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G-CSF THERAPY FOR CARDIAC REPAIR AFTER ACUTE MYOCARDIAL INFARCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

BACKGROUND—Small clinical studies of granulocyte colony stimulating factor (G-CSF) therapy for cardiac repair after acute myocardial infarction (MI) have yielded divergent results. The effect of G-CSF therapy on left ventricular (LV) function and structure in these patients remains unclear.

METHODS—We searched MEDLINE, EMBASE, Science Citation Index, CINAHL, and the Cochrane CENTRAL database of controlled clinical trials (July 2007) for randomized controlled trials of G-CSF therapy in patients with acute MI. We conducted a fixed-effects meta-analysis across 8 eligible studies (n=385 patients).

RESULTS—Compared with controls, G-CSF therapy increased LV ejection fraction (EF) by 1.09%, increased LV scar size by 0.22%, decreased LVEDV by 4.26 ml, and decreased LVESV by 2.50 ml. None of these effects was statistically significant. The risk of death, recurrent MI, and in-stent restenosis was similar in G-CSF-treated patients and controls. Subgroup analysis revealed a modest but statistically significant increase in EF (4.73%, $P<0.0001$) with G-CSF therapy in studies that enrolled patients with mean EF <50% at baseline. Subgroup analysis also showed a significant increase in EF (4.65%, $P<0.0001$) when G-CSF was administered relatively early (≤ 37 hours) after the acute event.

CONCLUSIONS—G-CSF therapy in unselected patients with acute MI appears safe but does not provide an overall benefit. Subgroup analyses suggest that G-CSF therapy may be salutary in acute MI patients with LV dysfunction and when started early. Larger randomized studies may be conducted to evaluate the potential benefits of early G-CSF therapy in acute MI patients with LV dysfunction.

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Keywords

meta-analysis; G-CSF; cytokine; acute myocardial infarction; cardiac repair

INTRODUCTION

Recent evidence from small clinical trials indicates that therapy with bone marrow cells (BMCs) affords modest benefits in patients with acute myocardial infarction (MI)¹. Because of promising results from animal studies^{2–6}, and because BMC mobilization using G-CSF obviates bone marrow aspiration and repeated cardiac catheterization, the feasibility, safety, and efficacy of granulocyte colony-stimulating factor (G-CSF) therapy for cardiac repair in humans are being actively investigated. However, the small clinical trials completed thus far have yielded disparate results, and the impact of G-CSF therapy in patients with acute MI remains unclear. To our knowledge, there are no comprehensive analyses of these data. Therefore, we performed a meta-analysis of the results of the randomized controlled trials (RCTs) investigating the potential therapeutic benefits of G-CSF therapy for cardiac repair in patients with acute MI.

METHODS

A detailed description of Methods is provided in the online supplement.

Study Selection and Data Collection

The review question was: To what extent does therapy with G-CSF affect cardiovascular outcomes in patients with acute MI? This protocol-driven meta-analysis was performed according to the Quality of Reporting of Meta-analysis (QUOROM)⁷ statement.

The complete search strategy is available upon request from the authors. We searched MEDLINE, the Cochrane databases, EMBASE, CINAHL, the US FDA Web site (<http://www.fda.gov>) and BIOSIS Previews (all until July 2007) using database-appropriate terms. One reviewer (A.A.L.) judged eligibility of studies. Because of the fundamentally different approach, we excluded studies that injected G-CSF-mobilized BMCs via the intracoronary route. We also identified 2 RCTs^{8,9} that included patients with chronic ischemic cardiomyopathy (ICM). Given the major differences in cardiac milieu between acute MI and chronic ICM, which may profoundly influence homing of stem/progenitor cells, we performed separate meta-analyses of RCTs without (Table 1) as well as with (supplemental Table 1) patients with ICM. Thus, the primary meta-analysis examining the effects of G-CSF therapy on cardiovascular outcomes in patients with acute MI alone was limited to 8 eligible RCTs. Two reviewers (A.A.L. and B.D.) working in duplicate and independently used a standardized form to abstract data from each study. When data were available from more than one follow-up time points^{10, 11}, the longest follow-up data were used. We used the criteria of Juni *et al.*¹² to ascertain the methodological quality of included RCTs¹². The authors' statements regarding blinding and other methods in the original manuscripts were accepted verbatim. In addition, we applied the Jadad scale¹³ for quantifying the study quality.

