ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 2049–2050
Published online 5 April 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13812

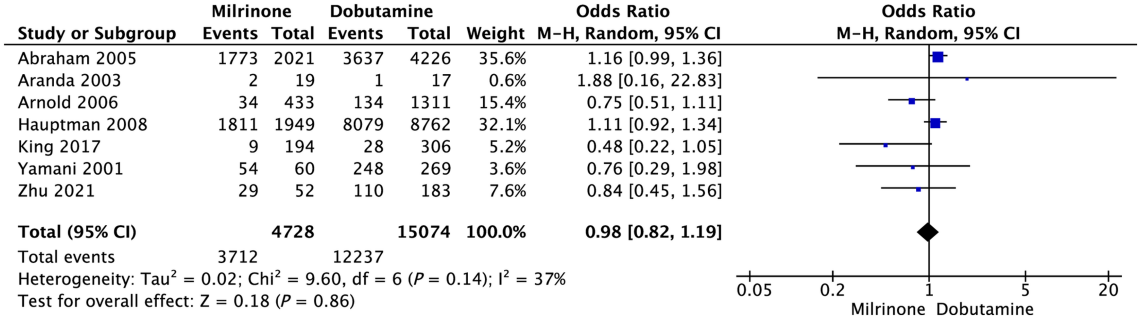
Milrinone or dobutamine in patients with heart failure: evidence from meta-analysis

Heart failure (HF) is one of the most prevalent causes of hospital admissions, especially among the elderly. Although the therapy for HF exacerbation primarily consists of restoring euvolemia with diuretics, inotropes are still needed for treatment of patients with low cardiac output and hypotension.[1] Dobutamine improves myocardial contractility via activation of β1-adrenergic receptors in cardiomyocytes, which can cause sinus tachycardia, arrhythmias and myocardial ischaemia, thus increasing mortality.[2] Type-3-phosphodiesterase inhibitor milrinone improves contractility without affecting the β1-receptors and may therefore be preferred over dobutamine, especially for patients on beta-blockers. On the other hand, excessive peripheral vasodilation and hypotension can be major limitations of milrinone, especially when administered at high doses. In some studies, patients with acute HF receiving milrinone demonstrated improved survival rates compared with the patients treated with dobutamine.[3,4] In other studies, milrinone did not show a significant advantage over dobutamine with regard to either clinical outcomes or adverse effects, making the use of dobutamine more attractive due to lower cost.[5,6] Given the role that inotropes play in acute HF, the high prevalence of their use, and the discrepancies in cost between them, it is crucial to determine the differences between the efficacy and safety of these drugs to optimize HF therapy. We performed a systematic review and meta-analysis of randomized and non-randomized trials to compare the effect of milrinone and dobutamine on survival outcomes and adverse events in adult patients with HF.

This systematic review and meta-analysis complied with the widely recognized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The PubMed, Embase, and Cochrane Library electronic databases were searched for articles published from database inception until 10 August 2021 performed by two independent reviewers (L. S. and M. P.). Keywords and phrases used for search queries included 'milrinone', 'dobutamine', and 'heart failure'. All results are presented as mean difference (MD) or odds ratio (OR) or risk ratios (RR) with their 95% confidence interval (CI). All reported *P*-values were two-sided, and $P < 0.05$ were considered statistically significant. Statistical analyses were performed using RevMan5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark).

Nine studies including 19 045 patients were selected for meta-analysis.[1–9] All studies reported the use of milrinone vs. dobutamine in HF patients (Supporting Information, *Table S1*). Survival to hospital discharge was reported in seven studies[1–3,6–9] and was 78.5% for the milrinone group, compared with 81.2% for dobutamine (OR = 0.98; 95% CI: 0.82 to 1.19; *P* = 0.86; *Figure 1*). The 180 day survival rate was reported in one study[1] and was 11.9% for milrinone and 18.0% for dobutamine group (OR = 0.61; 95% CI: 0.36 to 1.04; *P* = 0.07). Pooled analysis of 1 year survival rate for milrinone and dobutamine was 62.7% vs. 43.0% (OR = 2.23; 95% CI:

Figure 1 Forest plot of survival to hospital discharge in milrinone and dobutamine group. The centre of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.



