The effect of milrinone on mortality in adult patients: A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis

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Abstract

OBJECTIVE: Milrinone is commonly used for patients performed coronary artery bypass graft surgery (CABG) because of its effectiveness in decreasing cardiac index and mitral regurgitation. This study was to perform a systematic meta-analysis of existing studies in the past 20 years to evaluate the impact of milrinone on mortality in patients undergoing CABG surgery. EASUREMENTS AND MAIN RESULTS: The network meta-analysis included 723 patients from 16 randomized clinical trials. Overall, there was no significantly difference in mortality between the milrinone group and the placebo/standard care group 11/352 (3.13%) vs. 9/346 (2.60%), risk ratio = 1.18 (0.53–2.62), p for effect = 0.69, I² = 0 % when patients underwent CABG surgery. Besides that, 9 trials (with 440 randomized patients), 4 trials (with 212 randomized patients), and 10 trials (with 470 randomized patients) reported that the occurrence of myocardial infarction (MI), myocardial ischemia, and arrhythmias in the milrinone group were decreased in comparison with the placebo/standard care group, respectively. Between the milrinone treatment and placebo/standard care groups, the occurrence of myocardial infarction was 5/219 (2.28 %) vs. 25/212 (17.79 %), odds ratio(OR) = 0.19 (0.08–0.49), p value = 0.0005, I² = 5%, the occurrence of myocardial ischemia was 12/106 (11.32 %) vs. 41/106 (36.68 %), OR = 0.20 (0.10–0.42), p value <0.0001, I² = 0 % and the occurrence of arrhythmias was 16/234 (6.84 %) vs. 31/236 (13.14 %), OR= 0.46 (0.24–0.88), p value = 0.02, I² =0 %. However, the occurrence of stroke and renal failure, duration of inotropic support (h), need for intra-aortic balloon pump (IABP), and mechanical ventilation (h) between these two groups showed no differences. CONCLUSION: Based on the current results, milrinone might be unable to decrease the mortality in adult CABG surgical patients, but can significantly ameliorate the occurrence of MI, myocardial ischemia, and arrhythmias compared with placebo-treated patients. These results provide evidence for further clinical application of
milrinone and therapy strategies for CABG surgery. However, along with milrinone application in clinical use, sufficient randomized clinical trials need to be collected, and the potential benefit and adverse effects should be analyzed and reevaluated.

Background

In 2017, the World Health Organization (WHO) reported that nearly 17.7 million people death from cardiovascular diseases (CVDs) every year, accounting for 31% of all global deaths. Coronary artery disease (CAD) refers to the class of diseases of vascular stenosis or obstruction caused by coronary artery atherosclerotic lesions, resulting in myocardial ischemia, hypoxia or necrosis, including stable and unstable angina, myocardial infarction (MI), and sudden cardiac death. Meanwhile, CAD can cause serious complications from multiple risk factors such as heart attack, damaged heart muscle, and irregular heartbeats and result in sudden death. At present, coronary artery bypass grafting (CABG) surgery, are primary strategies for CAD treatment. CABG surgery is a surgical procedure, which the grafted vein was used to establish a vascular access between the root of ascending aorta and the distal end of the lesion site, so that blood can bypass the coronary artery lesion site, flow to the distal end of coronary artery stenosis or obstruction, and reach the ischemic myocardium, improving coronary perfusion and increasing myocardial oxygen supply. Although CABG surgery has been reported with respect to low costs, superior outcomes, and particularly to short-term mortality, multiple complications such as myocardial infarction (MI), myocardial ischemia, arrhythmias, stroke, and acute renal failure (ARF) are impossible to ignore and still perplex researchers and clinical doctors. 8, 18-21 To minimize the occurrence of postoperative complications, pre- and/or postoperative medicinal applications, such as phosphodiesterase (PDE) III inhibitors, have
been primary strategies until now.\textsuperscript{22-24}

By reducing the inactivation of cyclic adenosine phosphate (cAMP) in cardiomyocytes, PDE III inhibitors enhance myocardial contractility and produce positive inotropic effects;\textsuperscript{25, 26} a higher concentration of cAMP results in contractility, increasing myocardial tissue and the vasodilatory effect on vascular smooth muscle.\textsuperscript{27, 28} Milrinone, one of the PDE III inhibitors, primarily used after open-heart surgery because it can avoid cardiopulmonary bypass,\textsuperscript{29} enhances cardiac contractility,\textsuperscript{30} prevents vasospasm,\textsuperscript{31} and ameliorates low output syndrome (LOS).\textsuperscript{(32)} However, recent studies have demonstrated that the efficacy and safety profile of milrinone remain controversial, although it is implemented in several guidelines.\textsuperscript{33, 34} In some cardiac surgeries, the tendency of increasing mortality and incidence of arrhythmia was found in milrinone group, comparing with control agents.\textsuperscript{35, 36} However, another study evaluating milrinone for acute heart failure treatment revealed that milrinone might be safe and effective.\textsuperscript{37} All contradictory outcomes result from a limited number of included patients\textsuperscript{35} and lack of key methodological criteria\textsuperscript{38} not based on previously published protocol.\textsuperscript{36} No study has assessed the incidence of postoperative complications.

