Adult Bone Marrow–Derived Cells for Cardiac Repair

A Systematic Review and Meta-analysis

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Background: The results from small clinical studies suggest that therapy with adult bone marrow (BM)–derived cells (BMCSs) reduces infarct size and improves left ventricular function and perfusion. However, the effects of BMCS transplantation in patients with ischemic heart disease remains unclear.

Methods: We searched MEDLINE, EMBASE, Science Citation Index, CINAHL (Cumulative Index to Nursing and Allied Health), and the Cochrane Central Register of Controlled Trials (CENTRAL) (through July 2006) for randomized controlled trials and cohort studies of BMCS transplantation to treat ischemic heart disease. We conducted a random-effects meta-analysis across eligible studies measuring the same outcomes.

Results: Eighteen studies (N=999 patients) were eligible. The adult BMCSs included BM mononuclear cells, BM mesenchymal stem cells, and BM-derived circulating progenitor cells. Compared with controls, BMCS transplantation improved left ventricular ejection fraction (pooled difference, 3.66%; 95% confidence interval [CI], 1.93% to 5.40%; P<.001); reduced infarct scar size (−5.49%; 95% CI, −9.10% to −1.88%; P=.003); and reduced left ventricular end-systolic volume (−4.80 mL; 95% CI, −8.20 to −1.41 mL; P=.006).

Conclusions: The available evidence suggests that BMCS transplantation is associated with modest improvements in physiologic and anatomic parameters in patients with both acute myocardial infarction and chronic ischemic heart disease, above and beyond conventional therapy. Therapy with BMCSs seems safe. These results support conducting large randomized trials to evaluate the impact of BMCS therapy vs the standard of care on patient-important outcomes.

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Ischemic heart disease (IHD) is a major cause of mortality and morbidity worldwide and accounts for approximately 20% of all deaths in the United States.""
complete search strategy is available on request from the authors.

DATA ABSTRACTION

Two reviewers (A.A.-L. and I.M.T.) working in duplicate and independently used a standardized form to abstract the data from each study. The corresponding author (B.D.) solved disagreements that could not be solved by consensus. When necessary, LV end-diastolic volume was estimated from LV end-diastolic volume index, and infarct volume/mass was converted to infarct size expressed as a percentage of LV by calculating total LV myocardial volume from LV mass index. Data from echocardiography and cardiac magnetic resonance imaging were considered equivalent. When both echocardiographic and cardiac magnetic resonance imaging functional data were available, cardiac magnetic resonance imaging data were preferentially used.

QUALITY ASSESSMENT

We used the criteria by Juni et al\textsuperscript{11} to ascertain the methodological quality of included randomized trials\textsuperscript{12} and a modified Newcastle-Ottawa scale\textsuperscript{13} to assess the quality of cohort studies.

DATA ANALYSIS

Meta-analyses

The main outcomes of our review were change from baseline in mean LV ejection fraction, infarct scar size, LV end-systolic volume, and LV end-diastolic volume. We conducted random-effects meta-analyses to pool these outcomes across included studies, estimating weighted mean differences between BMC-treated patients and control patients and their associated 95% confidence intervals (CIs). We estimated the proportion of between-study inconsistency due to true differences between studies (rather than differences due to random error or chance) using the I\(^2\) statistic,\textsuperscript{13} with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. Funnel plots graphically explored publication bias. We used RevMan version 4.2.7 (Cochrane Collaboration, 2004) for these analyses.

Subgroup Analyses

We conducted planned subgroup analyses and tested for treatment-subgroup interactions. Planned subgroups comprised the types of study design (RCTs vs cohort studies); the clinical scenario in which BMCs were used (acute MI vs chronic IHD); timing of BMC transplantation after MI and/or percutaneous coronary intervention (<5 days vs within 5-30 days); the number of cells injected (above vs below the median of 80 x 10^6 BMCs used in the eligible studies); and the population of BMCs used (BM mononuclear cells vs nonmononuclear cells, including mesenchymal stem cells and BM-derived circulating progenitor cells). Because most of the included studies used the intracoronary route for BMC transplantation, the impact of the route of transplantation on outcomes could not be assessed.

