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Original Article

Safety and efficacy of granulocyte colony stimulating factor in patients with acute myocardial infarction

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Abstract: This meta-analysis was aimed to evaluate the safety and clinical efficacy of granulocyte colony stimulating factor (G-CSF) in acute myocardial infarction (AMI). Relevant studies were identified by both database searches and manual searches. The randomized controlled trial (RCT) studies related to G-CSF in AMI treatment were selected. The effects of healthcare interventions were evaluated by Cochrane quality evaluation. The safety indices including mortality, reinfarction, restenosis, major cardiovascular events (MACE), as well as therapeutic effect indices including left ventricular ejection fraction (LVEF), Left Ventricular End-Systolic Volume (LVESV) and Left Ventricular End-Diastolic Volume (LVEDV) were analyzed by using RevMan 5.2 software. The comparison of binary variable was evaluated by relative risk (RR) and 95% confidence interval (CI). While the comparison of continuous variable was evaluated by weighted mean difference (WMD) and 95% CI. The funnel plot was used to evaluate the possibility of publication bias. A total of 12 publications including 727 subjects were enrolled. The meta-analysis revealed that the weighted mean difference (WMD) for LVEDV was -3.87 (95% CI: [-7.20, -0.54)], P = 0.02), suggesting that G-CSF could ameliorate the condition of LVEDV. The effect of G-CSF on safety indices like mortality, reinfarction, restenosis, MACE and LVEF were not significant (all P > 0.05). G-CSF therapy did not improve mortality, MACE, reinfarction, LVESV nor LVEF, but improved LVEDV. G-CSF therapy might be an adjuvant therapy for AMI.

Keywords: Granulocyte colony stimulating factor, acute myocardial infarction, safety and clinical efficacy, meta-analysis

Introduction

Acute myocardial infarction (AMI), commonly known as heart attack, causes heart failure, irregular heartbeat and cardiac arrest [1]. In the developed world, the risk of death in those who have had an AMI is about 10% [2], and the incidence rates of AMI for a given age have decreased globally during 1990 and 2010 [3]. The risk factors of AMI are various, including lifestyle [4], disease [5], genetic variants [6] and family history [7]. Traditional therapies like drugs and surgery have been widely applied for AMI [2, 8], however, these therapies could not regenerate the dead myocardium caused by ischemic damage.

Stem cells have the potential to regenerate damaged myocardium. They can be mobilized from the bone marrow by granulocyte colony stimulating factor (G-CSF) [9]. G-CSF, first recognized and purified in 1983, is a glycoprotein that stimulates the bone marrow to produce granulocytes [10]. G-CSF was proven to have beneficial effects on cardiac regeneration after myocardial infarction [11]. In patients with AMI in a large area of the anterior wall, G-CSF could prevent left ventricular remodeling [12]. Despite the potential benefit of G-CSF therapy in patients with AMI, the safety and clinical efficacy of G-CSF in regenerating the heart after AMI remains controversial. Sato *et al*., indicated that G-CSF could mobilize bone marrow-derived cells to the peripheral circulation but could not promote the recruitment to the infarcted myocardium [13]. Kang *et al.* confirmed that the combination of darbepoetin and G-CSF was safe and more effective in mobilizing and recruiting proangiogenic cells than G-CSF alone in patients with AMI [14]. Given the conflicting data, this meta-analysis was conducted to investigate the value of G-CSF for the treatment of AMI.