Data Analysis

Meta-analyses—The main outcomes of our analyses were change from baseline in mean LV ejection fraction (LVEF), infarct scar size, LVEDV, LVESV, and the relative risk (RR) for adverse events, including death, recurrent MI, and in-stent restenosis. We conducted meta-analyses using both 'fixed-effects' and 'random-effects' models, and the results were similar

with respect to the major outcomes. Since we excluded studies that included chronic ICM patients, we felt that the use of the fixed-effects model was justified.

For data regarding clinical outcome variables, the effect measures estimated were the RR for dichotomous data, which we report with 95% CI. The RR indicates the risk of death, recurrent MI, or in-stent restenosis in an individual receiving G-CSF compared with the respective risk in an individual not receiving G-CSF. We also calculated the absolute risk reduction (ARR), i.e. risk difference (RD), and the 'numbers needed to harm' (NNH) to assess the clinical significance of the outcome. The RRs from separate studies were combined according to a fixed-effects model (Mantel-Haenszel method^{14, 15}).

The Review Manager software (RevMan version 4.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2006) was used for all of the analyses. The proportion of between-study inconsistency due to true differences between studies (rather than differences due to random error or chance) was estimated by the I^2 statistic¹⁶. Funnel plots were used to explore any publication bias.

Stratified Analyses—We conducted planned subgroup analyses and examined potential treatment-subgroup interactions. Planned subgroups comprised the mean LVEF at baseline (using LVEF of 50% as cut-off^{17, 18}), the average time between the acute event (acute MI or PCI) and the first dose of G-CSF (using the median initiation time of 37 hours as cut-off), the dose of G-CSF (using the median of 10 µg/kg/day as cut-off), and the peak white blood cell (WBC) and CD34+ cell counts as indicators of BMC mobilization efficacy with G-CSF therapy.

RESULTS

Of the 112 articles retrieved during the initial search (Figure 1), 29 were not reports of original investigations (reviews and editorials), 41 were conducted in animals, 4 were cohort studies, 7 injected mobilized BMCs, 4 lacked a control group, 6 used G-CSF for indications other than treatment of AMI, 3 did not report the end-points, 2 included ICM patients, and 8 were performed *in vitro* or without transplantation. Eight RCTs^{10, 19–25} with a total of 385 patients were eligible for review.

Table 1 summarizes the characteristics of all studies included in our meta-analysis. Notably, the sample size in each study was relatively small (range 18–114 patients; median 40 patients), and the follow-up duration was relatively short (range 1–12 months; median 6 months). Although the majority of studies used 10 µg/kg/day of G-CSF for 5–6 days, a few studies used as low as 2.5 µg/kg/day (median 10 µg/kg/day for 5 days). Consequently, the peak WBC count varied from 29.4×10^3 to 55.0×10^3 WBCs/µl of blood (median 42.0×10^3 WBCs/µl). The time of initiation of G-CSF therapy also varied from 1.4 hours to 120 hours after acute MI (median 37 hours).

Study Quality

Table 2 describes the methodological quality of the included studies. At least 4 of the included studies failed to blind the participants and caregivers to study allocation. Importantly, in all studies the outcome ascertainment was performed in a blinded fashion. The inter-reviewer agreement on these quality domains was greater than 90%.

Meta-analyses

Efficacy—Compared with controls, in G-CSF-treated patients the LVEF increased by 1.09% (CI: -0.21 to 2.38; $P=0.10$; Figure 2), infarct size increased by 0.22% (CI: -1.34 to 1.78;

$P=0.78$; Figure 3), LVEDV decreased by 4.26 ml (CI: -9.73 to 1.21 ; $P=0.13$; Figure 4), and LVESV decreased by 2.50 ml (CI: -7.81 to 2.81 ; $P=0.36$; Figure 5). Thus, G-CSF therapy failed to significantly improve any of the primary surrogate end-points.

