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Heart Connections

Integrating Organ, Environmental, and Mental Health Impacts

Meta-analysis & systematic reviews

META-ANALYSIS

Effect of Inotropes in Patients with Advanced Heart Failure: A Meta-Analysis of Randomized Trials

L'effet des inotropes chez les patients atteints d'insuffisance cardiaque avancée : Une méta-analyse d'essais randomisés

Racha Ghabara[1], Badereddine Ben kaab[1], Saoussen Antit[1], Ilhem Boussabeh[1], Sabrine Bousnina[1], Chadli Dziri[2], Lilia Zakhama[1]

1. University of Tunis El Manar, Faculty of Medicine of Tunis, Cardiology Department, Security Forces Hospital, Tunis, Tunisia
2. University of Tunis El Manar, Faculty of Medicine of Tunis, Tunis, Tunisia

Abstract

Introduction : Advanced heart failure (AHF) is associated with high morbidity and mortality. Inotropic agents such as dobutamine, levosimendan, and milrinone are commonly used to improve cardiac output, but their impact on mortality remains controversial due to limited head-to-head comparisons.

Aim : To compare the effectiveness of inotropes (dobutamine, levosimendan, milrinone) versus placebo or each other in reducing mortality in patients with AHF.

Methods : This systematic review and meta-analysis followed PRISMA guidelines and was registered with PROSPERO (CRD42024584389). We searched Scopus, CENTRAL, Google Scholar, PubMed, and clinical trial registries up to December 2024 for randomized controlled trials (RCTs) published from 2000 onward. Eligible studies included adults (≥18 years) with AHF and cardiorenal syndrome. Risk differences (RD) with 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity was assessed with the Cochrane Q-test, Tau^2, and I^2. Subgroup analyses and meta-regression were performed. Publication bias was evaluated using funnel plots and Duval and Tweedie's trim-and-fill method.

Results : Twenty-four RCTs involving 2,862 participants were included. The pooled RD for mortality was -0.023 (95% CI: -0.046 to 0.000; p=0.055), indicating no significant difference. Subgroup analysis by control (inotropes vs. placebo) showed similar non-significant results. Meta-regression for moderators (age, LVEF, systolic blood pressure) did not explain heterogeneity. The funnel plot suggested asymmetry, indicating potential publication bias.

Conclusions : Inotropic agents showed a non-significant trend toward reduced mortality in AHF patients. Heterogeneity limits firm conclusions. Larger RCTs are needed to identify subgroups that may benefit.

Keywords : Advanced heart failure; inotropes; dobutamine; levosimendan; milrinone; meta-analysis; mortality.

Résumé

Introduction : L'insuffisance cardiaque avancée (ICA) demeure associée à une morbidité et une mortalité élevées. Les agents inotropes tels que la dobutamine, le lévosimendan et la milrinone sont utilisés pour améliorer le débit cardiaque, mais leur effet sur la mortalité reste incertain, faute de comparaisons directes.

Objectif : Évaluer l'efficacité des inotropes (dobutamine, lévosimendan, milrinone) par rapport au placebo ou entre eux sur la mortalité chez les patients atteints d'ICA.

Méthodes : Une revue systématique et méta-analyse a été menée selon les recommandations PRISMA et enregistrée sur PROSPERO (CRD42024584389). Les bases de données Scopus, CENTRAL, Google Scholar, PubMed et les registres d'essais cliniques ont été consultés jusqu'en décembre 2024. Ont été inclus les essais contrôlés randomisés (ECR) publiés depuis 2000 chez des adultes (≥18 ans) présentant une ICA avec syndrome cardio-rénal. Les différences de risque (DR) et leurs intervalles de confiance (IC) à 95 % ont été estimées à l'aide d'un modèle à effets aléatoires. L'hétérogénéité (Q, Tau^2, I^2) et le biais de publication (diagramme en entonnoir, méthode trim-and-fill) ont été évalués.

Résultats : Vingt-quatre ECR totalisant 2 862 participants ont été inclus. La DR combinée pour la mortalité était de -0,023 (IC 95 % : -0,046 à 0,000 ; p = 0,055), sans différence significative. Les analyses de sous-groupes (inotropes vs placebo) et les méta-régressions (âge, fraction d'éjection, pression systolique) n'ont pas modifié ces résultats. Une asymétrie du diagramme en entonnoir suggère un biais de publication.

