

Effect of milrinone on cardiac functions in patients undergoing coronary artery bypass graft: a meta-analysis of randomized clinical trials

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Background and aim: Inotropes are commonly used to treat myocardial dysfunction, which is the major complication after coronary artery bypass graft (CABG). Milrinone, a phosphodiesterase 3 inhibitor, is one of these inotropes. Recently, a number of clinical studies have been carried out to evaluate the effects of milrinone on cardiac function in patients with low ventricular ejection fraction undergoing CABG. However, it has been inconclusive because of the inconsistent results. In addition, some studies found that milrinone increased the incidence of postoperative atrial arrhythmias and did not show any long-term beneficial effects on survival. Therefore, it is very important to perform a meta-analysis to summarize the results so as to determine the clinical efficacy and safety of milrinone.

Method: Several databases and websites for clinical trials were searched until October 2015 for prospective clinical studies comparing milrinone versus placebo on cardiac functions in patients undergoing CABG.

Results: Four articles were identified by our search strategy. 1) Milrinone decreased incidence of myocardial ischemia and myocardial infarction (15.6% versus 44.4%; 4.7% versus 18% in milrinone and control group, respectively). 2) Milrinone decreased duration of inotropic support (95% confidence interval [CI]: -6.52 to -1.68; $P=0.0009$) and mechanical ventilation (h) support (95% CI -5.00 to -0.69; $P=0.010$), but did not decrease the requirement for intra-aortic balloon pump or inotropic support ($P>0.05$). 3) Milrinone did not decrease the overall mortality or morbidity, intensive care unit stay ($P>0.05$).

Conclusion: Perioperative continuous infusion of milrinone is effective to lower incidence of myocardial ischemia and myocardial infarction in patients post-CABG, but it was unable to improve the overall morbidity and mortality or decreased duration of intensive care unit stay. The available sample size is small; therefore, future studies should be directed toward a better understanding of the benefit of milrinone to CABG patients.

Keywords: inotropic support, intra-aortic balloon pump, cardiac function, clinical trial, meta-analysis

Introduction

Myocardial dysfunctions, myocardial ischemia, and infarction are major complications after coronary artery bypass graft (CABG) that needs inotropic support.¹⁻³ Currently, there are three main treatment methods for these complications which include the following: 1) optimization of loading conditions; 2) inotropic support to increase myocardial contraction; and 3) mechanical support. Milrinone is a phosphodiesterase 3 inhibitor, which provides an alternative means of inotropic support via non- β 1-adrenergic pathways and vasodilatation.⁴⁻⁵ It also improves hemodynamic parameters and increases blood flow of the grafted internal mammary arteries as well

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as middle cerebral arteries during CABG.⁶ Previous studies indicated that milrinone is valuable in cardiac surgery by facilitating weaning from cardiopulmonary bypass.⁷⁻⁸

In recent years, a number of clinical studies have been carried out to evaluate the effects of milrinone on cardiac function in patients with low ventricular ejection fraction (LVEF) undergoing CABG. Milrinone may reduce the incidence of postoperative myocardial ischemia and infarction in patients with impaired left ventricular function undergoing CABG surgery. The results reported by Jebeli et al⁹ suggest that perioperative administration of milrinone in patients undergoing on-pump CABG, especially those with LVEF, is beneficial. Hadadzadeh et al¹⁰ reported that administration of milrinone in patients undergoing off-pump CABG with LVEF is useful and effective.¹⁰

There are a few studies evaluating the effects of milrinone on cardiac function in patients with low output syndrome who undergo CABG, which have reported diverse results. In this manuscript, we performed a meta-analysis to summarize the results of these clinical trials so as to determine the clinical efficacy and safety of milrinone, in terms of intra-aortic balloon pump (IABP), inotropic support requirement, myocardial ischemia, myocardial infarction, duration of inotropic support, duration of intensive care unit (ICU) stay, mortality, and morbidity rate. The results of this meta-analysis will provide evidence-based information on administration of milrinone in patients undergoing CABG with LVEF.