Since the variability in G-CSF dosage might have influenced the outcomes of our analysis, in a separate meta-analysis we examined the pooled outcomes of studies that used a uniform G-CSF dose of 10 $\mu\text{g/kg/day}$. However, the outcomes (supplemental Figures 1–5) were similar to those derived from the analysis that included all G-CSF dosages. Furthermore, when data from all studies (a total of 10 RCTs, including patients with acute MI as well as chronic ICM [451 patients]) were analyzed using a random-effects model, the outcomes did not differ from those obtained with an analysis restricted to acute MI patients alone (supplemental Figures 6–10). We drew funnel plots (supplemental Figure 11) to seek evidence of publication bias; where inconsistency was high, the funnel plots were not interpretable; where inconsistency was low, the funnel plots were inconclusive.

Stratified Analysis—A statistically significant and clinically relevant improvement in LVEF (mean increase of 4.73% [CI: 2.67 to 6.79; $P<0.0001$]) was noted in G-CSF-treated patients in studies that included patients with mean LVEF of $<50\%$ at baseline (Table 3 and Figure 6). Significant improvements were observed in other surrogate parameters, including LVEDV (mean decrease by 7.82 ml [CI: -14.68 to -0.96 ; $P<0.03$]) and LVESV (mean decrease by 10.07 ml [CI: -18.88 to -1.26 ; $P<0.04$]) (Table 3). On the other hand, G-CSF therapy failed to halt the deterioration in LVEF as well as other functional parameters when given to patients with normal LVEF ($>50\%$) at baseline (Table 3 and Figure 6). The treatment-subgroup interaction was also statistically significant ($P<0.0001$; Table 3). In addition, we observed a statistically significant and clinically relevant improvement in LVEF (mean increase of 4.65% [CI: 2.51 to 6.80; $P<0.0001$]) in G-CSF-treated patients when G-CSF therapy was started early after acute MI or PCI (≤ 37 hours) as compared with later initiation (Table 3 and Figure 7). The treatment-subgroup interaction was also statistically significant ($P<0.0001$; Table 3). However, in four studies^{10, 21, 23, 24} that included patients with low LVEF and in three studies^{10, 23, 24} in which G-CSF therapy was started early after the acute event, the patients and/or the caregivers were apparently not blinded (Table 2). Therefore, despite the large observed benefits, we cannot entirely exclude the role of performance bias influencing the results.

Safety—No significant differences in the incidence of death (RR 1.08; CI: 0.34 to 3.43) or recurrent MI (RR 1.49; CI: 0.36 to 6.12) between G-CSF-treated patients and controls were observed (Figure 8). The crude rate of in-stent restenosis was also not different between the 2 groups (23% in both G-CSF-treated and placebo groups). The pooled analysis of 328 patients demonstrated no difference in the in-stent restenosis risk (RR 0.92; CI: 0.62 to 1.37).

DISCUSSION

Despite the completion of several relatively small clinical trials, the effect of G-CSF therapy on cardiac repair remains controversial. The overall results of our meta-analysis indicate that administration of G-CSF in unselected patients with acute MI fails to improve any of the clinically relevant primary end-points examined. The observed differences achieved neither statistical nor clinical significance. Although the results of subgroup analysis should be interpreted with caution, they suggest that G-CSF may be potentially beneficial in patients with lower LVEF ($<50\%$) at baseline and if given earlier (≤ 37 hours) after acute MI/PCI. Importantly, the pooled estimates of potential side effects demonstrate that G-CSF therapy is relatively safe. The results presented herein may be useful for the design of future clinical trials of G-CSF therapy for cardiac repair.

