REVIEW ARTICLE

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 (BMCs) reduces infarct size and improves left ventricular function and perfusion. However, the effects of BMC 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 BMC 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 BMCs included BM mononuclear cells, BM mesenchymal stem cells, and BM-derived circulating progenitor cells. Compared with controls, BMC 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 BMC 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 BMCs seems safe. These results support conducting large randomized trials to evaluate the impact of BMC 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.[1-3] Despite significant advances in medical therapy and interventional strategy, the prognosis of millions of patients with acute myocardial infarction (MI) and ischemic cardiomyopathy remains dismal.[4,5] Although the underlying mechanism remains controversial, numerous studies in animals have documented that transplantation of bone marrow (BM)–derived cells (BMCs) following acute MI and in ischemic cardiomyopathy is associated with a reduction in infarct scar size and improvements in left ventricular (LV) function and perfusion.[6] In humans, transplantation of BMCs and BM-derived circulating progenitor cells (CPCs) in patients with acute MI as well as chronic IHD has yielded similar encouraging results.[7,8]

However, these studies in humans are heterogeneous in their methods and have yielded disparate results. These studies have each enrolled a small number of patients and have fallen short of providing conclusive results. Thus, the extent to which BMC transplantation can improve outcomes in patients with IHD remains unclear. To our knowledge, there are no comprehensive syntheses of these data. Therefore, we performed a systematic review of the literature and meta-analysis to critically evaluate and summarize the potential therapeutic benefits of BMC transplantation for cardiac repair in patients with IHD.

METHODS

REVIEW QUESTION AND STUDY PROTOCOL

The review question was to what extent does BMC transplantation affect cardiovascular outcomes in patients with IHD? We report this protocol-driven systematic review according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[9] and Quality of Re-

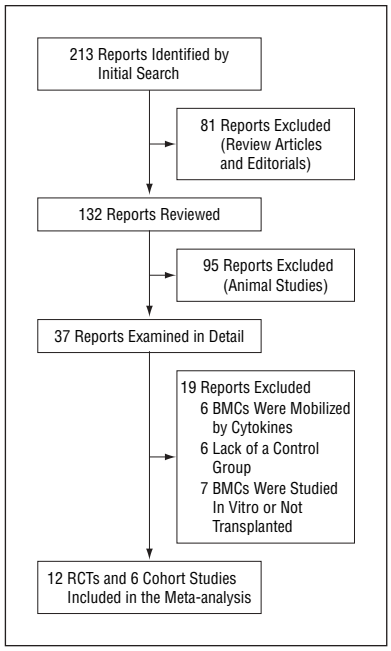

Figure 1. Flow diagram of eligible studies of bone marrow–derived cells (BMCs) transplantation in patients with acute myocardial infarction and chronic ischemic heart disease. RCTs indicates randomized controlled trials.

porting of Meta-analysis (QUOROM)[10] statements.

ELIGIBILITY CRITERIA

Two reviewers (A.A.-L. and I.M.T.) judged eligibility of studies in duplicate and independently. Eligible studies were randomized controlled trials (RCTs) and cohort studies examining the effects of BMC transplantation on cardiovascular outcomes in patients with IHD. Because cytokines may exert cardiovascular effects, we excluded studies of cardiac repair solely via the mobilization of endogenous BMCs with systemic administration of cytokines.

SEARCH STRATEGY

We searched MEDLINE (January 1980 to July 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) (July 2006), EMBASE (January 1980 to July 2006), CINAHL (Cumulative Index to Nursing and Allied Health) (January 1982 to July 2006), the US Food and Drug Administration Web site (http://www.fda.gov), and BIOSIS Previews (January 1980 to July 2006) using the following database-appropriate terms: *coronary artery disease*, *myocardial infarction*, *stem cells*, *progenitor cells*, *bone marrow*, *circulating progenitor cells*, *myocardial regeneration*, and *cardiac repair*. We sought additional studies by reviewing the reference lists of eligible studies and relevant review articles. The 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 Jüni et al[11] to ascertain the methodological quality of included randomized trials[11] and a modified Newcastle-Ottawa scale[12] 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,[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 80×10^6 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, 2×10^6 to 60×10^9 cells [median, 80×10^6 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,

