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# Recovery of Microcirculation After Intracoronary Infusion of Bone Marrow Mononuclear Cells or Peripheral Blood Mononuclear Cells in Patients Treated by Primary Percutaneous Coronary Intervention

## The Doppler Substudy of the Hebe Trial

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**Objectives** In the present substudy of the Hebe trial, we investigated the effect of intracoronary bone marrow mononuclear cell (BMMC) and peripheral blood mononuclear cell (PBMC) therapy on the recovery of microcirculation in patients with reperfused ST-segment elevation myocardial infarction (STEMI).

**Background** Several studies have suggested that cell therapy enhances neovascularization after STEMI.

**Methods** Paired Doppler flow measurements were available for 23 patients in the BMMC group, 18 in the PBMC group, and 19 in the control group. Coronary flow was assessed at 3 to 8 days after primary percutaneous coronary intervention (PCI) and repeated at 4-month follow-up, with intracoronary Doppler flow measurements.

**Results** At baseline, the coronary flow velocity reserve was reduced in the infarct-related artery and improved over 4 months in all 3 groups. The increase of coronary flow velocity reserve did not significantly differ between the 2 treatment groups and the control group (BMMC group: 2.0 ± 0.5 to 3.1 ± 0.7; PBMC group: 2.2 ± 0.6 to 3.2 ± 0.8; control group: 2.0 ± 0.5 to 3.4 ± 0.9). Additionally, the decrease in hyperemic microvascular resistance index from baseline to 4-month follow-up was not statistically different between the 2 treatment groups and the control group.

**Conclusions** In STEMI patients treated with primary PCI in the Hebe trial, adjuvant therapy with BMMCs or PBMCs does not improve the recovery of microcirculation. Therefore, our data do not support the hypothesis of enhanced neovascularization after this mode of cell therapy. (Multicenter, randomised trial of intracoronary infusion of autologous mononuclear bone marrow cells or peripheral mononuclear blood cells after primary percutaneous coronary intervention [PCI]; ISRCTN95796863) (J Am Coll Cardiol Intv 2011;4:913–20) © 2011 by the American College of Cardiology Foundation

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In patients with acute ST-segment elevation myocardial infarction (STEMI), timely restoration of the myocardial perfusion by advanced revascularization therapies has resulted in increased survival. Although this has been a major progress in the treatment of STEMI patients, long-term morbidity remains high. In many patients, the intrinsic reparative mechanisms fail to prevent further deterioration of cardiac function after the acute ischemic event, putting the patient at risk for progression to post-infarct heart failure. Therefore, augmentation of the healing response is an appealing concept to improve clinical outcome.

Cell-based therapies have evoked great interest as an adjuvant therapy in patients with STEMI. Several experimental studies have shown that bone marrow mononuclear cell (BMMC) therapy enhances neovascularization and improves functional cardiac outcome after acute myocardial infarction (1–4). Whereas some of these experimental studies report that BMMCs stimulate neovascularization in the peri-infarct zone through incorporation into the microvasculature (2,3), other studies suggested paracrine effects (5). In patients, evidence for this hypothesis is scarce. The large randomized REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) trial reported a significant improvement in left ventricular ejection fraction after BMMC therapy (6). In addition, an increased recovery of microcirculation in the infarcted area was found, supporting the hypothesis of enhanced neovascularization after this mode of therapy (7). Other clinical studies investigating BMMC therapy obtained contradicting results with regard to functional cardiac outcome (8–11). To assess the effect of BMMC therapy on the recovery of microcirculation, we examined coronary flow with intracoronary Doppler flow measurements in STEMI patients that participated in the Hebe trial. The Hebe trial was a randomized controlled trial, evaluating the effect of intracoronary BMMC infusion and intracoronary peripheral blood mononuclear cell (PBMC) infusion on cardiac recovery in patients with STEMI treated by primary percutaneous coronary intervention (PCI) (12). Although the Hebe trial showed no beneficial effects of BMMC therapy or PBMC therapy with regard to functional cardiac outcome measured by cardiovascular magnetic resonance imaging (CMR) at short-term follow up (13), cell therapy might have influenced neovascularization in the infarcted area, resulting in improved recovery of microcirculation.