The overall outcome showing no beneficial effect of G-CSF therapy in unselected patients with acute MI is somewhat incongruent with the modest salutary effects of BMC transplantation in humans¹. In animal models, G-CSF or combinatorial cytokine therapies have been found to result in myocardial homing of mobilized BMCs, repair of the infarcted myocardium, and improvement in LV structural and functional parameters as well as survival^{2–6}. The homing of c-kit positive cells in the myocardium was found to be increased when G-CSF was combined with stromal derived factor-1 (SDF-1)²⁶, emphasizing the well-known role of the SDF-1/CXCR4 axis in homing of pluripotent cells. The addition of stem cell factor or Flt-3 ligand to G-CSF therapy also resulted in improved outcomes⁶. Although G-CSF therapy effectively mobilizes BMCs, it is plausible that the lack of benefit in the clinical trials may be due, at least in part, to myocardial homing of relatively small number of stem/progenitor cells. Indeed, it has been reported that the expression of surface markers responsible for homing on mobilized cells varies depending on the cytokine regimen⁶. Moreover, different cytokines are known to preferentially mobilize somewhat different subsets of BMCs^{27, 28}. Future studies investigating the characteristics of G-CSF-mobilized cells will be necessary to glean additional mechanistic insights in this regard.

The variable dose/duration (2.5 to 10 µg/kg/day) of G-CSF therapy and the consequent variability in CD34+ cell count (15±19 to 72±154 cells/µl) and the peak WBC count (29.4 ±9×10³ to 55±8×10³ cells/µl, Table 1) might also have influenced the overall results. In a dose escalating study, Ellis *et al.*¹⁹ did not observe differences between the effects of low and high dose G-CSF therapy. Also, Takano *et al.*²³ did not find a correlation between the peak CD34+ cell count and improvement in LVEF after G-CSF therapy. However, in an observational non-blinded study, a correlation between the spontaneously mobilized CD34+ cell count and the improvement in regional as well as global LV function after acute MI was noted²⁹. When we separately analyzed data from RCTs that used a uniform G-CSF dose of 10 µg/kg/day (supplemental Figures 1–5), the outcomes were similar to those from the analysis that included all G-CSF dosages. Consistent with these observations, in subgroup analyses, we did not observe any correlation between the G-CSF dose or the peak WBC/CD34+ cell counts and the change in any of the examined parameters.

The lack of overall efficacy of G-CSF therapy might also have resulted from the differences in methodology and patient characteristics in these trials. In the study by Kang *et al.*⁸, the authors found an initial correlation between the baseline LVEF and subsequent improvement with G-CSF therapy at 6 and 12 month follow-up. After correction for the variable baseline data, this continued to be the only independent correlation. It is quite conceivable that G-CSF therapy will fail to improve an LVEF that is already normal or near-normal (>50%). Indeed, in the subgroup analysis based on baseline LVEF (using a cut-off of 50%), we found that G-CSF therapy improved LVEF in studies of patients with worse LV function (mean LVEF <50%) (Table 3 and Figure 6). The interaction between baseline LVEF and subsequent improvement with G-CSF therapy was statistically significant. These observations are consonant with the results obtained with BMC transplantation in the REPAIR-AMI study³⁰. However, since these are *post hoc* analyses of published data rather than individual patient data, and since the influence of performance bias on the interaction cannot be entirely excluded, larger double-blind RCTs specifically designed to address this question will be necessary.

We also observed a statistically significant and clinically relevant improvement in LVEF in treated patients when G-CSF administration was initiated early (≤37 hours after the acute event) (Table 3 and Figure 7). The subgroup-treatment interaction was also statistically significant. However, these results could also be biased by the apparent lack of blinding the patients/caregivers in three of the included studies. In animal studies, the beneficial effects of G-CSF were observed when therapy was started before² or shortly after^{3, 6} ischemic injury, and early initiation of G-CSF therapy resulted in better outcomes⁵. Myocardial expression of

chemoattractants, such as SDF-1, LIF, and HGF, peaks at 24–72 hours after acute MI^{31–33}. Therefore, greater myocardial homing of mobilized BMCs would be expected when the peak BMC mobilization coincides temporally with the peak expression of myocardial homing factors. However, since G-CSF therapy also upregulates Akt³⁴, resulting in a significant reduction in apoptosis, and activates the myocardial JAK/STAT pathway⁵, the overall effects of G-CSF therapy may depend not only on the mobilization of BMCs but also on the influence of these signaling events in the infarcted myocardium. The optimal timing of G-CSF therapy remains to be determined in future basic as well as clinical studies.

