

ORIGINAL ARTICLE

Intracoronary Bone Marrow–Derived Progenitor Cells in Acute Myocardial Infarction

Volker Schächinger, M.D., Sandra Erbs, M.D., Albrecht Elsässer, M.D., Werner Haberbosch, M.D., Rainer Hambrecht, M.D., Hans Hölschermann, M.D., Jiangtao Yu, M.D., Roberto Corti, M.D., Detlef G. Mathey, M.D., Christian W. Hamm, M.D., Tim Süselbeck, M.D., Birgit Assmus, M.D., Torsten Tonn, M.D., Stefanie Dimmeler, Ph.D., and Andreas M. Zeiher, M.D., for the REPAIR-AMI Investigators*

ABSTRACT

BACKGROUND

Pilot trials suggest that the intracoronary administration of autologous progenitor cells may improve left ventricular function after acute myocardial infarction.

METHODS

In a multicenter trial, we randomly assigned 204 patients with acute myocardial infarction to receive an intracoronary infusion of progenitor cells derived from bone marrow (BMC) or placebo medium into the infarct artery 3 to 7 days after successful reperfusion therapy.

RESULTS

At 4 months, the absolute improvement in the global left ventricular ejection fraction (LVEF) was significantly greater in the BMC group than in the placebo group (mean [\pm SD] increase, $5.5 \pm 7.3\%$ vs. $3.0 \pm 6.5\%$; $P=0.01$). Patients with a baseline LVEF at or below the median value of 48.9% derived the most benefit (absolute improvement in LVEF, 5.0%; 95% confidence interval, 2.0 to 8.1). At 1 year, intracoronary infusion of BMC was associated with a reduction in the prespecified combined clinical end point of death, recurrence of myocardial infarction, and any revascularization procedure ($P=0.01$).

CONCLUSIONS

Intracoronary administration of BMC is associated with improved recovery of left ventricular contractile function in patients with acute myocardial infarction. Large-scale studies are warranted to examine the potential effects of progenitor-cell administration on morbidity and mortality. (ClinicalTrials.gov number, NCT00279175.)

From the Department of Internal Medicine III, Johann Wolfgang Goethe University, Frankfurt (V.S., B.A., S.D., A.M.Z.); the Department of Cardiology, Herzzentrum Leipzig, Leipzig (S.E., R.H.); the Department of Cardiology, Kerckhoff Klinik, Bad Nauheim (A.E., C.W.H.); the Department of Internal Medicine, Zentralklinikum Suhl, Suhl (W.H.); the Department of Cardiology, Universitätsklinikum Gießen, Giessen (H.H.); the Department of Cardiology, Zentralklinikum, Bad Berka (J.Y.); the Hamburg University Cardiovascular Center, Hamburg (D.G.M.); the Department of Cardiology, Universitätsklinikum, Mannheim (T.S.); and the Institute for Transfusion Medicine and Immunohematology, Red Cross Blood Donor Service Baden–Württemberg–Hessen, Frankfurt (T.T.) — all in Germany; and the Department of Cardiology, Universitätsspital, Zurich, Switzerland (R.C.). Address reprint requests to Dr. Zeiher at the Department of Internal Medicine III, J.W. Goethe University, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany, or at zeiher@em.uni-frankfurt.de.

*Members of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) study group are listed in the Appendix.

N Engl J Med 2006;355:1210-21.

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PROMPT REPERFUSION OF THE INFARCT-related coronary artery has considerably improved the clinical outcome in patients with acute myocardial infarction.¹ Although contemporary reperfusion strategies using stent implantation and aggressive inhibition of platelet aggregation have been shown to increase myocardial salvage,² improvements in global left ventricular function are rather modest, despite the use of optimal reperfusion therapy.^{3,4} Heart failure that develops after infarction remains a major cause of morbidity and mortality.^{5,6}

Experimental studies suggested that intravascular or intramyocardial administration of progenitor cells derived from bone marrow (BMC) or blood may contribute to functional regeneration of infarcted myocardium and enhance neovascularization of ischemic myocardium.⁷⁻¹⁰ Moreover, clinical pilot studies demonstrated that intracoronary infusion of progenitor cells is feasible and may improve the recovery of left ventricular contractility in patients with acute myocardial infarction.¹¹⁻¹⁶ We therefore designed a double-blind, placebo-controlled, randomized multicenter trial — the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial — to determine whether intracoronary infusion of enriched BMC is associated with improved global left ventricular function in patients with myocardial infarction treated with state-of-the-art methods.