**Abbreviations and Acronyms**

**BMMC** = bone marrow mononuclear cell

**CFVR** = coronary flow velocity reserve

**CMR** = cardiovascular magnetic resonance imaging

**HMRI** = hyperemic microvascular resistance index

**PBMC** = peripheral blood mononuclear cell

**STEMI** = ST-segment elevation myocardial infarction

## Methods

**Study population and procedures.** This pre-specified substudy was part of the Hebe trial. The design and main results of the Hebe trial have been reported previously (12,13). Briefly, between August 2005 and April 2008, a total of 200 patients with first STEMI that were successfully treated with primary PCI were included in this multicenter, randomized, open trial with blinded evaluation of endpoints. All patients underwent CMR and were randomly assigned in a 1:1:1 ratio to treatment with intracoronary infusion of autologous BMMCs, intracoronary infusion of autologous PBMCs, or standard therapy. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by institutional review boards of the participating institutes. Patients enrolled in the Academic Medical Center, University of Amsterdam and VU University Medical Center (both Amsterdam, the Netherlands) underwent cardiac catheterization at baseline to assess intracoronary flow. In patients randomized to BMMC and PBMC therapy, baseline intracoronary flow measurements were performed before intracoronary cell therapy. In the control group, catheterization was performed for intracoronary flow measurements only. For preparation of the cell suspension, either 60 ml heparin anticoagulated bone marrow aspirate (BMMC group) or 150 to 200 ml venous heparin anticoagulated blood (PBMC group) was collected and sent to a single cell processing laboratory. Mononuclear cells were isolated by density gradient centrifugation and prepared for intracoronary infusion the same day. The detailed cell processing and cell characterization protocols have been reported previously (12,14). At 4-month follow-up, intracoronary flow measurements were repeated to assess the recovery of the intracoronary flow in the 3 treatment groups (Fig. 1).

**Intracoronary Doppler flow measurements and data analysis.** Cardiac catheterization was performed by standard techniques. A bolus of 0.1 mg nitroglycerin was administered into the coronary circulation to induce vasodilation of the coronary arteries before intracoronary Doppler flow measurements. To assess coronary flow, a 0.014-inch Doppler-tipped guidewire (Flowire, Volcano Corporation, Rancho Cordova, California) was positioned in the infarct-related artery, distal to the previously implanted stent. After optimization of the Doppler signal, average peak flow velocity recordings were obtained at baseline and during induction of maximal hyperemia by an intracoronary bolus of 20 to 40 $\mu$g adenosine. Doppler flow measurements were repeated at least 3 times. Coronary flow was also measured in a reference artery. The position of the Doppler-tipped guidewire in the infarct-related artery as well as the reference artery was angiographically documented. At 4-month follow-up, the Doppler flow measurements were repeated and coronary flow was assessed at the same position as