To avoid bias results best from any unclear risk of bias that were included, our objective was to conduct a systematic review and meta-analysis of existing randomized controlled trials (RCTs) and assessed the mortality between milrinone-treated cases and placebo/standard care. Postoperative complications, such as MI, myocardial ischemia, arrhythmias, stroke, and AKI incidences, were estimated simultaneously.

\textbf{Methods}

\textbf{Search strategy}
The search strategy aimed to include any RCTs conducted among adult patients undergoing CABG surgery and treated with milrinone, compared to those treated only with placebo/standard care. A pertinent study search was independently conducted in BioMed Central, PubMed, Embase, and the Cochrane Central Register (all searches updated in November, 2017) by 3 trained investigators [Lan-fang Li, Guo-liang Cheng, and Ying Sun]. No language restrictions were imposed, and non-English-language articles were translated before analysis.

**Study Selection**

References retrieved using the literature searches and databases were screened. When potentially pertinent studies were found, complete articles were retrieved. The inclusion criteria comprised: random allocation to treatment, group receiving milrinone compared with group receiving placebo/standard care with no restriction in dose and time of administration, CABG surgery performed in adult patients, and information provided on primary outcome (endpoint). The exclusion criteria were as follows: lack of outcome (mortality) data, duplicate publication, animal experimental studies, article published as abstract only, pediatric population. Three investigators independently assessed compliance to selection criteria and selected studies for the final analysis and divergences resolved by consensus, and if issues persisted, the reference evaluated by 4 investigators, independently.

**Data extraction and study characteristics**

The following details were extract from retrieved studies: number of patients, surgical type, clinical setting, milrinone dosage, treatment duration, follow-up, mortality, and operative complications (such as MI, myocardial ischemia, arrhythmias, stroke, and AKI incidences) were independently extracted by 4 trained investigators. The primary endpoint of current analysis was mortality. And MI (per author definition), acute renal failure (per
author definition), myocardial ischemia, arrhythmias, stroke, AKI, mechanical ventilation, and length of intensive care unit and hospital stay were subsequent endpoint.

Quality assessment

We assessed the included trials according to the Cochrane Collaboration methods for evaluating risk of bias and the internal validity by 3 independent reviewers.

Data analysis and synthesis

RevMan (Review Manager, version 5.2, Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, 2012) and Stata (Stata Statistical Software: release 13, StataCorp LP, College Station, Texas) will be utilized to deal with data extracted from selected articles. Q-test was applied to measure statistical heterogeneity and $I^2$ as a quantitative measure of the degree of heterogeneity. Date on mortality was estimated to compute the individual and pooled relative risks (RR) with 95% confidence interval (CI), by means of Mantel-Haenszel method. The presence of heterogeneity across trials was also evaluated, with $I^2 <$ 25% indicating no significant heterogeneity, where the fixed-effects model was used. In contrast, in case of a moderate or substantial heterogeneity ($I^2 > 25$%), a random-effects model was used. Funnel plots were used to explore small study risk bias and by analytic appraisal based on the Peters’ regression asymmetry test.

The Cochrane Collaboration principal and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were complied as standard for the current study. The two-tailed 0.05 and 0.1 level were set for statistical significance limit of hypothesis and heterogeneity analysis, respectively. The p values are not revised throughout assess.

Results

A total of 1,463 articles were identified and screened. After exclusion by 1,301 irrelevant
titles or abstracts, 162 studies were eligible in full-text and assessed according to the selection criteria (Figure 1). Of these, the most common reasons for exclusion were: valid date could not be obtained by the authors (87 studies), comparison of milrinone with other drugs (17 studies), pediatric population (11 studies), nonrandomized controlled trails (9 studies), crossover studies (5 studies), published as abstract only (4 studies), mechanical devices as control (4 studies), inhaled milrinone (3 studies), randomizing brain-dead organ donors (3 studies), animal studies (2 studies) and healthy volunteers (1 study). Ultimately, sixteen randomized clinical trials were assessed in compliance with inclusion (Table 1).

32, 39-52

**Study characteristics**

The total number of patients in 16 included trials was 698, undergoing CABG surgery (346 treated with placebo/standard care and 352 treated with milrinone) (Table 2 and Table 3). Five of these studies performed off-pump CABG32, 42, 46, 47, 50 and 11 performed on-pump CABG surgery. (39-45, 48, 49, 51, 52) Mode of administration included bolus (39-43, 45, 48, 49), continuous infusion (40-42, 44-60), preceded in 7 studies by an initial bolus, (40-42, 45, 48, 49) which dose varied from 30 to 75 μg/kg in the way of bolus or from 0.25 to 0.75 μg/kg/min as a continuous infusion. The quality of current results presented variable. Although 3 RCTs were considered as high quality, there were a large number of studies lacked important details which to evaluate the risk of selection, performance, attrition, or detection biases (Figure 2).