An increased albeit statistically insignificant risk of in-stent restenosis has been reported with G-CSF therapy⁸. In contrast, G-CSF therapy was not associated with increased in-stent restenosis in 41 patients in the STEMMI trial²², which carefully evaluated neo-intimal hyperplasia at 5 months using angiography and intravascular ultrasound³⁵. Furthermore, an individual patient-data meta-analysis of the adverse effects of G-CSF in the setting of acute MI including 106 patients showed no increased risk of in-stent restenosis, reduction in minimal luminal diameter, stent thrombosis, or reinfarction³⁶. Importantly, the development of in-stent restenosis is influenced by multiple factors, such as the patient population, lesion type, and technical competency. When we analyzed the reported risk of in-stent restenosis across the included studies, totaling 284 patients, we found no difference in in-stent restenosis risk between the treatment and the placebo/control arms. Moreover, the incidence of in-stent restenosis in this setting decreases considerably after a few months. In our meta-analysis, none of the included studies reported an increased incidence of serious side-effects beyond minor systemic side-effects, such as bone ache and malaise. However, the risk of side-effects associated with G-CSF therapy needs to be evaluated during longer follow-up periods.

Limitations

Although the total number of patients in the meta-analysis is relatively small, our analysis effectively summarizes the available data, reaches valid conclusions regarding the efficacy of G-CSF therapy, and provides important insights. Despite the significant interaction between baseline LVEF and timing of therapy with the observed benefits, we cannot entirely exclude the role of performance bias in influencing the results. Also, since our meta-analysis was based on published data rather than individual patient data, in subgroup analyses, the ability to precisely identify the best time to initiate G-CSF therapy and the LVEF cut-off was limited. Finally, the duration of the follow-up in the studies included in this meta-analysis was relatively short.

Conclusions

The results of this meta-analysis suggest that G-CSF therapy does not improve LV function and structure in unselected patients with acute MI. However, G-CSF may potentially benefit acute MI patients with impaired baseline LVEF and when therapy is initiated early. G-CSF therapy appears to be safe. The results presented herein may be useful for the design of future clinical trials of G-CSF therapy for cardiac repair.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Selection of trials for inclusion in meta-analysis

Figure 1. Selection of trials for inclusion in meta-analysis. mPBCs, mobilized peripheral blood cells; RCT, randomized controlled trial.

Outcome: Mean change in LVEF **Figure 2.**

Mean change in LVEF. Forest plot of unadjusted difference in mean (with 95% CIs): G-CSF therapy resulted in a 1.09% (95% CI: -0.21 to 2.38; $P=0.10$) increase in mean LVEF. The imaging modality is specified within parentheses. FU, follow-up; WMD, weighted mean difference.

Outcome: Mean change in infarct scar Size **Figure 3.**

Mean change in infarct scar Size. Forest plot of unadjusted difference in mean (with 95% CIs): G-CSF therapy resulted in a 0.22% (95% CI: -1.34 to 1.78; $P=0.78$) increase in mean infarct scar size. The imaging modality is specified within parentheses. WMD, weighted mean difference.

Outcome: Mean change in LVEDV **Figure 4.**

Mean change in LVEDV. Forest plot of unadjusted difference in mean (with 95% CIs): G-CSF therapy resulted in a 4.26 ml (95% CI: -9.73 to 1.21; $P=0.13$) reduction in mean LVEDV. The imaging modality is specified within parentheses. FU, follow-up; WMD, weighted mean difference.

Outcome: Mean change in LVESV **Figure 5.**

Mean change in LVESV. Forest plot of unadjusted difference in mean (with 95% CIs): G-CSF therapy resulted in a 2.50 ml (CI: -7.81 to 2.81; $P=0.36$) reduction in LVESV. The imaging modality is specified within parentheses. WMD, weighted mean difference.

Outcome: Mean change in LVEF according to baseline LVEF

Mean LVEF < 50% at baseline

P for interaction <0.0001

Mean LVEF $\geq$ 50% at baseline

Figure 6.

Mean change in LVEF according to baseline LVEF. Forest plots of unadjusted difference in mean (with 95% CIs) change in LVEF in G-CSF-treated patients compared with controls stratified by the mean LVEF in G-CSF-treated groups at baseline. The interaction between the baseline LVEF and the change in LVEF was also statistically significant ($P < 0.0001$). FU, follow-up; WMD, weighted mean difference.