Methods

Search strategy

References for this meta-analysis were obtained from PubMed and EMBASE searches of literature published until October 2015 and websites for clinical trials including <http://www.clinicaltrials.gov/>, using the key words “milrinone”, “CABG”, “clinical trial”, and “cardiac function”. Eligible studies were selected based on the following criteria: 1) study design: double-blind, placebo control, and randomized clinical trials; 2) subjects: eligible patients underwent CABG; 3) interventions: patients received milrinone or placebo/nesiritide. The primary outcomes included requiring of IABP, inotropic support, incidence of myocardial ischemia and myocardial infarction. The secondary outcomes were duration of inotropic support, duration of ICU stay, and mortality and morbidity rate. If these inclusion criteria were not met, the studies were excluded from the analysis. All authors independently conducted study selection based on these criteria. Any discrepancy was resolved by group discussion of all authors.

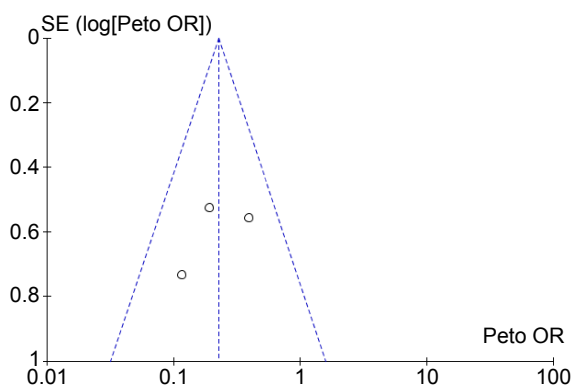


Figure 1 Funnel plot comparing the requirement of intra-aortic balloon pump (%) between milrinone group and control/nesiritide group.

Abbreviations: OR, odds ratio; SE, standard error.

Data collection and statistical analysis

The following information was extracted from selected studies: authors, publication year, study design, number of patients analyzed, treatment regimen, and primary and secondary outcomes. The meta-analyses were performed using the Review Manager, version 5.1.0 (Cochrane Collaboration, Oxford, UK). Dichotomous outcomes were presented as an event with a 95% confidence interval (CI). The presence of heterogeneity across trials was also evaluated, with $I^2 > 50\%$ indicating a substantial heterogeneity, where a random-effects model was used. In the case of $I^2 < 50\%$, which indicates no significant heterogeneity, a fixed-effects model was used, P -value < 0.05 was considered statistically significant. Peto-statistical models were used for the meta-analysis. The publication bias was assessed by funnel plot (Figure 1), which did not show any evidence of publication bias.

Results

Identification of relevant studies

A total of 53 published articles evaluated the effect of milrinone on cardiac functions in patients with post-CABG. Finally, only four articles were identified by our search strategy, which were double-blinded, placebo-controlled trials. A flow chart of study selection is shown in Figure 2. However, for some end points in final meta-analysis, we only used two to three available clinical trials, which provided those results.

1. IABP: 75 patients in each group who received milrinone or placebo were included in the statistical analysis. There was no significant difference between the two groups requiring of IABP. Four out of 75 patients (5.3%) in the milrinone group versus eleven out of 75 patients (14.7%) in the control group ($P=0.06$; Figure 3A).
2. Inotropic support requirement: Similar result was observed in two groups. A 62 out of 106 patients (58.5%)

