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Stem Cell Mobilization by Granulocyte Colony-Stimulating Factor for Myocardial Recovery After Acute Myocardial Infarction

A Meta-Analysis

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Objectives The objective of this meta-analysis was to evaluate the effect of stem cell mobilization by granulocyte colony-stimulating factor (G-CSF) on myocardial regeneration on the basis of a synthesis of the data generated by randomized, controlled clinical trials of G-CSF after acute myocardial infarction (AMI).

Background Experimental studies and early-phase clinical trials suggest that stem cell mobilization by G-CSF may have a positive impact on cardiac regeneration after AMI. The role of G-CSF in patients with AMI remains unclear considering the inconsistent results of several clinical trials.

Methods For our analysis, PubMed, the Cochrane Central Register of Controlled Trials, conference proceedings from major cardiology meetings, and Internet-based sources of information on clinical trials in cardiology from January 2003 to August 2007 served as sources. Two reviewers independently identified studies and abstracted data on sample size, baseline characteristics, and outcomes of interest. Eligible studies were randomized trials with stem cell mobilization by G-CSF after reperfused AMI that reported data regarding the change in left ventricular ejection fraction (LVEF) at follow-up.

Results Ten trials using stem cell mobilization by G-CSF, including 445 patients, met the inclusion criteria. Significant improvement in LVEF at follow-up was observed in both the G-CSF and placebo groups. Compared with placebo, stem cell mobilization by G-CSF did not enhance the improvement of LVEF at follow-up (mean difference 1.32% [95% confidence interval −1.52 to 4.16; p = 0.36]). Moreover, the mean difference of reduction of infarct size between the treatment and placebo groups was −0.15 (95% confidence interval −0.38 to 0.07, p = 0.17).

Conclusions Cumulatively, available evidence does not support a beneficial effect of G-CSF in patients with AMI after reperfusion. (J Am Coll Cardiol 2008;51:1429–37) © 2008 by the American College of Cardiology Foundation

Heart failure develops in a relevant number of patients with acute myocardial infarction (AMI) caused by irreversible myocardial damage and ventricular remodeling despite early reperfusion strategies (1,2). Cell-based therapeutic strategies seem to be a promising tool to beneficially influence ventricular remodeling after AMI. Although the underlying mechanism remains controversial, numerous animal studies have documented that cytokine-induced mobilization of bone marrow–derived stem cells after AMI is associated with a reduction in infarct size, improvement in left ventricular ejection fraction (LVEF), and survival (3–6). Moreover, a meta-analysis recently showed a moderate benefit from intracoronary stem cell transplantation in patients with AMI after successful reperfusion (7).

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Granulocyte colony-stimulating factor (G-CSF) is an effective stimulus for mobilization of bone marrow-derived stem cells into the peripheral blood. A number of recent studies, mostly involving limited numbers of patients, have evaluated the use of G-CSF as a less invasive stem cell-based strategy for myocardial regeneration in patients with AMI after successful reperfusion (8–17). However, these

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CD34 = cluster of differentiation 34
CI = confidence interval
G-CSF = granulocyte colony-stimulating factor
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
PCI = percutaneous coronary intervention
WMD = weighted mean differences

trials have obtained mixed results with respect to improvement of left ventricular (LV) function after G-CSF–induced stem cell mobilization. Moreover, in an early safety and feasibility study of stem cell mobilization in patients with AMI, G-CSF therapy was associated with an increased risk of restenosis (18). Therefore, we herein summarize available experience in this field in the form of a meta-analysis of the effect of stem cell mobilization by G-CSF on changes in LVEF and infarct size in patients with AMI.

Methods

Objective. The objective of our meta-analysis was to assess the efficacy and safety of G-CSF–induced stem cell mobilization for myocardial recovery in patients with AMI.

Criteria for study selection. For this meta-analysis, studies were selected that included patients with AMI who were assigned to stem cell mobilization by G-CSF in randomized, controlled trials. All studies had to report the outcomes of interest during a follow-up period of at least 1 month after the index procedure. No restriction criteria were imposed with regard to the form of study publication.

Outcomes and definitions. The primary outcome of interest was change in LVEF. The secondary end point was change in infarct size. The angiographic outcome of interest was binary restenosis, which was defined as diameter stenosis of at least 50% at follow-up, measured by quantitative angiography in the area, including the stented area as well as the 5-mm margins proximal and distal to the stent.

