

## Hemodynamic and Clinical Outcomes of Milrinone Compared to Dobutamine in Cardiogenic Shock: A – Systematic Review and Meta – Analysis

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### Abstract

**Background:** Despite years of clinical experience with the two most commonly used inotropes i.e. dobutamine and milrinone, in the cardiogenic shock setting, there is a lack of head-to-head comparison between inotropes in cardiogenic shock. We conducted a systematic review and meta-analysis on the comparison of hemodynamic and clinical effects of dobutamine and milrinone in cardiogenic shock.

**Methods:** A comprehensive literature search using PubMed and Scopus was performed. Among 40 studies retrieved from the database, 3 studies were included for hemodynamic comparison outcomes and 2 studies for clinical outcomes.

**Results:** Three studies with 101 patients were included for hemodynamic analysis and two studies with 146 patients for clinical analysis. We observed no significant difference between cardiac index, pulmonary capillary wedge pressure, and mean arterial pressure at 1 hour after milrinone and dobutamine administration. However, there is significantly lower mPAP after milrinone infusion compared to dobutamine (mean difference -8.7 (-9.97 to -7.43) mmHg,  $p < 0.01$ ). We also observed no significant difference in in-hospital mortality but significantly shorter ICU length of stay in the milrinone group (mean difference -1 (-1.92 to -0.08) days).

**Conclusion:** Administration of milrinone resulted in lower PA pressure and shorter ICU LOS compared to dobutamine in patients with cardiogenic shock.

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## Introduction

**C**ardiogenic shock is defined as a primary cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion. Clinical criteria include a systolic blood pressure of less than or equal to 90 mm Hg for greater than or equal to 30 minutes or support to maintain systolic blood pressure less than or equal to 90 mm Hg and urine output less than or equal to 30 mL/hr or cool extremities. Hemodynamic criteria include a depressed cardiac index (less than or equal to 2.2 liters per minute per square meter of body surface area) and an elevated pulmonary-capillary wedge pressure greater than 15 mm Hg.<sup>1</sup>

Cardiogenic shock is a clinical entity characterized by a low cardiac output state of circulatory failure that results in end-organ hypoperfusion and tissue hypoxia.<sup>2</sup> The most common cause of cardiogenic shock is acute myocardial infarction, though other disorders leading to impairment of the myocardium, valves, conduction system, or pericardium also can result in cardiogenic shock. Despite advances in reperfusion therapy and mechanical circulatory support treatments, morbidity, and mortality among patients with cardiogenic shock remain high.<sup>3</sup>

Although mechanical circulatory support for cardiogenic shock has garnered considerable attention, vasopressors and inotropes remain the cornerstone of therapy for most patients with this condition. Norepinephrine has emerged as a preferred vasopressor over epinephrine and dopamine. However, comparative data on other commonly used and widely available inotropes, such as milrinone and dobutamine, remain scarce.<sup>4</sup>

The two most commonly used inotropic agents are milrinone and dobutamine, in the cardiogenic shock setting. Milrinone is a phosphodiesterase III inhibitor, which increases intracellular cyclic AMP levels resulting in improved cardiac contractility, inotropy, and lusitropy with subsequent vasodilation of both systemic and pulmonary circulations.<sup>4</sup> Dobutamine is a synthetic catecholamine with an affinity for both beta-1 and beta-2 receptors; binding to cardiomyocytes results in improved myocardial inotropy, weak chronotropy, and mild systemic vasodilation.<sup>3</sup> However, in the absence of firm comparative data, the use of each agent is largely

based on clinician preference and theoretical benefits related to their mechanisms of action.<sup>4</sup> We conducted a systematic review and meta-analysis on the comparison of hemodynamic and clinical effects of dobutamine and milrinone in cardiogenic shock.

## Methods

### Data Sources

We conducted a systematic search on electronic databases including PubMed, and Scopus, up to 15 January 2021. The bibliography of all included studies was also checked to obtain higher accuracy. The whole study was designed and performed based on PRISMA guidelines.

### Search strategy

Search keywords were elected based on our PICO as P: patients with shock cardiogenic, I: Milrinone, C: Dobutamine, O: Hemodynamic, and Clinical Outcomes. For a better search result, we adjusted keywords and their combinations based on the requirements of each database. Only English studies were chosen for further evaluation.