**Quantitative data synthesis**

The overall analysis demonstrated that the mortality in patients receiving milrinone was not increased when compared to placebo/standard care [11/352 (3.13 %): death in the milrinone treatment group 9/346 (2.60 %) versus death in the control group, RR = 1.18
(0.53–2.62), p value = 0.69, p for heterogeneity = 0.91, $I^2 = 0 \%$] (Figure 3).

Sensitivity analysis and funnel plot inspection confirmed the overall robustness of the present findings and the lack of evidence for small study bias, respectively (Figure 5A).

The sub-analysis in different postoperative outcomes (Figure 4, Table 4) showed that a statistically significant effect of milrinone reduced the occurrence of MI [5/219 (2.28 %) in the milrinone treatment group versus 25/221 (11.31 %) in the control group, RR = 0.23 (0.10–0.54), p value = 0.0008, p for heterogeneity = 0.35, $I^2 = 9 \%$, with 9 studies included], myocardial ischemia [12/106 (11.32 %) in the milrinone treatment group vs. 41/106 (36.68 %) in the control group, RR = 0.29 (0.16–0.52), p value <0.0001, p for heterogeneity = 0.55, $I^2 = 0 \%$, with 3 studies included], and arrhythmias [16/234 (6.84 %) in the milrinone treatment group vs. 31/236 (13.14 %) in the control group, RR = 0.53 (0.31–0.91), p value= 0.02, p for heterogeneity = 0.55, $I^2 = 0 \%$, with 10 studies included].

Another sub-analysis showed a difference in the risk of stroke [2/86 (2.33 %) in the milrinone treatment group vs. 0/86 (0 %) in the control group, RR = 3.00 (0.32–27.88), p value = 0.33, p for heterogeneity = 1.00, $I^2 = 0 \%$, with 3 studies included], renal failure [9/151 (5.96 %) in the milrinone treatment group vs. 8/151 (5.30 %) in the control group, RR = 1.25 (0.45–2.81), p for effect = 0.80, p for heterogeneity = 0.64, $I^2 = 0 \%$, with 5 studies included]. Sensitivity analysis and funnel plot inspection confirmed the overall robustness of the present findings and the lack of evidence for small-study bias, respectively (Figure 5B).

Discussion

In this study, we conducted a systematic meta-analysis of all existed, enrolled and randomized studies, comparing treatment with milrinone to placebo/standard care in
patients who underwent CABG surgery. The result showed that compared with placebo treatment, milrinone has no contribution to mortality. Although milrinone failed to reduce the mortality, the risk of postoperative complications, such as MI, myocardial ischemia, and arrhythmias were significantly decreased when patients underwent CABG surgery. About 110 million people were affected by CAD, which resulted in 8.9 million deaths in 2015. 53 CAD is considered the most common cause of death globally because of its high mortality risk (15.9 %). 54 From 1980 to 2010, the number of cases and risk of death from CAD for a given age both declined, especially in developed countries. 55, 56 Some well-determined risk factors, including high blood pressure, smoking, diabetes, obesity, family history, and excessive alcohol were controlled. About half of the cases result from genetics among all these factors. 57-59 Obesity and smoking are associated about 20 % and 36 % of cases, respectively. 60 The typical pathophysiological character of CAD is limited blood flow to the heart, which may result in ischemia and long-term oxygen deficit of the heart muscle, leading to cell death and, finally, causing myocardial infarction (MI). Besides that, transient ischemia resulting from coronary artery stenosis may lead to ventricular arrhythmia, devolve into a dangerous heart rhythm, and lead to death, which is known as ventricular fibrillation. 61 Although a Cochrane review in 2015 suggests that combining preventive strategies such as persisting appropriate physical exercise, maintaining a healthy diet, treating hypertension, reducing cholesterol and quit smoking could effectively prevent the risk of CAD; 62-66 there was insufficient evidence to prove an impact on mortality or actual cardiovascular events. 67 Until now, the most effective treatment options for moderate to severe CAD are medications (such as statins, nitroglycerin, calcium channel blockers, and/or beta-blockers, and aspirin) 68-70 and
surgery (such as CABG).\textsuperscript{71-73} CABG surgery is performed to treat coronary artery disease (CAD) by using a grafted vein to establish a vascular access between the root of ascending aorta and the distal end of the lesion site, so that blood can bypass the coronary artery lesion site, and reach the ischemic myocardium, improving coronary perfusion and increasing myocardial oxygen supply, which the process also called as myocardial revascularization.\textsuperscript{74, 75} Numerous studies in the reference have demonstrated that CABG surgery is associated with low mortality (in both the short term and the long-term) and cognitive and renal function benefits.\textsuperscript{76, 77} However, multiple complications (involving MI, myocardial ischemia, arrhythmias, stroke, and renal kidney) are common postoperative syndromes.\textsuperscript{8, 18, 20, 21, 78} Surgery, combined with medication pre- and/or post-operatively, such as inotropic agents, which could increase myocardial contractility that in most cases results in increasing intracellular cAMP levels, could effectively avoid or ameliorate these unwanted outcomes.\textsuperscript{79-81} Increased cAMP subsequently stimulates adenylate cyclase and inhibits PDE III simultaneously.\textsuperscript{82} Despite (or because of) their effectiveness, inotropic agents face various substantial limitations, such as acute myocardial β-adrenergic receptor desensitization, limiting the function for post-bypass cardiac failure,\textsuperscript{83} and more observational data suggest that inotropic agents are contributed to worse clinical outcomes, due to higher incidence of renal dysfunction and death ratio.\textsuperscript{84-87}