RESULTS

SEARCH RESULTS

Of 213 articles retrieved during the initial search (Figure 1), 81 were not reports of original investigations (review articles and editorials), 95 were conducted in animals, 6 used mobilization rather than transplantation of BMCs, 6 lacked control groups, and 7 were performed in vitro. Eighteen studies (12 RCTs and 6 cohort studies) with a total of 999 patients were eligible for review. The interreviewer agreement on study eligibility was 100%.

STUDY CHARACTERISTICS

Table 1 summarizes the characteristics of all studies included in our meta-analysis. Notably, the sample size in each study was relatively small (range, 20-204 patients; median, 36 patients), and the follow-up duration was relatively short (range, 3-18 months; median, 4 months). There was considerable heterogeneity in the timing of cell transplantation after MI or percutaneous coronary intervention (range, 1 day to 81 months; median, 9.8 days) and in the number of BMCs used (range, 2 x 10^6 to 60 x 10^6 cells [median, 80 x 10^6 BMCs]).

STUDY QUALITY

Table 2 describes the methodological quality of the RCTs, and Table 3 describes the quality of the cohort studies. All cohort studies and at least 6 RCTs failed to blind participants and caregivers,
and at least 2 RCTs and 3 cohort studies failed to blind outcome assessors. The follow-up was complete in all eligible studies. The interreviewer agreement on these quality domains was greater than 90%.

**META-ANALYSES AND EFFICACY**

Compared with control, BMC transplantation improved LV ejection fraction by 3.66% (95% CI, 1.93% to 5.40%; \( I^2 = 71\% \), \( P < .001 \); **Figure 2**), reduced infarct scar size by 5.49% (95% CI, −9.10% to −1.88% \( I^2 = 66\% \), \( P < .003 \); **Figure 3**); reduced LV end-systolic volume by 4.80 mL (95% CI, −8.20 to −1.41 mL; \( I^2 = 0\% \), \( P = .006 \); **Figure 4**); and reduced LV end-diastolic volume by

### Table 1. Characteristics of Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Mean Follow-up Duration, mo</th>
<th>Study Design</th>
<th>Cell Type</th>
<th>No. of Cells Transplanted</th>
<th>Route of Injection</th>
<th>Clinical Scenario</th>
<th>Time From PCI and/or MI to Transplantation, d*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmus et al,14 2006</td>
<td>92</td>
<td>3</td>
<td>RCT</td>
<td>BMMNC and CPC</td>
<td>(22 \pm 11 \times 10^6) (CPC), (205 \pm 110 \times 10^6) (BMMNC)</td>
<td>IC</td>
<td>ICM</td>
<td>2348 ± 2318 (CPC), 2470 ± 2196 (BMMNC)</td>
</tr>
<tr>
<td>Bartunk et al,15 2005</td>
<td>35</td>
<td>4</td>
<td>Cohort</td>
<td>BMMNC (CD133+)</td>
<td>(12.6 \pm 2.2 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>11.6 ± 1.4</td>
</tr>
<tr>
<td>Chen et al,16 2004</td>
<td>69</td>
<td>6</td>
<td>RCT</td>
<td>MSC</td>
<td>(48-60 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>18.4 ± 0.5</td>
</tr>
<tr>
<td>Erbs et al,17 2005</td>
<td>26</td>
<td>3</td>
<td>RCT</td>
<td>CPC</td>
<td>(69 \pm 14 \times 10^6)</td>
<td>IC</td>
<td>ICM</td>
<td>225 ± 87</td>
</tr>
<tr>
<td>Ge et al,18 2006</td>
<td>20</td>
<td>6</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(40 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>1</td>
</tr>
<tr>
<td>Hendrikse et al,19 2006</td>
<td>20</td>
<td>4</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(60.25 \pm 31 \times 10^6)</td>
<td>IM</td>
<td>ICM</td>
<td>217 ± 162</td>
</tr>
<tr>
<td>Janssens et al,20 2006</td>
<td>67</td>
<td>4</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(172 \pm 72 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>1-2 (Range)</td>
</tr>
<tr>
<td>Kang et al,21 2006</td>
<td>82</td>
<td>6</td>
<td>RCT</td>
<td>CPC</td>
<td>(14 \pm 5 \times 10^6)</td>
<td>IC</td>
<td>AMI/ICM</td>
<td>7 ± 1 (AMI), 517 ± 525 (OMI)</td>
</tr>
<tr>
<td>Katritsis et al,22 2005</td>
<td>22</td>
<td>4</td>
<td>Cohort</td>
<td>MSC and EPC</td>
<td>(2-4 \times 10^6)</td>
<td>IC</td>
<td>AMI/ICM</td>
<td>224 ± 470</td>
</tr>
<tr>
<td>Lunde et al,23 2006</td>
<td>100</td>
<td>6</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(87 \pm 47.7 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>6 ± 1.3</td>
</tr>
<tr>
<td>Meyer et al,24 2006</td>
<td>60</td>
<td>18</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(24.6 \pm 9.4 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>4.8 ± 1.3</td>
</tr>
<tr>
<td>Mocini et al,25 2006</td>
<td>36</td>
<td>3</td>
<td>Cohort</td>
<td>BMMNC</td>
<td>(292 \pm 232 \times 10^6)</td>
<td>IM</td>
<td>ICM</td>
<td>NR</td>
</tr>
<tr>
<td>Perin et al,26 2004</td>
<td>20</td>
<td>12</td>
<td>Cohort</td>
<td>BMMNC</td>
<td>(25.5 \pm 6.3 \times 10^6)</td>
<td>IM</td>
<td>ICM</td>
<td>NR</td>
</tr>
<tr>
<td>Ruan et al,27 2005</td>
<td>20</td>
<td>6</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(236 \pm 174 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>Schächinger et al,28 2006</td>
<td>204</td>
<td>4</td>
<td>RCT</td>
<td>BMMNC</td>
<td>(28 \pm 22 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Strauer et al,29 2002</td>
<td>20</td>
<td>3</td>
<td>Cohort</td>
<td>BMMNC</td>
<td>(90 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>823.5 ± 945.5</td>
</tr>
<tr>
<td>Strauer et al,30 2005</td>
<td>36</td>
<td>3</td>
<td>Cohort</td>
<td>BMMNC</td>
<td>(72.5 \pm 73.3 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Li et al,31 2006</td>
<td>70</td>
<td>6</td>
<td>RCT</td>
<td>CPC (PBSC)</td>
<td>(72.5 \pm 73.3 \times 10^6)</td>
<td>IC</td>
<td>AMI</td>
<td>72.5 ± 73.3 \times 10^6</td>
</tr>
</tbody>
</table>