### Eligible Studies

We included clinical trials if they reported cardiogenic shock (SCAI classification C-E), hemodynamic and clinical outcomes. Case reports, letters, and review articles were excluded. Patients were excluded if they had no hemodynamic evidence of cardiogenic shock, the presence of a ventricular assist device or intra-aortic balloon pump (IABP), concomitant milrinone and dobutamine therapy at initiation, CS of a mixed or noncardiac origin, or cardiac arrest before initiation of inotrope therapy.

All adult patients age greater than 18 who received milrinone or dobutamine as initial inotrope therapy for CS were included. Hemodynamic and clinical outcomes were defined as 1) cardiac index, 2) pulmonary capillary wedge pressure, 3) mean arterial pressure, 4) pulmonary artery pressure, 5) hospital mortality, and 6) intensive care unit (ICU) length of stay.

### Quality Assessment and Data Extraction

We conducted data extraction independently using prespecified inclusion and exclusion criteria. Furthermore, discrepancies were resolved by consensus.

### Statistical Analysis and Data Synthesis

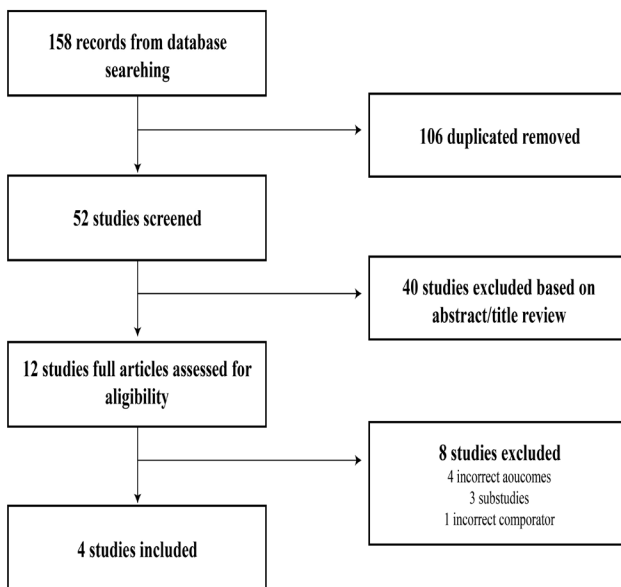
All Statistical analyses were performed by Comprehensive meta-analysis software version 2 (CMA-2). For all analyses random effects model was applied. Heterogeneity tests were used including I<sup>2</sup>, Cochran Q test statistic, and associated P-values.

## Results

From 158 studies identified, we included 2 RCTs and 2 observational studies. We specifically identified a study that compared dobutamine and milrinone in patients with cardiogenic shock (Table 1).<sup>4-7</sup>

### Search result

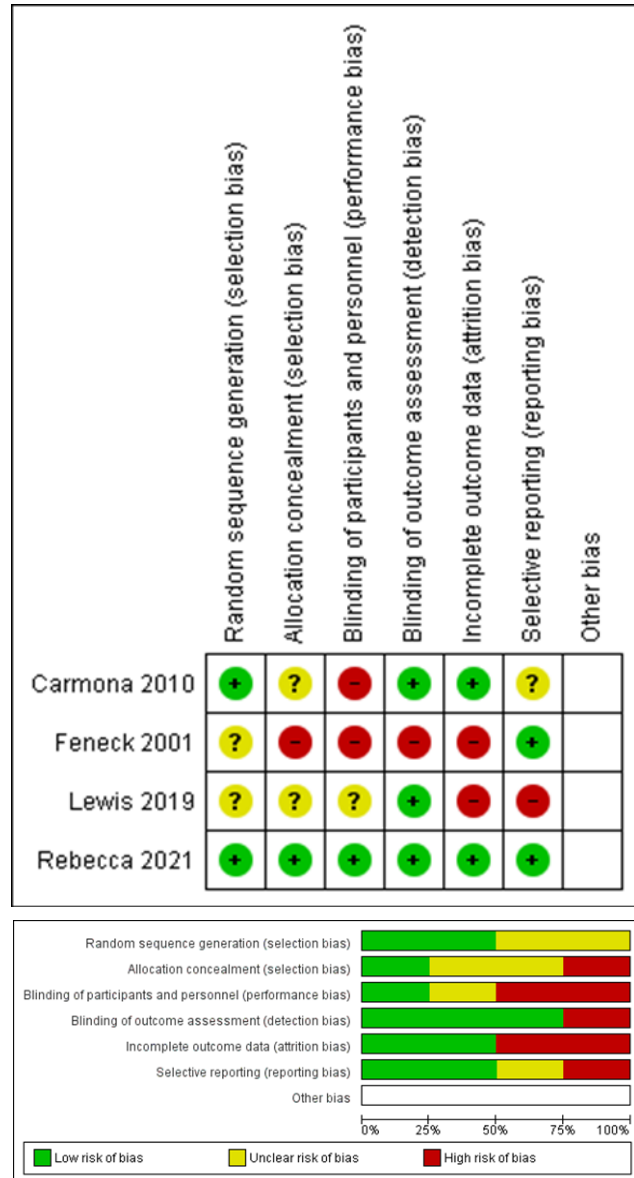
Table 1. PRISMA flow diagram.



