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Letter

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# The Mortality Benefit of Milrinone as a Continuous Outpatient Intravenous Inotrope Therapy in Advanced Heart Failure: A Systemic Review and Meta-Analysis

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Advanced (stage D) heart failure (AHF) is defined by severe and refractory symptoms, not responding to maximum guideline-directed medical therapy, that markedly interfere with daily life and lead to recurrent hospitalizations.[1] According to the AHA/ACC/ESFA 2022 guideline, continuous outpatient intravenous inotrope therapy is a strategy used as in interim treatment to those with AHF awaiting for mechanical circulatory support or cardiac transplantation (class IIa recommendation) and palliative treatment to improve symptom and functional status (class IIb recommendation).[1] Milrinone and dobutamine are the most frequently used intravenous inotropes.[2] Despite the aforementioned recommendation, there's a sparsity of data comparing the benefit between those inotropic agents. Recent randomized-controlled trial and meta-analyses did not show an advantage of milrinone over dobutamine with regards to in-hospital mortality in patients with acute cardiogenic shock[3-5]; however, there was an increasing mortality benefit of milrinone over time, suggesting the possibility of time-dependent effect.[4] A systemic review and meta-analysis was, therefore, performed to compare the mortality benefit between continuous outpatient intravenous therapy with milrinone and dobutamine.

We independently searched for published studies and abstracts indexed in PubMed database from inception to December 2022 using the terms "advanced heart failure," "milrinone," and "dobutamine" (**Figure 1**). Studies were included if they compared continuous outpatient intravenous milrinone against dobutamine therapy and evaluated the clinical outcome of all-cause mortality in patients with AHF. Pooled odd ratios (OR) and adjusted hazard ratios (HR) for mortality with their respective 95% confidence interval (CIs) were estimated using Der Simonian and Laird random-effects model. $I^2$ statistic was used to quantify the heterogeneity of effect size estimates across included studies, ranging from 0% to 100% (<25%, low; 25–50%, moderate; >50%, substantial). A p value of <0.05 was considered statistically significant. All data analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA). The review protocol was registered on PROSPERO (CRD42022334045).

