

## ORIGINAL ARTICLE

# Transcoronary Transplantation of Progenitor Cells after Myocardial Infarction

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## ABSTRACT

**BACKGROUND**

Pilot studies suggest that intracoronary transplantation of progenitor cells derived from bone marrow (BMC) or circulating blood (CPC) may improve left ventricular function after acute myocardial infarction. The effects of cell transplantation in patients with healed myocardial infarction are unknown.

**METHODS**

After an initial pilot trial involving 17 patients, we randomly assigned, in a controlled crossover study, 75 patients with stable ischemic heart disease who had had a myocardial infarction at least 3 months previously to receive either no cell infusion (23 patients) or infusion of CPC (24 patients) or BMC (28 patients) into the patent coronary artery supplying the most dyskinetic left ventricular area. The patients in the control group were subsequently randomly assigned to receive CPC or BMC, and the patients who initially received BMC or CPC crossed over to receive CPC or BMC, respectively, at 3 months' follow-up.

**RESULTS**

The absolute change in left ventricular ejection fraction was significantly greater among patients receiving BMC (+2.9 percentage points) than among those receiving CPC (−0.4 percentage point,  $P=0.003$ ) or no infusion (−1.2 percentage points,  $P<0.001$ ). The increase in global cardiac function was related to significantly enhanced regional contractility in the area targeted by intracoronary infusion of BMC. The crossover phase of the study revealed that intracoronary infusion of BMC was associated with a significant increase in global and regional left ventricular function, regardless of whether patients crossed over from control to BMC or from CPC to BMC.

**CONCLUSIONS**

Intracoronary infusion of progenitor cells is safe and feasible in patients with healed myocardial infarction. Transplantation of BMC is associated with moderate but significant improvement in the left ventricular ejection fraction after 3 months. (ClinicalTrials.gov number, NCT00289822.)

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**C**HRONIC HEART FAILURE IS COMMON, and its prevalence continues to increase.<sup>1</sup> Ischemic heart disease is the principal cause of heart failure.<sup>2</sup> Although myocardial salvage due to early reperfusion therapy has significantly reduced early mortality rates,<sup>3</sup> postinfarction heart failure resulting from ventricular remodeling remains a problem.<sup>4</sup> One possible approach to reversing postinfarction heart failure is enhancement of the regeneration of cardiac myocytes as well as stimulation of neovascularization within the infarcted area. Initial clinical pilot studies have suggested that intracoronary infusion of progenitor cells is feasible and may beneficially affect postinfarction remodeling processes in patients with acute myocardial infarction.<sup>5-9</sup> However, it is currently unknown whether such a treatment strategy may also be associated with improvements in cardiac function in patients with persistent left ventricular dysfunction due to healed myocardial infarction with established scar formation.

Therefore, in the prospective TOPCARE-CHD (Transplantation of Progenitor Cells and Recovery of LV [Left Ventricular] Function in Patients with Chronic Ischemic Heart Disease) trial, we investigated whether intracoronary infusion of progenitor cells into the infarct-related artery at least 3 months after myocardial infarction improves global and regional left ventricular function.

## METHODS

### PATIENTS

Between January 2002 and December 2004, a total of 92 patients who had had a myocardial infarction at least 3 months previously were recruited into the study at a single center. Patients between 18 and 80 years of age were eligible for inclusion in the study if they had had a documented myocardial infarction at least 3 months before inclusion and had a well-demarcated region of left ventricular dysfunction and a patent infarct-related artery. Exclusion criteria were the presence of acutely decompensated heart failure with a New York Heart Association (NYHA) class of IV, a history of other severe chronic diseases or cancer, or unwillingness to participate. The ethics review board of the Johann Wolfgang Goethe University in Frankfurt, Germany, approved the protocol; the trial was registered according to the German Drug Law (accession numbers, 0703/01 and 0704/01); and the study was conducted in

accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

### STUDY DESIGN

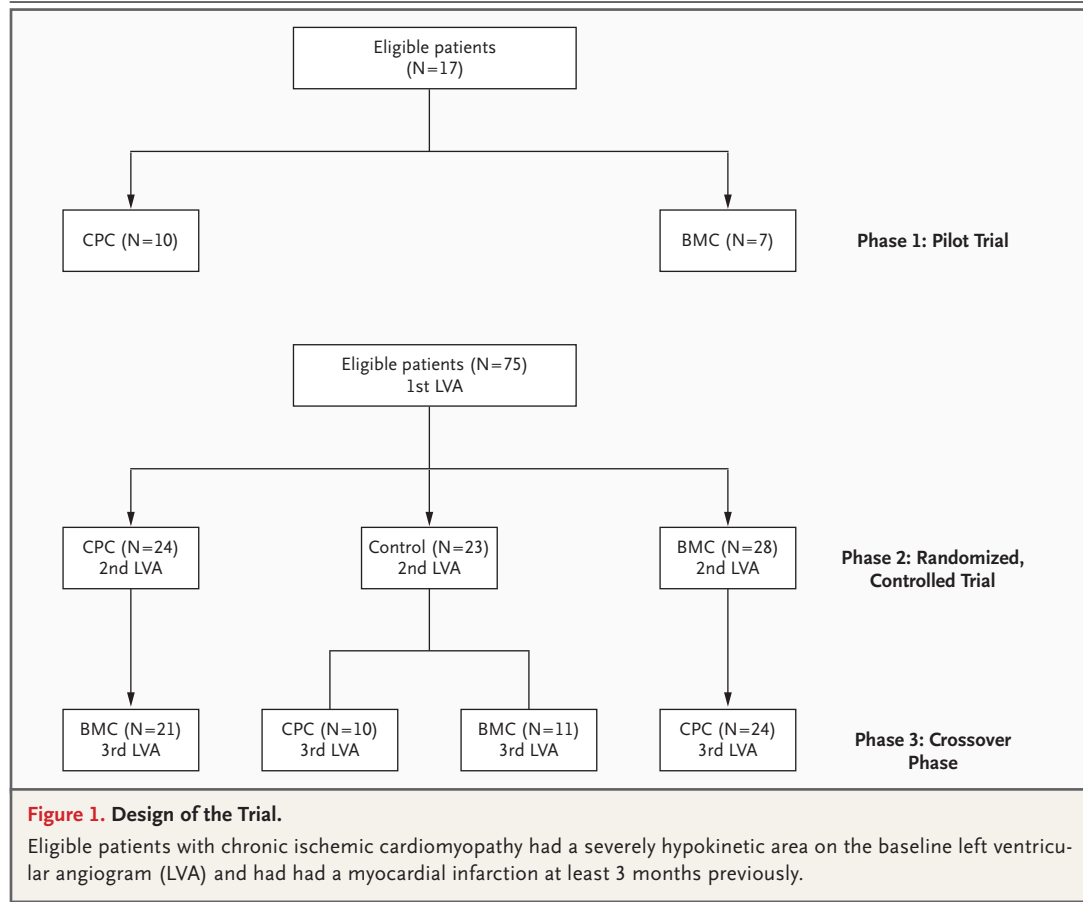
The study consisted of three phases: a pilot trial comprising 17 patients (7 receiving progenitor cells derived from bone marrow [BMC] and 10 receiving progenitor cells derived from circulating blood [CPC]); a second phase, in which 75 patients were randomly assigned to receive intracoronary infusion of BMC (28 patients) or CPC (24) or no cell infusion (23); and a third phase, in which the 75 randomly assigned patients crossed over to one of the active treatments if they had originally been in the control group or to the alternate cell type if they had initially received intracoronary cell infusion (Fig. 1).

The primary end point of the study was the absolute change in global left ventricular ejection fraction (LVEF) as measured by quantitative left ventricular angiography 3 months after cell infusion. Secondary end points included quantitative variables relating to the regional left ventricular function of the target area, as well as left ventricular volumes derived from serial left ventricular angiograms. In addition, functional status was assessed by NYHA classification. Finally, event-free survival was defined as freedom from death, myocardial infarction, stroke, or rehospitalization for worsening heart failure. Causes of rehospitalization during follow-up were verified by review of the discharge letters or charts of hospital stays.

### PREPARATION AND TRANSPLANTATION OF PROGENITOR CELLS

For patients assigned to receive CPC, mononuclear cells were isolated by Ficoll density-gradient centrifugation of 270 ml of venous blood and cultured for 3 days *ex vivo*, as previously reported.<sup>6,7,9-12</sup> A mean of  $22 \times 10^6 \pm 11 \times 10^6$  CPC were infused. For patients assigned to receive BMC, 50 ml of bone marrow aspirate was obtained while the patients were under local anesthesia on the morning of cell-transplantation day. BMC were isolated by Ficoll density-gradient centrifugation, as previously reported.<sup>6,7,9</sup> We infused a mean of  $205 \times 10^6 \pm 110 \times 10^6$  BMC, of which on average less than 1% were positive for the hematopoietic progenitor-cell marker CD34.