### Risk of Bias

All trials except that of Rebecca et al had high or unclear risk of bias for at least 3 domains (Table 2). Table 2 lists the quality of evidence for each outcome.

Table 1. Risk of Bias.



### Meta-analysis for Cardiac Index

Three studies reported measuring cardiac index by use of inotrope and were included in the primary efficacy analysis. Comparatively, there was no observed difference

between dobutamine (93 patients) and milrinone (101 patients) on Cardiac Index (mean Difference -12.56, 95% CI -26.61 - 1.49,  $p=0.08$ , (Figure 1).

### Meta-analysis for Pulmonary Capillary Wedge Pressure

Pulmonary capillary wedge pressure was reported in three studies. There was no difference in pulmonary capillary wedge pressure between milrinone (101 patients) and dobutamine (93 patients) (mean difference -12.56, 95% CI -26.61 - 1.49,  $p=0.65$ , (Figure 2).

### Meta-analysis for Mean Arterial Pressure

No difference in clinically significant mean arterial pressure was noted between milrinone (70 patients) and dobutamine (70 patients) in the three studies (mean difference -12.86, 95% CI -35.29 - 9.57,  $p= 0.26$ , (Figure 3).

### Meta-analysis for Mean Pulmonary Artery Pressure

Results associated with mean pulmonary artery pressure from one study showed with a P value= <0.001, there is a significant difference in mean pulmonary artery pressure between milrinone (91 patients) and dobutamine (83 patients). As seen in the forest plot in Figure 4, with a mean difference of -8.70 (95% CI -9.97, -7.43). It can be concluded that patients who were administered with milrinone have a lower mean pulmonary artery pressure in comparison to patients who were administered with dobutamine (Figure 4).

### Meta-analysis for In Hospital Mortality

Both two studies were eligible for this meta-analysis too. As seen in Figure 5, there is no statistically significant difference (P-value=0.33) in-hospital mortality between milrinone (36 patients) and dobutamine (46 patients) (OR 0.56, 95% CI 0.17, 1.81, (Figure 5).

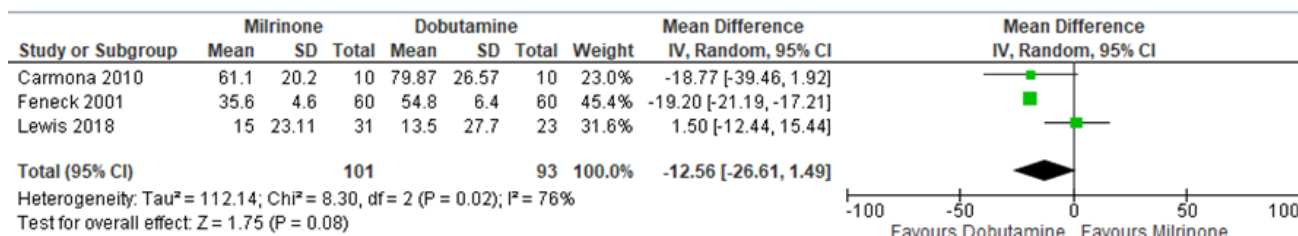


Figure 1. Forest Plot for Cardiac Index.