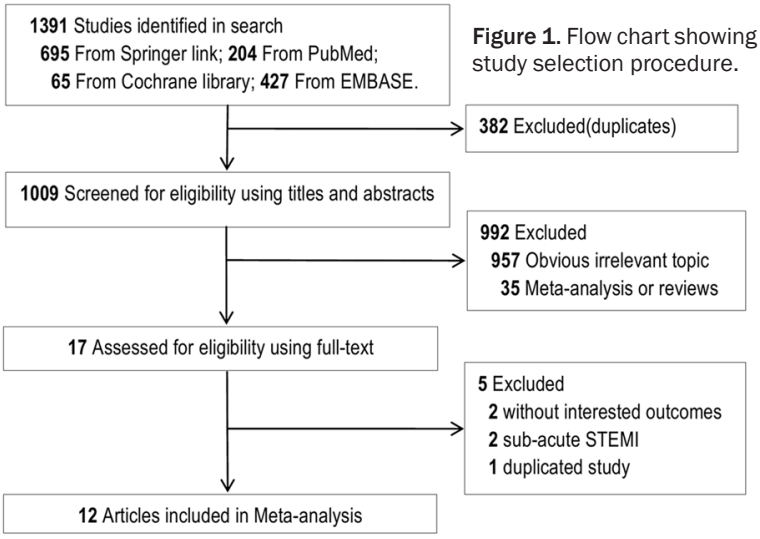

Figure 1. Flow chart showing study selection procedure.

Materials and methods

Data sources and keywords

A comprehensive search of bibliographic databases (PubMed, Embase, Springer link, and the Cochrane Library) was conducted to identify relevant studies. The search terms were: ("granulocyte colony stimulating factor" OR "GCSF" OR "G-CSF") and ("acute myocardial infarction" OR "AMI"). Restriction on language was not applied. The retrieval time was updated to August 20th, 2015. Manual searches were used for screening and selection of other eligible studies from the reference of included studies.

Study selection

The inclusion criteria for the present meta-analysis were: 1) randomized controlled trial (RCT) studies; 2) included patients with AMI after percutaneous coronary stent intervention (PCI); 3) patients treated with G-CSF were included in the case group, while patients accepted placebo were included in the control group; 4) high integrity data that suitable formortality, reinfarction, restenosis, major cardiovascular events (MACE), left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). Studies with incomplete data, literature reviews, letters, comments and repeat publications were excluded. Furthermore, if several studies were based on the same group of patients, only one study with the most complete information and longest research time was included.

Data extraction and quality assessment

Two investigators independently extracted the data information from all selected studies in order to reduce bias. All investigators reached a consensus on all included studies items via discussion. The following information were extracted from each eligible study: surname of first author, year of publication, country (or area), pathological type, the number of cases, age and gender of subjects, the dose of G-CSF and study outcomes.

Methodological quality assessment were based on the guidelines of the Cochrane [15], an official document that describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions. The standard criteria of the Cochrane systematic reviews were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Statistical analysis

RevMan 5.2 software was used for statistical analysis. The safety indices including mortality, reinfarction, restenosis, MACE, as well as therapeutic effect indices including LVEF, LVESV and LVEDV were analyzed. The comparison of binary variable was evaluated by relative ratio (RR) and 95% confidence interval (CI). While the comparison of continuous variable was evaluated by weighted mean difference (WMD) and 95% CI. Heterogeneity was evaluated using Cochran's Q statistic and I^2 [16]. The random-effects model was applied if significant heterogeneity was found ($Q < 0.05$ or $I^2 > 50\%$). Otherwise, the fixed-effects model was used ($Q \geq 0.05$ or $I^2 \leq 50\%$). The funnel plot was used to evaluate the publication bias.

Results

Included studies

As shown in **Figure 1**, the present meta-analysis initially retrieved 1391 studies from data-