Outcome: Mean change in LVEF according to onset of G-CSF therapy

G-CSF therapy initiated ≤ 37 hours after acute MI/PCI

G-CSF therapy initiated > 37 hours after acute MI/PCI

Figure 7.

Mean change in LVEF according to onset of G-CSF therapy. Forest plots of unadjusted difference in mean (with 95% CIs) change in LVEF in G-CSF-treated patients compared with controls stratified by the timing of G-CSF therapy. The interaction between the timing of G-CSF therapy and the change in LVEF was also statistically significant ($P < 0.0001$). FU, follow-up; WMD, weighted mean difference.

Outcome: Relative risk of adverse clinical outcomes

Figure 8. Relative risk of adverse clinical outcomes. Forest plot of unadjusted risk ratio (RR, with 95% CIs) for major reported adverse effects, namely, death, recurrent MI, and in-stent restenosis in G-CSF-treated patients compared with controls. None of these end-points were significantly different between groups. FU, follow-up; RR, risk ratio.

Table 1

Characteristics of studies included in the meta-analysis.

	Ellis, 2006 ¹⁹	Engelmann, 2006 ²⁰	Ince, 2005 ¹⁰	Leone, 2007 ²¹	Ripa, 2006 ²²	Takano, 2006 ²³	Valimijeli, 2005 ²⁴	Zohlhofer, 2006 ²⁵
Sample size	18	44	30	41	78	40	20	114
Clinical scenario	AMI	AMI	AMI	AMI	AMI	AMI	AMI	AMI
G-CSF dose ($\mu\text{g}/\text{kg}$)	5/10	10	10	10	10	2.5	5	10
Duration of G-CSF therapy (days)	5	5	6	5	6	5	4	5
Time from PCI/MI to G-CSF (hours)	38±8 (5 $\mu\text{g}/\text{kg}$) 41±6 (10 $\mu\text{g}/\text{kg}$)	31±24	1.4±0.5	≥ 5 days	29.6	21	37±66	120
Peak WBC count ($10^3/\mu\text{l}$)	35±14 (5 $\mu\text{g}/\text{kg}$) 42±7.6 (10 $\mu\text{g}/\text{kg}$)	42.9±25.7	55±8	NR	51±8	29.4±9	35±11	48±15
Peak number of CD34 ⁺ cells in the treatment arm (n/ μl)	37±30 (5 $\mu\text{g}/\text{kg}$) 29±14 (10 $\mu\text{g}/\text{kg}$)	CD34 ⁺ /CD133 ⁺ 46.1 ±33 CD34 ⁺ /CD31 ⁺ 46.4 ±32.9 CD34 ⁺ /CD117 ⁺ 41.2 ±26.8	66±54	50.3±35	55±45	15±18.9	33.6±8.7	72±154
Mean follow-up duration (months)	1	12	12	6	6	6	6	4-6
Jadad Score	5	4	4	4	5	3	3	5

Data are mean±SD. AMI, acute MI; LVEF, left ventricular ejection fraction; NR, not reported; PCI, percutaneous coronary intervention; WBC, white blood cell.

Table 2
Quality assessment scale for RCTs included in the meta-analysis

Source of Bias	Ellis, 2006 ¹⁹	Engelmann, 2006 ²⁰	Ince, 2005 ¹⁰	Leone, 2007 ²¹	Ripa, 2006 ²²	Takano, 2006 ²³	Valimijeli, 2005 ²⁴	Zohlnhöfer, 2006 ²⁵
Selection	Was allocation adequate?	Y	Y	Y	Y	Y	Y	Y
	Was an adequate method of randomization described?	Y	N	N	Y	Y	Y	Y
	Were groups similar at the start of the study?	Y	Y	Y	Y	Y	Y	Y
Performance	Were the patients/caregivers blinded to the intervention?	Y	Y	N	Y	N	N	Y
Detection	Was the outcome ascertained blindly?	Y	Y	Y	Y	Y	Y	Y
Attrition	What percentage was lost to follow-up?	0%	16%	0%	10%	12.5%	0%	3%
	Were all patients analyzed in the group to which they were assigned (intention-to-treat analysis)?	Y	Y	Y	Y	Y	Y	Y

* “Adequate” means the use of central site, numeric code, opaque envelopes, drugs prepared by pharmacy, and other appropriate procedures. Adapted from Juni *et al.*¹².