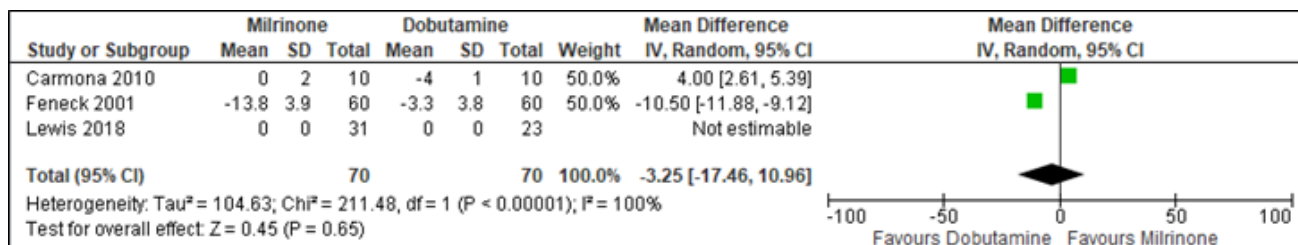


Figure 2. Forest Plot for Pulmonary Capillary Wedge Pressure.

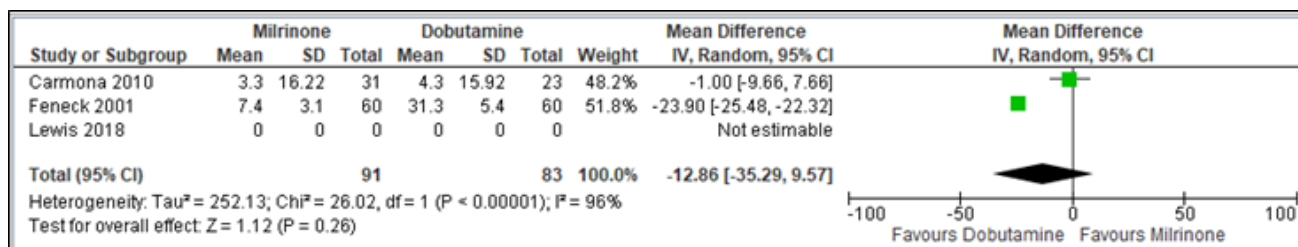


Figure 3. Forest Plot for Mean Arterial Pressure.

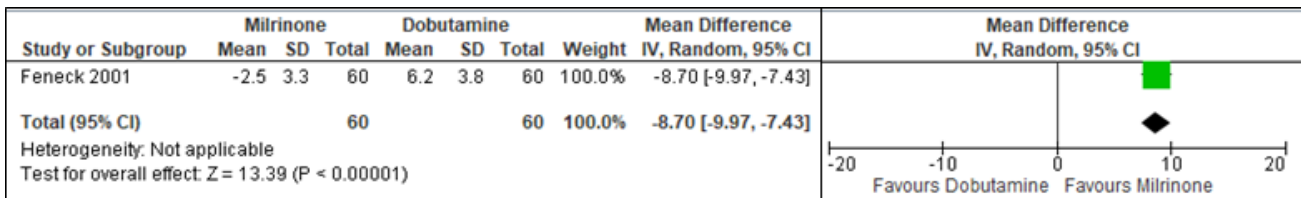


Figure 4. Forest Plot for Mean Pulmonary Artery Pressure.