We also analyzed clinical end points such as target vessel revascularization, myocardial infarction (MI), death, and the composite of death or MI.

Data sources. We searched PubMed and the Cochrane Central Register of Controlled Trials for trials comparing stem cell mobilization with G-CSF versus placebo treatment in patients with AMI. In addition, we searched conference proceedings from the American College of Cardiology, American Heart Association, and European Society of Cardiology. Searches were restricted to the period from January 2003 to August 2007. We reviewed the peer-reviewed publications identified through searches using the following key words: "granulocyte colony stimulating factor," "G-CSF," "cytokine," "stem cells," "coronary artery disease," "acute myocardial infarction," "primary percutaneous coronary intervention" (PCI), and "primary PCI." Relevant reviews and editorials from major medical journals published within the last year were identified and assessed for possible information on trials of interest. Internet-based sources of information on the results of clinical trials in cardiology were also searched.

Data collection and assessment of quality. Studies were selected and data were extracted independently by 2 reviewers (D.Z., A.D.). Disagreements were resolved by consensus. We recorded the following characteristics, in addition to the number of participating patients: LV function at baseline and follow-up, infarct size at baseline and follow-up, angiographic restenosis, target vessel revascularization, MI, death, and the composite of death and MI. Raw data obtained from source information of the individual studies were used for all analyses.

Statistical analysis. Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were computed as summary statistics. A random-effects model using the method of DerSimonian and Laird was used to calculate pooled WMD (19). Heterogeneity was explored using the chi-square test. The quantity of heterogeneity across trials was measured by the I^2 statistic as proposed by Higgins et al. (20). We assessed publication bias with respect to the primary outcome of interest, increase in LVEF, using the Begg adjusted rank correlation test according to the method of Begg and Mazumdar (21) and regression asymmetry test by Egger et al. (22). A sensitivity analysis was performed by assessing the contribution of individual studies to the summary effect estimate with respect to the primary outcome. This was done by excluding each trial 1 at a time and computing meta-analysis estimates for the remaining studies. The effect of study variables was assessed using meta-regression. Results were considered statistically significant at $p < 0.05$. Statistical analyses were performed with Stata software, version 9.2 (Stata Corp., College Station, Texas).

Results

Randomized trials investigating the effect of G-CSF after AMI. Our search identified 10 randomized trials that investigated the effect of G-CSF–induced stem cell mobilization in 445 patients with AMI after successful reperfusion (8–17) (Table 1).

The G-CSF treatment resulted in a dose-dependent mobilization of cluster of differentiation 34 positive ($CD34^+$) stem cells from the bone marrow to the peripheral blood (Table 2). The lowest $CD34^+$ cell count was seen in the study with the lowest G-CSF dose and the shortest duration of G-CSF treatment (14), whereas it was highest in the study with the highest dose and longest duration of treatment (17) (Table 2).

Among the 10 included trials, 4 were double-blinded (REVIVAL-2 [Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells] [10], STEMMI [Stem Cells in Myocardial Infarction] [11], G-CSF-STEMI [Granulocyte Colony-Stimulating Factor ST-Segment Elevation Myocardial Infarction] [12], and the trial by Ellis et al. [13]). The remaining 6 trials did not have a

Table 1 Main Characteristics of the Trials

Trial	Double Blinding	Number of Patients	Therapy	Reperfusion Treatment	Primary End Point	Method	Duration of Follow-Up (Months)
Valgimigli et al. (8)	No	20	G-CSF	PCI*	Safety and feasibility	SPECT	6
FIRSTLINE-AMI (9)	No	50	G-CSF	PCI	Safety and left ventricular function	ECHO	4
REVIVAL-2 (10)	Yes	114	G-CSF	PCI	Change in infarct size	MRI	4
STEMMI (11)	Yes	78	G-CSF	PCI	Change in systolic wall thickening	MRI	6
G-CSF-STEMI (12)	Yes	44	G-CSF	PCI	Change in ejection fraction and systolic wall thickening	MRI	3
Ellis et al. (13)	Yes	18	G-CSF	PCI	Safety and change in ejection fraction	ECHO	1
Takano et al. (14)	No	40	G-CSF	PCI	Changes in left ventricular function and volume	SPECT	6
Rigenera (15)	No	41	G-CSF	PCI	Change in ejection fraction and left ventricular volume	ECHO	5
MAGIC Cell 1 (16)	No	20	G-CSF	PCI	Change in ejection fraction	SPECT	24
Suarez de Lezo et al. (17)	No	20	G-CSF	PCI	Change in ejection fraction	Ventriculography	3

*Seven patients per group had PCI.