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

Source	Sample Size	Mean Follow-up Duration, mo	Study Design	Cell Type	No. of Cells Transplanted	Route of Injection	Clinical Scenario	Time From PCI and/or MI to Transplantation, d*
Assmus et al,[14] 2006	92	3	RCT	BMMNC and CPC	$22 \pm 11 \times 10^6$ (CPC), $205 \pm 110 \times 10^6$ (BMMNC)	IC	ICM	2348 ± 2318 (CPC), 2470 ± 2196 (BMMNC)
Bartunek et al,[15] 2005	35	4	Cohort	BMMNC ($CD133^+$)	$12.6 \pm 2.2 \times 10^6$	IC	AMI	11.6 ± 1.4
Chen et al,[16] 2004	69	6	RCT	MSC	$48\text{-}60 \times 10^9$	IC	AMI	18.4 ± 0.5
Erbs et al,[17] 2005	26	3	RCT	CPC	$69 \pm 14 \times 10^6$	IC	ICM	225 ± 87
Ge et al,[18] 2006	20	6	RCT	BMMNC	40×10^6	IC	AMI	1
Hendrikx et al,[19] 2006	20	4	RCT	BMMNC	$60.25 \pm 31 \times 10^6$	IM	ICM	217 ± 162
Janssens et al,[20] 2006	67	4	RCT	BMMNC	$172 \pm 72 \times 10^6$	IC	AMI	1-2 (Range)
Kang et al,[21] 2006	82	6	RCT	CPC	$14 \pm 5 \times 10^8$	IC	AMI/ICM	7 ± 1 (AMI), 517 ± 525 (OMI)
Katritsis et al,[22] 2005	22	4	Cohort	MSC and EPC	$2\text{-}4 \times 10^6$	IC	AMI/ICM	224 ± 470
Lunde et al,[23] 2006	100	6	RCT	BMMNC	$87 \pm 47.7 \times 10^6$	IC	AMI	6 ± 1.3
Meyer et al,[24] 2006	60	18	RCT	BMMNC	$24.6 \pm 9.4 \times 10^8$	IC	AMI	4.8 ± 1.3
Mocini et al,[25] 2006	36	3	Cohort	BMMNC	$292 \pm 232 \times 10^6$	IM	ICM	NR
Perin et al,[26] 2004	20	12	Cohort	BMMNC	$25.5 \pm 6.3 \times 10^6$	IM	ICM	NR
Ruan et al,[27] 2005	20	6	RCT	BMC	NR	IC	AMI	1
Schächinger et al,[28] 2006	204	4	RCT	BMMNC	$236 \pm 174 \times 10^6$	IC	AMI	4.3 ± 1.3
Strauer et al,[29] 2002	20	3	Cohort	BMMNC	$28 \pm 22 \times 10^6$	IC	AMI	8 ± 2
Strauer et al,[30] 2005	36	3	Cohort	BMMNC	90×10^6	IC	ICM	823.5 ± 945.5
Li et al,[31] 2006	70	6	RCT	CPC (PBSC)	$72.5 \pm 73.3 \times 10^6$	IC	AMI	7 ± 5

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

	Selection			Performance	Detection	Attrition	
Source of Bias	Was Allocation Adequate?*	Was an Adequate Method of Randomization Described?	Were Groups Similar at the Start of the Study?	Were the Patients/Caregivers Blinded to the Intervention?	Was the Outcome Ascertained Blindly?	What Percentage Was Lost to Follow-up?	Were All Patients Analyzed in the Group to Which They Were Assigned (Intention-to-Treat Analysis)?
Assmus et al,[14] 2006	Y	N	Y	N	Y	4	Y
Chen et al,[16] 2004	Y	N	Y	Y	Y	0	Y
Erbs et al,[17] 2005	Y	N	Y	Y	Y	0	Y
Ge et al,[18] 2006	Y	Y	Y	N	Y	0	Y
Hendrikx et al,[19] 2006	Y	Y	Y	N	Y	0	Y
Janssens et al,[20] 2006	Y	Y	Y	Y	Y	0	Y
Kang et al,[21] 2006	N	Y	Y	N	N	0	Y
Lunde et al,[23] 2006	Y	Y	Y	N	Y	0	Y
Meyer et al,[24] 2006	Y	Y	Y	Y	Y	0	Y
Ruan et al,[27] 2005	Y	N	Y	Y	Y	0	Y
Schächinger et al,[28] 2006	Y	Y	Y	Y	Y	0	Y
Li et al,[31] 2006	Y	N	Y	N	N	17	Y

*"Adequate" means the use of central site, numeric code, opaque envelopes, drugs prepared by pharmacy, and other appropriate procedures (adapted from Jüni et al[11]).