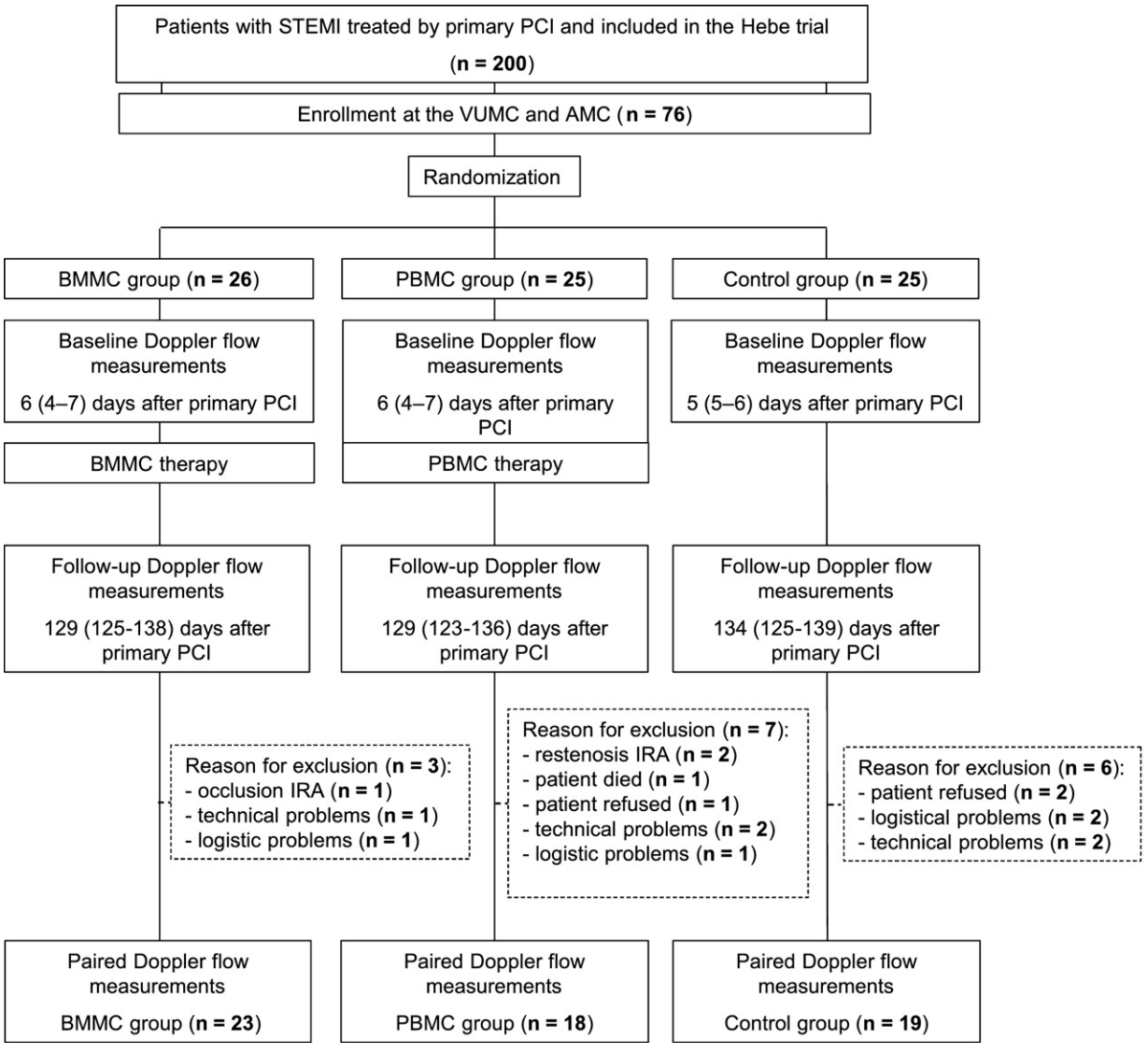


**Figure 1. Study Flow Diagram**

AMC = Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; BMMC = bone marrow mononuclear cell; IRA = infarct-related artery; PBMC = peripheral blood mononuclear cell; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; VUMC = VU University Medical Center, Amsterdam, the Netherlands.

during cardiac catheterization at baseline. Flow velocities were recorded continuously on videotape (FloMap, Jomed, Rancho Cardova, California) and analyzed by an independent investigator. Absolute coronary flow velocity reserve (CFVR) was determined as the ratio of the hyperemic to baseline average peak flow velocity. Relative CFVR was calculated as the absolute CFVR in the infarct-related artery divided by the absolute CFVR in the reference artery. The hyperemic microvascular resistance index (HMRI) was defined as the ratio of mean aortic pressure to the average peak flow velocity during maximum hyperemia. Patients with ≥70% stenosis in the infarct-related artery or the reference artery at 4-month follow-up were excluded to avoid confounding effects.

**Statistical analysis.** Data with normal distribution are expressed as mean ± SD, and data with non-normal distribution are given as median value (25th to 75th percentile). Categorical data are presented as number (%). For categorical variables, a chi-square test was used to test for differences between groups. For continuous variables, a Student *t* test or a 1-way analysis of variance was used to compare data with a normal distribution, whereas a nonparametric Kruskal-Wallis test was used to compare data with a non-normal distribution. For the comparison of changes in

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flow parameters between groups, analysis of covariance was used, including treatment group as the main factor and each baseline variable as a covariate. Linear multivariable regression models were used to further investigate the relation between cell therapy and the change in CFVR and HMRI when adjusting for baseline variables. A 2-sided p value $<0.05$ was considered statistically significant. Statistical analysis was performed with Statistical Package for Social Sciences software (SPSS for Windows, version 16.0, SPSS, Inc., Chicago, Illinois).

## Results

**Patient demographic and clinical characteristics.** Of the 76 patients included in the Academic Medical Center and VU University Medical Center, 16 did not have paired intracoronary flow measurements and were excluded from this analysis (Fig. 1). Of the 60 patients with paired measurements, 23 were allocated to BMMC therapy, 18 to PBMC therapy, and 19 patients to no cell therapy (control group). Baseline demographic and clinical characteristics are summarized in Table 1. The mean age in the study group was 55 years, and 83% were men. Baseline demographic and clinical characteristics were comparable across the 3 treatment groups, except for a lower incidence of hypertension in the PBMC group and a higher incidence of Thrombolysis In Myocardial Infarction flow grade 2 after primary PCI in the BMMC group. No differences were found in baseline demographic and clinical characteristics between the 16 excluded patients and the study group (data not shown). Furthermore, no clinical, electrocardiographic, or enzymatic evidence of reinfarction was observed in any patient between primary PCI and the cardiac catheterization at 4-month follow-up.