For cell transplantation, arterial puncture



was followed by the administration of 7500 to 10,000 U of heparin and (in 89% of the cell-treated patients) a bolus of abciximab (0.25 mg per kilogram of body weight). Cells were infused into the vessel supplying the most dyskinetic left ventricular area by means of a balloon catheter with a stop-flow technique, as previously described.<sup>6</sup>

#### EVALUATION OF SAFETY AND FEASIBILITY

Clinical, laboratory, and safety-related data were prospectively collected. Follow-up visits after 3 months were performed by physicians. Procedural complications were defined as any ventricular arrhythmia, visible thrombus formation, distal embolization, or injury of the coronary artery associated with the cell-infusion catheterization procedure. For patients undergoing bone marrow aspiration, potential bleeding complications were assessed. During hospitalization, telemetry was routinely performed for 24 hours after the procedure in all patients.

#### LEFT VENTRICULAR ANGIOGRAPHY

Left ventricular angiograms were obtained at the time of the baseline procedure and at 3 months' follow-up. Quantitative analysis of paired left ventricular angiograms recorded in identical projections was performed by an investigator who was blinded to the individual patients' treatments; the analysis was performed with QCA-CMS software (version 5.2, Medis), as described elsewhere.<sup>6,7,9</sup>

#### MAGNETIC RESONANCE IMAGING

In a subgroup of 35 patients who did not have implanted defibrillators or pacemakers and who consented to and tolerated the imaging procedure, cardiac magnetic resonance imaging (MRI) (a 1.5-T system; Magnetom Sonata, Siemens Medical Solutions) was performed at baseline and at 3 months' follow-up. The results were analyzed as previously described<sup>7</sup> by an experienced investigator who was blinded to the type of cells infused.

**DETECTION OF VIABLE MYOCARDIUM**

All patients underwent low-dose dobutamine stress echocardiography, combined thallium single-photon-emission computed tomography and [<sup>18</sup>F]fluorodeoxyglucose positron-emission tomography, or both, as previously described.<sup>6</sup> It was possible to analyze regional left ventricular viability in 80 patients (87%).

**STATISTICAL ANALYSIS**

Continuous variables are presented as means ( $\pm$ SD), unless otherwise noted. Categorical variables were compared with use of the chi-square test or Fisher's exact test. Statistical comparisons between initial and follow-up data were performed in a nonparametric, paired fashion with use of the Wilcoxon signed-rank test. Nonparametric Mann-Whitney U tests and Kruskal-Wallis tests were used to compare continuous variables with categorical variables as well as to compare the results between treatment groups. Bonferroni-adjusted analysis-of-variance testing was used for between-group analysis of quantitative left ventricular angiographic results in phases 1 and 2 (the pilot phase and first randomized phase). For multivariate analysis, the treatment groups were categorized as follows: control, 0; CPC, 1; and BMC, 2. The multivariate analysis was performed with use of a stepwise linear regression model with a forward-entry stepping algorithm; variables with a P value of  $\leq 0.05$  on univariate analysis were entered in the model. Statistical significance was assumed for P values of less than 0.05. All statistical analyses were performed with SPSS software (version 12.0).

**RESULTS****BASELINE CHARACTERISTICS OF THE PATIENTS**

A total of 92 patients were enrolled in the study. Of these, 35 patients received BMC as their initial treatment (in phases 1 and 2 of the trial), 34 patients received CPC (in phases 1 and 2), and 23 patients received no intracoronary cell infusion (in phase 2, as the control group). Table 1 illustrates that the three groups of patients were well matched.

**EFFECTS OF PROGENITOR-CELL INFUSION***Quantitative Characteristics of Left Ventricular Function*

Patients with an adverse clinical event (six), subtotal stenosis of the target vessel at follow-up

(three), an intraventricular thrombus precluding performance of left ventricular angiography (one), or atrial flutter or fibrillation at follow-up (one) were excluded from the exploratory analysis. In addition, of the 81 eligible patients, left ventricular angiograms could not be quantitatively analyzed in 4 because of inadequate contrast opacification, in 1 because of ventricular extrasystoles, and in 4 because of the patients' refusal to undergo invasive follow-up. Thus, a total of 72 of 81 serial paired left ventricular angiograms were available for quantitative analysis (28 in the BMC group, 26 in the CPC group, and 18 in the control group).

Table 2 summarizes the angiographic characteristics of the 75 patients included in the randomized phase of the study. At baseline, the three groups did not differ with respect to global LVEF, the extent or magnitude of regional left ventricular dysfunction, left ventricular volumes, or stroke volumes.