Conclusions : Les inotropes montrent une tendance non significative à la réduction de la mortalité dans l'ICA. L'hétérogénéité des études limite la robustesse des conclusions. Des essais de plus grande envergure sont nécessaires pour identifier les sous-groupes susceptibles d'en bénéficier.

Mots-clés : Insuffisance cardiaque avancée ; inotropes ; dobutamine ; lévosimendan ; milrinone ; méta-analyse ; mortalité.

Correspondance
Racha Ghabara
University of Tunis El Manar, Faculty of Medicine of Tunis, Cardiology Department, Security Forces Hospital, Tunis, Tunisia
Email: racha.ghabara@fmt.utm.tn

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Introduction

Advanced heart failure (AHF) is a global health challenge affecting millions, with high morbidity and mortality despite therapeutic advances(1). Inotropic agents, including catecholamines (e.g., dobutamine), calcium sensitizers (e.g., levosimendan), and phosphodiesterase III inhibitors (e.g., milrinone), are used to enhance cardiac output and support organ function, such as renal perfusion, in AHF patients(2). Clinical trials have evaluated their effects on mortality and renal protection in acute or chronic heart failure(3,4), but results are inconsistent due to a lack of direct comparisons(5).
To inform treatment strategies and patient outcomes, understanding the safety and renoprotective effects of these agents is crucial. This systematic review and meta-analysis synthesizes evidence on their impact on mortality, aiming to guide clinical practice, update guidelines, and identify research gaps.
The primary aim was to compare the effectiveness of inotropes (dobutamine, levosimendan, milrinone) versus placebo in reducing mortality in patients with AHF.

Methods

Study Design

This systematic review and meta-analysis evaluated the comparative efficacy of inotropes (dobutamine, levosimendan, milrinone) and noradrenaline in AHF patients. It adhered to PRISMA guidelines for transparency and reproducibility. The protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO (CRD42024584389).
Key elements included:
• Systematic review: Comprehensive database searches for relevant RCTs.
• Meta-analysis: Data pooling for comparisons, assuming sufficient homogeneity.

Data Sources and Searches

Databases searched included Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and PubMed up to December 2024. Secondary sources were clinical trial registries (e.g., ClinicalTrials.gov). Search terms combined heart failure, inotropes or noradrenaline, and cardiorenal syndrome. PubMed terms: (("Heart Failure"[Mesh]) OR ("Cardio-Renal Syndrome"[Mesh])) AND ((((("Cardiotonic Agents"[Mesh]) OR "Cardiotonic Agents" [Pharmacological Action]) OR "Dobutamine"[Mesh]) AND "Simendan"[Mesh]) OR "Milrinone"[Mesh]) OR "Norepinephrine"[Mesh]) Filters: Randomized Controlled Trial, from 2000–2024. Google Scholar: ("Heart failure" OR "congestive heart failure" OR "cardiac failure") AND ("inotropes" OR "calcium sensitizer" OR "catecholamines" OR "phosphodiesterase III inhibitors" OR "noradrenaline") AND ("randomized controlled trial" OR "RCT"). Reference lists of retrieved articles were hand-searched. Non-relevant references provided contextual support.

Study Selection

Inclusion criteria: RCTs published from 2000 onward comparing specified inotropes with placebo or each other. No language restrictions; non-English studies were translated as needed. Exclusion: Observational studies, non-randomized trials, case reports, non-comparative studies.

Study Population

Adults (≥18 years) with AHF and cardiorenal syndrome. AHF defined as: (a) severe symptoms (NYHA III/IV); (b) severe dysfunction (Left Ventricular Ejection Fraction (LVEF) ≤30%, high BNP/NT-proBNP, structural abnormalities); (c) congestion or low output requiring diuretics/inotropes; (d) impaired function (6-minute walk test, peak VO2). Cardiorenal syndrome: HF-induced renal impairment (reduced GFR, elevated creatinine)(6). Exclusions: Pediatric populations, mild/moderate HF, no clear cardiorenal syndrome diagnosis, or hemodynamically unstable patients (e.g., cardiogenic shock).
Interventions and Comparators
Intervention: Inotropes (dobutamine, levosimendan, milrinone) to improve contractility and perfusion. Primary comparator: Placebo or noradrenaline. Secondary: Head-to-head inotrope comparisons.

Outcomes

Primary: Mortality, comparing inotropes for relative effectiveness.