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 3. Modified Newcastle-Ottawa Quality Assessment Scale[12] for Cohort Studies Included in the Meta-analysis

	Selection*					Outcome‡		
Source	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Incident Disease	Comparability†	Assessment of Outcome	Length of Follow-up	Adequacy of Follow-up
Bartunek et al,[15] 2005	A	A	A	A	A	B	A	A
Katritsis et al,[22] 2005	A	A	A	A	A	A	A	A
Mocini et al,[25] 2006	A	A	A	A	A	A	A	A
Perin et al,[26] 2004	A	A	A	NR	A	A	A	A
Strauer et al,[29] 2002	A	A	A	A	A	B	A	A
Strauer et al,[30] 2005	A	A	A	A	A	B	A	A

Abbreviation: NR, not reported.

*Selection: (1) *Representativeness of the exposed cohort:* A, truly representative of the average patient with ischemic heart disease; B, somewhat representative of the average patient with ischemic heart disease; C, selected group; and D, no description of the derivation of the cohort. (2) *Selection of the nonexposed cohort:* A, drawn from the same community as the exposed cohort; B, drawn from a different source; and C, no description of the derivation of the nonexposed cohort. (3) *Ascertainment of exposure:* A, secure record (eg, surgical records); B, structured interview; C, written self-report; and D, no description. (4) *Demonstration that outcome of interest was not present at start of study:* A, yes; B, no.

†Comparability: *Comparability of cohorts on the basis of the design or analysis:* A, study controls for comorbidities; B, study controls for additional risk factors (such as age and severity of illness); and C, not done.

‡Outcome: (1) *Assessment of outcome:* A, independent blind assessment; B, record linkage; C, self-report; and D, no description. (2) *Was follow-up long enough for outcomes to occur:* A, yes; B, no. (3) *Adequacy of follow-up of cohorts:* A, complete follow-up—all subjects accounted for; B, subjects lost to follow-up unlikely to introduce bias (small number lost), follow-up rate higher than 90%, or description provided of those lost; C, follow-up rate 90% or lower (select an adequate percentage) and no description of those lost; and D, no statement.