PDE III inhibitors such as milrinone provide an alternative option to inotropic support\textsuperscript{83} because it not only has positive inotropic effect but also vasodilatory effects.\textsuperscript{82, 88} Pre-emptive use of milrinone was beneficial to renal tubular injury.\textsuperscript{84} Unlike dobutamine, milrinone does not increase heart rate and myocardial oxygen consumption,\textsuperscript{89} and some
studies reported that milrinone could significantly reduce the risk of postoperative myocardial ischemia and infarction in patients undergoing CABG surgery. However, one of the current controversies or open questions in milrinone application is whether it is associated with mortality. A recent meta-analysis by Zangrillo A et al. has shown that milrinone had tendency to increase mortality and incidence of arrhythmia in patients underwent cardiac surgery, comparing with control agents [13/249 (5.2 %) in milrinone vs. 6/269 (2.2 %) in the control arm, OR = 2.67 (1.05–6.79), p for effect = 0.04, p for heterogeneity = 0.23, I² = 25 %]. However, in their study, 13 trials were included and involved different control agents (3 with levosimendan, 2 with nesiritide, 7 with placebo, and 1 with nothing). These factors may induce bias risk. For instance, a sub-analysis with placebo or nothing as control demonstrated no difference in the risk of mortality [4/165 (2.4 %) with milrinone vs. 3/164 (1.8 %) in the control arm, OR = 1.27 (0.28–5.84), p for effect = 0.76, p for heterogeneity = 0.45, I² = 0 %, 329 patients and 8 studies included]. Besides that, an updated meta-analysis (35) showed that neither the overall nor the subgroup (adult patients) mortality in the milrinone-treated group was significantly different from the control group (mortality, 2.2 % vs. 2.1 %, p = 0.70 overall, 3 % vs. 2.4%, p = 0.70 in adult patients). However, the sensitivity analysis with a low risk of bias showed a trend, but not statistical significance, toward an increase in mortality with milrinone [8/153 (5.2 %) in the milrinone arm vs. 2/152 (1.3 %) in the control arm, RR = 2.71 (0.82–9), p for effect = 0.10]. Meanwhile, the most recent studies, respectively published in 2015(90) and 2016, demonstrated that there were no differences in mortality of patients administrated milrinone compared to control groups. All these reasons may induce bias risk.

To avoid these interference factors, we enrolled 16 trials with a randomized total of 698
patients undergoing CABG surgery (346 treated with placebo or standard care and 352 treated with milrinone); the results showed that there was no difference in mortality between the group receiving milrinone and the placebo/standard care group. Nevertheless, the sub-analysis demonstrated that the occurrence of myocardial infarction, myocardial ischemia, and arrhythmias decreased significantly with milrinone treatment compared to the placebo or standard care group. However, the occurrence of stroke and renal failure, need for IABP, and duration of inotropic support (h) and mechanical ventilation (h) between these two groups showed no differences. Although the evidence in the present study demonstrated that milrinone failed to show an advantage in mortality in adult CABG patients, it significantly reduced the occurrence of MI, myocardial ischemia, and arrhythmias compared to placebo-treated patients. All these findings may be helpful for clinical application of milrinone and provide therapy strategies for CABG surgery. Meanwhile, along with clinical milrinone application, sufficient randomized clinical trials need to be collected and the potential benefit or adverse effects should be analyzed and reevaluated.

Limitations
Our study has several limitations. First, the authors acknowledge that only 4 of the 16 studies included in this meta-analysis were of high quality. Second, in enrolled RCTs, the doses of milrinone were between 30 and 75 μg/kg (as an intravenous bolus) and between 0.5 and 0.75 μg/kg/min (as continuous infusion). This fact suggested that the current reference lacks generalizability of milrinone at doses beyond the range of 0.3 - 0.75 μg/kg/min. Third, our study on the incidence of myocardial ischemia, stroke, and renal failure were performed using a small number of studies and patients. Therefore, the current result should not be conclusive due to possibility of inducing error. Finally, only one trial evaluated with a 1-year follow-up, so defection in short follow-up could
potentially impact on our mortality analyses.

Conclusions

This meta-analysis suggests that, compared to placebo or standard care, milrinone neither significantly increases nor decreases the risk of dying in adult patients undergoing CABG surgery, but milrinone could efficiently ameliorate the incidence of postoperative complications, including MI, myocardial ischemia, and arrhythmias.