FIRSTLINE-AMI = Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction trial; G-CSF = granulocyte colony-stimulating factor; ECHO = echocardiography; G-CSF-STEMI = Granulocyte Colony-Stimulating Factor ST-Segment Elevation Myocardial Infarction trial; MAGIC Cell 1 = Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion 1 trial; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; REVIVAL-2 = 22 Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells trial; SPECT = single-photon emission computed tomography; STEMMI = Stem Cells in Myocardial Infarction trial.

double-blinded design: FIRSTLINE-AMI (Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction) (9), the Rigenera study (15), MAGIC Cell 1 (Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion 1) (16), as well as the trials by Valgimigli et al. (8), Takano et al. (14), and Suarez de Lezo et al. (17) all had a randomized control group (Table 1).

Concerning the primary end points, G-CSF studies varied considerably (Table 1). Change in ejection fraction was the primary end point in 6 trials: the G-CSF-STEMI trial, the MAGIC Cell 1 trial, the Rigenera trial, and the trials by Ellis et al., Takano et al., and Suarez de Lezo et al. (12–17). Two trials did not specify a primary end point because they were mainly designed as safety and feasibility studies (8,9). One trial investigated reduction in infarct size as a primary end point and a change in LVEF as a secondary end point (10). The STEMMI trial measured the change in systolic wall thickening as the primary end point (11).

Moreover, trials used varying imaging modalities to measure LVEF (Table 1). The LVEF was measured by magnetic resonance imaging in 3 trials (10–12), by echocardiography in 3 trials (9,13,15), by single-photon emission computed tomography in 3 trials (8,14,16), and by left ventriculography in the trial by Suarez de Lezo et al. (17).

Reperfusion treatment and time of reperfusion differed between the trials (Table 1). In most trials except for the trial by Valgimigli et al. (8) and the Rigenera trial (15), patients had successful mechanical reperfusion after AMI. In the study by Valgimigli et al. (8), only 14 (i.e., those presenting during the acute phase of MI) of 20 patients underwent primary PCI. Likewise, in the Rigenera trial 29% of patients in the G-CSF compared with 44% in the control group were treated by primary PCI (15).

Table 2 G-CSF Therapy

Trial	G-CSF Dosage (μg/kg/day)	Duration of G-CSF Administration (day)	Number of Cells/μl (CD34$^+$)	
			G-CSF	Control
Valgimigli et al. (8)	5	4	28 ± 8	7 ± 2
FIRSTLINE-AMI (9)	10	5	65 ± 37	4 ± 2
REVIVAL-2 (10)	10	5	72 ± 154	5 ± 6
STEMMI (11)	10	6	55 ± 53	4 ± 2
G-CSF-STEMI (12)	10	5	46 ± 33	2 ± 1
Ellis et al. (13) (5 μg G-CSF)	5	5	37 ± 30	7 ± 7
Ellis et al. (13) (10 μg G-CSF)	10	5	29 ± 14	7 ± 7
Takano et al. (14)	2.5	5	15 ± 19	2 ± 1
Rigenera (15)	10	5	50 ± 35	2 ± 2
MAGIC Cell 1 (16)	10	4	—	—
Suarez de Lezo et al. (17)	10	10	88 ± 79	—

CD34 = cluster of differentiation 34; other abbreviations as in Table 1.

Time from onset of symptoms to PCI also varied among the studies (Table 3). In the G-CSF-STEMI trial investigating the effect of G-CSF after subacute MI undergoing late revascularization, the time from symptom onset to PCI was 32 ± 45 h in the G-CSF and 51 ± 53 h in the control group (12). In the FIRSTLINE-AMI trial, time from symptom onset to PCI was within 5 h in both groups (9).

Likewise, the mean time from PCI to G-CSF administration differed considerably among the trials (Table 3). Whereas in the FIRSTLINE-AMI trial, G-CSF treatment started very early within 89 ± 35 min after successful PCI (9), in the REVIVAL-2 trial (10) and in the MAGIC Cell 1 trial (16), G-CSF was given as late as 5 days after PCI.