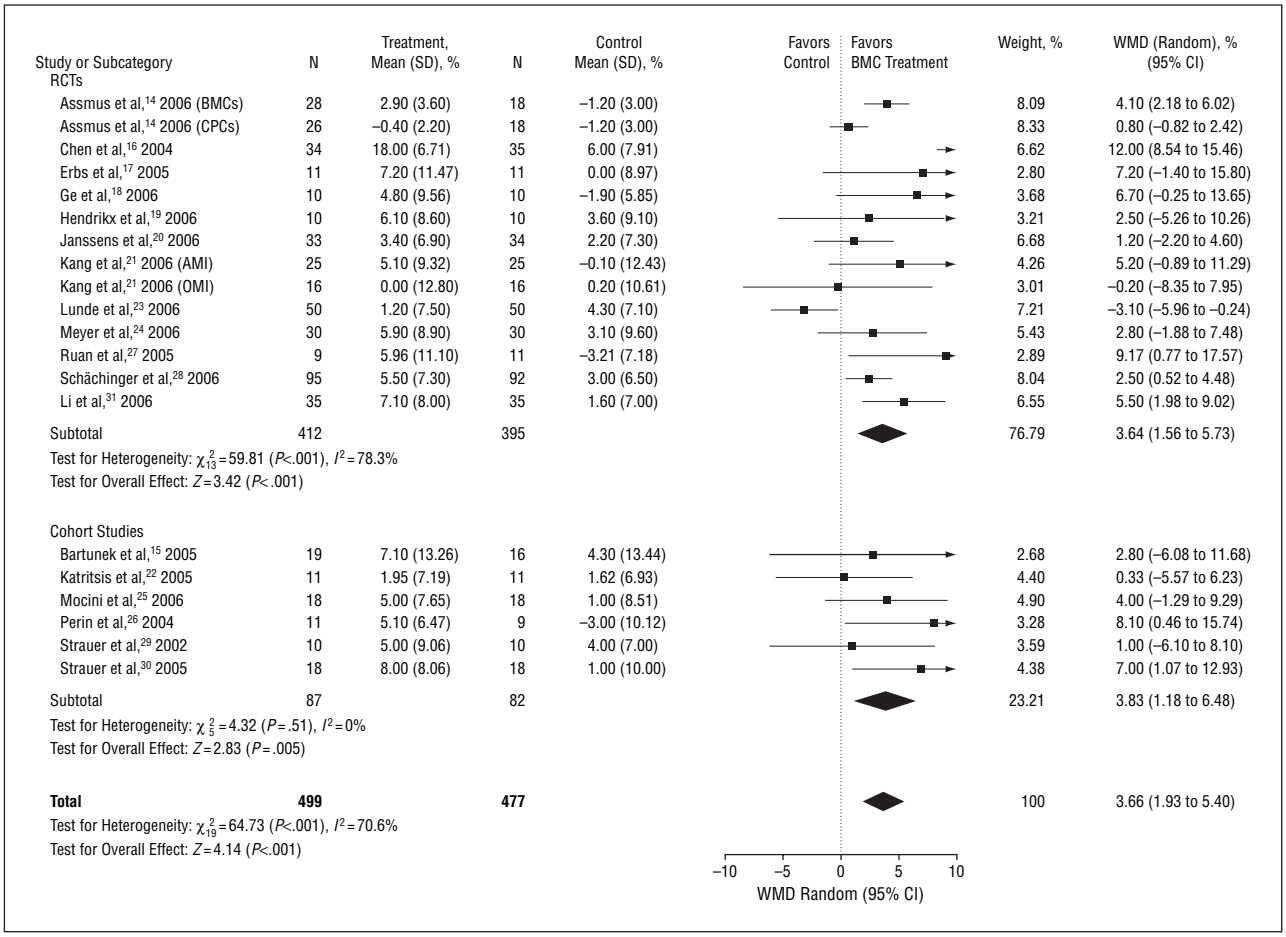

Figure 2. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) improvement in left ventricular ejection fraction (LVEF) in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled 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.