The absolute change in global LVEF from baseline to 3 months did significantly differ among the three groups of patients. Patients receiving BMC had a significantly larger change in LVEF than patients receiving CPC ( $P=0.003$ ) and those in the control group ( $P<0.001$ ). Similar results were obtained when patients from the first two phases of the study (the pilot phase and the randomized phase) were pooled. The results did not differ when patients without evidence of viable myocardium before inclusion were analyzed separately. The change in LVEF was  $-0.3\pm 3.4$  percentage points in the control group (9 patients),  $+0.4\pm 3.0$  percentage points in the CPC group (18 patients), and  $+3.7\pm 4.0$  percentage points in the BMC group (18 patients) ( $P=0.02$  for the comparison with the control group and  $P=0.02$  for the comparison with the CPC group).

In the subgroup of 35 patients who underwent serial assessment of left ventricular function by MRI, MRI-derived global LVEF increased significantly, by  $4.8\pm 6.0\%$  ( $P=0.03$ ) among those receiving BMC (11 patients) and by  $2.8\pm 5.2\%$  ( $P=0.02$ ) among those receiving CPC (20 patients), whereas no change was observed in 4 control patients ( $P=0.14$ ). Thus, MRI-derived assessment of left ventricular function further corroborated the results obtained from the total patient population.

Analysis of regional left ventricular function revealed that BMC treatment significantly increased contractility in the center of the left ventricular target area (Table 2). Likewise, MRI-derived

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Control Group (N=23)	CPC Group (N=34)	BMC Group (N=35)	P Value
<b>Demographic and laboratory characteristics</b>				
Age — yr	61±9	56±12	60±11	0.32
Female sex — no. (%)	0	6 (18)	4 (11)	0.11
Blood pressure — mm Hg				
Systolic	117±21	109±20	109±22	0.28
Diastolic	66±11	63±10	62±14	0.48
Heart rate — beats/min	68±12	65±8	64±11	0.56
Body-mass index†	28±3	27±4	27±4	0.37
NYHA class — no. (%)				
1	7 (30)	7 (21)	5 (14)	0.34
2	11 (48)	13 (38)	18 (51)	
3	5 (22)	12 (35)	12 (34)	
4	0	2 (6)	0	
Serum creatinine — mg/dl‡	1.1±0.3	1.1±0.2	1.1±0.4	0.71
<b>Risk factors</b>				
Hypertension — no. (%)	16 (70)	19 (56)	21 (60)	0.58
Diabetes mellitus — no. (%)	5 (22)	9 (26)	10 (29)	0.84
Current or former smoking — no. (%)	19 (83)	28 (82)	27 (77)	0.78
Hypercholesterolemia — no. (%)§	20 (87)	28 (82)	27 (77)	0.31
Family history of coronary artery disease — no. (%)	10 (43)	24 (71)	21 (60)	0.12
<b>Medical history</b>				
Previous MI — no. (%)				
Anterior	9 (39)	22 (65)	20 (57)	0.34
Inferior	12 (52)	8 (24)	13 (37)	
Lateral	0	1 (3)	0	
Anterior and inferior	2 (9)	3 (9)	2 (6)	
Time since most recent MI — mo				
Mean	81±101	77±76	81±72	0.59
Median	24	50	60	
Range	3–358	3–276	4–300	

regional analysis of left ventricular function revealed that the number of hypocontractile segments was significantly reduced, from  $10.1\pm 3.6$  to  $8.7\pm 3.6$  segments ( $P=0.02$ ), and the number of normocontractile segments significantly increased, from  $3.8\pm 4.5$  to  $5.4\pm 4.6$  segments ( $P=0.01$ ), in the BMC group, whereas no significant changes were observed in the CPC group. MRI-derived infarct size, as measured by late enhancement volume normalized to left ventricular mass, remained constant both in the CPC group ( $25\pm 18\%$  at baseline and  $23\pm 14\%$  at 3 months, 13

patients) and in the BMC group ( $20\pm 10\%$  at both time points, 9 patients). Thus, taken together, the data suggest that intracoronary infusion of BMC is associated with significant improvements in global and regional left ventricular contractile function among patients with persistent left ventricular dysfunction due to prior myocardial infarction.