1.74 to 2.85; $P < 0.001$), and the 2 year survival rate was 46.8% vs. 33.7%, respectively (OR = 1.06; 95% CI: 1.35 to 2.23; $P < 0.001$).[4] Length of hospital stay was reported in five studies and was 12 (17) vs. 10.5 (10.6) days respectively for milrinone and dobutamine groups (MD = 3.12; 95% CI: 0.43 to 5.80; $P = 0.02$).

A full overview of adverse events is presented in Supporting Information, *Table S2*. The use of milrinone compared with dobutamine was associated with more frequent 30 day readmission (9.5% vs. 5.0%; RR = 1.91; 95% CI: 1.31 to 2.78; $P < 0.001$). Conversely, in the case of hypertension, the reverse trend was observed (13.3% vs. 40.0%; RR = 0.33; 95% CI: 0.16 to 0.68; $P = 0.003$).

In conclusion, in our analysis involving 19 045 patients, the survival to hospital discharge was comparable in HF patients receiving milrinone or dobutamine. The 180 day survival outcomes showed a trend towards better results with milrinone, compared with dobutamine, but they also did not reach statistical significance. In contrast, a pooled analysis of 1 year and 2 year survival showed a clear advantage of milrinone over dobutamine, indicating better long-term outcomes in HF patients treated with milrinone. Interestingly, patients on milrinone had less episodes of hypertension, but a higher incidence of 30 day hospital readmissions. Our analysis indicated the need to conduct further randomized clinical trials to clearly answer the question about the advantages of milrinone over dobutamine in long-term survival in HF patients.

Supporting information

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

Table S1. Main characteristics of the studies comparing Milrinone and Dobutamine in heart failure patients.
Table S2. Characteristics of the adverse events in Milrinone and Dobutamine groups.

Lukasz Szarpak
Maria Sklodowska-Curie Medical Academy, Warsaw, 03-411, Poland
Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
E-mail: lukasz.szarpak@gmail.com

Piotr Szwed
1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Aleksandra Gasecka
1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Zubaid Rafique
Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA

Michal Pruc
Polish Society of Disaster Medicine, Warsaw, Poland

Krzysztof J. Filipiak
Maria Sklodowska-Curie Medical Academy, Warsaw, 03-411, Poland

Milosz J. Jaguszewski
First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland

References

1. King JB, Shah RU, Sainski-Nguyen A, Biskupiak J, Munger MA, Bress AP. Effect of inpatient dobutamine versus milrinone on out-of-hospital mortality in patients with acute decompensated heart failure. *Pharmacotherapy* 2017; **37**: 662–672.
2. Zhu Y, Yin H, Zhang R, Ye X, Wei J. The effect of dobutamine versus milrinone in sepsis: a big data, real world study. *Int J Clin Pract* 2021; **75**: e14689.
3. Arnold LM, Crouch MA, Carroll NV, Oinonen MJ. Outcomes associated with vasoactive therapy in patients with acute decompensated heart failure. *Pharmacotherapy* 2006; **26**: 1078–1085.
4. Mody BP, Khan MH, Zaid S, Ahn C, Lloji A, Aronow WS, Gupta CA, Levine A, Gass AL, Cooper HA, Lanier GM. Survival with continuous outpatient intravenous inotrope therapy in the modern era. *Am J Ther* 2020; **28**: 1–10.
5. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. *J Cardiothorac Vasc Anesth* 2001; **15**: 306–315.
6. Yamani MH, Haji SA, Starling RC, Kelly L, Albert N, Knack DL, Young JB. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: hemodynamic efficacy, clinical outcome, and economic impact. *Am Heart J* 2001; **142**: 998–1002.
7. Aranda JM, Schofield RS, Pauly DF, Cleeton TS, Walker TC, Monroe VS, Leach D, Lopez LM, Hill JA. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J* 2003; **145**: 324–329.
8. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, Lejemtel TH, Cheng ML, Wynne J, ADHERE Scientific Advisory Committee and Investigators, ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the acute decompensated heart failure National Registry (ADHERE). *J Am Coll Cardiol [Internet]* 2005; **46**: 57–64.
9. Hauptman PJ, Swindle J, Burroughs TE, Schnitzler MA. Resource utilization in patients hospitalized with heart failure: insights from a contemporary national hospital database. *Am Heart J* 2008; **155**: 978–985.e1.