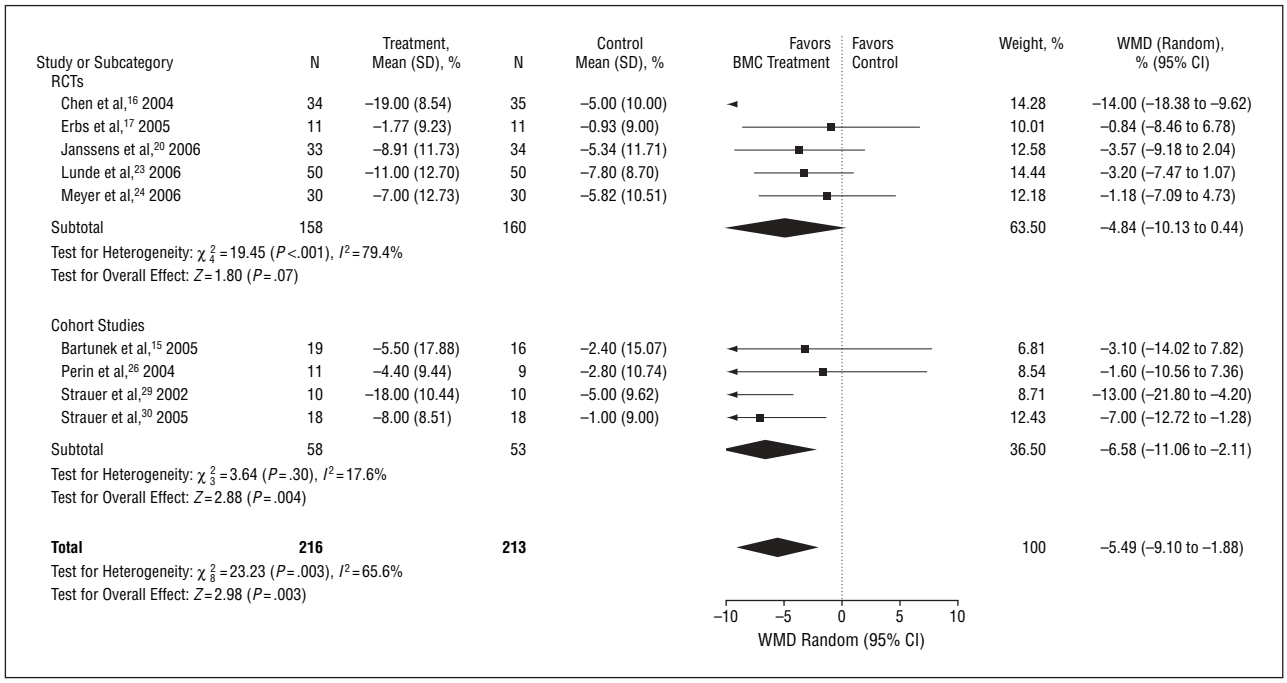

Figure 3. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) change in infarct scar size in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled trials (RCTs). Transplantation 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.

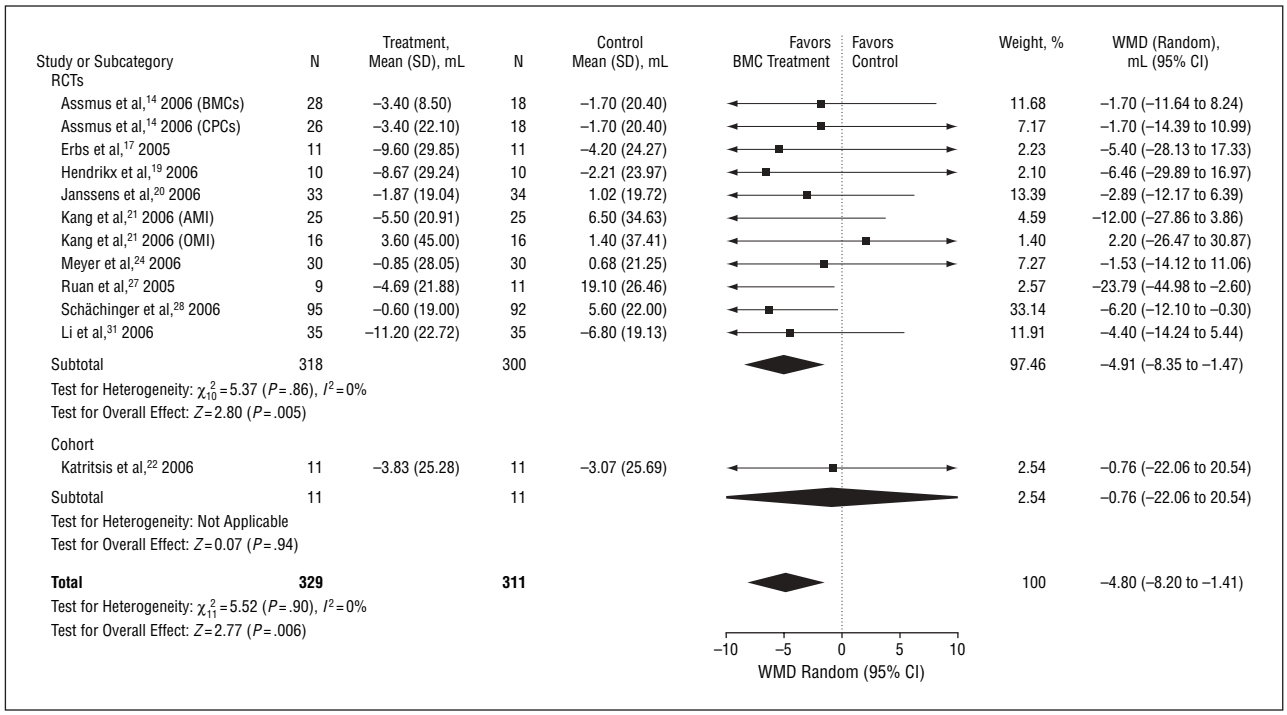

Figure 4. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) change in left ventricular end-systolic volume (LVESV) in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled 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 therapy. AMI indicates acute myocardial infarction; CPCs, circulating progenitor cells; OMI, old myocardial infarction; and WMD, weighted mean difference.