To identify independent predictors of improved global LVEF, a stepwise multivariate regression analysis was performed; it included classic determinants of LVEF as well as various baseline char-

**Table 1. (Continued.)**

Characteristic	Control Group (N=23)	CPC Group (N=34)	BMC Group (N=35)	P Value
Extent of coronary artery disease — no. (%)				0.07
One vessel	2 (9)	10 (29)	10 (29)	
Two vessels	9 (39)	5 (15)	15 (43)	
Three vessels	12 (52)	19 (56)	10 (29)	
Target vessel — no. (%)				0.35
Left anterior descending artery	13 (57)	22 (65)	17 (49)	
Left circumflex artery	5 (22)	3 (9)	4 (11)	
Right coronary artery	5 (22)	9 (26)	14 (40)	
Coronary-artery bypass grafting — no. (%)	5 (22)	10 (29)	7 (20)	0.63
Concomitant PCI — no. (%)				
Target vessel	4 (17)	9 (26)	10 (29)	0.61
Vessel other than the target vessel	1 (4)	2 (6)	3 (9)	0.80
Pacemaker or implantable cardioverter-defibrillator — no. (%)	5 (22)	7 (21)	12 (34)	0.37
Evidence of viable myocardium — no. (%)¶	5 (28)	9 (28)	8 (27)	0.99
<b>Current medication</b>				
Antiplatelet therapy: aspirin, clopidogrel, or both — no. (%)	22 (96)	32 (94)	31 (89)	0.54
Beta-blocker — no. (%)	22 (96)	33 (97)	33 (94)	0.85
ACE inhibitor or angiotensin-receptor blocker — no. (%)	21 (91)	33 (97)	33 (94)	0.64
Spironolactone — no. (%)	6 (26)	12 (35)	11 (31)	0.76
Diuretics — no. (%)	17 (74)	25 (74)	28 (80)	0.79
Warfarin — no. (%)	6 (26)	7 (21)	13 (37)	0.30
Statin — no. (%)	21 (91)	32 (94)	30 (86)	0.49

\* Plus-minus values are means ±SD. MI denotes myocardial infarction, PCI percutaneous coronary intervention, and ACE angiotensin-converting enzyme.

† Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

§ Hypercholesterolemia was defined by a low-density lipoprotein level of more than 130 mg per deciliter (3.4 mmol per liter) or the use of lipid-lowering therapy.

¶ Viability could be analyzed in 80 patients (18 in the control group, 32 in the CPC group, and 30 in the BMC group).

acteristics of the three groups (Table 3). The multivariate analysis identified the type of progenitor cell infused and the baseline stroke volume as the only statistically significant independent predictors of LVEF recovery.

*Functional Status*

The functional status of the patients, as assessed by NYHA classification, improved significantly in the BMC group (from 2.23±0.6 to 1.97±0.7, P=0.005). It did not improve significantly either in the CPC group (class, 2.16±0.8 at baseline and 1.93±0.8 at 3 months; P=0.13) or in the control group (class, 1.91±0.7 and 2.09±0.9, respectively; P=0.27).

**RANDOMIZED CROSSOVER PHASE**

Of the 24 patients who initially were randomly assigned to CPC infusion, 21 received BMC at the time of their first follow-up examination. Likewise, of the 28 patients who initially were randomly assigned to BMC infusion, 24 received CPC after 3 months. Of the 23 patients of the control group, 10 patients received CPC and 11 received BMC at their reexamination at 3 months (Fig. 1). As illustrated in Figure 2, regardless of whether patients received BMC as initial treatment, as crossover treatment after CPC infusion, or as crossover treatment after no cell infusion, global LVEF increased significantly after infusion of BMC. In contrast, CPC treatment did not sig-

**Table 2. Quantitative Variables Pertaining to Left Ventricular Function, as Assessed by Left Ventricular Angiography.\***

Variable	Baseline	3 Months' Follow-up	Absolute Change	P Value
Global LVEF (%)				
Control group	43±13	42±13	-1.2±3.0	0.12
CPC group	39±10	39±10	-0.4±2.2	0.60
BMC group	41±11	43±10	+2.9±3.6	0.001
P value for all 3 groups	0.68	0.31	0.001	
Regional contractility in central target area (SD from normal/chord)				
Control group	-1.55±0.40	-1.50±0.47	-0.06±0.33	0.62
CPC group	-1.72±0.36	-1.75±0.41	-0.03±0.30	0.70
BMC group	-1.63±0.40	-1.38±0.42	+0.26±0.43	0.006
P value for all 3 groups	0.44	0.03	0.09	
Extent of regional left ventricular dysfunction (% circumference)				
Control group	45±24	45±22	0±5	0.41
CPC group	52±18	50±19	-3±6	0.15
BMC group	45±18	42±19	-3±10	0.31
P value for all 3 groups	0.51	0.50	0.37	
End-diastolic volume (ml/m <sup>2</sup> of BSA)				
Control group	90±38	87±33	-3±17	0.45
CPC group	96±34	93±30	-3±18	0.47
BMC group	79±29	79±29	0±10	0.95
P value for all 3 groups	0.14	0.26	0.62	
End-systolic volume (ml/m <sup>2</sup> of BSA)				
Control group	55±36	55±32	-1±12	0.91
CPC group	62±31	60±26	-2±13	0.57
BMC group	49±26	47±26	-2±5	0.09
P value for all 3 groups	0.21	0.26	0.83	
Stroke volume (ml/m <sup>2</sup> of BSA)				
Control group	34±7	32±4	-2±7	0.22
CPC group	35±8	34±8	-1±7	0.31
BMC group	30±9	32±8	+2±7	0.21
P value for all 3 groups	0.08	0.78	0.09	
Left ventricular end-diastolic pressure (mm Hg)				
Control group	14±9	12±6	-2±7	0.15
CPC group	12±7	12±6	0±6	0.84
BMC group	12±8	12±7	0±7	0.91
P value for all 3 groups	0.64	0.61	0.42	