METHODS

STUDY POPULATION AND PROTOCOL

We enrolled the first patient in the study on April 16, 2004, and the last 4-month angiographic follow-up was performed on October 31, 2005. The definition of primary and secondary end points, as well as the prespecified subgroup analyses, have been published previously.¹⁷ In brief, patients 18 to 80 years of age were eligible for the study if they had had an acute ST-elevation myocardial infarction that had been successfully reperfused by means of stent implantation and had a substantial residual left ventricular regional wall-motion abnormality (as defined by an ejection fraction $\leq 45\%$ according to a visual estimate). Written informed consent was obtained within 3 days after the reperfusion therapy if the patients no longer required intravenous pressor substances or mechanical hemodynamic support. The ethics review

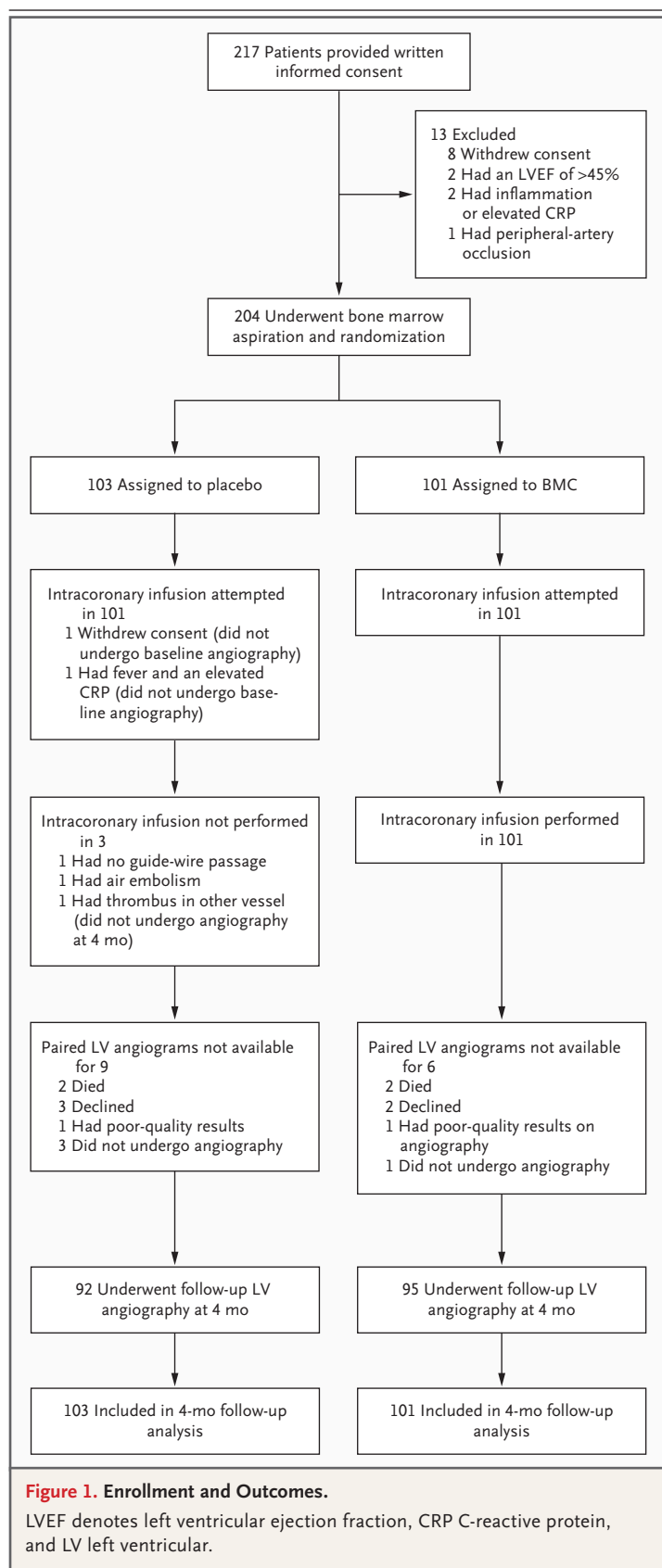
board at each participating center approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. A total of 16 centers in Germany and 1 in Switzerland participated in this investigator-initiated trial.

All patients underwent bone marrow aspiration 3 to 6 days after receiving reperfusion therapy for acute myocardial infarction. The bone marrow aspirate was sent by courier to the central cell-processing laboratory (Institute for Transfusion Medicine, Frankfurt, Germany), where patients were randomly assigned to receive placebo medium or BMC, and the study medication was sent back to the centers. Temperature-registering isolation boxes were used for the shipment of bone marrow aspirates and the study medication to monitor the quality of the materials during transportation. Baseline left ventricular angiography was performed at the time of intracoronary infusion of study medication and was repeated in identical projections at 4 months of follow-up (Fig. 1). All patients undergoing bone marrow aspiration underwent randomization, and clinical follow-up started at the time of bone marrow aspiration.

CELL PREPARATION AND ADMINISTRATION

A total of 50 ml of bone marrow was aspirated into heparin-treated syringes from the iliac crest with the use of local anesthesia. The bone marrow aspirate was shipped at room temperature together with 20 ml of venous blood used to produce patients' own serum to the central cell-processing laboratory. Progenitor cells were isolated and enriched with the use of Ficoll-Hypaque centrifugation procedures.¹⁴ The cell suspension consisted of a heterogeneous cell population including hematopoietic, mesenchymal, and other progenitor cells, as well as mononuclear cells. The cells were suspended in 10 ml of X VIVO 10 medium (a serum-free medium containing pharmaceutical-grade human components, Cambrex), including 2 ml of the patient's own serum. The placebo medium consisted of the 10 ml of X VIVO 10 medium, including 2 ml of the patient's own serum (without BMC). Frequencies of BMC were assessed according to the guideline of the International Society of Hematotherapy and Graft Engineering.¹⁸