Patients were frequently treated with aspirin, clopidogrel, beta-blockers, statins, and angiotensin-converting enzyme inhibitors as standard optimal medical heart failure treatment. Only in the trials by Ellis et al. (13) and Takano et al. (14) were patients not frequently treated with beta-blockers, whereas in the STEMMI trial only 40% to 50% of patients were treated with angiotensin-converting enzyme inhibitors. Diuretics, including an aldosterone antagonist, were not given frequently.

Effect of G-CSF treatment on LV recovery. Compared with control conventional treatment, stem cell mobilization by G-CSF had a beneficial effect on neither LV function nor infarct size. As expected, in both groups LVEF increased during the follow-up period (Table 3). In only 1 trial, the FIRSTLINE-AMI, LV function significantly deteriorated in the control group, whereas it improved in the treatment group (9).

The weighted mean difference of improvement of LVEF between the treatment and control groups was 1.32% (95% CI −1.52 to 4.16, p = 0.36) (Fig. 1). There was considerable heterogeneity between the trials (p < 0.001 from the chi-square test, I^2 = 71.4%). The sensitivity analysis showed that omission of the study of Ince et al. (9) had a more pronounced effect on the pooled result compared with other studies (WMD 0.17%, 95% CI −1.82 to 2.17). Choosing to omit this study from the analysis was associated with a dramatic reduction of heterogeneity of the meta-analysis (p = 0.14 from chi-square test, I^2 = 34.4%). Metaregression indicated that $CD34^+$ cell count, number of study patients, duration of study follow-up, method used to measure LVEF, lack of double blinding, and change of LV function in the control group had no effect on the pooled result. The Begg adjusted rank correlation test showed no evidence of significant bias (p = 0.53), whereas the Egger test was marginally significant (p = 0.044).

The weighted mean difference of LVEF at the end of the follow-up period between the treatment and control groups was 2.04% (95% CI −1.59 to 5.66, p = 0.27) (Fig. 2). There was considerable heterogeneity between the trials (p < 0.001 from the chi-square test, I^2 = 72.5%). The sensitivity analysis showed that omission of the study of Ince et al. (9) had a more pronounced effect on the pooled result compared with other studies (WMD 0.93%; 95% CI −1.57

Table 3 Change in EF From Baseline to Follow-Up

	EF Baseline		EF Follow-Up		ΔEF		Time (h) From AMI to PCI		Time (h) From PCI to G-CSF		Time (h) From AMI to G-CSF	
	G-CSF	Control	G-CSF	Control	G-CSF	Control	G-CSF	Control	G-CSF	Control	G-CSF	Control
Valgimigli et al. (8)	41 ± 10	42 ± 7	50 ± 15	48 ± 9	9 ± 5	6 ± 3	<12	<12	37 ± 66	—	—	—
FIRSTLINE-AMI (9)	48 ± 4	47 ± 5	54 ± 8	43 ± 5	6 ± 9	−4 ± 7	5 ± 2	5 ± 2	1 ± 1	—	—	—
REVIVAL-2 (10)	51 ± 8	49 ± 9	52 ± 8	51 ± 9	1 ± 4	2 ± 5	<12	<12	114 ± 31	114 ± 27	—	—
STEMMI (11)	51 ± 15	55 ± 11	60 ± 12	62 ± 12	9 ± 11	8 ± 10	4	4	30	28	—	—
G-CSF-STEMI (12)	41 ± 12	44 ± 9	47 ± 12	50 ± 12	6 ± 9	5 ± 10	32 ± 45	51 ± 53	31 ± 24	39 ± 28	—	—
Ellis et al. (13) (5 μg G-CSF)	37 ± 8	33 ± 2	41 ± 10	42 ± 8	5 ± 11	8 ± 10	6 ± 4	15 ± 18	—	—	38 ± 8	42 ± 11
Ellis et al. (13) (10 μg G-CSF)	34 ± 5	34 ± 2	39 ± 7	42 ± 8	5 ± 7	8 ± 10	12 ± 17	15 ± 18	—	—	41 ± 6	42 ± 11
Takano et al. (14)	47 ± 11	46 ± 10	52 ± 11	49 ± 14	5	3	7 ± 6	5 ± 3	<24	<24	<21	<21
Rigenera (15)	40 ± 6	38 ± 6	45 ± 6	38 ± 8	5 ± 9	0 ± 6	—	—	≥120	—	—	—
MAGIC-CELL 1 (16)	53 ± 14	44 ± 9	53 ± 13	51 ± 9	0	8 ± 7	—	—	—	—	—	—
Suarez de Lezo et al. (17)	37 ± 5	39 ± 6	42 ± 14	45 ± 8	4 ± 13	6 ± 10	—	—	—	—	<120	—

AMI = acute myocardial infarction; EF = ejection fraction; other abbreviations as in Table 1.