Data Extraction and Risk of Bias Assessment

Two investigators (RG, BBK) extracted data using a standardized form, with cross-verification; discrepancies resolved by a third (CD). Extracted: Study characteristics (author, year, design, setting, country), participant details (sample size, age, sex, HF classification, renal function), intervention (type, dose, duration, co-interventions), comparators (dose, duration), outcomes (As listed under the eligibility criteria, with specific metrics and measurement time points).
Risk of bias: Assessed using the Jadad scale (randomization, blinding, withdrawals/dropouts; score 0–5, ≥3 indicating high quality). Disagreements resolved by discussion or third reviewer.

Statistical Analysis

Evaluation of effect size: Overall estimates of mortality effect size were calculated, using Risk difference (RD) with their 95 % confidence intervals (CIs) for dichotomous variables. Forest plots summarized the data using a random model.
Publication bias was evaluated using the Funnel plot followed by the Duval and Tweedie's Trim & Fill methods.

Assessment of heterogeneity: We calculated the Cochrane Chi2 test (Q-test), Tau2 and 95 % predictive interval (PI). Reasons for heterogeneity were investigated by testing interactions between relevant factors termed moderators (age, LVEF, PAS) and effect size. We performed subgroup analysis based on inotrope type (dobutamine Vs levosimendan Vs. milrinone), and patient characteristics (age, severity of heart failure). Comprehensive meta-analysis software version 4 was used for all calculations.

Results

Study Characteristics

Twenty-four unique RCTs involving 2,862 participants were included (Figure 1). Most participants had AHF. Four inotropic agents (levosimendan, milrinone, dobutamine, dopamine) were analyzed. Doses: Levosimendan 0.1–0.6 µg/kg/min ± bolus 6–24 µg/kg for 10 min; dobutamine 1.4–10 µg/kg/min ± bolus; dopamine 2–5 µg/kg/min without bolus; milrinone 0.25–1 µg/kg/min with bolus.

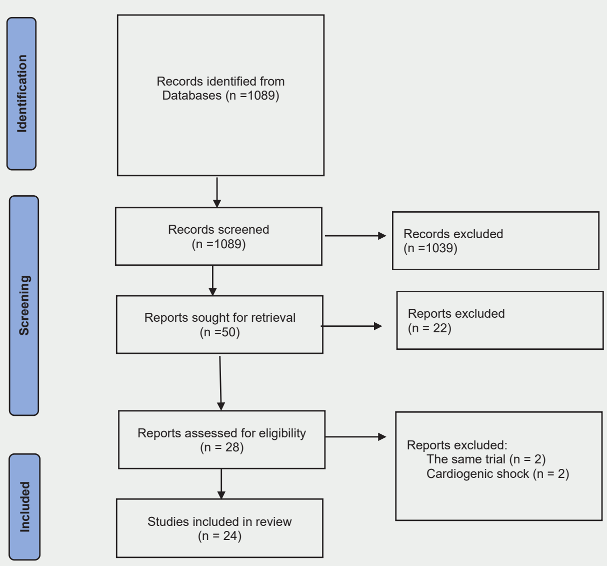

Figure 1. Flow diagram of randomized controlled trials included and excluded.

Overall Analysis: Mortality

A total of 24 studies were included in the meta-analysis. The individual estimates of risk difference (RD) and their corresponding 95% confidence intervals (CIs) are displayed in Figure 2. Several studies, including those by Nanas (2003), Tereschenko (2011), demonstrated a significant reduction in risk associated with inotropic therapy compared to the control group ($p < 0.05$). However, most studies reported non-significant results, with confidence intervals crossing null.

The pooled analysis, utilizing a random-effects model, yielded an overall RD of –0.023 (95% CI: –0.082 to 0.037, p=0.055), indicating no statistically significant difference between inotropic therapy and the control group. The prediction interval crossed the null line, further illustrating the significant heterogeneity and uncertainty in treatment effects across the studies. Overall, these findings suggest that inotropic therapy does not provide a consistent benefit compared to the control group.

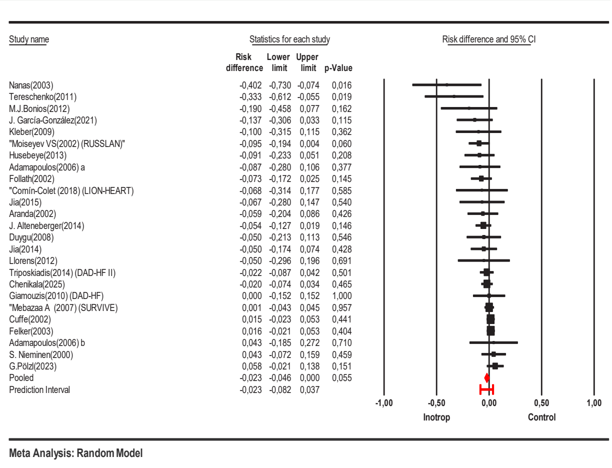

Figure 2. Forest plot of the effect of inotropic therapy versus control group on mortality.