1.92 mL (95% CI, −6.31 to 2.47 [I^2=0%; P=.39]; **Figure 5**). We drew funnel plots 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 (available at: www.louisville.edu/medschool/medicine/cardiology

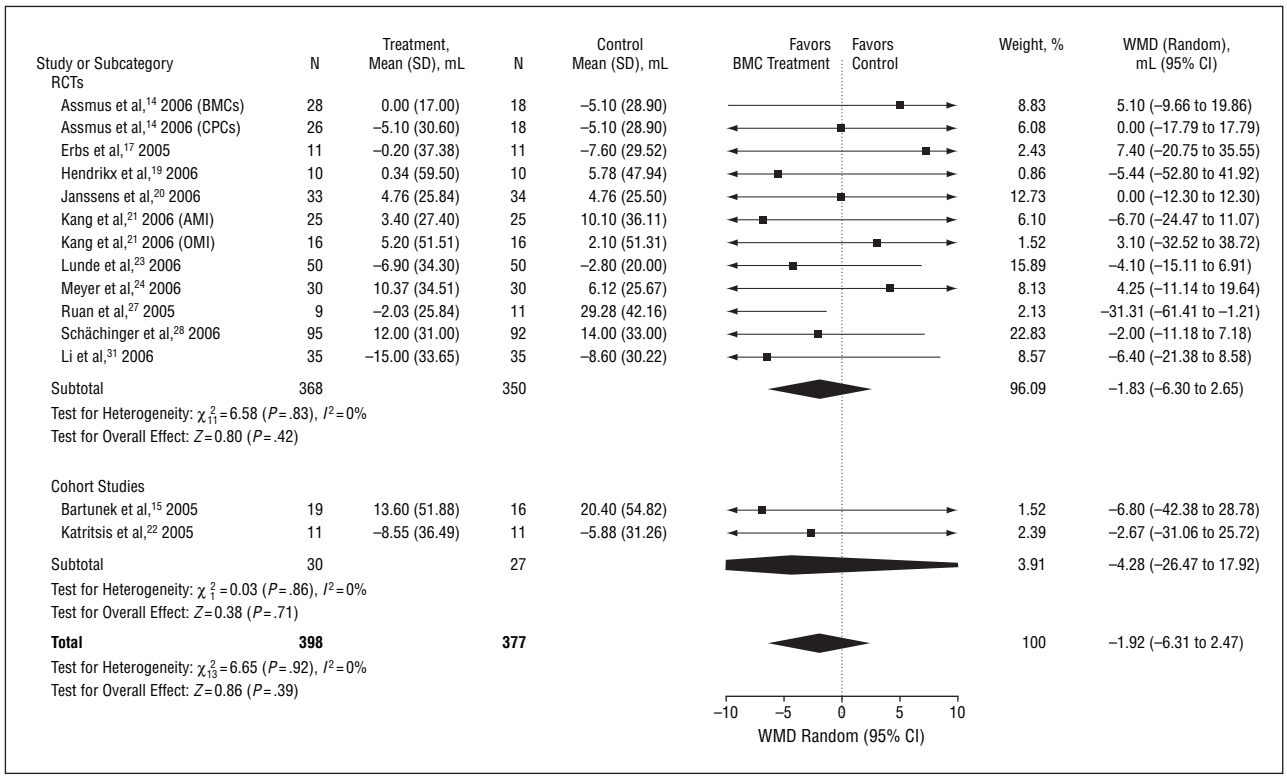

Figure 5. Forest plot of unadjusted difference in mean (with 95% confidence intervals [CIs]) change in left ventricular end-diastolic volume (LVEDV) in patients treated with bone marrow–derived cells (BMCs) compared with controls. The figure shows the summary of cohort studies and randomized controlled trials (RCTs). BMC transplantation resulted in a 1.92 mL (95% CI, –6.31 to 2.47) decrease in mean LVEDV. The overall effect was in favor of BMC therapy (not statistically significant). AMI indicates acute myocardial infarction; CPCs, circulating progenitor cells; OMI, old myocardial infarction; and WMD, weighted mean difference.

/Archinternmed_2007_supplemental_data.pdf).

SUBGROUP ANALYSES AND SAFETY

We did not find any treatment-subgroup interaction through any of our planned subgroup analyses (**Table 4**).