Table 1. Characteristics of included studies

Study	Country	Type of case	n, M/F		Age, y (mean ± SD)		G-CSF dose (μg/kg)	Follow-up duration (M)	Outcomes
			G-CSF	Control	G-CSF	Control			
Ince, H 2005 [21]	Germany	Acute STEMI	25, 23/2	25, 23/2	50.5 ± 7.9	49.6 ± 7.6	10, subcutaneously, QD, 6 d; Initiated 89 ± 35 minutes of PCI	4	Mortality, reinfarction, restenosis, MACE, LVEF
Valgimigli, M 2005 [25]	Italy	Acute STEMI	10, 8/2	10, 8/2	62 ± 9	61 ± 10	10, subcutaneously, QD, 6 d; Initiated 37 ± 66 hours of PCI	6	Restenosis, MACE, LVEF, LVEDV
Ripa, R. S 2006 [27]	Denmark	Acute STEMI	39, 28/11	39, 34/5	57.4 ± 8.6	54.7 ± 8.1	10, subcutaneously, QD, 6 d; Initiated within 48 hours of PCI	6	Restenosis, LVEF, LVESV, LVEDV
Ellis, S. G 2006 [18]	USA	Acute STEMI	12, 11/1	6, 6/0	56.5 ± 13.1	62 ± 12	5/10, subcutaneously, QD, 5 d; Initiated within 48 hours of PCI	12	Mortality, reinfarction, MACE, LVEF, LVESV
Zohlnhofer, D 2006 [26]	Germany	Acute STEMI	56, 44/12	58, 46/12	59.4 ± 12.0	59.8 ± 10.3	10, subcutaneously, QD, 5 d; Initiated within 5 days of PCI	6	Mortality, reinfarction, restenosis, MACE, LVEF, LVESV, LVEDV
Takano, H 2007 [24]	Japan	Acute STEMI	18, 14/4	22, 18/4	61 ± 8	63 ± 11	2.5, subcutaneously, QD, 5 d; Initiated within 24 hours of PCI	6	Mortality, reinfarction, restenosis, MACE, LVEF, LVESV, LVEDV
Leone, A. M 2007 [12]	Italy	Acute STEMI	14, 13/1	27, 27/0	53 ± 11	56 ± 11	10, subcutaneously, QD, 5 d; Initiated 5 days of PCI	6	Restenosis, MACE, LVEF, LVESV, LVEDV
Guo, S. Z 2010 [19]	China	Acute STEMI	17, 10/7	16, 12/4	66.7 ± 8.5	64.8 ± 7.2	10 subcutaneously, QD, 7 d; Initiated between 3 and 5 days of PCI	6	Restenosis, MACE, LVEF, LVEDV
Kang, H. J 2012 [22]	South Korea	AMI	57, 48/9	60, 43/17	57.5 ± 10.9	57.5 ± 11.9	10, subcutaneously, QD, 4 d; Initiated within 14 days of PCI	60	Mortality, reinfarction, MACE, LVEF, LVEDV
Ripa, R. S 2013 [23]	Denmark	Acute STEMI	39, 28/11	39, 34/5	57.4 ± 8.6	54.7 ± 8.1	10, subcutaneously, QD, 6 d; Initiated within 48 hours of PCI	60	All-cause mortality, reinfarction, major cardiovascular events
Achilli, F 2014 [17]	Italy	Acute STEMI	29, 29/0	25, 23/2	61 ± 8	62 ± 10	5, subcutaneously, BID, 5 d; Initiated within 12 hours of PCI	36	Mortality, reinfarction, restenosis, MACE, LVEF, LVESV, LVEDV
Hibbert, B 2014 [20]	Canada	Acute STEMI	42, 35/7	42, 34/8	53.3 ± 8.7	57.0 ± 9.2	10, subcutaneously, QD, 4 d; Initiated 3-4 days after PCI	6	Mortality, reinfarction, MACE, LVEF

STEMI, ST-elevation myocardial infarction; LVEDV, Left Ventricular End-Diastolic Volume; LVESV, Left Ventricular End-Systolic Volume; AMI, acute myocardial infarction; MACE, major cardiovascular events; QD, once/day; BID, twice/day; M, month.