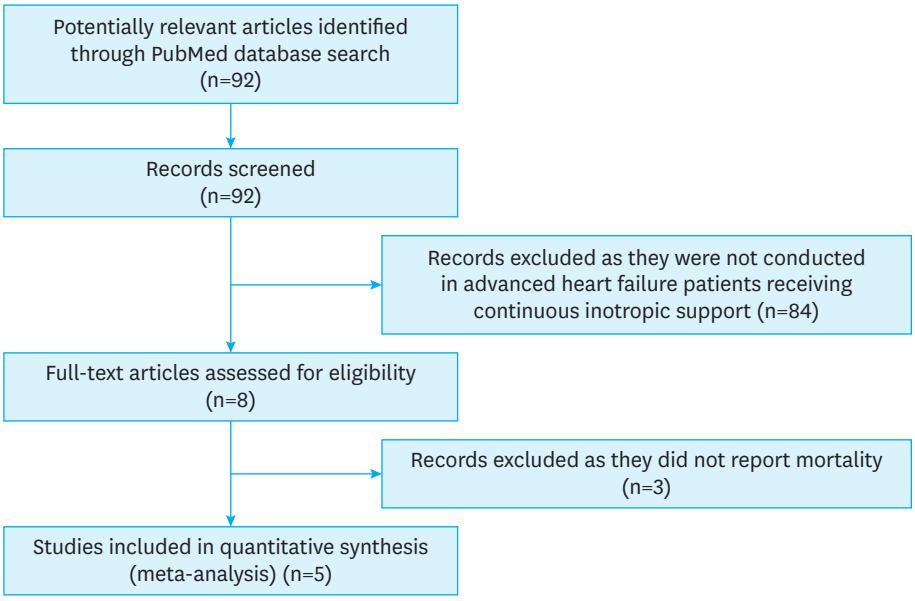


**Figure 1.** PRISMA flow diagram demonstrating search methodology and selection process.

A total of 5 cohort studies from 2009 to 2022 comprising 4,841 patients with AHF (3,312 received milrinone and 1,529 received dobutamine) were included (**Table 1**). Follow-up duration was 4-12 months. The crude mortality was lower in those receiving continuous outpatient intravenous milrinone compared to dobutamine (25% vs. 44%; pooled OR, 0.41; 95% CI, 0.26–0.66; $I^2$, 86.4%, p<0.05; **Figure 2A**). From multivariable analysis, patients who received intravenous milrinone also showed a significantly lower mortality rate than patients who received dobutamine (pooled adjusted HR, 0.61; 95% CI, 0.46–0.81; $I^2$, 58.6%; p<0.05; **Figure 2B**).

A retrospective analysis of 112 patients with AHF, conducted by Gorodeski et al.,[7] showed that dobutamine was associated with higher mortality rate (unadjusted HR, 1.63; 95% CI, 1.03–2.59; p=0.04). However, after adjustment for age and gender, there was no longer an association between dobutamine and mortality (HR, 1.09; 95% CI, 0.64–1.85; p=0.75).[7] Data from another retrospective analysis of 222 patients with AHF showed that, despite the differences in survival by treatment became insignificant over time, milrinone was associated with lower overall mortality and longer survival time.[10] Other studies uniformly demonstrated a significant mortality benefit in favor of milrinone.[6-8]

Milrinone exerts its inotropic and vasodilatory effects via inhibition of the intracellular phosphodiesterase-3 enzyme, resulting in elevated intracellular cyclic adenosine monophosphate (cAMP) levels and subsequent increased protein kinase A activity.[2] Elevated cAMP levels lead to vasodilation in both systemic and pulmonary vasculature by reducing the activity of myosin light chain kinase in the vascular smooth muscle.[11] Dobutamine, on the contrary, is a catecholaminergic agent with β-1 and, less predominantly, β-2 and α-1 adrenergic agonist properties.[2]

The detrimental effect of dobutamine may be associated with increased myocardial oxygen consumption.[12,13] Alternately, it could be the differences in the site of action that makes dobutamine less favorable than milrinone. Although both drugs exert their inotropic effect vias increase in cAMP levels, dobutamine action is dependent on stimulation of β-adrenergic receptors (β-ARs) in the myocardial cells. Whether the use of beta-blockers, which are known to improve morbidity and mortality, will negate its action remains controversial.[14] The hemodynamic effects of dobutamine were blunted in heart failure patients chronically treated with carvedilol, while the favorable effects on pulmonary pressures persisted with milrinone.[14]

Prolonged dobutamine infusion has also been associated with eosinophilic myocarditis as manifested by eosinophilia, worsening ejection fraction, and rehospitalization.[15] The incidence was as high as 14% with median duration of therapy of only 41 days as opposed to milrinone group, in which there was no incidence.[15]

A retrospective cohort of 69 patients with AHF listed for transplant who were bridged with continuous milrinone infusion showed that milrinone was associated with approximately 20% reduction in both ventricular pressures, pulmonary, and systemic vascular resistance, together with almost 20% increase in cardiac index.[16] Concurrent use of beta-blockers and milrinone might decrease ar-

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**Table 1.** The methodology and the population characteristics of included studies