After undergoing arterial puncture, all patients received 7500 to 10,000 U of heparin, and the first 85 patients received a bolus of abciximab



(0.25 mg per kilogram of body weight). Cells were infused with the use of a stop-flow technique through an over-the-wire balloon catheter (Open-sail, Guidant) positioned within the segment containing the stent, as described previously.¹²

LEFT VENTRICULAR ANGIOGRAPHY

Left ventricular angiograms were obtained in identical standard projections at the time of the baseline procedure (immediately before intracoronary cell infusion) and at 4 months. An experienced investigator in a central core laboratory who was unaware of the patient's treatment assignment quantitatively analyzed the left ventricular angiograms from individual patients with the use of CMS software (version 6.0, Medis), as previously described.¹² Left ventricular ejection fraction (LVEF) and left ventricular volumes were calculated with the use of the area-length method, and regional wall motion in the infarcted zone was determined with the use of the center-line chord method.¹²

END POINTS

The primary end point was the absolute change in global LVEF from baseline to 4 months, as measured by quantitative left ventricular angiography.¹⁷ Secondary end points included changes in left ventricular end-diastolic and end-systolic volume and changes in regional wall motion. Prespecified subgroup analyses were conducted to determine whether there was an interaction of the primary end point with baseline LVEF and the time to intracoronary-infusion therapy. Prespecified clinical end points included major adverse events (defined as death, recurrence of myocardial infarction, or any revascularization procedure) and rehospitalization for heart failure. Other clinical events or combined end points were assessed as a post hoc analysis. Only the first event for each patient was included in the analysis. As of June 16, 2006, 1-year clinical follow-up data were available for 168 patients.

STATISTICAL ANALYSIS

Continuous variables are presented as means \pm SD (unless stated otherwise). Analysis-of-variance testing was used to compare the incidence of the primary end point — the change in LVEF — between the groups. For subgroup analyses, subgroup variables were entered as effects into the univariate analysis-of-variance model to determine whether there was an interaction with the treatment assignment. An analysis-of-variance model

was used to adjust for effects, and an analysis-of-covariance model was used to adjust for covariates. To estimate the treatment effect, differences in least-square means and corresponding 95% confidence intervals (CIs) were calculated on the basis of the analysis-of-variance model. All other analyses were performed in a nonparametric paired fashion with the use of the Wilcoxon signed-rank test, if not stated otherwise. Nonparametric Mann-Whitney U and Kruskal-Wallis tests were used to compare continuous with categorical variables. Categorical variables were compared with the chi-square test or Fisher's exact test, as appropriate. Spearman's correlation coefficient was used to correlate continuous data. A P value of less than 0.05 was considered to indicate statistical significance. All reported P values are two-sided. Statistical analyses were performed with SPSS software (version 13.0, SPSS).

RESULTS

ENROLLMENT AND BASELINE CHARACTERISTICS

A total of 217 patients with an acute myocardial infarction successfully reperfused by means of stent implantation gave written informed consent to participate in the trial. Of these patients, 13 were excluded before undergoing bone marrow aspiration (Fig. 1). Of the remaining 204 patients undergoing bone marrow aspiration, 103 were randomly assigned to receive an infusion of placebo medium and 101 to receive a BMC infusion into the infarct-related coronary artery. The two groups were well matched with respect to baseline characteristics and procedural characteristics of the reperfusion therapy and concomitant pharmacologic therapy during the study (Table 1). The characteristics of the BMC are provided in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

PROCEDURAL RESULTS OF INTRACORONARY INFUSION

After bone marrow aspiration, one patient withdrew consent and one patient was excluded owing to fever and an increase in the level of C-reactive protein. No patient had bleeding complications or hematoma formation at the bone marrow puncture site. Intracoronary infusion was successful in all patients in the BMC group. In the placebo group, intracoronary infusion was not performed in three patients: in one the guidewire could not be advanced into the infarct-related ar-

tery, one had an air embolism during initial angiography before the guidewire could be advanced, and one had angiographic evidence of a thrombus in a non-infarct-related artery.

QUANTITATIVE VARIABLES OF LEFT VENTRICULAR FUNCTION

Baseline measurements of left ventricular function and volumes did not differ significantly between the two groups (Table 1). At 4 months, paired left ventricular angiograms with adequate contrast opacification for quantitative analysis were available for 95 patients in the BMC group and 92 patients in the placebo group. Paired left ventricular angiograms were not available for the two patients in each group who died, five patients (three in the placebo group and two in the BMC group) who declined to undergo angiography at follow-up, three patients who missed one angiographic session (two patients in the placebo group and one patient in the BMC group), and one patient with left ventricular thrombus in the placebo group. In addition, in one patient in each group, poor contrast opacification precluded quantitative analysis of the left ventricular angiogram (Fig. 1).