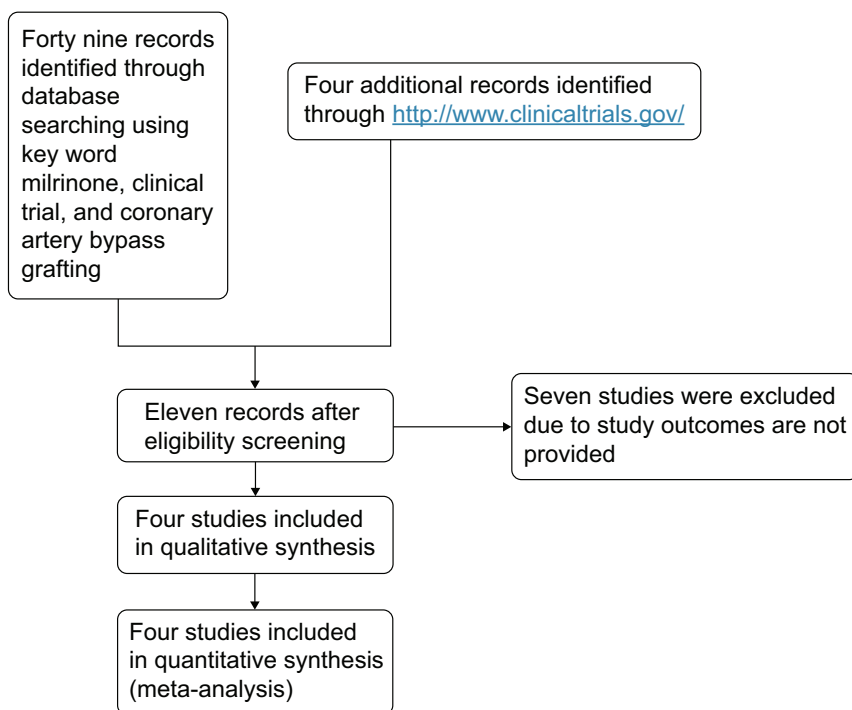


Figure 2 Flow diagram of study selection.