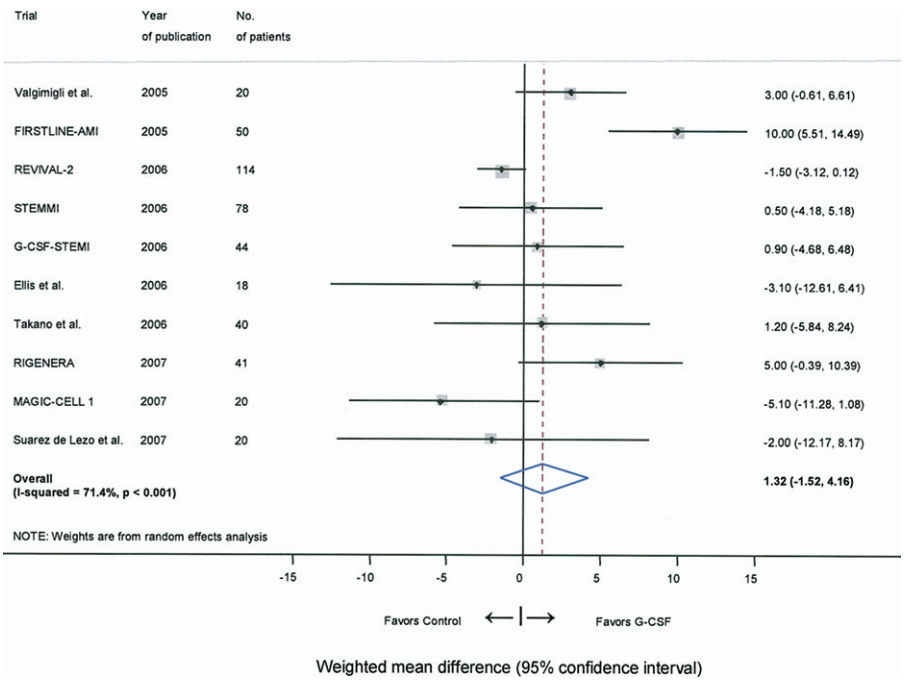

Figure 1 **The Effect of Stem Cell Mobilization by G-CSF on Change of Left Ventricular Ejection Fraction**

Compared with control conventional treatment, stem cell mobilization by G-CSF had no additional beneficial effect on change in left ventricular function at follow-up as shown by the weighted mean difference for change in left ventricular ejection fraction between treatment and control groups in individual trials. FIRSTLINE-AMI = Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction trial; G-CSF = granulocyte colony-stimulating factor; G-CSF-STEMI = Granulocyte Colony-Stimulating Factor ST-Segment Elevation Myocardial Infarction trial; MAGIC Cell 1 = Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion 1 trial; REVIVAL-2 = Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells trial; STEMMI = Stem Cells in Myocardial Infarction trial.

to 3.44). Choosing to omit this study from the analysis was associated with a dramatic reduction of heterogeneity of the meta-analysis ($p = 0.19$ from chi-square test, $I^2 = 28.2\%$).

Information about infarct size at the end of the follow-up period was available for 6 trials. The standardized mean difference of reduction of infarct size between the treatment and control groups was −0.15 (95% CI −0.38 to 0.07, $p = 0.17$). There was no evidence of heterogeneity between the trials ($p = 0.58$ from chi-square test, $I^2 = 0.0\%$).