Global LVEF increased from a mean of $46.9 \pm 10.4\%$ at baseline to $49.9 \pm 13.0\%$ at 4 months in the placebo group. In the BMC group, global LVEF increased from $48.3 \pm 9.2\%$ to $53.8 \pm 10.2\%$ (Table 2). At 4 months, LVEF was significantly higher in the BMC group than in the placebo group ($P=0.02$). The absolute increase in LVEF was significantly greater in the BMC group than in the placebo group (2.5%; 95% CI, 0.5 to 4.5; $P=0.01$).

In order to document that the primary end point of the study was not affected by the subtle, nonsignificant differences in both baseline variables and clinical end points during follow-up between the two groups, we reanalyzed the data after adjustment for a variety of effects or covariates (Fig. 2). None of the adjustments altered the primary finding that intracoronary administration of BMC was associated with a significantly greater increase in global LVEF than was placebo.

Selective analysis of the infarcted zone revealed a significantly greater improvement in regional contractility in the BMC group than in the placebo group (Table 2). End-diastolic volumes slightly increased in both groups (Table 2). In contrast, left ventricular end-systolic volumes remained

Table 1. Baseline Characteristics of the Patients and Concomitant Therapy.*

Characteristic	Placebo (N=103)	BMC (N=101)	P Value
Risk factor			
Age — yr			
Mean	57±11	55±11	0.39
Median	55	56	
Male sex — no. (%)	84 (82)	83 (82)	0.91
Hypertension — no. (%)	62 (60)	55 (54)	0.41
Hyperlipidemia — no. (%)	61 (59)	53 (52)	0.33
Diabetes — no. (%)	22 (21)	12 (12)	0.07
Insulin-dependent	8 (8)	3 (3)	
Smoking (current or former) — no. (%)	70 (68)	74 (73)	0.41
Family history of coronary heart disease — no. (%)	37 (36)	35 (35)	0.85
Coronary artery disease — no. (%)			0.36
1-Vessel disease	60 (58)	61 (60)	
2-Vessel disease	32 (31)	24 (24)	
3-Vessel disease	11 (11)	16 (16)	
Infarct treatment			
Infarct-related vessel — no. (%)			0.09
Left anterior descending coronary artery	78 (76)	65 (64)	
Left circumflex artery	4 (4)	11 (11)	
Right coronary artery	21 (20)	25 (25)	
PCI for additional stenoses in non-infarct-related vessels — no. (%)	12 (12)	10 (10)	0.69
Time from symptom onset to first reperfusion therapy — hr			
Mean	7.0±6.5	7.5±8.0	0.87
Median	4.5	4.5	
TIMI flow grade before PCI			
Mean	0.75±1.1	0.85 ±1.2	0.57
Median	0	0	
Drug-eluting stent — no. (%)	13 (13)	16 (16)	0.51
GP IIb/IIIa inhibitor during acute PCI — no. (%)	81 (79)	82 (81)	0.65
Intravenous catecholamines — no. (%)	8 (8)	5 (5)	0.41
Maximal creatine kinase — ×ULN			
Mean	19.3±13.7	19.8±17.2	0.53
Median	16.2	14.6	
Cell therapy			
Time from reperfusion to infusion of study therapy — days			
Mean	4.4±1.4	4.3±1.3	0.61
Median	4.0	4.0	
TIMI flow grade before study therapy			
Mean	2.94±0.34	2.97±0.22	0.43
Median	3	3	
TIMI flow grade after study therapy			
Mean	2.99±0.10	2.98±0.20	1.0
Median	3	3	
No. of BMC injected — ×10 ⁻⁶			
Mean	—	236±174	
Median	—	198	

Table 1. (Continued.)			
Characteristic	Placebo (N=103)	BMC (N=101)	P Value
CD34+CD45+ — %			
Mean	—	1.5±0.7	
Median	—	1.4	
Absolute no. — ×10⁻⁶			
Mean	—	3.6±3.6	
Median	—	2.5	
CD34+CD133+CD45+ — %			
Mean	—	0.99±0.47	
Median	—	0.93	
Absolute no. — ×10⁻⁶			
Mean	—	2.5±2.5	
Median	—	1.8	
Viability of cells — %			
Mean	—	98±1.2	
Median	—	99	
Baseline quantitative left ventricular angiography†			
Ejection fraction — %			
Mean	46.7±10.3	47.5±10.0	0.57
Median	47.5	49.7	
End-diastolic volume — ml			
Mean	138±45	129±37	0.12
Median	132	120	
End-systolic volume — ml			
Mean	74.2±31	68.4±27.1	0.16
Median	68.4	62.2	
Medication at discharge — no. (%)‡			
Aspirin	99 (97)	100 (100)	0.25
Clopidogrel	102 (100)	100 (100)	1.0
ACE inhibitor or AT II blocker	99 (97)	97 (97)	1.0
Beta-blocker	102 (100)	97 (97)	0.12
Digitalis	8 (8)	2 (2)	0.10
Aldosterone antagonist	16 (16)	5 (5)	0.01
Statin	100 (98)	100 (100)	0.50
Medication at 4 mo — no. (%)§			
Aspirin	96 (95)	98 (99)	0.21
Clopidogrel	84 (83)	81 (82)	0.80
ACE inhibitor or AT II-receptor blocker	98 (97)	96 (97)	1.0
Beta-blocker	96 (95)	92 (93)	0.53
Digitalis	5 (5)	1 (1)	0.21
Aldosterone antagonist	13 (13)	5 (5)	0.05
Statin	90 (89)	95 (96)	0.07

* Plus-minus values are means ±SD. TIMI denotes Thrombolysis in Myocardial Infarction, PCI percutaneous coronary intervention, GP glycoprotein, ULN upper limit of the normal range, ACE angiotensin-converting-enzyme, and AT angiotensin.