Abbreviations

AKI, Acute Kidney Injury; ARF, Acute Renal Failure; CABG, Coronary Artery Bypass Graft surgery; CAD, Coronary Artery Disease; cAMP, cyclic Adenosine Phosphate; CVDs, Cardiovascular Diseases; LOS, Low Output Syndrome; MI, Myocardial Infarction; WHO, World Health Organization; PDE, Phosphodiesterase; RCTs, Randomized Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data and materials are available.

Competing interests

The authors declare that they have no competing interests.

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**Authors' contributions**

YS R, GM Z, and J L designed the study. LF L, GL C, and Y S performed and collected the data. YJ T, T P, and GL C analyzed the data. YS R, GM Z, and J L wrote the manuscript. All authors approved the contents of the manuscript.

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Tables

Table 1. A Description of the Studies Included in the Meta-Analysis.
| First Author | Journal                                      | Year | Procedures               | Control  | Inclusion Criteria                                                                 |
|--------------|----------------------------------------------|------|--------------------------|----------|-----------------------------------------------------------------------------------|
| Arbeus M     | Journal of Cardiothoracic and Vascular       | 2009 | Elective CABG            | Placebo  | Stable angina, LVEF (%) > 30 %, Sinus rhythm.                                     |
|              | Anesthesia                                   |      |                          |          |                                                                                   |
| Couture P    | Canadian Journal of Anaesthesia              | 2007 | Elective CABG            | Placebo  | Ischemic heart disease, LV diastolic dysfunction.                                 |
| Doolan LA    | Journal of Cardiothoracic and Vascular       | 1997 | Elective CABG and valvular surgery | Placebo  | LVEF (%) ≤ 35 %, Mean PAP ≥ 20 mmHg.                                            |
| Guo Yj       | Chinese Heart Journal                        | 2014 | Elective CABG            | Placebo  | CABG surgery, LVEF (%) < 35 %,                                                   |
|              |                                              |      |                          |          |                                                                                   |
| Hadadzadeh M | Acta medica Iranica                          | 2013 | Elective CABG (off-pump) | Placebo  | Severe myocardium dysfunction (LVEF (%) < 35 %)                                  |
| Hamada Y     | Japanese circulation journal                 | 1999 | Elective CABG and valvular surgery | Standard treatment | Unspecified                                                             |
| Hayashida N  | Annals of Thoracic Surgery                   | 1999 | Elective CABG            | Standard treatment | Isolated CABG surgery                                                          |
| Jebeli M     | Cardiology Journal                          | 2010 | Elective CABG            | Placebo  | LVEF (%) < 35 %,                                                               |
| Jo HR        | Korean Journal of Anesthesiology            | 2010 | Elective CABG (off-pump) | Placebo  | CABG surgery, Normal LV function.                                              |
| Kwak YL      | European journal of cardio-thoracic surgery  | 2004 | Elective CABG (off-pump) | Placebo  | Unspecified                                                             |
| Lee JH       | Journal of korean medical science            | 2006 | Elective CABG (off-pump) | Placebo  | RVEF (%) < 35 %,                                                          |
| Möllhoff T   | Anesthesiology                               | 1999 | Elective CABG            | Placebo  | Elective CABG                                                               |
| Shi YF       | Journal of Thoracic and Cardiovascular Surgery | 2006 | Elective CABG            | Placebo  | Elective CABG                                                               |
| Song JW      | Korean Journal of Anesthesiology            | 2011 | Elective CABG (off-pump) | Placebo  | E/e’ value > 15                                                             |
| Yamaguchi A  | Annals Of Thoracic And Cardiovascular Surgery | 2009 | Elective CABG and valvular surgery | Standard treatment | Elective CABG concomitant LVR, LV dysfunction (LVEF (%) < 30 %), LVESVI > 100 ml/m² |
| Yamaura K    | Journal of Cardiothoracic and Vascular       | 2001 | Elective CABG            | Standard treatment | Cardiac Surgery                                                                |
|              | Anesthesia                                   |      |                          |          |                                                                                   |