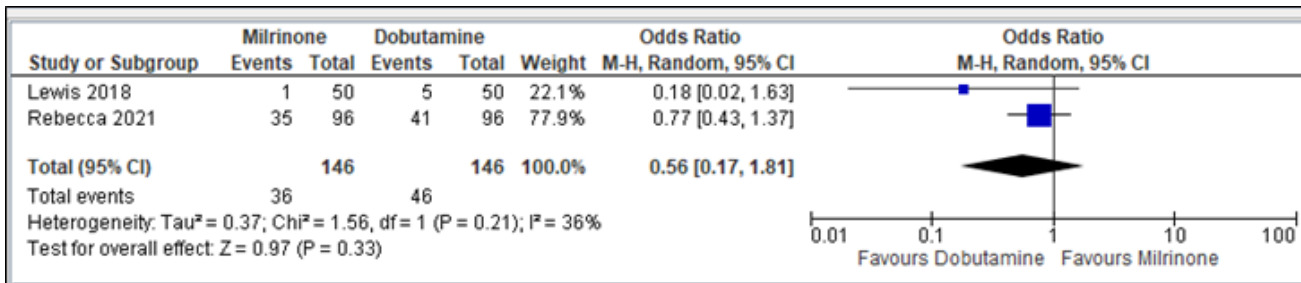


Figure 5. Forest Plot for In Hospital Mortality.

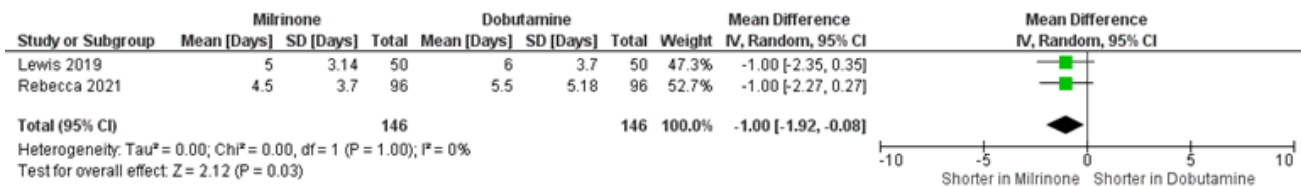


Figure 6. Forest Plot for ICU Length of Stay.

### Meta-analysis for ICU Length Of Stay

Total ICU length of stay was reported in two studies. Both studies reported the outcome, LOS-ICU was shorter with milrinone (146 patients) compared with dobutamine (146 patients) by nearly one day (mean difference -1.00, 95% CI -1.92, -0.08, (Figure 6).

## Discussion

Clinicians are often faced with the complexity of patients in cardiac ICUs. Furthermore, they had to choose between inotropic therapies without a sizeable body of evidence upon which to make a selection. There is a lack of comparison between inotropes in hospitalized patients in critical care settings, especially cardiogenic shock. We report the summary of all studies evaluating the hemodynamic and clinical effects using milrinone and dobutamine.

Dobutamine is a direct-acting synthetic catecholamine. The principal effect of dobutamine is an increase in myocardial contractility and ventricular ejection mediated by its  $\beta_1$  effects. Dobutamine generally reduces SVR by a combination of direct vasodilation and a reflex decrease in sympathetic vascular tone. This might be offset by the increase in cardiac output, leading to no change or a decrease in MAP. Dobutamine generally decreases cardiac filling pressures and PVR. Dobutamine has a variable effect on heart rate, but it can significantly increase heart rate (particularly at the higher concentrations used in stress echocardiography). However, dobutamine can produce tachycardia, arrhythmias, and hypertension. Dobutamine can exacerbate myocardial ischemia in susceptible patients by increases in heart rate and contractility. The usual infusion dose of dobutamine is 2.5–20  $\mu\text{g}/\text{kg}$  per minute intravenously.<sup>8,9</sup>

Milrinone is a phosphodiesterase type III inhibitor, and as such is a synthetic non-catecholamine indicator.

Milrinone increases cardiac index with reductions in arterial pressure, left ventricular end-diastolic pressure, and PVR. Milrinone is attractive for use in right heart failure by increasing ventricular contractility and decreasing PVR. However, milrinone-induced decreases in SVR and arterial blood pressure might offset these benefits and worsen the supply and demand balance in the failing right heart. For this reason, milrinone is often combined with norepinephrine or vasopressin in an attempt to offset peripheral vasodilation. The most common adverse effect of milrinone is arterial hypotension; milrinone should be used carefully especially in patients with already hypotensive, though this is often a desired effect. Milrinone use is an independent risk factor for the development of atrial fibrillation after cardiac surgery, but the incidence is less than with dobutamine. Milrinone is typically given intravenously, but it can also be nebulized. Intravenous dosing of milrinone is initiated with a loading dose of 20 to 50  $\mu\text{g}/\text{kg}$  over 10 minutes, followed by an infusion of 0.2 to 0.75  $\mu\text{g}/\text{kg}$  per minute. Owing to the high degree of renal clearance, the dose should be reduced in patients with reduced creatinine clearance.<sup>8</sup>

In the present article, we reviewed the current evidence on outcomes of vasopressors and inotropes in patients with cardiogenic shock and found that dobutamine and milrinone were partially associated with hemodynamic and clinical outcomes. These were associated with significant differences in mean pulmonary artery pressure and Total ICU length of stay. However, we found no significant difference in cardiac index, pulmonary capillary wedge pressure, and pulmonary artery pressure.