† The analysis included 100 patients in the placebo group and 99 in the BMC group.

‡ The analysis included 102 patients in the placebo group and 100 in the BMC group.

§ At 4 months, two patients in each group had died.

Variable	Placebo (N=92)	BMC (N=95)	P Value
Global LVEF (%)			
Baseline			
Mean	46.9±10.4	48.3±9.2	0.31
Median	47.5	50.6	
4 Mo			
Mean	49.9±13.0	53.8±10.2	0.02†
Median	53.2	54.7	
Absolute difference			
Mean	3.0±6.5	5.5±7.3	0.01‡
Median	4.0	5.0	
P value (baseline vs. 4 mo)	<0.001	<0.001	
End-diastolic volume (ml)			
Baseline			
Mean	139±46	128±38	0.09
Median	132	121	
4 Mo			
Mean	153±57	141±43	0.09
Median	138	134	
Difference			
Mean	14±33	12±31	0.64
Median	12	13	
P value (baseline vs. 4 mo)	<0.001	<0.001	
End-systolic volume (ml)			
Baseline			
Mean	75±32	67±26	0.09
Median	69	62	

constant in the BMC group but increased in the placebo group. The absolute change in left ventricular end-systolic volumes differed significantly between the two groups (Table 2).

INTERACTION BETWEEN CHANGE IN LVEF AND BOTH BASELINE LVEF AND TIME TO INFUSION

There was a significant inverse relation between baseline LVEF and the absolute change in LVEF at 4 months in the BMC group ($r=-0.21$, $P=0.04$) but not in the placebo group ($r=+0.11$, $P=0.31$). When the total patient population was dichotomized according to the median value of LVEF at baseline, there was a significant interaction between the treatment effect of the BMC infusion and the baseline LVEF ($P=0.02$). Among patients with a baseline LVEF at or below the median value (48.9%), patients in the BMC group had an ab-

solute increase in LVEF that was three times that in the placebo group (Fig. 3A): $7.5\pm7.1\%$ as compared with $2.5\pm7.7\%$ (absolute difference, 5.0% ; 95% CI, 2.0 to 8.1). Among patients with a baseline LVEF above the median, the absolute difference between groups was 0.3% (95% CI, -2.2 to 2.8), with an absolute improvement in LVEF in the placebo group of $3.7\pm4.6\%$, as compared with $4.0\pm7.1\%$ in the BMC group.

Correlating the absolute changes in LVEF at 4 months with the time from reperfusion therapy to intracoronary infusion of BMC or placebo medium revealed a significant interaction, with a progressive increase in BMC-associated recovery of contractile function as the interval between reperfusion therapy and BMC infusion increased ($P=0.01$) (Fig. 3B). In fact, the beneficial effects of BMC infusion on the recovery of contractile

Table 2. (Continued.)

Variable	Placebo (N=92)	BMC (N=95)	P Value
4 Mo			
Mean	80±45	67±30	0.01‡
Median	66	59	
Difference			
Mean	5.6±22	-0.6±19	0.04¶
Median	1.5	-2.6	
P value (baseline vs. 4 mo)	0.02	0.76	
Regional wall-motion analysis in infarcted zone			
Contractility in infarcted zone (SD from normal/chord)**			
Baseline			
Mean	-1.54±0.42	-1.54±0.42	0.27
Median	-1.53	-1.49	
4 Mo			
Mean	1.27±0.60	-1.17±0.60	<0.001
Median	-1.29	-1.20	
Difference			
Mean	0.28±0.52	0.37±0.53	<0.001
Median	0.23	0.28	
P value (baseline vs. 4 mo)	<0.001	<0.001	

* Plus-minus values are means ±SD. P values were determined by analysis of variance.
 † P=0.05 by nonparametric testing.
 ‡ P=0.04 by nonparametric testing.
 § P=0.07 by nonparametric testing.
 ¶ P=0.06 by nonparametric testing.
 || P=0.09 by nonparametric testing.
 ** Values represent the cumulative analysis of all chords in the infarct area.