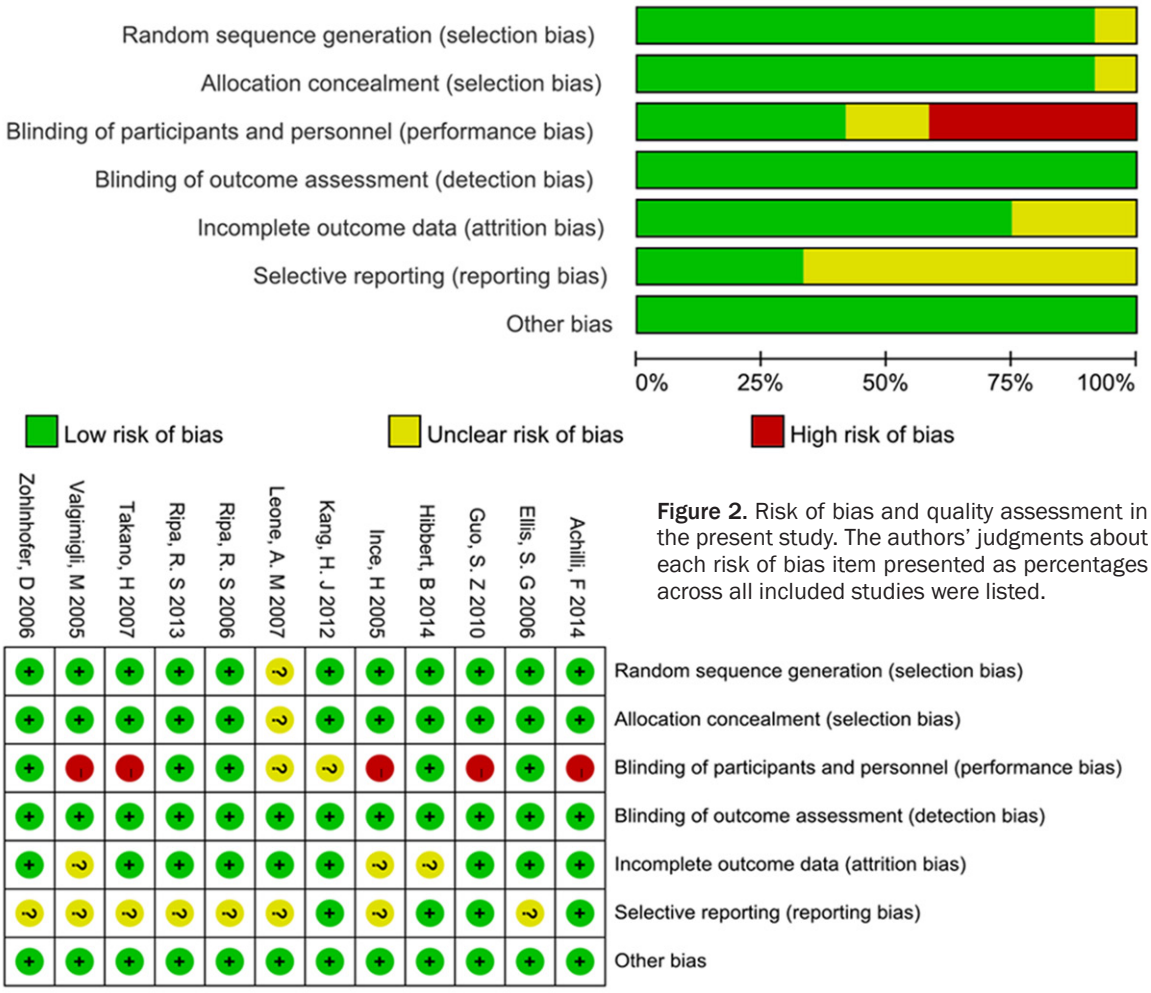

Figure 2. Risk of bias and quality assessment in the present study. The authors' judgments about each risk of bias item presented as percentages across all included studies were listed.

base searches and manual searches. After removing the duplicates (n = 382), studies unrelated to the research topics (n = 957), and other meta-analysis or reviews (n = 35), the remaining 17 studies were reviewed. Among these studies, 5 studies were excluded because of missing of interested outcomes (n = 2), studies on sub-acute STEMI (n = 2), or duplicated study (n = 1). Finally, a total of 12 publications with sufficient data were enrolled [12, 17-27]. The selected 12 studies included a total of 727 subjects (358 patients treated with G-CSF and 369 placebo controls). These studies were performed in Europe (n = 7), Asia (n = 3) and North America (n = 2). There was no significant difference on age and sex ratio at baseline between the case group and control group. The baseline characteristics of these studies are presented in **Table 1**. Acute STEMI was the object of all studies except for Kang 2012 [22]. The follow-up time for these studies ranged from 4 to 6 months. Cochrane quality evaluation results showed that all studies were with high quality and only small bias existed in single-blind studies (**Figure 2**).