\* Plus-minus values are means ±SD. BSA denotes body-surface area.

nificantly alter LVEF when given either before or after BMC.

Thus, the inpatient comparison of the different treatment strategies not only documents the superiority of intracoronary infusion of BMC over the infusion of CPC for improving global left ventricular function, but also corroborates our findings in the analysis of data according to initial treatment assignment. The preserved improvement in cardiac function observed among patients who initially received BMC treatment and then crossed over to CPC treatment demonstrates that the initially achieved differences in cardiac function persisted for at least 6 months after intracoronary infusion of BMC.

**PROCEDURAL SAFETY AND CLINICAL OUTCOMES**

In 3 of the 135 intracoronary progenitor-cell-infusion procedures (pooled data from all study phases), local dissection of the coronary arterial wall was angiographically visible after inflation of the balloon during cell infusion; in these cases the dissection was successfully treated with immediate stent implantation. However, two of these three patients had subsequent elevations in creatine kinase (Table 4). The further clinical course of these three patients was uneventful. One additional patient required defibrillation from his implanted defibrillator for ventricular fibrillation during induction of myocardial ischemia by transient balloon occlusion for cell infusion. The clinical events before and after discharge from the hospital are listed in Table 4.

Therefore, potential confounding effects relating to ischemic preconditioning or microvascular activation can be ruled out in accounting for the improved cardiac function observed in the group treated with BMC. Moreover, inpatient comparison in the crossover phase of the trial rules out the possibility that differences in the patient populations studied may have affected outcomes. However, the mechanisms involved in mediating improved contractile function after intracoronary progenitor-cell infusion are not well understood.

Experimentally, although there is no definitive proof that cardiac myocytes may be regenerated, BMC were shown to contribute to functional recovery of left ventricular contraction when injected into freshly infarcted hearts,<sup>13-15</sup> whereas CPC profoundly stimulated ischemia-induced neovascularization.<sup>16,17</sup> Both cell types were shown to prevent cardiomyocyte apoptosis and reduce the development of myocardial fibrosis and thereby improve cardiac function after acute myocardial infarction.<sup>18,19</sup> Indeed, in our TOPCARE-AMI (Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction) studies,<sup>6,7,9</sup> intracoronary infusion of CPC was associated with functional improvements similar to those found with the use of BMC immediately after myocardial infarction. In the current study, however, which involved patients who had had a myocardial infarction at least 3 months before therapy, transcoronary administration of CPC was significantly inferior to ad-