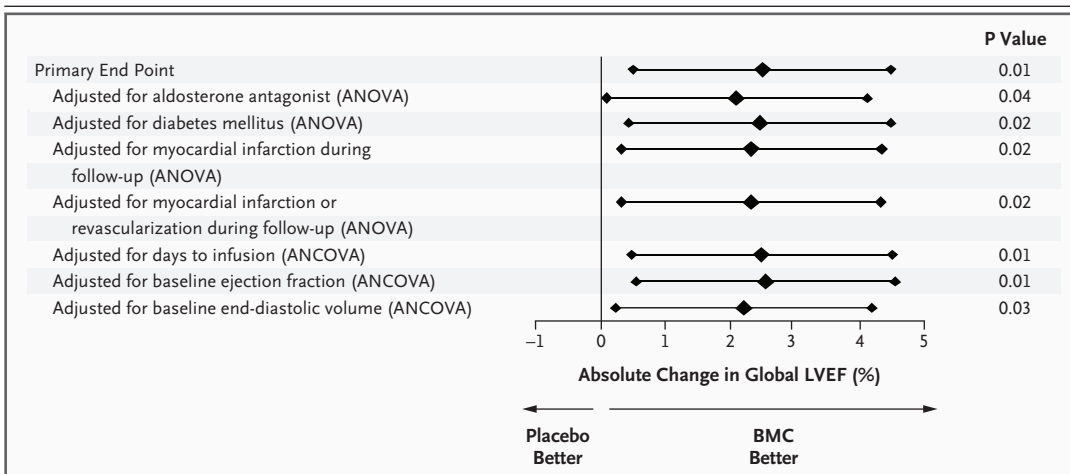
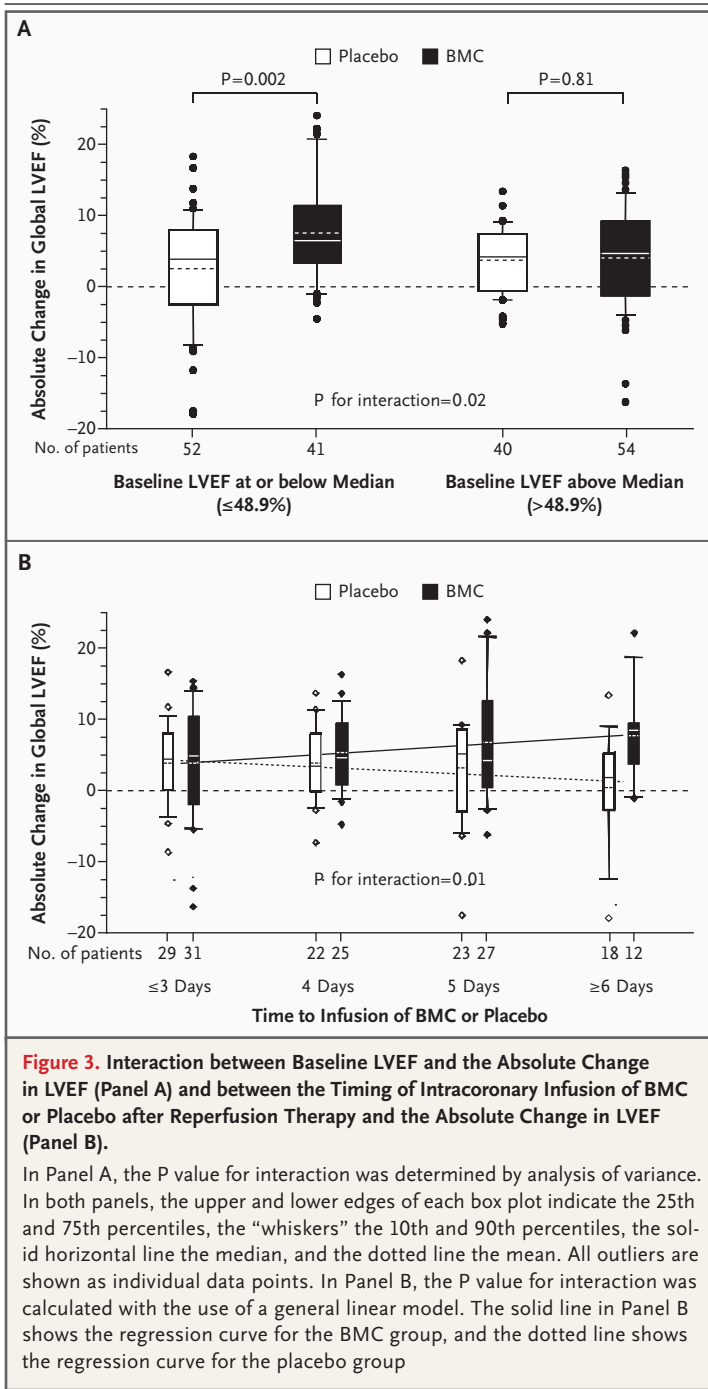


Figure 2. Effect of BMC Therapy as Compared with Placebo on the Primary End Point of the Absolute Change in the Global LVEF from Baseline to 4 Months.

The primary end point is shown before and after adjustment for effects according to analysis of variance (ANOVA) or analysis of covariance (ANCOVA). The large diamonds show the absolute change in LVEF, and the small diamonds show the 95% CI.



BMC group; $P=0.004$), whereas no benefit was observed in patients treated up to day 4 after reperfusion (treatment-associated increase in LVEF, 0.6%; 95% CI, -1.8 to 3.0 ; absolute improvement in LVEF, $3.9 \pm 5.4\%$ in the placebo group vs. $4.5 \pm 6.8\%$ in the BMC group; $P=0.62$). The interaction between the BMC treatment effect and the timing of the procedure (≤ 4 days vs. ≥ 5 days) was significant ($P=0.03$) and remained significant when baseline LVEF was also entered into the model as a covariate ($P=0.04$).