The funnel plot showed an asymmetric distribution of studies. Most studies cluster towards the top of the funnel, indicating higher precision (Figure 3).

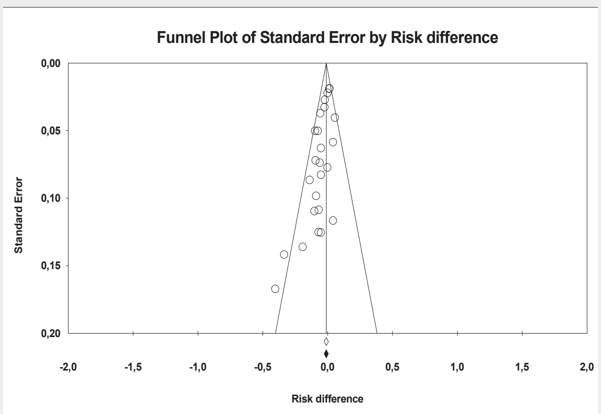

Figure 3. Funnel plot assessing publication bias in the meta-analysis concerning mortality.

Subgroup Analysis: Mortality

In the subgroup comparing inotropes directly, seven studies were included. The pooled estimate indicated a non-significant reduction in risk associated with inotropic therapy (Risk Difference [RD] = –0.036, 95% CI: –0.079 to 0.007, p=0.099). None of the individual trials in this subgroup showed a consistent benefit.

In the placebo-controlled subgroup, 17 studies were analyzed, resulting in a pooled analysis that yielded an RD of –0.018 (95% CI: –0.047 to 0.010, p=0.212), indicating no statistically significant benefit.

Table 1. The characteristics of included trials

Study	Study design	Inclusion criteria	Outcomes	Jadad score
Cuffe (2002)(7)	Randomized, double-blind, multicenter study	Patients with acute exacerbation of chronic HF (NYHA III IV, mean LVEF 23%)	Mortality (2m)	3
Moiseyev VS (2002) (RUSSLAN) (8)	Randomized, double-blind, multicenter study	Patients with left ventricular failure due to an acute myocardial infarction	Mortality (3m)	5
Nanas(2004)(9)	randomized, double-blind study	patient with decompensated chronic HF (NYHA IV)	Mortality (12m)	5
Mebazaa A (2007) (SURVIVE)(3)	Randomized, double-blind, multicentre study	Patients with acute decompensated HF (LVEF ≤30%, NYHA class III or IV)	Mortality (3m)	5
Nieminen (2000)(10)	Randomized, study	Patient with chronic HF (NYHA II-IV and LVEF ≤40%)	Mortality	3
Comín-Colet (2018) (LION-HEART)(11)	Randomized, double-blind, multicentre study	Patients with advanced HF (EF ≤35%, NYHA class III or IV)	Mortality	2
Jia (2014)(12)	Randomized, single-blind, single-center study	Patients with HF complicated by acute myocardial infarction (EF ≤40%)	Mortality (6m)	2
Jia (2015)(13)	Randomized, single-blind study	Patients with acute decompensated HF (EF ≤35%, NYHA class III or IV)	Mortality (3m)	3
Follath (2002) (LIDO study)(14)	Randomized, double-blind, multicentre study	patients with severe low-output HF (EF ≤ 35%)	Mortality (3m)	5
Aranda (2002)(15)	Randomized, open-labeled study	Patients with decompensated HF awaiting cardiac transplantation	Mortality (Followed until death, transplantation or cardiac support)	2
Llorens(2012)(16)	Randomized, triple-blind, single center study	Patients with decompensated acute HF (NYHA III-IV)	Mortality (6m)	5
Bonios MJ (2012)(17)	Randomized, open-labeled study	Patients with decompensated, end stage chronic HF (NYHA class IV) and refractory to standard therapy weaned from an inotrope infusion during 72 h from their initial hospitalization	Mortality (3m)	2
Giamouzis (2010) (DAD-HF)(18)	Randomized, double-blind study	Patients with acutely decompensated HF	Mortality (2m)	5
Triposkiadis (2014) (DAD-HF II)(19)	Randomized, single blind, multicenter study	Patients with acutely decompensated HF	Mortality (12m)	5
Husebye (2013) (LEAF)(20)	Randomized, double-blind, single center study	Patients with acute HF following primary PCI treated acute STEMI	Mortality (6m)	4
Kleber(2002)(21)	randomized, double-blind study	Patient with right HF due to pulmonary hypertension (NYHA III-IV)	Mortality (2m)	4
G.Pölzl(2023)(22)	Multicenter, randomized, double-blind, placebo-controlled, two-arm trial	Patient hospitalized for acute HF event requiring i.v. vasodilators, i.v. inotropic therapy, or any combination with LVEF ≤30%	Mortality (3m)	5
Duygu(2008)(23)	Randomized controlled trial	Patient with chronic heart failure with NYHA functional class III to IV symptoms and LVEF <40%	Mortality (1m)	4
J. García-González(2021)(24)	Multicenter Randomized Double-blind Placebo-controlled	Patients with advanced heart failure with NYHA Class III or IV, evidence of severe left ventricular dysfunction of any etiology, and at least one episode of acute decompensation requiring hospital admission within the previous 6 months.	Mortality (3m)	5
Felker(2003)(25)	Randomized, double-blinded trial.	Patients with systolic dysfunction and decompensated heart failure.	Mortality (2m)	5
J. Alteneberger (2014)(26)	Randomized, double-blind, placebo-controlled	Patients with chronic HF (NYHA class III or IV) with LVEF of ≤35%	Mortality	5
Adamapoulous (2006)(27)	Randomized, placebo-controlled trial	Patients with symptoms of NYHA class III or IV Admitted for acute decompensated heart failure with documented LVEF ≤30%	Mortality (4m)	5
Tereschenko(2011) (28)	Randomized controlled trial	Patients with resistant cardiac failure (RCF)	Mortality (6m)	3
Chenikala (2025)(29)	Randomized controlled trial	patients undergoing off-pump coronary artery bypass grafting (OPCAB) with LVEF≤40%	Mortality (6m)	3