Clinical outcome after G-CSF treatment. Data on angiographic restenosis were available in 9 trials (8–12,14–17), whereas data on target vessel revascularization were available in 7 trials (8,10–12,15–17). In this meta-analysis, the restenosis rate as well as the rate of target vessel revascularization did not significantly differ between the G-CSF and the control groups (Figs. 3 and 4). The overall adverse event rate was low in all trials analyzed. Adverse events of all trials have been summarized in Table 4. Altogether, 5 patients died: 3 in the G-CSF group and 2 in the control group. In the G-CSF group, 1 patient died of ventricular fibrillation 12 days after enrollment (10), and for 2 patients who died, the cause of death was unclear because an autopsy was not performed (12,14). In the control population, 1 patient progressed to cardiogenic shock and died 2 days after PCI (11), and 1 patient died of chronic heart failure after 13 months (13).

Discussion

The main findings of this meta-analysis suggest that stem cell mobilization by G-CSF is safe and feasible but neither improves LV function nor reduces infarct size in patients with AMI after reperfusion.

There was a significant heterogeneity across trials regarding treatment effect size. Limited sample size of available trials, differences in the nature of randomization (double blind or open label), and variation in the methods used for measurement of LVEF and in the timing of both reperfusion and application of G-CSF therapy might have well contributed to this heterogeneity, although our metaregression analysis could not discern any factor significantly associated with treatment effect size. However, sensitivity analysis showed that the study by Ince et al. (9) had a more pronounced effect on the pooled result compared with other studies and that omitting this study from the analysis was associated with a dramatic reduction of heterogeneity of the meta-analysis. The FIRSTLINE-AMI trial, which included 50 patients in the 6-month follow-up and 30 patients in the 1-year follow-up, was a phase-1 randomized but open-label trial of G-CSF treatment initiated within

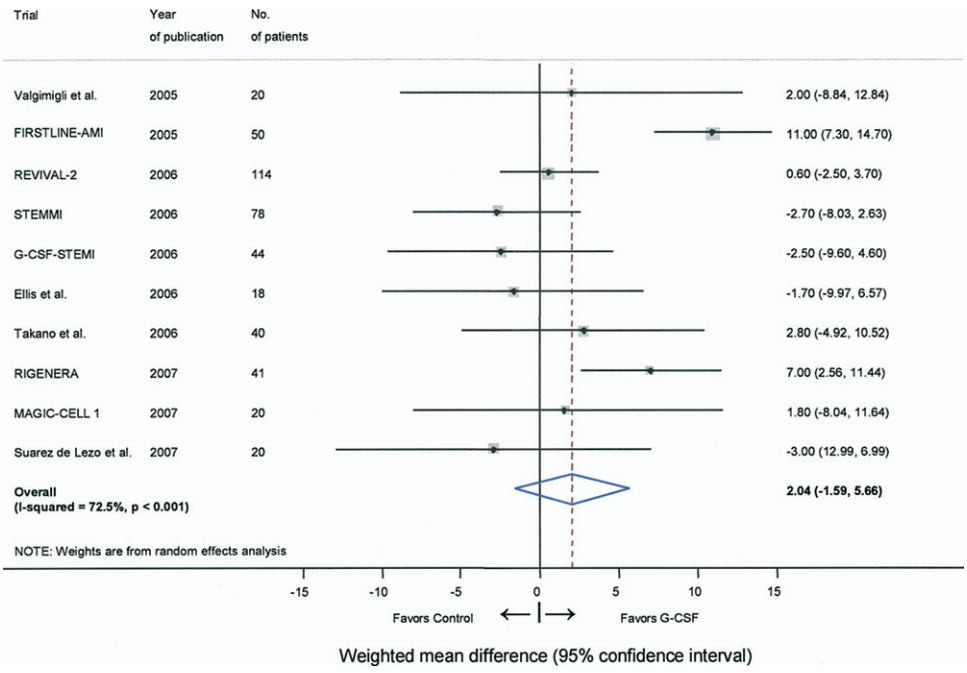

Figure 2 **The Effect of G-CSF on Left Ventricular Ejection Fraction at Follow-Up**

Compared with control groups, G-CSF had no beneficial effect on left ventricular function at follow-up as shown by the weighted mean difference of left ventricular ejection fraction at follow-up between treatment and control groups. Abbreviations as in Figure 1.

90 min after primary PCI in patients with AMI. In this trial, the G-CSF–treated patients had a significant improvement in LV function resulting in an improvement in ejection fraction. In contrast, the control group had a decrease in ejection fraction after 6-month and 12-month follow-up (9).