Table 3

Subgroup analysis examining the impact of baseline LVEF, duration between acute event/PCI and the start of G-CSF therapy, G-CSF dose, and peak white blood and CD34+ cell counts on outcome variables.

Outcome	Difference in mean or RR	95% Confidence Interval	Difference in mean	95% Confidence Interval	P value for Interaction
LVEF	4.73	2.67,6.79	-1.34	-3.01,0.34	<0.0001
Infarct scar size	0.94	-1.44,3.32	-0.32	-2.38,1.74	0.43
LVEDV	-7.82	-14.68,-0.96	1.95	-7.11,11.01	0.09
LVEFV	-10.07	-18.88,-1.26	1.83	-4.83,8.48	0.03
Death	1.16	0.27,4.98	0.96	0.14,6.49	0.88
Recurrent MI	2.52	0.43,14.88	0.35	0.01,8.30	0.31
ISR	0.78	0.41,1.49	1.03	0.63,1.70	0.50
Starting G-CSF ≤37 hours after acute MI/PCI					
LVEF	4.65	2.51,6.80	-0.98	-2.61,0.65	<0.0001
Infarct scar size	0.65	-1.11,2.42	-1.30	-4.61,2.01	0.31
LVEDV	-4.19	-10.52,2.14	-4.47	-15.36,6.41	0.96
LVEFV	-1.51	-10.05,7.03	-3.12	-9.90,3.66	0.77
Death	1.44	0.23,8.86	0.72	0.04,11.86	0.68
Recurrent MI	3.12	0.34,28.73	0.77	0.08,6.98	0.38
ISR	0.81	0.45,1.48	1.05	0.63,1.77	0.52
G-CSF dose ≥ 10 µg/kg/day					
LVEF	-0.72	-2.25,0.81	1.99	-1.42,5.40	0.16
Infarct scar size	-0.20	-2.22,1.65	1.14	-1.48,3.75	0.39
LVEDV	-2.94	-11.03,5.14	-5.37	-12.80,2.05	0.66
LVEFV	-1.27	-7.04,4.50	-9.31	-22.90,4.27	0.29
Death	1.32	0.27,6.48	3.53	0.15,8.11	0.58
Recurrent MI	0.97	0.14,6.96	3.53	0.15,8.11	0.49
ISR	0.97	0.63,1.51	0.75	0.31,1.84	0.61
Peak WBC count ≤ 42×10³ cells/µl					
LVEF	1.45	-1.76,4.66	0.72	-0.75,2.19	0.69
Infarct scar size	1.14	-1.48,3.75	-0.28	-2.22,1.65	0.39
LVEDV	-5.37	-12.80,2.05	0.23	-8.31,8.78	0.33
LVEFV	-7.58	-18.97,3.80	1.34	-4.97,7.66	0.18
Death	0.82	0.15,4.48	1.32	0.27,6.48	0.69
Recurrent MI	2.41	0.28,20.73	0.97	0.14,6.96	0.54
ISR	0.75	0.31,1.84	0.97	0.63,1.51	0.61
Peak CD34+ cells < 37 cells/µl					
LVEF	1.83	-1.51,5.17	0.96	-0.49,2.41	0.63
Infarct scar size	1.14	-1.48,3.75	-0.32	-2.38,1.74	0.39
LVEDV	-5.37	-12.80,2.05	-2.23	-10.67,6.20	0.58
LVEFV	-2.90	-16.01,10.22	-2.36	-8.43,3.71	0.94
Death	3.53	0.15,8.11	0.96	0.14,6.49	0.49
Recurrent MI	3.53	0.15,8.11	0.35	0.01,8.30	0.33
ISR	0.75	0.31,1.84	1.03	0.64,1.66	0.54

G-CSF, granulocyte colony-stimulating factor; ISR, in-stent restenosis; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume; LVEFV, LV end-systolic volume; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk; WBC, white blood cell.