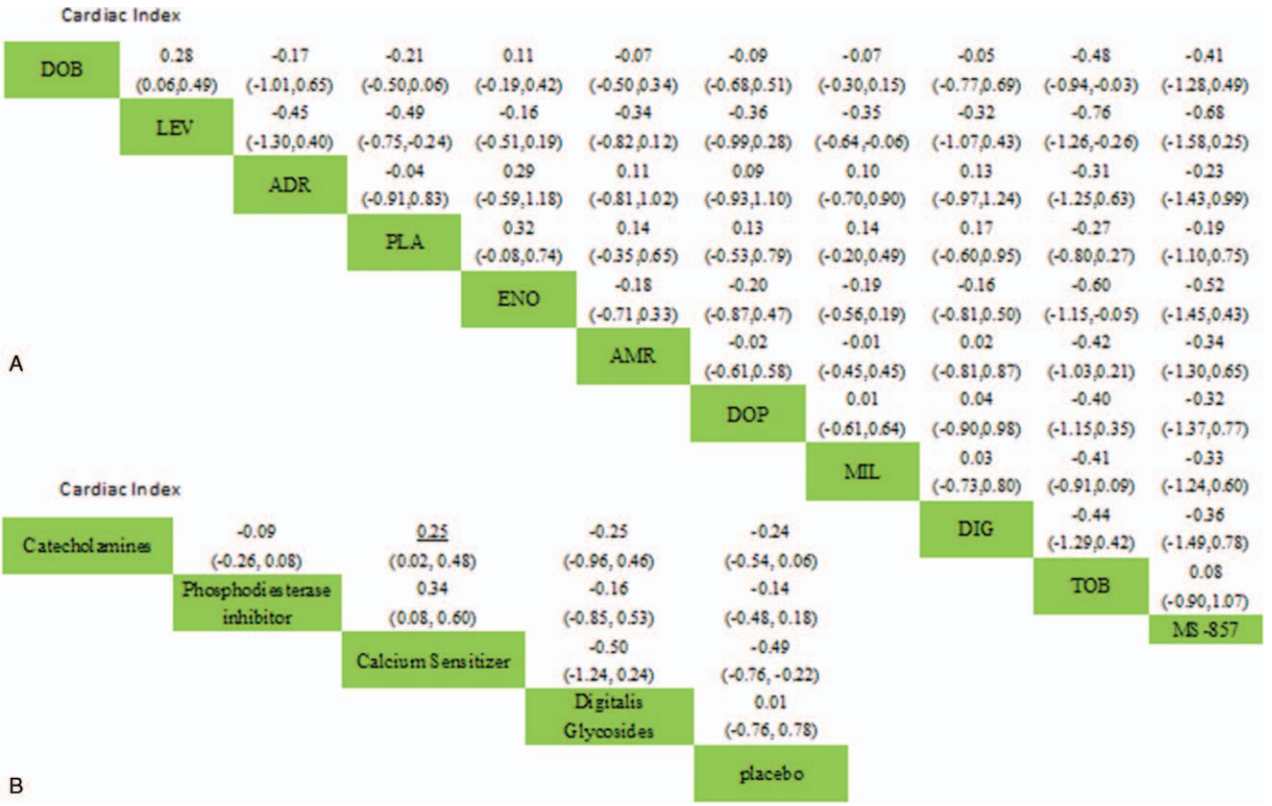

Figure 4. League tables for CI in patients were treated by different inotropic drugs. Note: ADR = adrenaline, AMR = amrinone, DIG = digoxin, DOB = dobutamine, DOP = dopamine, ENO = enoximone, LEV = levosimendan, MIL = milrinone, PLA = placebo, TOB = toborinone.