DISCUSSION

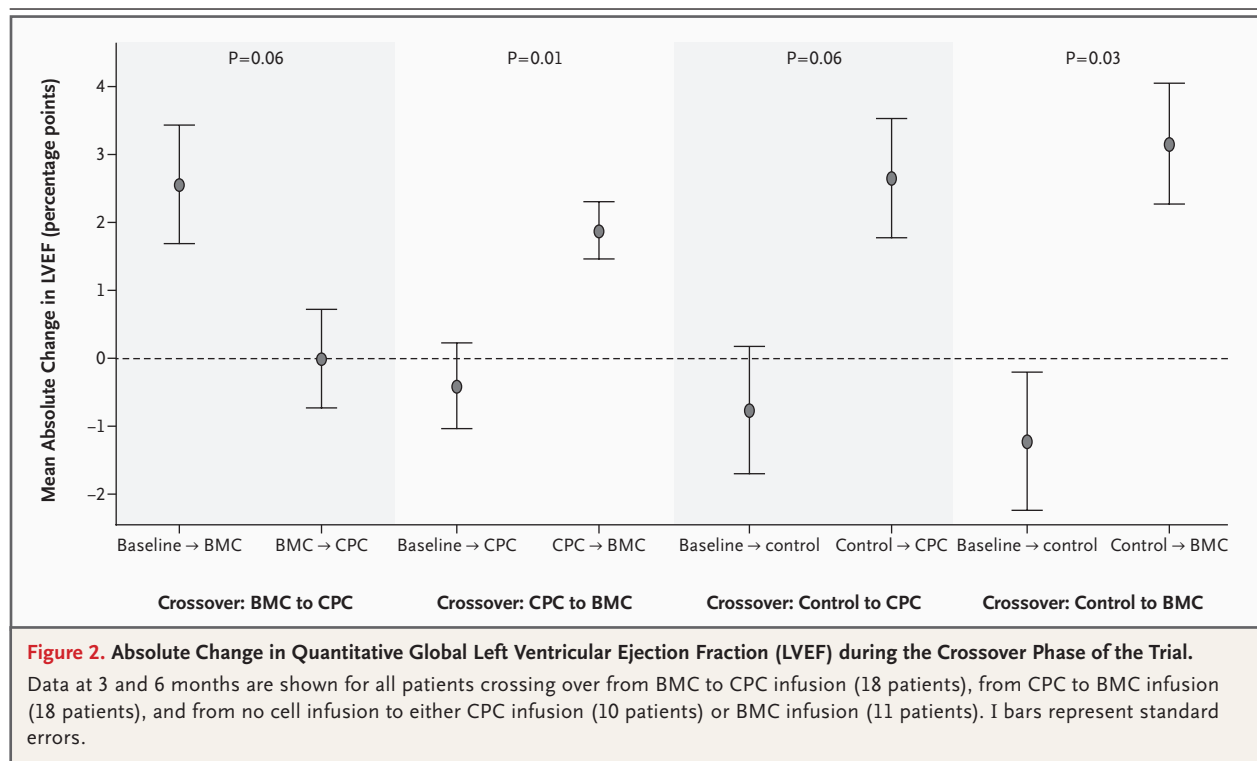
Using a randomized, controlled trial design, we examined the effects of intracoronary infusion of adult progenitor cells on global and regional left ventricular function in patients with chronic ischemic heart disease who had had a myocardial infarction at least 3 months previously. Our results demonstrate that infusion of BMC into the infarct-related artery is associated with moderate but significant improvements in both global and regional left ventricular contractile function. These improvements were observed in the presence of full conventional pharmacologic treatment and lasted at least 6 months.

The application procedures, infusion media, and infused volumes of cell suspension were identical in the two intracoronary-infusion groups.

**Table 3. Stepwise Linear Regression Analysis for Predictors of Improvement in Global Left Ventricular Ejection Fraction.\***

Variable	Nonstandardized Coefficient B	95% CI for B	P Value
Treatment group	1.49	0.53 to 2.46	0.003
Baseline stroke volume	-0.13	-0.22 to -0.05	0.002
No. of cardiovascular risk factors			0.76
Time since most recent MI			0.48
Concomitant PCI			0.60
Age			0.82
Baseline ejection fraction			0.72
Baseline end-diastolic volume			0.88

\* Values are shown only for significant differences. MI denotes myocardial infarction, and PCI percutaneous coronary intervention. For the overall model, the adjusted R<sup>2</sup> was 0.29; P<0.001 by analysis of variance.



ministration of BMC in altering global left ventricular function.

This study does not explain the cellular mechanisms associated with the significantly improved left ventricular function in the patients treated with BMC, nor does it explain the responses to CPC infusion, which were of only borderline significance. It is likely that the smaller number of progenitor cells derived from 270 ml of venous blood, which was 1/10 the number of monocytic cells obtained from 50 ml of bone marrow aspirate, may have contributed to the smaller effects of CPC in improving left ventricular contractile function. Moreover, CPC obtained from patients with chronic ischemic heart disease show profound functional impairments,<sup>20,21</sup> which might limit their recruitment, after intracoronary infusion, into chronically reperfused scar tissue many months or years after myocardial infarction. Thus, additional studies in which larger numbers of functionally enhanced CPC are used will be required to increase the response to intracoronary infusion of CPC.