Meta-analysis for safety indices

The comparison of mortality were reported in 7 studies [17, 18, 21-24, 26]. The I^2 and *P* value of heterogeneity test was 1% and 0.41 respectively, thus the fixed-effect model was adopted. The RR for mortality was 1.11 (95% CI: [-0.45, 2.76], P = 0.82) (**Figure 3A**). The comparison of reinfarction was reported in 8 studies [17, 18, 20-22, 24, 26, 27]. The meta-analysis revealed that RR for reinfarction was 0.68 (95% CI: [0.22, 2.07], P = 0.50) (**Figure 3B**). The comparison of restenosis was reported in 8 studies [12, 17, 19, 21, 24-27]. The RR for restenosis was 1.00 (95% CI: [0.71, 1.42], P = 0.98) (**Figure 4A**). The difference of MACE was reported in a total of 11 studies [12, 17-26]. The RR for MACE was 0.96 (95% CI: [0.64, 1.14], P = 0.30) (**Figure 4B**).

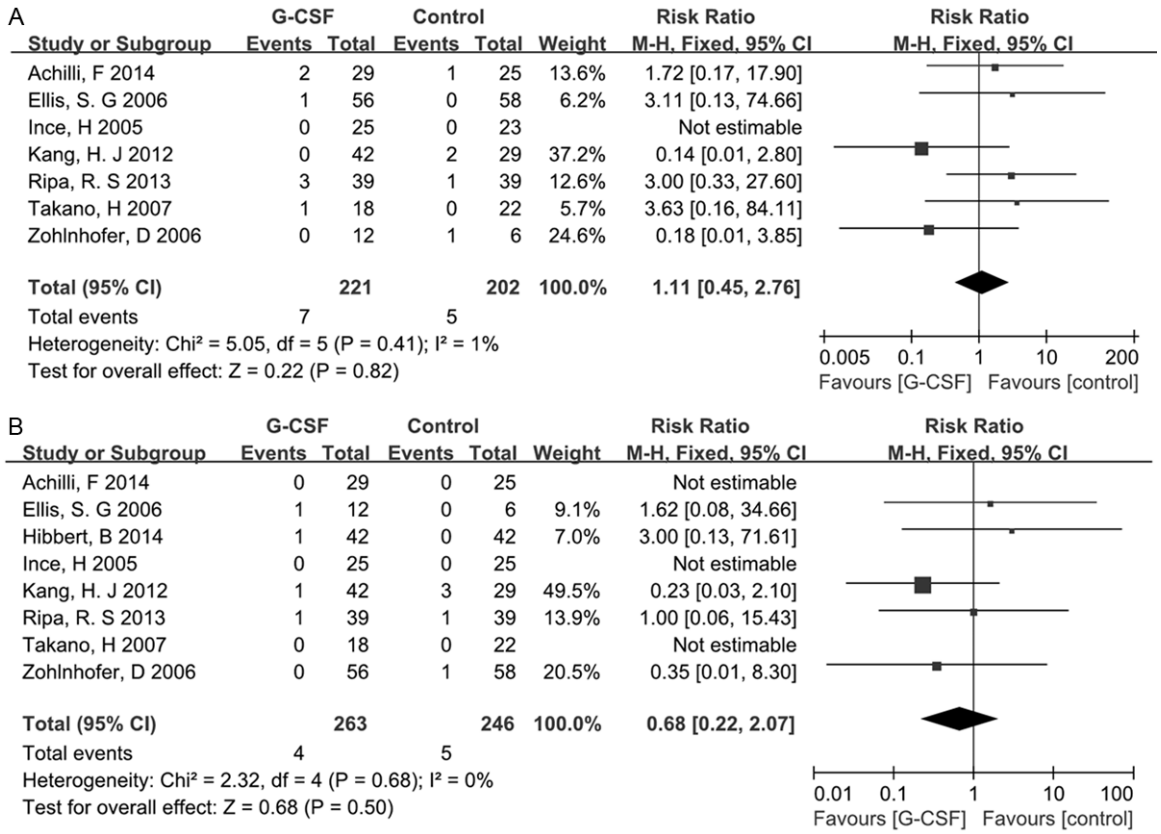

Figure 3. Result of overall effect size for mortality (A) and reinfarction (B) in the present meta-analysis.