The main difference between the FIRSTLINE-AMI trial and the rest of the studies included in the meta-analysis

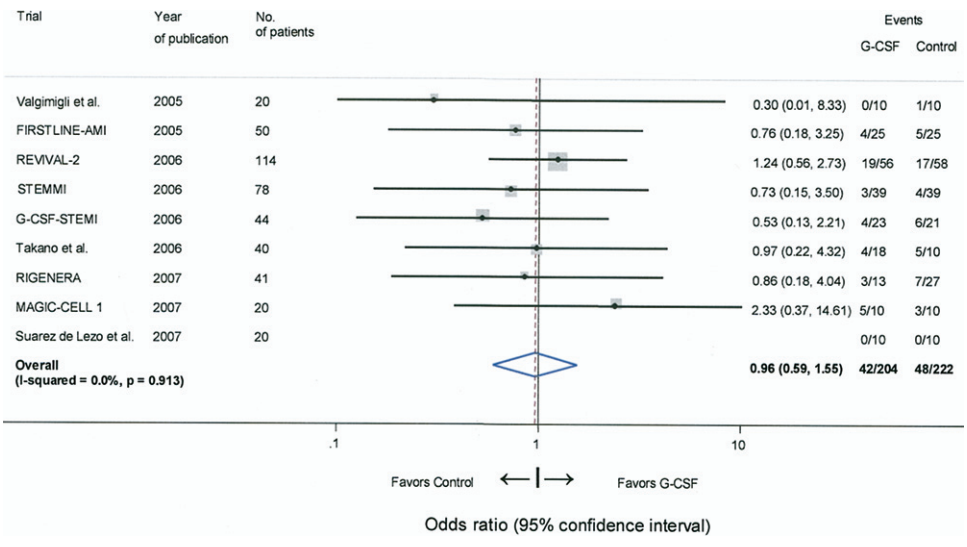

Figure 3 **The Effect of Stem Cell Mobilization on Angiographic Restenosis**

Stem cell mobilization by G-CSF had no effect on angiographic restenosis rate as shown by the odds ratios for angiographically assessed binary restenosis. Abbreviations as in Figure 1.

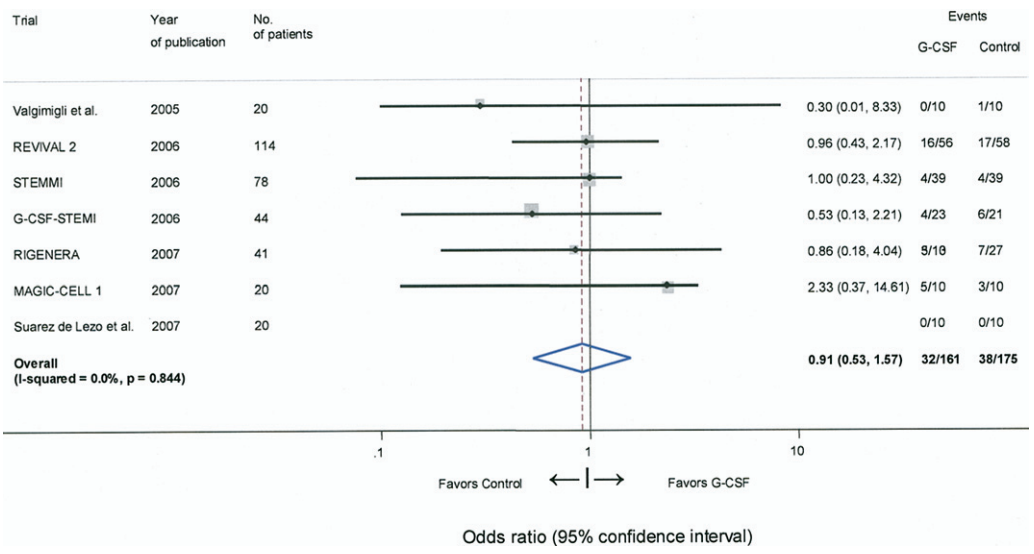

Figure 4 The Effect of G-CSF on Target Vessel Revascularization

The G-CSF therapy had no effect on target vessel revascularization as shown by the odds ratios for target vessel revascularization. Abbreviations as in Figure 1.

was seen in the control group. It has been shown recently that patients with AMI show an improvement in LV function and a reduction in infarct size within 6 months after coronary reperfusion (23). Accordingly, in the REVIVAL-2 study (10), the STEMMI study (11), the G-CSF-STEMI study (12), the MAGIC CELL 1 study (16), and the Rigenera trial (15), as well as in the trials by Valgimigli et al. (8), Ellis et al. (13), and Takano et al. (14), patients in the control group showed a comparable improvement in cardiac function compared with the G-CSF–treated groups. However, the hitherto largest trial supporting a beneficial effect of G-CSF after AMI, the FIRSTLINE-AMI trial, showed a significant improvement in LV function in the G-CSF group compared with the control group (9). It is noteworthy that the positive effect of the G-CSF treatment was rather attributable to an unexpected worsening of the LV function in the control group during follow-up compared with the G-CSF group (9).