The magnitude of the improvement after intracoronary infusion of BMC, with absolute increases in global LVEF of approximately 2.9 percentage points according to left ventricular

angiography and 4.8 percentage points according to MRI, was modest. However, it should be noted that the improvement in LVEF occurred in the setting of full conventional pharmacologic treatment: more than 90% of the patients were receiving beta-blocker and angiotensin-converting-enzyme inhibitor treatment. Moreover, results from trials of contemporary reperfusion for the treatment of acute myocardial infarction, which is regarded as the most effective treatment strategy for improving left ventricular contractile performance after ischemic injury, have reported increases in global LVEF of 2.8% (in the CADILLAC [Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications] trial) and 4.1% (in the ADMIRAL [Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up] trial).<sup>22,23</sup>

The number of patients, as well as the duration of follow-up, is not sufficient to address the question of whether the moderate improvement in LVEF associated with one-time intracoronary BMC infusion is associated with reduced mortality and morbidity among patients with heart failure secondary to previous myocardial infarction. We conclude that intracoronary infusion of BMC

**Table 4. Clinical Events during the 3-Month Follow-up Period.\***

Event	Control Group (N=23)	CPC Group (N=34)	BMC Group (N=35)	P Value
	<i>number (percent)</i>			
In-hospital events				
Death	0	0	0	
MI	0	2	0	
Infarct-vessel stent thrombosis	0	1	0	
Stent thrombosis at a site other than the target vessel	0	0	0	
Cerebral infarction	0	0	0	
Ventricular arrhythmia (detected during monitoring)	1	1	0	
Cumulative total	1 (4)	3 (9)	0	0.20
Events after discharge				
Death	1	0	0	
MI	0	0	0	
Rehospitalization for heart failure	1	1	0	
Stent thrombosis after hospitalization	0	0	0	
Infarct-vessel revascularization†	0	2	4	
Coronary bypass surgery	0	0	0	
Cerebral infarction	1	1	0	
Syncope	0	2	0	
Documented ventricular arrhythmia	0	0	0	
Cumulative total	2 (9)	5 (15)	4 (11)	0.79
Cumulative events, before or after discharge				
Death or MI	1 (4)	2 (6)	0	0.37
Death, MI, or rehospitalization for heart failure	1 (4)	3 (9)	0	0.20
Death, MI, stroke, rehospitalization for heart failure, or ventricular tachycardia	3 (13)	5 (15)	0	0.07

\* For analysis of cumulative events, the first event per patient was counted. The number of events may exceed the cumulative total because some events may have occurred in the same patient. MI denotes myocardial infarction.

† This category includes revascularization due to in-hospital stent thrombosis as well as that due to restenosis.

is associated with persistent improvements in regional and global left ventricular function and improved functional status among patients who have had a myocardial infarction at least 3 months previously. Given the reasonable short-term safety profile of this therapeutic approach, studies on a larger scale are warranted to examine its potential effects on morbidity and mortality among patients with postinfarction heart failure.

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## REFERENCES

1. 2001 Heart and stroke statistical update. Dallas: American Heart Association, 2000.
2. Braunwald E. Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997;337:1360-9.
3. Lange RA, Hillis LD. Reperfusion therapy in acute myocardial infarction. *N Engl J Med* 2002;346:954-5.
4. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* 2000;101:2981-8.
5. Strauer BE, Brehm M, Zeus T, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation* 2002;106:1913-8.
6. Assmus B, Schachinger V, Teupe C, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation* 2002;106:3009-17.
7. Britten MB, Abolmaali ND, Assmus B, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. *Circulation* 2003;108:2212-8.
8. Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 2004;364:141-8.
9. Schachinger V, Assmus B, Britten MB, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. *J Am Coll Cardiol* 2004;44:1690-9.
10. Dimmeler S, Aicher A, Vasa M, et al. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. *J Clin Invest* 2001;108:391-7.
11. Vasa M, Fichtlscherer S, Adler K, et al. Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease. *Circulation* 2001;103:2885-90.
12. Vasa M, Fichtlscherer S, Aicher A, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res* 2001;89:E1-E7.
13. Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature* 2004;428:668-73.
14. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001;410:701-5.
15. Mangi AA, Noiseux N, Kong D, et al. Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. *Nat Med* 2003;9:1195-201.
16. Kalka C, Masuda H, Takahashi T, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. *Proc Natl Acad Sci U S A* 2000;97:3422-7.
17. Murohara T, Ikeda H, Duan J, et al. Transplanted cord blood-derived endothelial precursor cells augment postnatal neovascularization. *J Clin Invest* 2000;105:1527-36.
18. Kawamoto A, Gwon HC, Iwaguro H, et al. Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia. *Circulation* 2001;103:634-7.
19. Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med* 2001;7:430-6.
20. Rupp S, Badorf C, Koyanagi M, et al. Statin therapy in patients with coronary artery disease improves the impaired endothelial progenitor cell differentiation into cardiomyogenic cells. *Basic Res Cardiol* 2004;99:61-8.
21. Valgimigli M, Rigolin GM, Fucili A, et al. CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. *Circulation* 2004;110:1209-12.
22. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344:1895-903.
23. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346:957-66.

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