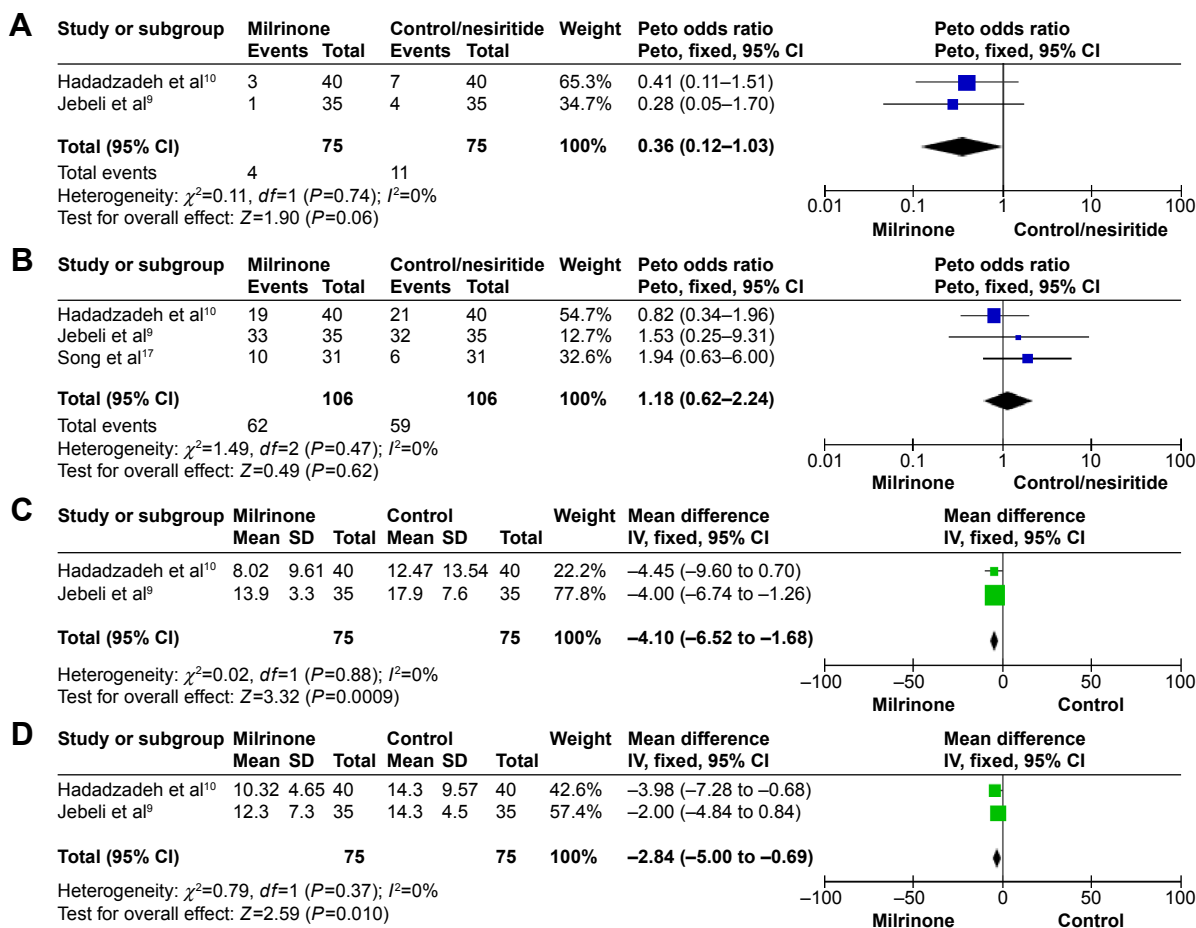


Figure 3 Forest plots comparing between milrinone group and placebo/nesiritide group the (A) requirement of intra-aortic balloon pump (%); (B) inotropic support requirement; (C) duration of inotropic support; (D) duration of mechanical ventilation support.

Abbreviation: CI, confidence interval.

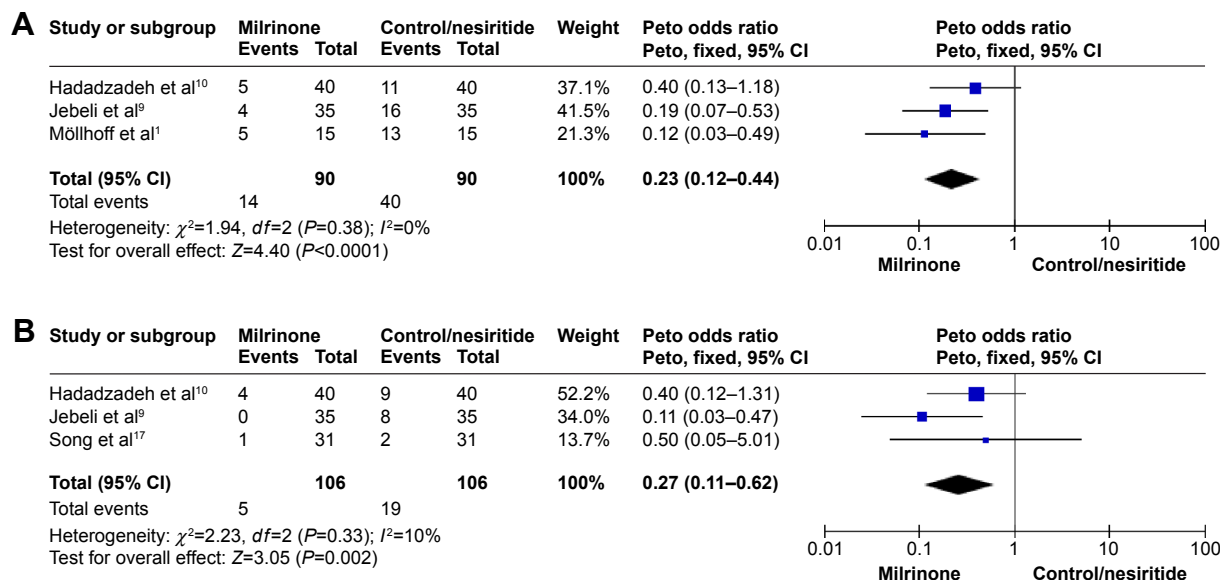


Figure 4 Forest plots comparing incidence of post-CABG complications between milrinone group and placebo/nesiritide group in (A) myocardial ischemia; (B) myocardial infarction.

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval.

- in milrinone group versus 59 out of 106 patients (55.7%) in control group who required inotropic support ($P=0.62$; Figure 3B).
- Duration of inotropic support (h): significant difference was observed in duration of inotropic support between milrinone and control group (risk ratio [RR] -4.10 ; 95% CI: -6.52 to -1.68 ; $P=0.0009$; Figure 3C).
 - Duration of mechanical ventilation (h): significant difference was observed in duration of inotropic support between milrinone and control group (RR -2.84 ; 95% CI: -5.00 to -0.69 ; $P=0.010$; Figure 3D).
 - Incidence of myocardial ischemia: 90 patients in each milrinone group and placebo group were analyzed for the incidence of myocardial ischemia. Significant difference was observed between milrinone and control group: 14 out of 90 patients (15.6%) in milrinone group had myocardial ischemia 24 hours after CABG, in contrast 40 out of 90 patients (44.4%) had it in control group, <0.0001 (Figure 4A).