Main treatment and results of included trials are summarized in table 2.

Table 2. The main treatment and results of included trials

Study	n	Drug	Administration dose	LVEF	Results
Cuffe (2002)(7)	477	Milrinone	loading dose: 50 µg/kg maintenance dose: 0.375-0.75 µg/kg/min for 48-72 hrs	NA	These results do not support the routine use of intravenous milrinone as an adjunct to standard therapy in chronic heart failure.
	472	Placebo		NA	
Moiseyev VS (2002) (RUSSLAN)(8)	402	Levosimendan	loading dose: 6-24 µg/kg for 10 mins maintenance dose: 0.1-0.4µg/kg/min for 5 hrs and 50 mins	NA	Levosimendan reduced the risk of worsening heart failure and death in patients with left ventricular failure complicating acute myocardial infarction.
	102	Placebo		NA	
Nanas (2004)(9)	16	Dobutamine	maintenance dose: 10 µg/kg/min for 8 hrs biweekly	22.7± 5.8%	Long-term intermittent dobutamine infusion combined with amiodarone improved the survival of patients with advanced HF.
	14	Placebo		23.9 ± 5%	
Mebazaa A (2007) (SURVIVE)(3)	664	Levosimendan	loading dose: 12 µg/kg for 10 mins maintenance dose: 0.1µg/kg/min for 50 mins	24± 5%	Levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes compared with dobutamine.
	663	Dobutamine	maintenance dose: 5 µg/kg/min for 24 hrs	24± 5%	
Nieminen (2000) (10)	23	Levosimendan	loading dose: 3, 6, 12, 24 µg/kg for 10 mins maintenance dose: 0.05, 0.1 ,0.2 ,0.4, 0.6 µg/kg/min for 24 hrs	26± 2%	There were no deaths during the treatment day, but two patients died during follow-up. One received dobutamine and the other received levosimendan.
	21	Placebo		27± 2%	
Comín-Colet (2018) (LION-HEART)(11)	48	Levosimendan	loading dose: NA maintenance dose: 0.2µg/kg/min for 6 hrs every 2 weeks over a 12-week period	27± 9%	Intermittent administration of levosimendan reduced plasma concentrations of NT-proBNP, worsening of HRQoL and hospitalization for heart failure.
	21	Placebo			
Jia (2014)(12)	80	Levosimendan	loading dose: 6 µg/kg for 10 mins maintenance dose: 0.1µg/kg/min for 24 hrs	28.5 ± 5.7%	Short-term intravenous infusion of levosimendan appears to be more effective than placebo for treating patients with heart failure complicated by AMI.
	80	Placebo		29.9 ± 5.3%	
Jia (2015)(13)	30	Levosimendan	loading dose: NA maintenance dose: 0.1µg/kg/min for 24 hrs	27.8 ± 6.8%	Levosimendan and nesiritide was superior to placebo and single drug therapies in terms of improvements in clinical conditions during the early stages of therapy.
	30	Placebo		29.6 ± 6.1%	
Follath (2002) (LIDO study)(14)	103	Levosimendan	loading dose: 24 µg/kg for 10 mins maintenance dose: 0.1µg/kg/min for 24 hrs	NA	Levosimendan showed better haemodynamic performance and lower mortality than dobutamine in patients with severe, low-output heart failure.
	100	Dobutamine	maintenance dose: 5 µg/kg/min for 24 hrs. The infusion rate was doubled if the response was inadequate at 2 h.	NA	
Aranda (2002)(15)	19	Milrinone	maintenance dose: 0.25-0.75 µg/kg/min	NA	Both dobutamine and milrinone can be used successfully as pharmacologic therapy for a bridge to heart transplantation.
	17	Dobutamine	maintenance dose: 2.5 - 10µg/kg/min	NA	
Llorens(2012)(30)	25	Levosimendan	loading dose: 6 µg/kg for 10 mins maintenance dose: 0.1µg/kg/min for 24 hrs	NA	Levosimendan produces no significant differences in readmission or mortality rates compared with placebo.
	20	Placebo		NA	
Bonios MJ (2012)(17)	19	Levosimendan	loading dose: NA maintenance dose: 0.6µg/kg/min for 6 hrs once weekly over a 6-month period	23.6 ± 7.8%	n patients with refractory end-stage heart failure, intermittent administration of levosimendan conferred survival and hemodynamic benefits in comparison to dobutamine, alone or in combination with levosimendan.
	12	Dobutamine	maintenance dose: 10 mg/kg/min for 6 hrs once weekly over a 6 months period	22.3 ± 5.5%	
Giamouzis (2010) (DAD-HF)(18)	30	Dopa	maintenance dose: 5 µg/kg/min	35.5 ± 11.2%	The combination of low-dose furosemide and low-dose dopamine is equally effective as high-dose furosemide but associated with improved renal function profile and potassium homeostasis.
	30	Diure		35.1 ± 13.1%	