| Ref | No. of patients | Period | Country | Study design | Patient population | Outcome | Mean dobutamine | Mean milrinone | Follow-up | Age | Female (%) | LVEF (%) | CAD (%) | BMI | Device (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mody et al.[6] (2020) | 1,149 | Jan 2015–May 2017 | USA | Retrospective cohort, registry | AHF who received interim therapy to decision, MCS, or transplant, or palliation | All-cause mortality | n/a | n/a | 2 years | 58.5±14.2 vs. 61.4±14.4 | 219 (29.5%) vs. 125 (30.7%) | n/a | n/a | n/a | n/a |
| Gorodeski et al.[7] (2009) | 112 | 2002–2007 | USA | Retrospective cohort, single-center | AHF patients who failed to wean inotrope in an intensive care unit and were not candidates for MCS or transplant | All-cause mortality | 5.4±2.5 μg/kg/min | 0.4±0.2 μg/kg/min | 130 days (2–2,345) | 53±12 vs. 60±13 | 12 (21%) vs. 8 (14%) | 16±8 vs. 17±9 | 41% vs. 41% | 27±8 vs. 26±7 | ICD: 37% vs. 40% CRT: 29% vs. 29% |
| Grazette et al.[8] (2022) | 3,110 | May 2009–June 2016 | USA | Retrospective cohort, registry | AHF patients who failed to wean inotrope in hospital | All-cause mortality | 4.22±2.94 μg/kg/min | 0.35±0.19 μg/kg/min | 171±231 days | 61.4±14.4 vs. 63.6±14.1 | 578 (25.2%) vs. 231 (28.3%) | n/a | n/a | n/a | n/a |
| Sami et al.[9] (2022) | 248 | Jan 2015–May 2019 | USA | Retrospective cohort, two-center | AHF patients who failed to wean inotrope in hospital and were not candidates for MCS or transplant | All-cause mortality | 4.2 μg/kg/min | 0.25 μg/kg/min | 1 year | 63.38±13.9 vs. 66.18±12.8 | 61.36% vs. 72.17% | 20.5±10.6 vs. 19.9±10.8 | 56% vs. 58.3% | 28.77±7.1 vs. 27.95±8.7 | ICD: 55.2% vs. 66.1% CRT: 42.5% vs. 31.2% |
| Eaton et al.[10] (2022) | 222 | Jan 2015–April 2020 | USA | Retrospective cohort, single-center | AHF patients who were on inotrope for palliation | All-cause mortality | 3 μg/kg/min | 0.3 μg/kg/min | 1 year | 59 [49–66] vs. 63 [53–72] | 31% vs. 27% | 18 vs. 18 | 53% vs. 64% | 29 [24–35] vs. 28 [25–34] | ICD: 77% vs. 64% |

Comparative data were represented as milrinone vs. dobutamine.
LVEF = left ventricular ejection fraction; CAD = coronary artery disease; BMI = body mass index; AHF = advanced heart failure; n/a = not available; MCS = mechanical circulatory support; ICD = implantable cardioverter-defibrillator; CRT = cardiac resynchronization therapy.

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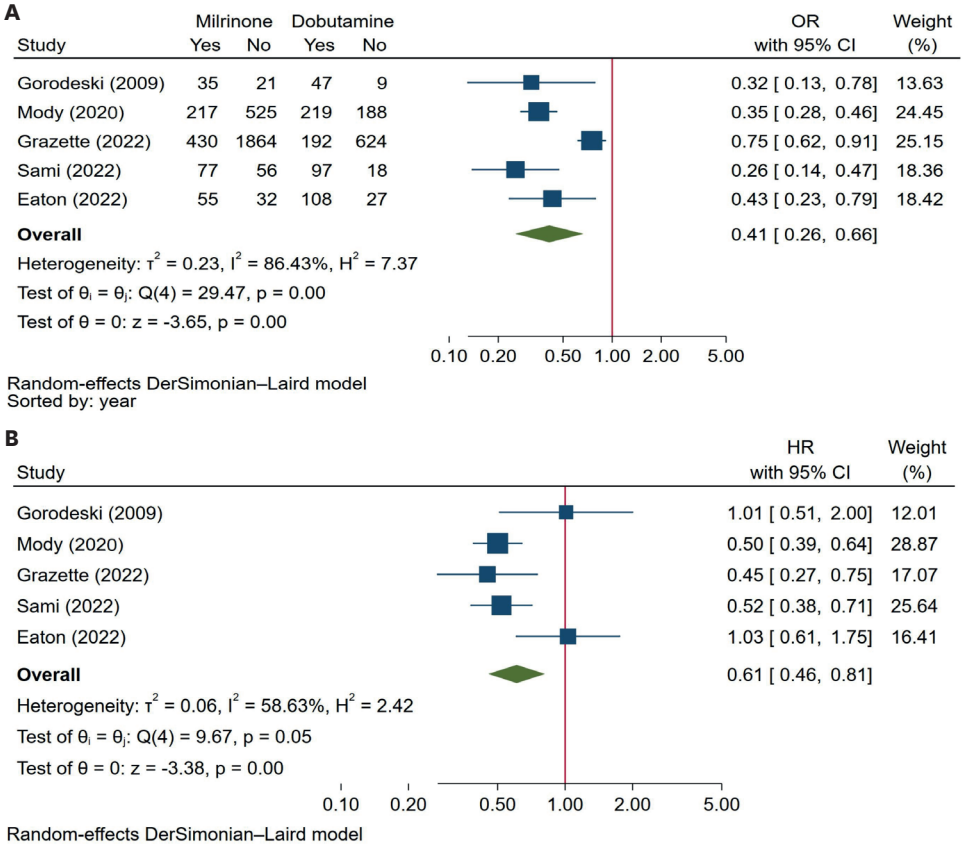