- Incidence of myocardial infarction: significant difference was observed in incidence of myocardial infarction between two groups. In milrinone group, five out of 106 patients (4.7%) had myocardial infarction 24 hours after CABG versus 19 out of 106 patients (18%) who had it in control group, $P=0.002$ (Figure 4B).
- ICU stay: no statistical difference was identified in ICU stay (RR -0.16 ; 95% CI: -0.52 to 0.19 ; $P=0.37$); between milrinone and control treatment (Figure 5).
- Mortality and morbidity: A total of 126 patients in each group were analyzed, no statistical significance was observed between milrinone and control group ($P=0.41$ for mortality and $P=0.31$ for morbidity).

Mortality: Two patients (1.6%) died in milrinone group and four patients (3.2%) died in control group, $P=0.41$ (Figure 6A).

Morbidity: These morbidities were bleeding, renal failure, and cerebrovascular accident. The most common morbidity was renal failure that occurred in eleven

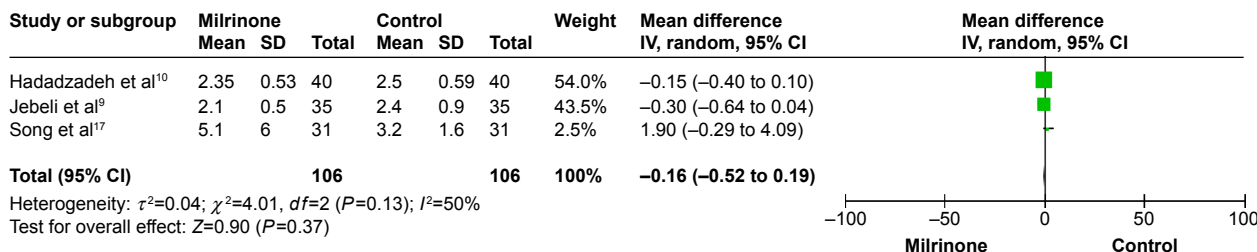


Figure 5 Forest plot comparing ICU stay between milrinone group and placebo/nesiritide group.

Abbreviations: CI, confidence interval; IV, independent variable; ICU, intensive care unit.