**Abbreviations:** AMI, acute myocardial infarction; BMC, bone marrow cell; BMMNC, bone marrow mononuclear cell; CPC, circulating progenitor cell; EPC, endothelial progenitor cells; IC, intracoronary injection; ICM, ischemic cardiomyopathy; IM, intramyocardial injection using electromechanical mapping system; MI, myocardial infarction; MSC, mesenchymal stem cell; NR, not reported; OMI, old myocardial infarction; PBSC, peripheral blood stem cells; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

*Values are given as mean ± SD unless otherwise specified.

### Table 2. Quality Assessment Scale for Randomized Controlled Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source of Bias</th>
<th>Selection</th>
<th>Performance</th>
<th>Detection</th>
<th>Attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was Allocation Adequate?*</td>
<td>Was an Adequate Method of Randomization Described?</td>
<td>Were Groups Similar at the Start of the Study?</td>
<td>Were the Patients/Caregivers Blinded to the Intervention?</td>
<td>Was the Outcome Ascertained Blindly?</td>
</tr>
<tr>
<td>Assmus et al,14 2006</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Chen et al,16 2004</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Erbs et al,17 2005</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Ge et al,18 2006</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Hendrikse et al,19 2006</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Janssens et al,20 2006</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Kang et al,21 2006</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Lunde et al,23 2006</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Meyer et al,24 2006</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Ruan et al,25 2005</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Schächinger et al,26 2006</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Li et al,27 2006</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

*“Adequate” means the use of central site, numeric code, opaque envelopes, drugs prepared by pharmacy, and other appropriate procedures (adapted from Jüni et al11).
Figure 2. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) improvement in left ventricular ejection fraction (LVEF) in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled trials (RCTs). Transplantation with BMCs resulted in a 3.66% (95% CI, 1.93% to 5.40%) increase in mean LVEF. The overall effect was statistically significant in favor of BMC therapy. AMI indicates acute myocardial infarction; CPCs, circulating progenitor cells; OMI, old myocardial infarction; and WMD, weighted mean difference.
Figure 3. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) change in infarct scar size in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled trials (RCTs). Transplantation with BMCs resulted in a 5.49% (95% CI, −9.10% to −1.88%) decrease in mean infarct scar size. The overall effect was statistically significant in favor of BMC therapy. WMD indicates weighted mean difference.