Table 2. (following)The main treatment and results of included trials

Study	n	Drug	Administration dose	LVEF	Results
Triposkiadis (2014) (DAD-HF II)(19)	56	Dopa	maintenance dose: 4-5 µg/kg/min	30 ± 4.5%	There were no significant differences between high- vs. low-dose furosemide infusion; the addition of low-dose dopamine infusion was not associated with any beneficial effects.
	50	Diuretics	high dose Furosemide	32 ± 5%	
Husebye (2013) (LEAF)(20)	30	Levosimendan	loading dose: NA maintenance dose: 0.2µg/kg/min for 1 hr thereafter decrease to 0.1µg/kg/min for 24 hrs	43%	Levosimendan improved contractility in post-ischaemic myocardium without any increase in arrhythmias and mortality.
	31	Place		40%	
Kleber (2002)(21)	18	Levosimendan	loading dose: 12 µg/kg for 10 mins maintenance dose: 0.1µg/kg/min for 50 mins and thereafter increase to 0.2µg/kg/min for 23 hrs 4 times at 2-week intervals as a continuous infusion of 0.2 µg/kg/min for 6 hours.	NA	One patient in placebo group died 10 days after completing the 24-hour infusion as a result of progression of heart failure and acute kidney failure.
	10	Place		NA	
G.Pölzl (2023)(22)	93	Levosimendan	6-hour infusion: 0.2 µg/kg/min every 2 weeks for 12 weeks 24-hour infusion: 0.1 µg/kg/min every 3 weeks for 12 weeks	24 ± 5%	The LeoDOR trial found that intermittent levosimendan therapy did not improve clinical stability in patients with advanced heart failure during the early discharge period after hospitalization for an acute heart failure event. The trial observed higher rates of cardiovascular events with levosimendan and lacked favorable effects on secondary endpoints.
	52	Placebo		24 ± 5%	
Duygu (2008)(23)	20	Levosimendan	10-min bolus infusion at 6-12 µg/kg, followed by continuous infusion at 0.1 µg/kg/min	28± 5%	Levosimendan significantly increased LVEF, Sm, DT, and Em, and decreased E/A ratio. Levosimendan did not alter heart rate or blood pressure; dobutamine increased these parameters. Clinical improvement in NYHA functional class with levosimendan.
	20	Dobutamine	Initial dose 5 µg/kg/min, increased to 10, 15, and 20 µg/kg/min if no adverse effects		
J. García-González (2021)(24)	70	Levosimendan	Dose of levosimendan: 0,1ug/kg/minAdministration: Continuous 24-hour intravenous infusion once monthly for 1 year		Cumulative incidence of acute decompensation of HF and/or death: Significantly lower in the levosimendan group at 1 and 3 months.