Abbreviations: CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiography; PAP, pulmonary arterial pressure; AF, atrial fibrillation; MI, myocardial infarction; E/e’, the ratio of the early transmitral flow velocity to the early diastolic velocity of the mitral annulus; LVR, left ventricular restoration; LVESVI, left ventricular end-systolic volume index.
| Author       | Group | Patients | Age  | Sex   | Time of administration                  |
|--------------|-------|----------|------|-------|-----------------------------------------|
| Arbeus M     | MIL   | 22       | 63 ± 10 | 20/2  | After release of aortic clamp           |
|              | Ctrl  | 22       | 62 ± 9  | 17/5  |                                         |
| Couture P    | MIL   | 25       | 67 ± 8  | 19/6  | After anesthesia induction              |
|              | Ctrl  | 25       | 70 ± 7  | 19/6  |                                         |
| Doolan LA    | MIL   | 15       | 65 ± 10.4 | 14/1 | 15 min before weaning from CPB         |
|              | Ctrl  | 15       | 67 ± 8.6 | 14/1 |                                         |
| Guo YJ      | MIL   | 31       | 56 ± 6  | 21/10 | After release of aortic clamp           |
|              | Ctrl  | 31       | 54 ± 6  | 20/11 |                                         |
| Hadadzadeh M | MIL   | 40       | 62 ± 10.7 | 31/9 | After anesthesia induction              |
|              | Ctrl  | 40       | 63 ± 9.6 | 26/14|                                         |
| Hamada Y     | MIL   | 10       | 66.2 ± 8.1 | 6/4 | After release of aortic clamp           |
|              | Ctrl  | 10       | 62.4 ± 6.5 | 6/4 |                                         |
| Hayashida N  | MIL   | 12       | 63.3 ± 2.8 | 7/5 | After anesthesia induction              |
|              | Ctrl  | 12       | 62.7 ± 2.8 | 9/3 |                                         |
| Jebeli M     | MIL   | 35       | 56.9 ± 9.7 | 25/10 | After release of aortic clamp           |
|              | Ctrl  | 35       | 58.2 ± 8.4 | 28/7 |                                         |
| Jo HR        | MIL   | 20       | 67.0 ± 9.2 | 12/8 | After sternotomy                        |
|              | Ctrl  | 20       | 64.1 ± 9.9 | 11/9 |                                         |
| Kwak YL      | MIL   | 29       | 61.5 ± 8.2 | 21/8 | After IMA harvest                      |
|              | Ctrl  | 33       | 60.4 ± 8.4 | 26/7 |                                         |
| Lee JH       | MIL   | 24       | 63 ± 8  | 20/4  | After sternotomy                        |
|              | Ctrl  | 26       | 62 ± 8  | 20/6  |                                         |
| Möllhoff T   | MIL   | 11       | 60 ± 8  | Not specified | After anesthesia induction          |
|              | Ctrl  | 11       | 61 ± 6  | Not specified |                                         |
| Shi Y        | MIL   | 25       | Not specified | Not specified | After anesthesia induction          |
|              | Ctrl  | 24       | Not specified | Not specified |                                         |
| Song JW      | MIL   | 31       | 67.2 ± 7.6 | 14/17 | After harvesting the left internal mammary artery |
|              | Ctrl  | 31       | 65.7 ± 7.9 | 21/10 |                                         |
| Yamaguchi A  | MIL   | 14       | 64.1 ± 8 | 13/1  | After induction of CPB                  |
|              | Ctrl  | 14       | 65.2 ± 8.5 | 13/1 |                                         |
| Yamaura K    | MIL   | 10       | 66 ± 6  | 7/3   | After induction of CPB                  |
|              | Ctrl  | 10       | 57 ± 16 | 6/4   |                                         |
### Table 3. Preoperative Ejection Fraction and Postoperative Causes of Death in the 2 Groups

| First Author | Preoperative EF (MIL Group) | Preoperative EF (Ctrl Group) | No. of Death (Death/Total, MIL Group) | No. of Death (Death/Total, Ctrl Group) | Cause |
|--------------|-----------------------------|-----------------------------|---------------------------------------|---------------------------------------|-------|
| Arbeus 39    | 59 ± 12                     | 63 ± 9                      | 1                                     | 22                                    | 0     |
| Couture 40   | 51 ± 15                     | 50 ± 13                     | 2                                     | 25                                    | 0     |
| Doolan 41    | Not specified               | Not specified               | 0                                     | 15                                    | 0     |
| Guo 9        | 35 ± 4                      | 35 ± 5                      | 1                                     | 31                                    | 1     |
| Hadadzadeh 42| 29 ± 5.5                    | 28.6 ± 5.6                  | 1                                     | 40                                    | 1     |
| Hamada 43    | Not specified               | Not specified               | 0                                     | 20                                    | 0     |
| Hayashida 44 | Not specified               | Not specified               | 0                                     | 12                                    | 0     |
| Jebeli 45    | 31.8 ± 3.2                  | 34.5 ± 1.4                  | 0                                     | 35                                    | 2     |
| Jo 46        | 45 ± 14                     | 51 ± 13                     | 0                                     | 20                                    | 0     |
| Kwak 47      | Not specified               | Not specified               | 0                                     | 29                                    | 0     |
| Lee 32       | 50 ± 17                     | 57 ± 8                      | 0                                     | 24                                    | 0     |
| Möllhoff 48  | Not specified               | Not specified               | 0                                     | 11                                    | 0     |
| Shi 49       | Not specified               | Not specified               | 1                                     | 25                                    | 1     |
| Song 50      | 55.3 ± 15.3                 | 51.5 ± 16.7                 | 1                                     | 31                                    | 1     |
| Yamaguchi 51 | 64.1 ± 8                    | 65.2 ± 8.5                  | 0                                     | 14                                    | 0     |
| Yamaura 52   | Not specified               | Not specified               | 0                                     | 10                                    | 0     |