Figure 4. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) change in left ventricular end-systolic volume (LVESV) in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled trials (RCTs). Transplantation of BMCs resulted in a 4.80-mL (95% CI, −8.20 to −1.41 mL) decrease in LVESV. The overall effect was statistically significant in favor of BMC treatment. Favors indicates the treatment favored BMC treatment over control; Weight, % indicates the percentage of total patients who were weighted in favor of BMC treatment; BMC Treatment indicates BMC treatment compared with control; WMD (Random), mL (95% CI) indicates weighted mean difference.
tions in BMC-treated patients and reported incidence of complications among BMC-treated and control patients. The incidence of other complications, such as recurrent angina, MI, and sustained or nonsustained supraventricular or ventricular arrhythmias, was not significantly different between BMC-treated patients and controls. A supplemental table of reported incidence of complications in BMC-treated patients and controls is available at: www . Louisville.edu/medschool/medicine /cardiology/Archinternmed_2007 _supplemental_data.pdf.

**COMMENT**

This systematic review and meta-analysis, the first, to our knowledge, to comprehensively summarize the available evidence of BMC transplantation in patients with IHD, indicates that BMC transplantation in patients with IHD is apparently safe and leads to modest benefits beyond those achieved with revascularization and conventional pharmacotherapy. Our results indicate that BMC transplantation may improve LV ejection fraction, infarct scar size, and LV end-systolic volume. However, the mechanisms explaining these benefits remain unclear.

Although the plasticity of adult stem cells remains debatable, extensive data from animal models indicate that BMCs are capable of differentiating into cells of cardiac and vascular lineages. Bone marrow–derived mesenchymal stem cells, mononuclear cells, and circulating endothelial progenitor cells have all been shown to differentiate into cardiomyocytes both in vitro and in vivo. Nevertheless, tracking cellular differentiation after transplantation in humans remains particularly difficult. Another potential mechanism is that transplanted BMCs may secrete a variety of growth factors and cytokines, thereby enhancing myocyte survival following ischemic injury and facilitating the migration of resident cardiac stem cells to the site of injury and their reparative activity. The finding of infarct scar size reduction with BMC therapy may signify new myocyte formation, superior preservation of existing myocytes, or both following BMC transplantation.

Beyond these mechanistic considerations, some technical issues remain unclear, such as the optimal number of BMCs, the optimal timing and route of transplantation, and the most effective type of BMC. Since only a small fraction of BMCs are retained in the myocardium following injection, we analyzed the pooled data based on the number of cells transplanted. There were no sig-
significant differences in outcomes between the groups that received less or more than the median number of cells. Although somewhat surprising, these findings perhaps underscore the importance of selective injection of the most efficacious cell subpopulation.

Furthermore, the impact of cell number may be affected by the timing and route of transplantation, both of which may influence cell retention. The retention of injected endothelial progenitor cells was much lower in sham-operated nude rats compared with nude rats 24 hours after acute MI. Furthermore, the benefits of BMC injection in the first few days after acute MI may be jeopardized by the local inflammation that renders the myocardium a hostile environment for the injected cells. In the Reinfusion of Enriched Progenitor Cells And Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial, the authors stratified data according to the time of BMC injection after acute MI. While there was no correlation between the timing of the procedure and LV contractile recovery in the placebo group, a significant correlation was observed in the BMC-treated group. Transplantation of BMCs was more beneficial when performed 5 days or later after acute MI. In our meta-analysis, injection of BMCs in the 5- to 30-day window resulted in a more than 3-fold greater reduction in infarct size and greater improvement in LV end-systolic volume compared with injection in the first 5 days after acute MI and/or percutaneous coronary intervention. Because the overall change in LV end-diastolic volume was not different between BMC-treated and control groups, a change in LV end-systolic volume may represent an improvement in global LV function. However, none of these interactions reached statistical significance, and the importance of these findings remains uncertain at this time. This lack of subgroup-treatment interaction may have resulted from a small number of studies with a small number of patients. Future meta-analyses with larger patient numbers or large randomized trials may identify potential interactions between treatment effects and the timing of BMC injection.