	27	Place			
Felker (2003)(25)	477	Milrinone	0.5 g/kg/min without a loading dose	NA	60-day mortality: 11.6% for ischemic patients, 7.5% for nonischemic patients (p=0.03)
	472	Placebo		NA	
J. Alteneberger (2014)(26)	63	Levosimendan	Dose per infusion: 0.2 µg/kg/min for 6 hours Number of infusions: Four cycles at 2-week intervals	24 ± 5%	Cumulative incidence of acute decompensation of HF and/or death: Significantly lower in the levosimendan group at 1 and 3 months.
	57	Placebo		24 ± 5%	
Adamapoulous (2006)(27)	23	Levosimendan	10-minute intravenous injection of 6 µg /kg followed by a continuous 24-hour infusion at 0.1 µg /kg/min	24%	Levosimendan significantly improved hemodynamic parameters: end-systolic wall stress, LVEF, pulmonary capillary wedge pressure, and cardiac index. Event-free survival was significantly longer in the levosimendan group.
	23	Dobutamine	A continuous infusion initially at 5 µg /kg/min without a loading dose	25%	
	23	Placebo		27%	
Tereschenko (2011)(28)	15	Levosimendan	Bolus: 12–24 µg/kg over 10 minutes. Infusion: continuous for 24 hours at 0.1 µg/kg/min.	NA	Levosimendan rapidly improves cardiac function, decreases vascular resistance, relieves symptoms, and appears to reduce short-term mortality compared to dopamine.
	15	Dopa	Continuous infusion for 24 hours. Mean dose: 2.2 µg/kg/min.	NA	
Chenikala (2025)(29)	50	Dobutamine	6–24 µg/kg over 10 minutes (many trials use 12 µg/kg). Continuous infusion: 0.05–0.2 µg/kg/min	NA	Mortality was lower in the levosimendan group, suggesting better early postoperative outcomes. These results indicate levosimendan is superior to dobutamine in this patient population for both hemodynamic and clinical endpoints
	50	Dopamine	2.5–20 µg/kg/min, titrated to effect/ BP (typical inpatient doses: 2.5–10 µg/kg/min).	NA	

LVEF=Left ventricular ejection fraction

Overall, the pooled estimate across all studies (n = 23) was –0.024 (95% CI: –0.047 to 0.000, p=0.051), which approached but did not achieve statistical significance.

The prediction intervals for both subgroups and the overall analysis crossed the line of no effect, highlighting heterogeneity regarding the true effect of inotropes.

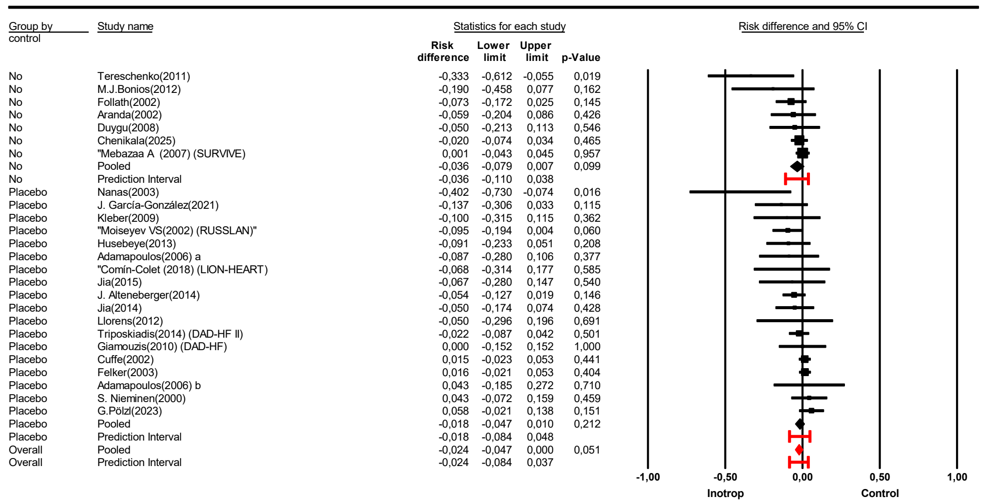

Figure 4. Forest plot of the effect of inotropic therapy versus control, stratified by inotropes or placebo use.