Meta-analysis for therapeutic effect indices

The comparison of LVEF was reported in 11 studies [12, 17-22, 24-27] with a WMD of 1.77 (95% CI: [-1.51, 5.05], P = 0.29) (**Figure 5A**). The comparison of LVESV was reported in 6 studies [17, 18, 21, 24, 26, 27] with a WMD of-5.30 (95% CI: [-12.39, 1.79, P = 0.14) (**Figure 5B**). The comparison of LVEDV were reported in 8 studies [12, 17, 19, 22, 24-27] with a WMD of-3.87 (95% CI: [-7.20, -0.54), P = 0.02) (**Figure 5C**), indicating that G-CSF could ameliorate the condition of LVEDV.

Publication bias analysis

Publication bias was assessed for the comparison of MACE, which involved the most number of studies. The result indicated that the likelihood of having publication bias was small (P = 0.86) (**Figure 6B**).

Discussion

AMI is one of the leading causes of death and morbidity globally [28]. Stem cell therapy like G-CSF has potential and promises for the treatment of AMI [29]. However, the safety and clinical efficacy of G-CSF in AMI treatment remains controversial. A total of 12 publications including 727 subjects were enrolled in the present study. The meta-analysis revealed that the WMD for LVEDV was -3.87 (95% CI: [-7.20, -0.54], P = 0.02), suggesting that G-CSF could improve LVEDV. The effect of G-CSF on mortality, reinfarction, restenosis, MACE and LVEF were not significant. These results indicated that G-CSF was safe and it had potential for the treatment of AMI.

G-CSF was proved to promote the recovery of myocardial function after myocardial infarction [23]. Previous study indicated that G-CSF enhanced the migration of systemically delivered MSCs from bone marrow to infarcted heart, but the effect of this migration was limited, since the cardiac function did not improve [30]. As an adjunctive therapy for AMI, G-CSF may be safe but there was not much supporting evidence that this treatment could improve LVEF [31]. Overgaard *et al.* indicated that in the time window from 17 to 65h after ST-elevation