**Figure 2.** Forest plot of included studies assessing the mortality comparing between milrinone and dobutamine. (A) showing pooled odd ratios and (B) showing adjusted HR.
OR = odds ratio; HR = hazard ratio; CI = confidence interval.

rhythmogenicity associated with uncontrolled β-ARs stimulation and subsequent increased calcium influx through L-type calcium current via cAMP-independent stimulatory G protein-coupled pathway, while preserving its cAMP-dependent inotropic effect.[17] Interestingly, Grazette et al.[8] revealed that concurrent use of beta-blockers was associated with lower mortality regardless of whether they received milrinone or dobutamine. This finding suggested that a higher mortality associated with dobutamine from previous studies might be, at least in part, attributed to the lower proportion of patients on beta-blockers.[9,10]

Despite robust data demonstrating survival benefit with milrinone, the result of this meta-analysis should be interpreted with caution as it only serves as a hypothesis generator. All included studies were observational and, thus, may be affected by confounding errors and biases. Publication bias cannot be accurately assessed due to insufficient number of included studies to reject the assumption of no funnel plot asymmetry. Clinical and methodological heterogeneity among studies should also be considered. We addressed these issues by using random-effects model and careful selection of eligible studies. The Newcastle–Ottawa quality assessment scale was used to assess each study's quality (**Table 2**). Additionally, the mortality benefit from milrinone existed in both unadjusted and adjusted analysis, suggesting ro-

**Table 2.** The Newcastle-Ottawa quality assessment scale of included studies

| Ref | Selection | | | | Comparability | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness | Selection of the non-exposed cohort | Ascertainment | Endpoint not presented at start | Comparability (confounding) | Assessment of outcome | Follow-up duration | Adequacy of follow-up | |
| Mody et al.[6] (2020) | x | x | x | x | | x | x | x | 7 |
| Gorodeski et al.[7] (2009) | x | x | x | x | x | x | x | x | 8 |
| Grazette et al.[8] (2022) | x | x | x | x | | x | | x | 6 |
| Sami et al.[9] (2022) | x | x | x | x | x | x | x | x | 8 |
| Eaton et al.[10] (2022) | x | x | x | x | x | x | x | x | 8 |


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bustness of the data. Further studies are needed to shed light on the mechanistic aspects underlying the difference in mortality outcomes between these inotropes. Subgroup analyses comparing between ischemic and non-ischemic cardiomyopathy would also provide clinically relevant information as coronary artery disease accounts for the vast majority of heart failure cases.

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**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Conceptualization: Del Rio-Pertuz G, Nair N; Data curation: Del Rio-Pertuz G, Phinyo P, Leelaviwat N, Mekraksakit P; Formal analysis: Del Rio-Pertuz G, Phinyo P, Leelaviwat N, Mekraksakit P, Benjanuwattra J; Methodology: Del Rio-Pertuz G; Supervision: Nair N; Validation: Nair N; Writing - original draft: Del Rio-Pertuz G, Benjanuwattra J; Writing - review & editing: Nair N, Benjanuwattra J.

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