The negative finding of our meta-analysis regarding the effect of G-CSF treatment on ventricular recovery after AMI could be explained by several factors. Mobilized stem cells might not have homed to the infarcted myocardium because of an unfavorable milieu at the time of stem cell mobilization. In patients with AMI, $CD34^+$ stem cell mobilization occurs naturally, peaking after 1 week (24,25). Moreover, the plasma level of the stem cell homing factor SDF-1 is up-regulated significantly from day 3 to day 28 after AMI (26,27), indicating that the milieu of the injured myocardium favors stem cell recruitment at this stage after AMI (26). Therefore, timing of cell therapy after reperfusion may well affect treatment efficacy because the myocardial milieu is likely to be more receptive at certain time

Table 4 Safety Characteristics of the Trials

	Binary Restenosis (%)		TVR (%)		Death and Recurrent MI (No. of Patients)		Death (No. of Patients)	
Trial	G-CSF	Control	G-CSF	Control	G-CSF	Control	G-CSF	Control
Valgimigli et al. (8)	0	10	0	10	0	1	0	0
FIRSTLINE-AMI (9)	16	20	—	—	—	—	—	—
REVIVAL-2 (10)	35	31	29	31	1	1	1	0
STEMMI (11)	10	13	10	10	0	1	0	1
G-CSF-STEMI (12)	21	29	21	29	2	2	1	0
Ellis et al. (13)	—	—	—	—	1	1	0	1
Takano et al. (14)	25	26	—	—	1	0	1	0
Rigenera (15)	21	26	21	26	0	0	0	0
MAGIC Cell 1 (16)	50	30	50	30	0	0	0	0
Suarez de Lezo et al. (17)	0	0	0	0	0	0	0	0

MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Table 1.

points. Although we did not see an effect of the timing of G-CSF treatment on LV recovery in our multivariate analysis, we cannot rule out that the milieu of the infarcted myocardium did not allow significant recruitment of stem cells at the time point of stem cell mobilization in the trials analyzed.

The functional activity of G-CSF–mobilized stem cells might have been compromised because of release of immature stem cells with limited capacity of homing to ischemic myocardium due to cleavage of the functional active CXCR4 surface receptor on G-CSF mobilized stem cells (28–30).

Study limitations. We cannot rule out that G-CSF itself does have a negative impact on cardiac regeneration after AMI, although treatment with G-CSF has inhibited apoptosis and improved survival of cardiomyocytes at a higher dose in mice after AMI (31). On the contrary, experimental studies in mice and early-phase clinical trials in patients with coronary artery disease suggest that G-CSF may promote atherosclerosis with the potential of adverse outcomes in these patients (32,33). However, the overall rate of major adverse cardiac events was very low in our meta-analysis and did not differ among patients treated with G-CSF and control. Therefore, our data are not in support of a harmful effect of G-CSF in patients with AMI.

In the trials included, CSF effectively mobilized $CD34^+$ bone marrow-derived stem cells into the circulation in a dose-dependent manner (Table 4). However, these $CD34^+$ cells do not completely fulfill the criteria of pluripotent stem cells with the potential to differentiate into all 3 germ layers. In fact, these bone marrow-derived $CD34^+$ cells rather correspond to multipotent hematopoietic and endothelial progenitor cells (1,28). Therefore, the $CD34^+$ cell count in the peripheral blood may not reliably reflect the number of available multipotent cells. This may explain the lack of impact of $CD34^+$ cell count on the treatment effect in our metaregression analysis.

Conclusions

This meta-analysis shows that G-CSF therapy to mobilize bone marrow–derived stem cells was feasible and safe, but on a cumulative basis it failed to improve LV recovery in patients with AMI after reperfusion.

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