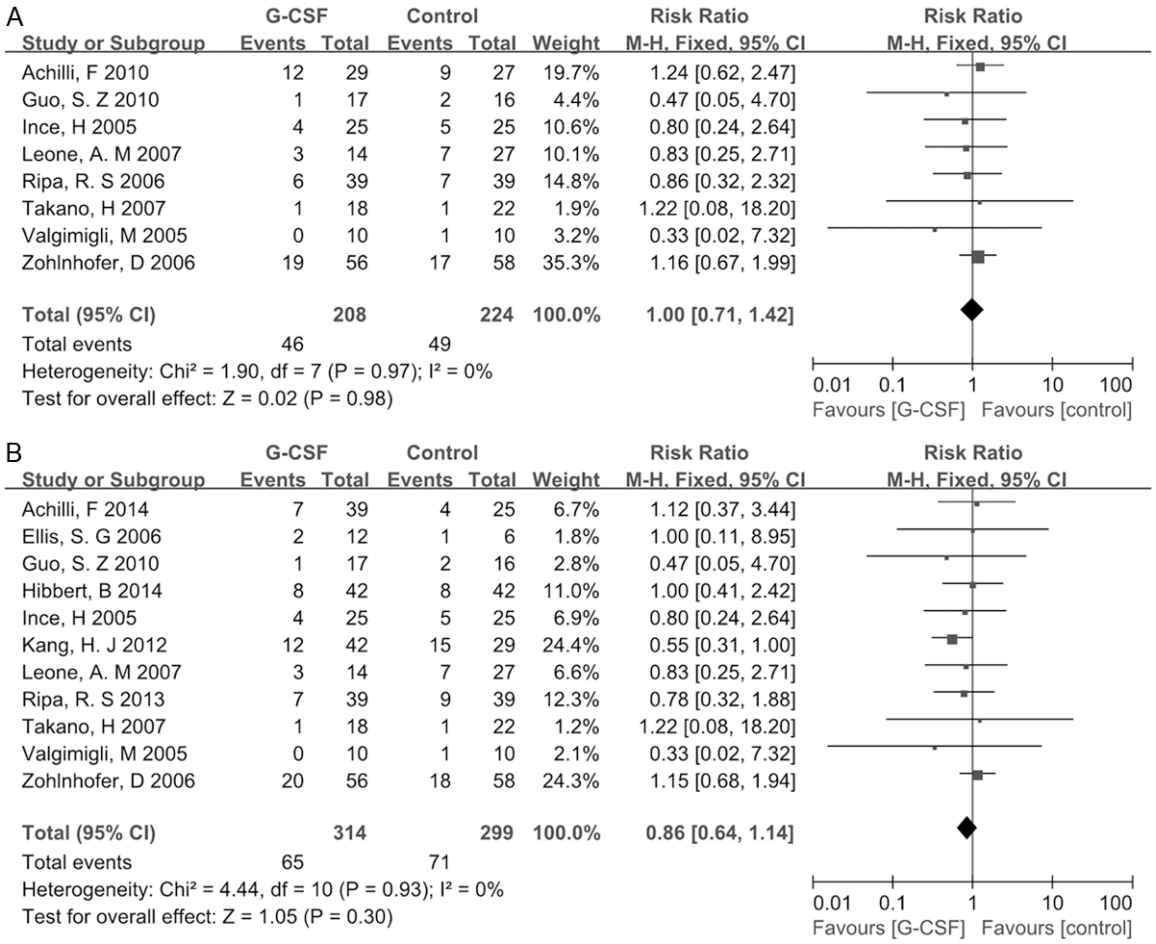

Figure 4. Result of overall effect size for restenosis (A) and MACE (B) in the present meta-analysis.

myocardial infarction (STEMI) treated with PCI, the timing of G-CSF treatment did not influence the recovery of LVEF [32]. For a period of time, researchers suggested that G-CSF was effective as an adjunctive therapy [33, 34]. However, previous studies indicated that it did not have additive benefit over monotherapy [35, 36]. Zohlnhofer *et al.* believe that the available evidence based on a meta-analysis does not support the use of G-CSF for AMI after reperfusion [37]. Our study indicated that G-CSF failed to improve neither functional cardiac parameters (LVEF, LVESV) nor clinical outcomes (death, reinfarction, restenosis, MACE). Furthermore, Takano *et al.*, indicated that no significant difference was observed for LVEDV between the G-CSF treatment group and control group [24]. At 6 month follow-up, patients who received G-CSF treatment had preferred recovery in terms of LVEDV [38]. The present study revealed that G-CSF could ameliorate the condition of LVEDV, which further confirmed findings of previous research. There were some limitations in the present study. First, the sample sizes of the enrolled studies were relatively small. Second, the follow-up time of included studies were mostly less than 1 year, which make it hard to assess the long-term effects of G-CSF. Therefore, further studies with larger sample size and longer follow-up are needed to confirm our findings.

In summary, G-CSF therapy is safe and is able to ameliorate the condition of LVEDV. Although G-CSF therapy does not improve mortality rate, MACE, reinfarction, LVESV nor LVEF, it can improve LVEDV. It might be a possible adjunctive therapy for AMI.