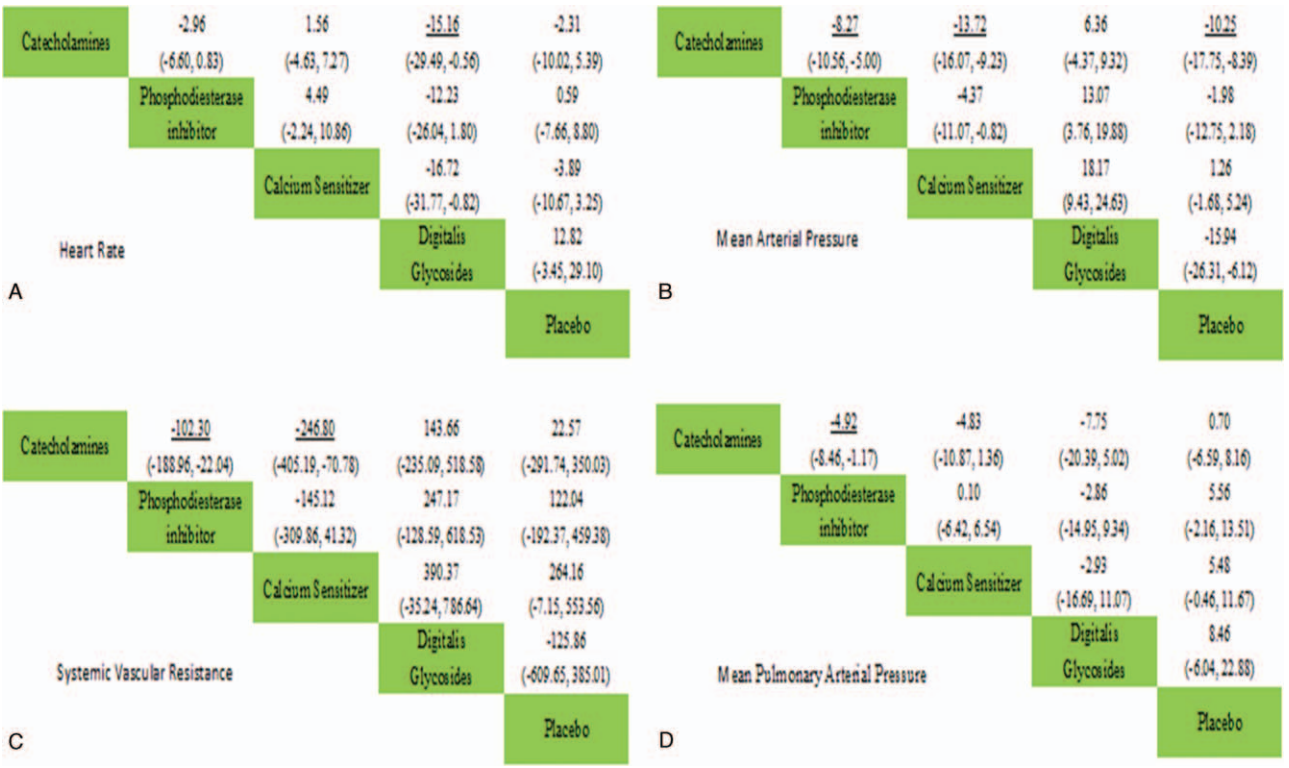

Figure 5. League tables for HR, MAP, SVR, mPAP in patients were treated by different inotropic drugs.

medications. In addition, phosphodiesterase inhibitors can cause vasodilation of the pulmonary and systemic circulations.[58] Indeed, phosphodiesterase inhibitors have been used in some studies to detect its benefits in patients with heart failure and reduced ejection fraction (HfrEF). In terms of improving hemodynamics, our study shows that phosphodiesterase inhibitors do not differ significantly from the other inotropic drugs and placebo. In a prospective randomized trial,[59] the all-cause mortality increased by 28% ($P=.038$) and the cardiovascular mortality increased by 34% ($P=.016$) in patients who received phosphodiesterase inhibitors compared to those who did not. Although higher doses have been associated with increased mortality[60] in another study of phosphodiesterase inhibitors in advanced heart failure trial,[61] there was no difference in all-cause mortality($P=.73$) or the combination endpoint of all-cause mortality or cardiovascular mortality($P=.71$) among subjects who received phosphodiesterase inhibitors.

Digitalis glycosides, is often considered separately from other drugs with positive inotropic effects and mediates its effects by inhibiting sodium potassium (Na^+/K^+)-ATPase. The subsequent rise in the concentration of intracellular calcium leads to an increase in myocardial contractility.[62] Although the use of digitalis glycosides could be traced back to publications published in 1785, some studies demonstrated the harmful effects of drugs withdrawal in subjects.[63,64] A randomized, double-blind, controlled trial[65] conducted to evaluate the effect of digitalis glycosides demonstrated that although digitalis glycosides had no effect on mortality, they did reduce hospitalization. Furthermore, the benefits of digitalis glycosides were observed among patients aged 65 years and older.[66] However another analysis suggested that the use of digitalis glycosides was associated with a higher risk of death in women.[67] In the current study, although digitalis glycosides were more efficacious than placebo, there were no significant differences in cardiac index, heart rate, systemic vascular resistance, mean pulmonary arterial pressure between digitalis and other inotropes.

In terms of improving cardiac index, only calcium sensitizers were more efficacious than placebo, and no significant differences were observed with the use of the other inotropes. Calcium sensitizers, such as levosimendan, can improve cardiac output without the most harmful side effects. However, evidence from several observational studies has shown that inotropes in general, and catecholamines in particular, can increase mortality.[68–70] In addition, a previous study[71] found a non-significant increase in mortality associated with the use of inotropes. Furthermore, several other relevant randomized trials have demonstrated a poor outcome in patients who received inotropic agents.[60,72] However, in some recent meta-analysis,[73,74] levosimendan improved survival in both cardiology and cardiac surgery settings; pulsed levosimendan has been shown to reduce mid-term mortality in advanced heart failure, and was the only drug that significantly improved survival. Levosimendan is thought to have a direct cardioprotective action by activating adenosine triphosphate-sensitive potassium channels in cardiac mitochondria.[75] Although, levosimendan has not yet been shown to improve survival in large, multicenter randomized clinical trials, a number of trials are currently ongoing, and the role of levosimendan in the treatment of critically ill patients is expected to be better defined in the near future.[76–78]

This review and meta-analysis has a number of limitations. First, we only included articles in English. Second, we investigated heterogeneous studies in that they included patients with heart failure from different causes. Third, the patients' dosage and dosing time varied widely among the different studies. Fourth, the measurement of the primary endpoint was not consistent throughout the included studies. Finally, we have to acknowledge that it is likely that statistically, the results have been influenced by the number of trials investigating different inotropes. Thus, more clinical studies are needed to further investigate the effects of different inotropic drugs on hemodynamics in patients who developed low cardiac output.

5. Conclusions

Clinicians believe that inotropic drugs can improve hemodynamics and increase patients' survival when used appropriately. However, the results of our study show that in the overall analyses and in different clinical settings, inotropes were benefit for hemodynamics compared with placebo. According to previously published studies, not any inotrope has an absolute advantage in improving hemodynamics. Therefore, an accurate evaluation of the benefits and risks, as well as the correct selection of the inotropic agent is required in all clinical settings.

Author contributions

Data curation: Hao-tian Zhao, Cong He.
Formal analysis: Li-min Shen.
Investigation: Hao-tian Zhao, Cong He, Shan Ren.
Methodology: Ling Long.
Supervision: Li-min Shen, He-ling Zhao.
Validation: He-ling Zhao.
Writing – original draft: Ling Long, Shan Ren.
Writing – review & editing: He-ling Zhao.

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