It is important to note that the majority of studies included in our review used unfractionated BM mononuclear cells and that BMC transplantation was reported safely in these studies. Although intracoronary injection of CD133+ BM mononuclear cells was associated with an increased incidence of in-stent restenosis, no other major adverse effects were noted in studies using different BMC populations. This safety profile of BMC transplantation as reported in these studies with follow-up durations of up to 18 months supports conducting further investigation of therapeutic efficacy. The possibility that reporting bias may be affecting the otherwise favorable safety picture emerging from our review, however, demands caution.

The duration of follow-up in the studies included in this meta-analysis was relatively short. Although the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial showed persistent benefits after 12 months of BMC and circulating progenitor cell therapy, a longer follow-up of 18 months failed to demonstrate statistically significant improvements with cell therapy in the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) study. Whether the benefits of BMC therapy are ephemeral remains to be assessed in larger trials with longer follow-up duration (e.g., 5 years). Moreover, a single dose of BMCs may not be sufficient for myocardial repair, and repeated infusions may result in sustained benefits over a longer time.
frame, but this remains speculative. Genetic modifications of BMCs prior to transplantation may also potentially improve their regenerative capability.44 These avenues may be explored in future trials. Overall, our findings support the recent consensus statement on the use of autologous adult stem cells for cardiac repair by the task force of the European Society of Cardiology that called for a pragmatic approach for demonstrating the efficacy of stem cell therapy in myocardial repair in humans.45

Limitations in study quality (namely, lack of blinding), unexpected between-study inconsistency, sparse evidence, and indirectness of the outcomes (ie, exclusive reliance on surrogate outcomes) weaken the inferences. The methods for evaluating LV function, the type of BMC used, and the interval between acute MI and/or percutaneous coronary intervention and BMC transplantation varied among the included studies (Table 1), all of which are potential sources of heterogeneity. However, the consistency of the beneficial effect of BMCs in most of the prespecified primary end points and subgroups suggests that the association is valid. The fact that the beneficial effect of BMCs persisted across different study designs, BMC lines, timings and routes of transplantation, and clinical scenarios suggest that the association can cautiously be generalized to different patient populations.

We believe that combining data from RCTs and cohort studies was justified because for both designs patients were followed prospectively, accurate methods were used to assess the primary end points, and few patients if any were lost to follow-up. Importantly, the results were consistent even when the analysis was restricted to RCTs or cohort studies alone (Table 4 and Figures 2-5), strengthening the fact that the results of the meta-analysis are cautiously generalizable.

In conclusion, the results of our systematic review and meta-analysis suggest that BMC transplantation in patients with acute MI as well as chronic IHD is reportedly safe and is associated with modest improvements in LV ejection fraction, infarct scar size, and LV end-diastolic volume, beyond those achieved with state-of-the-art therapy; however, there was no significant effect on LV end-diastolic volume. Although the benefits are modest, our results support the organization, funding, and conduct of larger randomized trials of BMC therapy designed to critically evaluate the long-term impact of BMC therapy on patient-important outcomes in patients with IHD.

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Author Contributions: Drs Abdel-Latif and Dawn had full access to all of the data in this study and take responsibility for its integrity and the accuracy of data analysis. Study concept and design: Abdel-Latif, Dawn, Bolli, Tleyjeh, and Hornung. Acquisition of data: Abdel-Latif, Tleyjeh, Perin, Zuba-Surma, Bolli, and Dawn. Analysis and interpretation of data: Abdel-Latif, Tleyjeh, Montori, Hornung, Perin, Bolli, Dawn, and Al-Mallah. Drafting of the manuscript: Abdel-Latif, Dawn, Zuba-Surma, Tleyjeh, Montori, Bolli, and Al-Mallah. Critical revision of the manuscript for important intellectual content: Dawn, Bolli, Montori, Abdel-Latif, Tleyjeh, Hornung, and Perin. Statistical analysis: Abdel-Latif, Montori, Tleyjeh, Hornung, and Dawn. Obtained funding: Bolli and Dawn. Administrative, technical, or material support: Bolli and Dawn. Study supervision: Dawn, Bolli, Hornung, and Perin.

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Additional Information: A supplementary table (reported incidence of complications in BMC-treated patients and controls) and figure (funnel plot [according to outcomes for studies included in the meta-analysis]) are available at: www.louisville.edu/medschool/medicine/cardiology/Archinternmed_2007_supplemental_data.pdf.

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