CLINICAL OUTCOMES

Table 3 summarizes the adverse clinical events during hospitalization for acute myocardial infarction, at 4 months, and at 1 year (data were available for 168 patients as of June 16, 2006). The occurrence of the individual major adverse cardiac events of death, recurrence of myocardial infarction, and rehospitalization for heart failure did not differ significantly between the two groups during follow-up. However, the incidence of the prespecified combined clinical end point of death, recurrence of myocardial infarction, and coronary revascularization was significantly lower in the BMC group than in the placebo group (Table 3). Likewise, the post hoc combined clinical end point of death, recurrence of myocardial infarction, and rehospitalization for heart failure occurred less frequently in the BMC group than in the placebo group.

DISCUSSION

The principal finding of our study is that intracoronary administration of BMC is associated with a significant increase in the recovery of left ventricular contractile function in patients with optimally treated acute myocardial infarction. Because the results of early pilot studies were promising,¹¹⁻¹⁶ we designed a placebo-controlled, double-blind, multicenter trial in which patients with acute myocardial infarction were randomly assigned to receive an infusion of either BMC or placebo medium in the infarct-related artery within 3 to 7 days after successful reperfusion therapy and the implantation of a stent. After 4 months, the global LVEF was significantly higher in the BMC group than in the placebo group. The enhanced recovery of global left ventricular contractile function after the intracoronary administra-

function were confined to patients who were treated more than 4 days after infarct reperfusion. BMC infusion on day 5 or later was associated with an absolute increase in LVEF of 5.1% (95% CI, 1.7 to 8.5; absolute improvement in LVEF, $1.9 \pm 7.6\%$ in the placebo group vs. $7.0 \pm 7.7\%$ in the

Table 3. Clinical Events during Follow-up.

Event	Placebo (N=103)	BMC (N=101)	P Value
	<i>no. of patients</i>		
Events before hospital discharge*			
Death	1	1	1.0†
Myocardial infarction	2	0	0.50†
4-Mo follow-up (cumulative)			
Death	2	2	1.0†
Myocardial infarction	5	0	0.06†
Rehospitalization for heart failure	2	0	0.50†
Revascularization	28	19	0.16‡
Target-vessel revascularization	20	15	0.39‡
Stent thrombosis	3	1	0.62†
Non–target-vessel revascularization	12	5	0.08‡
Cerebral infarction	0	0	
Documented ventricular arrhythmia or syncope	4	4	1.0†
Combined events			
Death and recurrence of myocardial infarction	7	2	0.17†
Death, recurrence of myocardial infarction, and any revascularization procedure	30	21	0.17‡
Death, recurrence of myocardial infarction, and infarct-vessel revascularization	22	17	0.41‡
Death, recurrence of myocardial infarction, and rehospitalization for heart failure	9	2	0.03‡
1-Yr follow-up (cumulative)§			
Death	6	2	0.28 †
Myocardial infarction	5	0	0.06†
Rehospitalization for heart failure	3	0	0.25 †
Revascularization	35	21	0.03‡
Target-vessel revascularization	24	16	0.18‡
Stent thrombosis	3	1	0.62†
Non–target-vessel revascularization	16	6	0.03‡
Cerebral infarction	1	1	1.0 †
Documented ventricular arrhythmia or syncope	5	5	1.0†
Combined events			
Death and recurrence of myocardial infarction	10	2	0.02 ‡
Death, recurrence of myocardial infarction, and any revascularization procedure	40	23	0.01 ‡
Death, recurrence of myocardial infarction, and infarct-vessel revascularization	29	18	0.08‡
Death, recurrence of myocardial infarction, and rehospitalization for heart failure	12	2	0.006‡

* These events occurred after bone marrow aspiration and randomization.

† Fisher's exact test was used.

‡ The chi-square test was used.

§ The mean follow-up was 10.7±3.3 months.

tion of BMC was due to a significant reduction in the extent and magnitude of regional left ventricular dysfunction within the territory of the infarct. Thus, segments with the most severe impairment in contractility at baseline appear to derive the greatest benefit from BMC administration. Moreover, intracoronary administration of BMC abrogated left ventricular end-systolic volume expansion after the infarction. Taken together, our findings indicate that when combined with optimal reperfusion therapy (stent implantation) and state-of-the-art medical treatment, intracoronary administration of BMC enhances the recovery of global and regional left ventricular function after myocardial infarction.

The results of our predefined subgroup analysis generate some important hypotheses essential for designing trials that address the clinical relevance of BMC administration. The magnitude of left ventricular contractile recovery was inversely related to the baseline LVEF, confirming similar observations in the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) pilot trial.¹⁴ Patients with the most severely depressed left ventricular contractile function had the greatest improvement in contractile function after the intracoronary administration of BMC. A reduced LVEF during the acute phase of myocardial infarction is the most important independent predictor of a poor outcome, even in the era of optimal reperfusion therapy with the use of stenting of the infarct-related artery.¹⁹ Thus, enhanced recovery of contractile function may be beneficial specifically in patients with large infarcts and depressed left ventricular function.