The cardiac index is a measurement of heart function based on the body size of the patient. Dobutamine and milrinone have different sites of binding that is dobutamine binds to adrenergic receptors and milrinone binds to phosphodiesterase III receptors (PDE Inhibitor). However, milrinone inhibits cAMP breakdown within the cell, thereby increasing cAMP levels, and producing similar effects on myocytes as  $\beta_1$ -adrenergic receptors agonists. As a result, no differences between dobutamine and milrinone on the cardiac index were identified in three studies that measured cardiac index using an inotrope.<sup>3,10</sup>

Pulmonary capillary wedge pressure (PCWP) is frequently used to assess left ventricular filling, represent

left atrial pressure, and assess mitral valve function. Milrinone as PDE inhibitors have more vasodilator and inodilator than dobutamine. This vasodilatory effect may cause hypotension and further peripheral and/or coronary hypoperfusion in patients who are already hypotensive and who have low ventricular filling pressures. Milrinone and dobutamine did not have a different pulmonary capillary wedge pressure.<sup>3</sup>

Mean arterial pressure (MAP) is the average arterial pressure throughout one cardiac cycle, systole, and diastole. In patients with symptoms of hypoperfusion, low CO, systemic hypertension, or pulmonary hypertension, milrinone may be preferable over dobutamine. However, milrinone therapy was significantly associated with increased hypotensive episodes and arrhythmias. It was similar to our study which showed that patients who received milrinone had a lower mean pulmonary artery pressure than those who received dobutamine.<sup>11</sup>

Hospital mortality is an indicator of a patient who died while admitted to a hospital. A study compared patients who received milrinone, dobutamine-treated patients had a higher risk of death from heart failure within the first 2 weeks after discharge with diminishing effects thereafter. It had a three-fold increased risk of death when patients were administered dobutamine instead of milrinone. We did not find a significant advantage of milrinone over dobutamine concerning hospital mortality. However, this association has not been established in patients with cardiogenic shock.<sup>12</sup>

Length of stay (LOS) is a clinical metric that measures the length of time elapsed between a patient's hospital admittance and discharge. Some studies are showing that patients administered with milrinone have longer LOS than dobutamine. On the other hand, two studies reported that LOS-ICU was shorter with milrinone compared with dobutamine by nearly one day.<sup>13</sup>

There are several limitations to our study. There were only four studies, which introduces numerous biases. It consists of two RCTs and two observational studies. Those had a high or unclear risk of bias for at least 3 domains. We had unbalanced patient populations based on the etiology of CS. A study is known that the parameters investigated are influenced by the level of anesthesia. In this study, the level of anesthesia was not monitored. Finally, our results were also limited as

hemodynamic parameters and clinical outcomes can be assessed more. Other clinical outcome parameters such as the use of renal replacement therapy, the incidence of cardiac arrest, and the use of mechanical ventilation.

Currently, there is no consensus on which inotropes is better and this study also showed that current evidence reveals no significant difference between dobutamine and milrinone and that the selection between dobutamine and milrinone should always be based on the patient's hemodynamic phenotype and physician should notice the higher incidence of arrhythmia in dobutamine and higher hypotension incidence in milrinone upon selection between dobutamine and milrinone.

## Conclusion

By this meta-analysis, a comparison of the Effects of dobutamine and milrinone on hemodynamic and clinical outcomes was no significant difference between cardiac index, pulmonary capillary wedge pressure, and mean arterial pressure. Although administration of milrinone resulted in lower PA pressure and shorter ICU LOS compared to dobutamine in patients with cardiogenic shock.

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