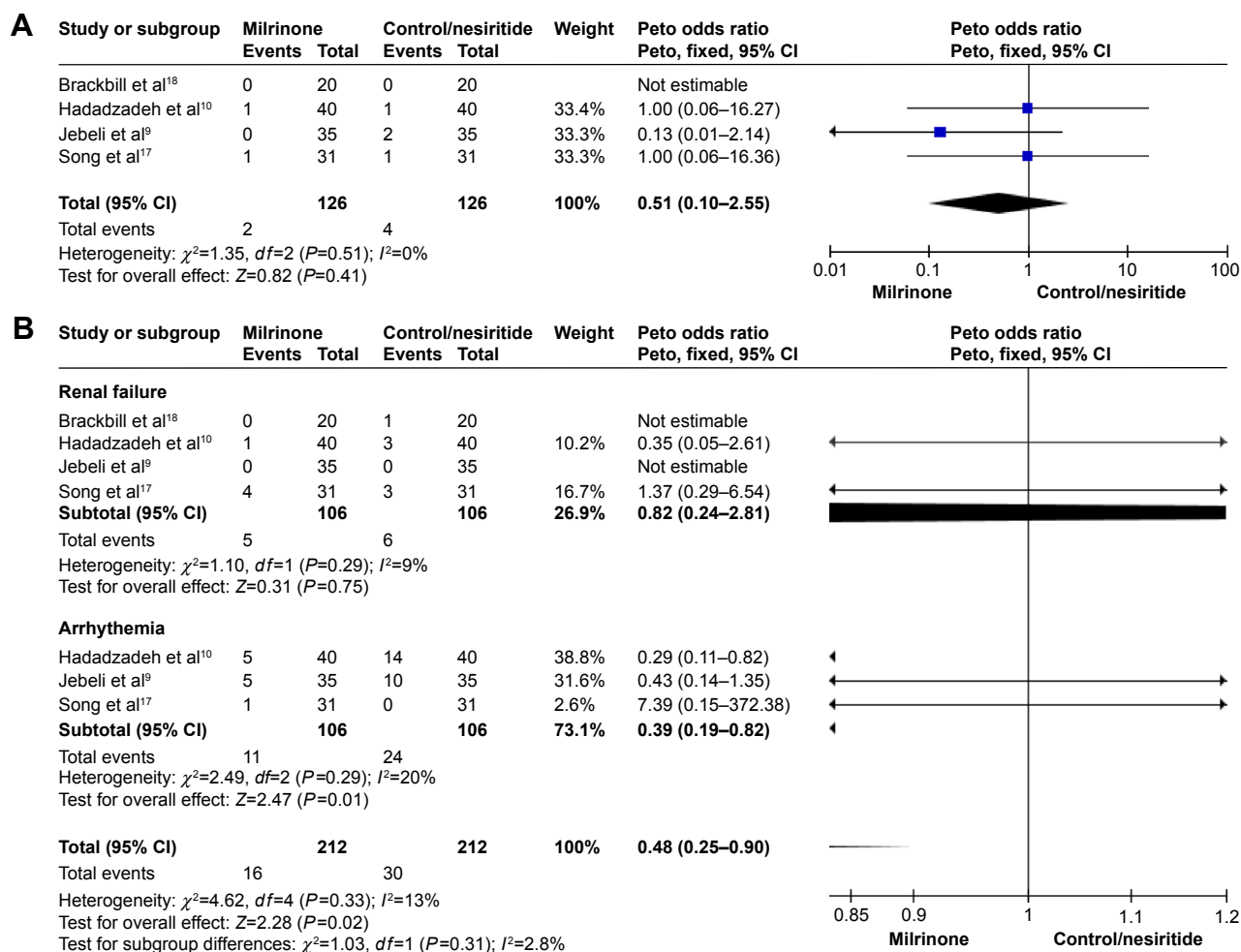


Figure 6 Forest plots comparing overall survival between milrinone group and placebo/nesiritide group in **(A)** mortality; **(B)** morbidity. **Abbreviations:** CI, confidence interval; IV, independent variable.

out of 212 patients (5.2%); five patients (4.7%) in milrinone group and six patients (5.7%) in the control group (Figure 6B).

Discussion

The results of this meta-analysis showed that administration of milrinone can protect against myocardial ischemia and myocardial infarction in patients undergoing CABG. Bailey et al¹¹ and Jebeli et al⁹ studies showed the similar results. Hadadzadeh et al¹⁰ study and Gorodeski et al¹² showed that there were no significant differences regarding incidence of myocardial ischemia and myocardial infarction in patients administered with milrinone.¹⁰ Even though it has a controversy, both Jebeli et al⁹ and Hadadzadeh et al¹⁰ studies revealed milrinone decreased creatine phosphokinase, creatine kinase-MB in CABG patients 4 and 24 hours after surgery. In the future, it may need multi-center studies with a large sample size to reach a solid conclusion.

Previous studies done by Kikura et al,⁴ Oztekin et al,¹³ and Yamaguchi et al¹⁴ indicated that milrinone decreased requirement of inotropic support after CABG surgery. Results of the meta-analysis study showed that there was no statistical significant difference regarding IABP requirement and inotropic support requirement between the two groups. However, the duration of inotropic requirement, duration of mechanical ventilation was lower in milrinone group, which was in accordance with the result of the study done by Levy et al.¹⁵ A study done by Konstam and Cody¹⁶ showed no significant difference in using IABP. This meta-analysis also found that it had no statistical difference in using of IABP or inotropic support requirement between both groups.

Song et al¹⁷ and Brackbill et al¹⁸ studies showed that there was no significant difference in mortality and morbidity between milrinone group and control group. Our analysis results also showed similar effect. However, those results are contradicted in with the study of Zangrillo et al,¹⁹ who

reported that milrinone may increase mortality in patients undergoing cardiac surgery.

Conclusion

Milrinone decreased incidence of myocardial ischemia and infarction, decreased duration of inotropic support and mechanical ventilation for the patient after CABG, but did not decrease the requirement of intra-aortic pump or inotropic support. In addition, milrinone did not improve the overall mortality/morbidity or decreased ICU stay duration. Therefore, administration of milrinone is beneficial and safe to patients undergoing CABG with LVEF overall even though it cannot improve mortality or morbidity.

Disclosure

The authors report no conflicts of interest in this work.

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