Meta-Regression Analysis: Mortality

Meta-regression for age, LVEF, and systolic blood pressure showed no significant associations, failing to explain heterogeneity.

Discussion

This meta-analysis found no significant reduction in mortality with inotropic agents in AHF patients, though a non-significant trend emerged (RD –0.023; p=0.055). Heterogeneity persisted despite subgroup and meta-regression analyses, with prediction intervals indicating uncertainty.

Previous meta-analyses have reported inconsistent findings. A large review of 177 trials (28,280 patients) found no mortality difference overall (RR 0.98; 95% CI 0.96–1.01) but suggested benefits in septic/vasoplegic shock subgroups (31).

In two key trials (32), participants were randomly assigned to receive either low-dose oral enoximone or a placebo (33). The results indicated that treatment with this phosphodiesterase inhibitor did not impact mortality rates or improve major clinical outcomes. Based on these findings and earlier studies, the use of inotropes may only be considered in situations requiring palliative care or bridge therapy.

For dobutamine specifically, an odds ratio of 1.47 (95% CI 0.98–2.21) indicated potential harm without significance (34). Pharmacological differences may contribute: dobutamine risks myocardial damage.

Some observational studies suggest that inotropes, particularly catecholamines, could increase mortality rates (35).

A post-hoc analysis of OPTIME-CHF study(7) suggested that milrinone could be harmful to patients with ischemic heart failure, while it might be beneficial for those with non-ischemic cardiomyopathy. The authors hypothesized that this effect could be due to accelerated apoptosis and a subsequent progression of heart failure in the chronically ischemic, hibernating myocardium, which may be mediated by adrenergic signaling pathways.

Some observational trials reported increased mortality associated with inotropes use in the setting of cardiac surgery (36,37).

The recent ROSE trial (38) examined the effects of dopamine, nesiritide, and a placebo on renal function in patients with decompensated heart failure. The study involved 360 randomized participants. The authors reported that there was no difference in mortality at the 180-day follow-up. However, it's important to note that dopamine was administered at a low dose of 2 µg/kg/min, and mortality was not the primary endpoint of the study.

Levosimendan has shown promise, with one meta-analysis reporting a 20% mortality reduction (RR 0.80; 95% CI 0.72–0.89) in heart failure and surgical settings (36) and another a 45% reduction with intermittent use (RR 0.55; 95% CI 0.37–0.84) (37). It offers myocardial protection (35). Intermittent intravenous administration can be considered in advanced heart failure, as meta-analyses suggest improved survival in both cardiology and cardiac surgery contexts, with pulsed regimens reducing mid-term mortality (39).

In cardiac surgery, inotropes are used in 20–90% of patients depending on preoperative status and surgical complexity (40). Their main indication is prevention or treatment of postoperative low-cardiac output syndrome, a complication associated with higher morbidity and mortality.

Levosimendan also appears renoprotective, potentially benefiting patients with advanced heart failure and cardiorenal syndrome (41). Studies by Fedele et al. (42)

and Lannemyr et al. (43) found that, unlike dobutamine, levosimendan significantly increased glomerular filtration rate. Proposed mechanisms include activation of ATP-dependent potassium channels causing peripheral and renal vasodilation, dilation of afferent arterioles improving glomerular ultrafiltration, and inhibition of angiotensin II–mediated mesangial contraction, increasing filtration surface area. Further meta-analyses are needed to confirm these effects.
Finally, among inotropes, meta-analyses indicate that levosimendan is the only agent associated with improved survival. However, large multicenter randomized trials have yet to confirm this benefit.

Limitations :
Our meta-analysis include small, single-center studies with short follow-up, potentially masking effects, and variability in comorbidities and co-therapies (e.g., beta-blockers). Publication bias and asymmetry in the funnel plot warrant caution.

Conclusion

Inotropic agents showed a non-significant trend toward reduced mortality in AHF. These findings indicate no consistent benefit. Future large-scale RCTs should focus on subgroups like severe left ventricular or perioperative dysfunction to assess survival benefits.

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