The mechanisms involved in mediating the recovery of contractile function after the intracoronary infusion of BMC are not well understood.²⁰ The microenvironment within the infarct tissue and the timing of cell delivery may be important determinants of the incorporation and effect of BMC.²⁰ We found that an intracoronary infusion of BMC within 4 days after reperfusion therapy for acute myocardial infarction had only marginal effects on the recovery of left ventricular contractile function. This finding is in agreement with the preliminary results of a small, randomized, placebo-controlled trial in which intracoronary infusion of bone marrow-derived mononuclear progenitor cells within 24 hours

after reperfusion therapy failed to improve left ventricular function in patients with acute myocardial infarction.²¹

Our study was not powered to assess whether intracoronary infusion of BMC can reduce the risk of complications and death among patients with acute myocardial infarction. However, the incidence of individual adverse clinical end points tended to be lower in the BMC group than in the placebo group. Thus, the intracoronary administration of BMC appears to be safe and feasible.

A major limitation of our study was the exclusive use of left ventricular angiography for the serial assessment of left ventricular function. Although angiography is well suited to delineate regional contractile function, the use of magnetic resonance imaging to assess global left ventricular function would have more precisely depicted changes in the distorted geometry of the infarcted hearts.

In summary, after acute myocardial infarction, the intracoronary administration of BMC enhances left ventricular contractile recovery. Given the safety profile of this treatment and the beneficial effects in patients with the most severely impaired left ventricular function, large-scale studies are warranted to examine the potential effects of this novel approach on the risk of death and complications in patients with large acute myocardial infarctions and depressed left ventricular contractile function.

Supported by an unrestricted research grant from Guidant. Guidant provided balloon catheters, and Eli Lilly provided the abciximab.

Dr. Schächinger reports having received consulting fees from Guidant and AstraZeneca and lecture fees from Pfizer, Novartis, Merck Sharp & Dohme, Lilly, Boehringer Ingelheim, Sanofi-Aventis, and Boston Scientific. Dr. Dimmeler reports having received consulting fees from Guidant and Genzyme and lecture fees from Medtronic. Dr. Zeiher reports having received consulting fees from Guidant. Dr. Haberbosch reports having received lecture fees from Takeda, Merck Sharp & Dohme, Essex, and Pfizer. Drs. Dimmeler and Zeiher report that they are cofounders of t2cure, a for-profit company focused on regenerative therapies for cardiovascular disease. They serve as scientific advisers and are shareholders. No other potential conflict of interest relevant to this article was reported.

We are indebted to Hans Martin (Department of Hematology) for expert advice, to Tina Rasper and Nicola Krzossok for technical assistance in cell processing, to Wilhelm Sauer mann for statistical advice, to Tayfun Aybek for database assistance, to Florian Seeger and Jörg Honold for logistic support, and to the following nonprofit research organizations, which supported the research leading to the initiation of the study: Alfried Krupp Stiftung, German Research Foundation, and European Vascular Genomics Network.

APPENDIX

The following investigators and committee members participated in the REPAIR-AMI study (numbers in parentheses are the numbers of patients enrolled): *Germany* — Herzzentrum, Leipzig (35) — S. Erbs, R. Hambrecht; J.W. Goethe Universität, Frankfurt (28) — V. Schächinger, A. Zeiher; Kerckhoff Klinik, Bad Nauheim (22) — A. Elsässer, M. Stanisch, C. Hamm; Zentralklinikum, Suhl (18) — W. Haberbosch; Universitätsklinikum, Giessen (15) — H. Hölschermann, H. Tillmanns; Zentralklinikum, Bad Berka (14) — J. Yu, B. Lauer; Hamburg University Cardiovascular Center, Hamburg (13) — D. Mathey, T. Tübler; Universitätsklinikum, Mannheim (11) — T. Süselbeck, M. Brückmann, K. Haase; Universitätsklinikum, Homburg/Saar (9) — G. Nickenig, N. Werner, M. Böhm; Kardiologisches Centrum Rotes Kreuz, Frankfurt (8) — J. Haase; Klinikum, Kassel (5) — C. Hansen, J. Neuzner; Bergmannshäel Klinik, Universität Bochum, Bochum (4) — A. Germing, A. Mügge; Herzzentrum Ludwigshafen (4) — B. Mark, J. Senges; Herzzentrum Nordrhein Westfalen, Bad Oeynhausen (3) — C. Hoffmann, M. Farr, D. Horstkotte; Klinikum, Lippe (1) — A. Cuneo, U. Tebbe; Universitätsklinik, Mainz (1) — S. Genth-Zotz, T. Münzel; *Switzerland* — Universitätsspital, Zurich (13) — R. Corti, T. Lüscher; *Steering Committee* — A.M. Zeiher (principal investigator), S. Dimmeler, V. Schächinger, W. Haberbosch, K.K. Haase, D. Mathey, R. Hambrecht; *Study Coordinating Center, Frankfurt, Germany* — H. Braun, V. Schächinger; *Angiographic Core Laboratory, Frankfurt, Germany* — B. Assmus, A.M. Zeiher; *Safety Committee* — T. Bonzel (Fulda, Germany), W. Kasper (Wiesbaden, Germany).

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