### Table 4. A Summary of the Global Effect of Different Outcomes.

| Patients (Studies) Included | Milrinone: Events (%) | Control: Events (%) | RR    | 95 % CI       |
|-----------------------------|-----------------------|---------------------|-------|---------------|
| Myocardial Infarction       | 440 (30)              | 5 (2.28 %)          | 25 (11.31 %) | 0.23          | 0.10-0.54    |
| Myocardial Ischemia         | 212 (53)              | 12 (11.32)          | 41 (36.68) | 0.29          | 0.16-0.52    |
| Arrhythmias                 | 470 (47)              | 16 (6.84)           | 31 (13.14) | 0.53          | 0.31-0.91    |
| Stroke                      | 172 (2)               | 2 (2.33)            | 0 (0)   | 3.00          | 0.32-27.88   |
| Renal Failure               | 302 (17)              | 9 (5.96)            | 8 (5.30) | 1.25          | 0.45-2.81    |

**Figures**
Figure 1

The flow diagram of study selection.

Figure 2
| Study                      | Random sequence generation | Allocation concealment (selective) | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data (attrition) | Selective reporting (reporting bias) | Other bias |
|----------------------------|----------------------------|-----------------------------------|---------------------------------------|-------------------------------|------------------------------------|--------------------------------------|------------|
| Arbeus M 2009              | ?                         | +                                 | +                                     | +                             | ?                                  | +                                    | +          |
| Couture P 2007             | +                         | +                                 | +                                     | +                             | ?                                  | +                                    | +          |
| Doolan LA 1997             | ?                         | ?                                 | +                                     | +                             | ?                                  | ?                                    | ?          |
| Guo YJ 2014                | +                         | -                                 | +                                     | ?                             | ?                                  | +                                    | +          |
| Hadadzadeh M 2013          | ?                         | ?                                 | +                                     | +                             | ?                                  | +                                    | ?          |
| Hamada Y 1999              | ?                         | ?                                 | ?                                     | ?                             | +                                  | +                                    | +          |
| Hayashida N 1999           | +                         | ?                                 | ?                                     | ?                             | ?                                  | ?                                    | +          |
| Jebeli M 2010              | ?                         | ?                                 | +                                     | ?                             | ?                                  | +                                    | +          |
| Jo HR 2010                 | ?                         | ?                                 | +                                     | ?                             | ?                                  | +                                    | +          |
| Kwak YL 2004               | ?                         | ?                                 | ?                                     | ?                             | +                                  | ?                                    | +          |
| Lee JH 2006                | ?                         | ?                                 | +                                     | ?                             | ?                                  | +                                    | +          |
| Mollhoff T 1999            | ?                         | ?                                 | ?                                     | ?                             | +                                  | ?                                    | +          |
| Shi Y 2006                 | ?                         | ?                                 | ?                                     | ?                             | +                                  | ?                                    | +          |
| Song JW 2011               | +                         | +                                 | +                                     | +                             | ?                                  | +                                    | +          |
| Yenamooli LA 2007          | ?                         | ?                                 | ?                                     | ?                             | ?                                  | ?                                    | ?          |
Figure 2
Risk of bias assessment. Review of authors’ judgements about each risk of bias domain for each included study. Red high risk, green low risk, yellow unclear.

Figure 3
A forest plot for the risk of mortality. CI, confidence interval; df, degrees of freedom.
### Figure 4

**Forest plot of all-cause mortality in trials stratified by intervention.**

#### Table 4.2.1: Myocardial infarction

| Study or Subgroup | Events | Total | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|------------|------------|
|                   |        |       | M-H Fixed, 95% CI | M-H Fixed, 95% CI |
| **Myocardial infarction** | | | | |
| Couture P 2007 | 0 | 25 | 0 | Not estimable |
| Guo YJ 2014 | 31 | 6 | 31 | 6.0% | 0.0769 | [0.0045, 1.3092] |
| Hadadazadeh M 2013 | 40 | 9 | 40 | 8.3% | 0.4444 | [0.1489, 1.3262] |
| Hamada Y 1999 | 0 | 10 | 0 | Not estimable |
| Hayashida N 1999 | 0 | 12 | 0 | Not estimable |
| Jebel M 2010 | 0 | 35 | 0 | 35 | 7.9% | 0.0588 | [0.0035, 0.9815] |
| Lee HJ 2006 | 0 | 24 | 0 | 26 | Not estimable |
| Möhlhoff T 1999 | 0 | 11 | 0 | Not estimable |
| Song JW 2011 | 1 | 31 | 2 | 31 | 1.9% | 0.5000 | [0.0478, 5.2337] |
| **Subtotal (95% CI)** | 219 | 221 | 24.1% | 0.2308 | [0.0982, 0.5422] |
| **Total events** | 5 | 25 | | |

Heterogeneity: Chi^2 = 3.28, df = 3 (P = 0.35); I^2 = 9%

Test for overall effect: Z = 3.38 (P = 0.0006)