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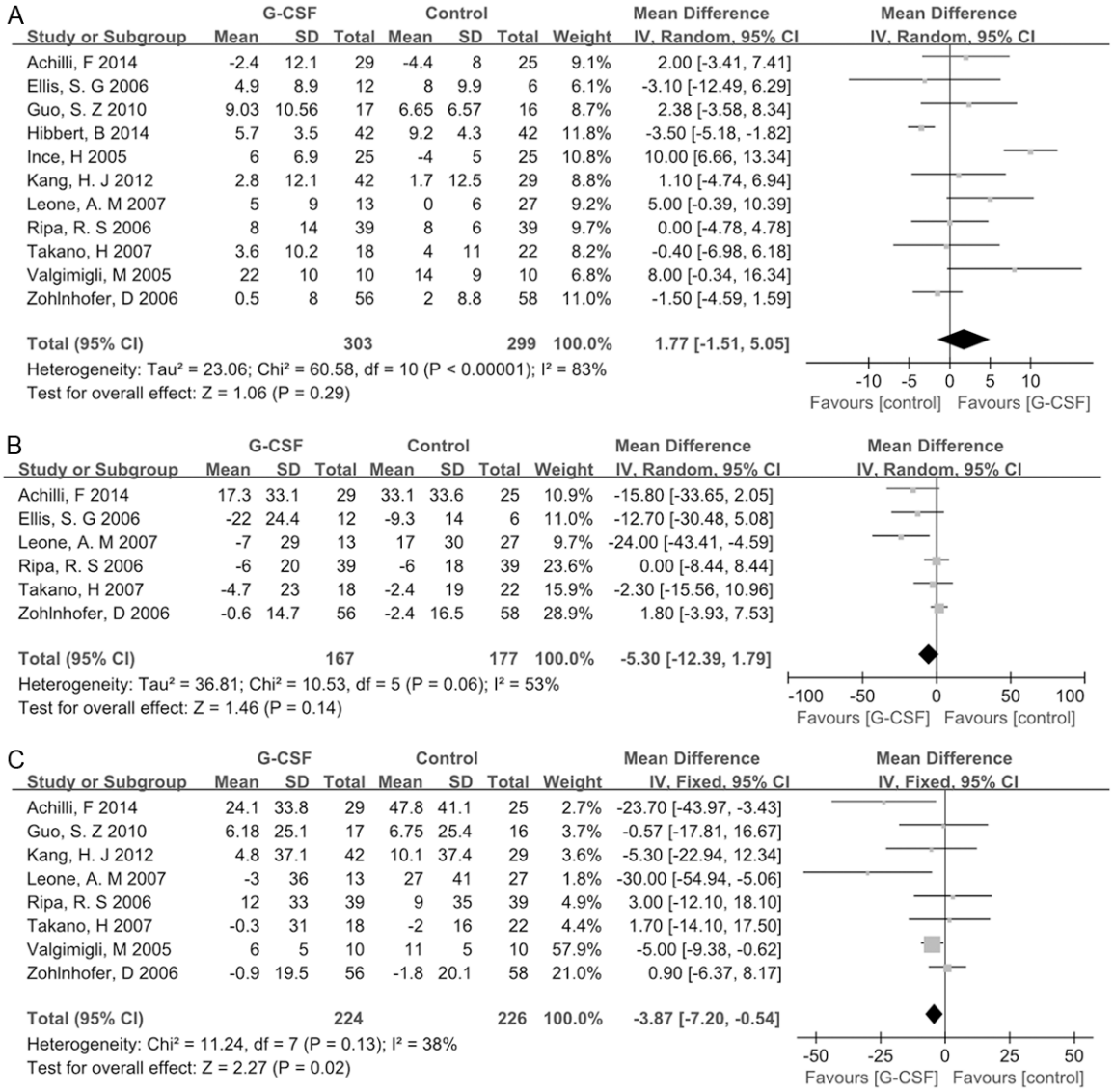

Figure 5. Result of overall effect size for LVEF (A), LVESV (B) and LVEDV (C) in the present meta-analysis.

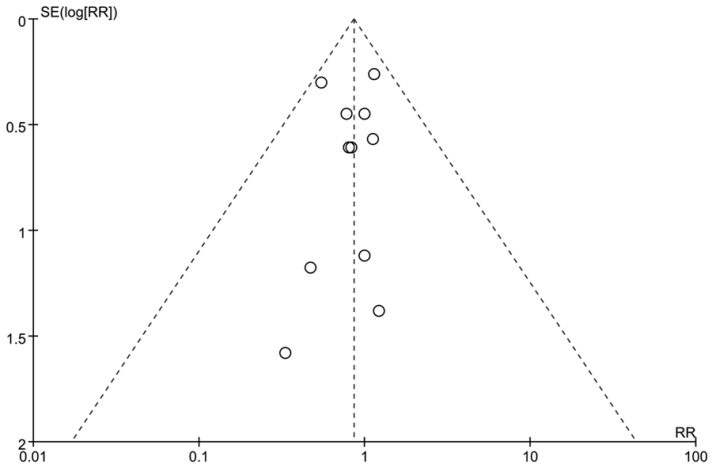

Figure 6. The funnel plot for publication bias analysis.

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Disclosure of conflict of interest

None.

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