The injection of BMCs was found to be safe without significantly greater risk of major local or systemic complications. Except for Bartunek et al,[15] who reported a higher incidence of in-stent restenosis in the BM mononuclear cell–treated group (9 of 19 patients vs 4 of 16 patients in the control group), the rate of restenosis was comparable 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.[32-38] 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.[7] 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,[39] thereby enhancing myocyte survival following ischemic injury and facilitating the migration of resident cardiac stem cells[40] 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,[41] we analyzed the pooled data based on the number of cells transplanted. There were no sig-

nificant 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[42] and route[41] 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.[42] 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.[28] 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.[28] 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.

Table 4. Subgroup Analysis Examining the Impact of Study Design, Underlying Type of Cardiomyopathy, Timing of Transplantation, Number of BMCs Transplanted, and Type of BMCs Transplanted on Outcome Variables

Outcome	Difference in Mean (95% Confidence Interval)		*P* Value for Interaction
	RCTs	**Cohort Studies**	
LVEF	3.64 (1.56 to 5.73)	3.83 (1.18 to 6.48)	.92
Infarct scar size	−6.49 (−10.23 to −2.75)	−6.31 (−10.27 to −2.35)	.94
LVESV	−4.91 (−8.35 to −1.47)	−0.76 (−22.06 to 20.54)	.71
LVEDV	−1.83 (−6.30 to 2.65)	−4.28 (−26.47 to 17.92)	.83
	Acute MI	**Chronic IHD**	
LVEF	3.95 (1.07 to 6.82)	3.45 (1.36 to 5.54)	.78
Infarct scar size	−6.45 (−11.55 to −1.36)	−4.12 (−8.20 to −0.05)	.48
LVESV	−5.82 (−9.80 to −1.84)	−2.22 (−9.07 to 4.63)	.37
LVEDV	−3.20 (−8.17 to 1.78)	0.72 (−8.18 to 9.62)	.45
	BMCs Injected <5 d After Acute MI and/or PCI	**BMCs Injected 5-30 d After Acute MI and/or PCI**	
LVEF	2.76 (1.05 to 4.47)	4.00 (−1.58 to 9.57)	.68
Infarct scar size	−2.44 (−6.51 to 1.63)	−8.80 (−15.20 to −2.40)	.10
LVESV	−5.64 (−11.00 to −0.29)	−6.51 (−14.87 to 1.85)	.86
LVEDV	−2.14 (−10.61 to 6.32)	−5.34 (−13.08 to 2.41)	.58
	No. of BMCs $<80 \times 10^6$	**No. of BMCs $\geq 80 \times 10^6$**	
LVEF	3.17 (1.01 to 5.33)	3.53 (0.90 to 6.16)	.84
Infarct scar size	−4.58 (−10.32 to 1.17)	−5.93 (−10.73 to −1.13)	.72
LVESV	−3.55 (−10.22 to 3.12)	−4.58 (−8.59 to −0.56)	.79
LVEDV	−2.67 (−12.05 to 6.72)	−0.89 (−5.92 to 4.15)	.74
	BMMNCs	**MSCs and CPCs**	
LVEF	2.69 (0.87 to 4.51)	4.89 (1.17 to 8.78)	.29
Infarct scar size	−4.37 (−7.01 to −1.73)	−7.80 (−20.68 to 5.07)	.61
LVESV	−4.27 (−8.40 to −0.14)	−5.91 (−11.88 to 0.05)	.66
LVEDV	−0.65 (−5.87 to 4.56)	−5.00 (−13.11 to 3.12)	.38

Abbreviations: BMCs, bone marrow–derived cells; BMMNCs, bone marrow mononuclear cells; CPCs, circulating progenitor cells; IHD, ischemic heart disease; MI, myocardial infarction; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MSC, mesenchymal stem cell; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

It is important to note that the majority of studies included in our review used unfractionated BM mononuclear cells[18,20,23-26,28-30] and that BMC transplantation was reportedly safe in these studies. Although intracoronary injection of $CD133^+$ BM mononuclear cells was associated with an increased incidence of in-stent restenosis,[15] 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,[43] 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.[24] Whether the benefits of BMC therapy are ephemeral remains to be assessed in larger trials with longer follow-up duration (eg, 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), unexplained 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-systolic 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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