#### Table 4.2.2: Myocardial ischemia

| Study or Subgroup | Events | Total | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|------------|------------|
|                   |        |       | M-H Fixed, 95% CI | M-H Fixed, 95% CI |
| **Myocardial ischemia** | | | | |
| Guo YJ 2014 | 3 | 31 | 14 | 31 | 13.0% | 0.2143 | [0.0683, 0.6722] |
| Hayashida N 1999 | 5 | 40 | 11 | 40 | 10.2% | 0.4546 | [0.1737, 1.1695] |
| Jebel M 2010 | 4 | 35 | 16 | 35 | 14.8% | 0.2500 | [0.0892, 0.6731] |
| **Subtotal (95% CI)** | 106 | 106 | 38.0% | 0.2927 | [0.1630, 0.5255] |
| **Total events** | 12 | 41 | | |

Heterogeneity: Chi^2 = 1.19, df = 2 (P = 0.55); I^2 = 0%

Test for overall effect: Z = 4.11 (P < 0.0001)

#### Table 4.2.3: Arrhythmias

| Study or Subgroup | Events | Total | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|------------|------------|
|                   |        |       | M-H Fixed, 95% CI | M-H Fixed, 95% CI |
| **Arrhythmias** | | | | |
| Couture P 2007 | 0 | 25 | 0 | Not estimable |
| Doolan LA | 1 | 15 | 0 | 15 | 0.5% | 3.0000 | [0.1319, 68.2587] |
| Guo YJ 2014 | 4 | 31 | 7 | 31 | 6.5% | 0.5714 | [0.1859, 1.7867] |
| Hadadazadeh M 2013 | 5 | 40 | 14 | 40 | 13.0% | 0.3571 | [0.1420, 0.8962] |
| Hamada Y 1999 | 0 | 10 | 0 | 10 | Not estimable |
| Hayashida N 1999 | 0 | 12 | 0 | 12 | Not estimable |
| Jebel M 2010 | 5 | 35 | 10 | 35 | 9.3% | 0.5000 | [0.1903, 1.3136] |
| Lee HJ 2006 | 0 | 24 | 0 | 26 | Not estimable |
| Möhlhoff T 1999 | 0 | 11 | 0 | 11 | Not estimable |
| Song JW 2011 | 1 | 31 | 0 | 31 | 0.5% | 3.0000 | [0.1269, 70.9156] |
| **Subtotal (95% CI)** | 234 | 236 | 29.6% | 0.5313 | [0.3108, 0.9081] |
| **Total events** | 16 | 31 | | |

Heterogeneity: Chi^2 = 3.07, df = 4 (P = 0.55); I^2 = 0%

Test for overall effect: Z = 2.31 (P = 0.02)

#### Table 4.2.4: Stroke

| Study or Subgroup | Events | Total | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|------------|------------|
|                   |        |       | M-H Fixed, 95% CI | M-H Fixed, 95% CI |
| **Stroke** | | | | |
| Jebel M 2010 | 0 | 35 | 0 | 35 | Not estimable |
| Jo HR 2010 | 1 | 20 | 0 | 20 | 0.5% | 3.0000 | [0.1295, 69.5153] |
| Song JW 2011 | 1 | 31 | 0 | 31 | 0.5% | 3.0000 | [0.1269, 70.9156] |
| **Subtotal (95% CI)** | 86 | 86 | 0.9% | 3.0000 | [0.3228, 27.8443] |
| **Total events** | 2 | 0 | | |

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 1.00); I^2 = 0%

Test for overall effect: Z = 0.97 (P = 0.33)

#### Table 4.2.5: Renal failure

| Study or Subgroup | Events | Total | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|------------|------------|
|                   |        |       | M-H Fixed, 95% CI | M-H Fixed, 95% CI |
| **Renal failure** | | | | |
| Couture P 2007 | 2 | 25 | 1 | 25 | 0.9% | 2.0000 | [0.1935, 20.6706] |
| Hadadazadeh M 2013 | 1 | 40 | 3 | 40 | 2.8% | 0.3333 | [0.0362, 3.0701] |
| Jebel M 2010 | 0 | 35 | 0 | 35 | Not estimable |
| Jo HR 2010 | 2 | 20 | 1 | 20 | 0.9% | 2.0000 | [0.1967, 20.3322] |
| Song JW 2011 | 4 | 31 | 3 | 31 | 2.8% | 1.3333 | [0.3250, 5.4708] |
| **Subtotal (95% CI)** | 151 | 151 | 7.4% | 1.1290 | [0.4503, 2.8168] |
| **Total events** | 9 | 8 | | |

Heterogeneity: Chi^2 = 1.6, df = 3 (P = 0.64); I^2 = 0%

Test for overall effect: Z = 0.25 (P = 0.80)

**Total (95% CI)**: 796 | 800 | 100.0% | 0.4352 | [0.3166, 0.5982]

**Total events**: 44 | 105

Heterogeneity: Chi^2 = 18.11, df = 17 (P = 0.38); I^2 = 6%

Test for overall effect: Z = 5.12 (P < 0.00001)

Test for subgroups differences: Chi^2 = 11.41, df = 4 (P = 0.02). I^2 = 65.0%
Figure 5

A funnel plot for the risk of mortality. SE, standard error. A. B.

Supplementary Files

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