**The effect of BMMC or PBMC therapy on the recovery of microcirculation.** Patients underwent baseline intracoronary Doppler flow measurements at a median of 6 (4 to 7) days after primary PCI. In the BMMC and PBMC groups, baseline intracoronary Doppler flow measurements were performed just before intracoronary cell infusion. Doppler flow measurements were repeated at a median of 132 (125 to 138) days after primary PCI. Coronary flow hemodynamic parameters are listed in Table 2. In summary, the baseline CFVR in the infarct-related artery was similar in the 3 groups (2.0 ± 0.5 in the BMMC group, 2.2 ± 0.6 in the PBMC group, and 2.0 ± 0.5 in the control group) as well as the HMRI (2.0 ± 0.5 mm Hg s/cm in the BMMC group, 1.9 ± 0.8 mm Hg s/cm in the PBMC group, and 1.9 ± 0.5 mm Hg s/cm in the control group). At 4-month follow-up, the CFVR in the infarct-related artery increased to levels similar to the reference artery (Fig. 2A, Table 2). The increase in CFVR in the infarct-related artery was not significantly different between the treatment groups and the control group (1.1 ± 0.7 in the BMMC group; 1.0 ± 0.8 in the PBMC group; 1.4 ± 0.9 in the control group) (Fig. 2B, Table 2). Furthermore, there was a trend toward a decrease in HMRI from baseline to follow-up in all 3 groups, which was only borderline significant in the control group, with no significant differences in change in HMRI between the treatment groups and the control group (2.0 ± 0.5 mm Hg s/cm to 1.8 ± 0.6 mm Hg s/cm in the BMMC group; 1.9 ± 0.8 mm Hg s/cm to 1.8 ± 0.6 mm Hg s/cm in the PBMC group; 1.9 ± 0.5 mm Hg s/cm to 1.7 ± 0.5 mm Hg s/cm in the control group) (Figs. 2C and 2D, Table 2). With regard to the reference artery, the change in coronary flow from baseline to 4-month follow-up was similar among the 3 groups (Table 2). Finally, no differences were found in improvement in relative CFVR among the 3 groups (0.2 ± 0.2 in the BMMC group, 0.1 ± 0.2 in the PBMC group, and 0.3 ± 0.3 in the control group) (Table 2). After adjustment for baseline variables, the results of the differences between treatment groups did not change, with regard to the change in CFVR and HMRI.

## Discussion

Intracoronary infusion of BMMCs or PBMC did not enhance the recovery of microcirculation after primary PCI in the present substudy of the Hebe trial. In accordance with other studies, the CFVR in the infarct-related artery was depressed in the early phase after primary PCI and increased to levels similar to the reference artery at 4 months of follow-up. Additionally, the increase in CFVR was comparable among the 3 groups. Also, the decrease in HMRI in the infarct-related artery was similar in the 3 groups. Taken together, it seems unlikely that BMMC or PBMC therapy enhanced post-infarct neovascularization in the Hebe study. This is also consistent with the CMR data from this trial, showing no beneficial effect of BMMC or PBMC therapy on global and regional cardiac function at 4 months of follow-up (13).

Our results are in contrast to data from the Doppler substudy of the REPAIR-AMI trial (7). Several factors might be responsible for these discrepant findings. In the present study, all patients received primary PCI according to the current guidelines to limit the extent of myocardial injury and to preserve the integrity of the microvasculature. Importantly, primary PCI was performed within 6 h after onset of symptoms in almost all patients, with a median of 3.1 h (2.2 to 4.1 h). In the REPAIR-AMI study, the mean time from symptom onset to reperfusion therapy was longer than 6 h, and some patients received fibrinolytic therapy before PCI (7). In a post hoc analysis of the REGENT (Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction) trial, the investigators found that patients with longer-than-median delay from the pain onset to reperfusion (5 h) were more likely to have significant improvement (11). Therefore, the potential benefit of intracoronary infusion of BMMCs on the recovery of microcirculation might have been different in our study.

**Table 1. Patient Demographic and Clinical Characteristics**

| Characteristic | BMMC Group (n = 23) | PBMC Group (n = 18) | Control Group (n = 19) | p Value |
|---|---|---|---|---|
| Age (yrs) | 55.2 ± 8.8 | 54.6 ± 11.0 | 54.2 ± 7.4 | 0.94 |
| Male | 19 (83) | 14 (78) | 17 (90) | 0.63 |
| Body mass index (kg/m$^2$) | 26.0 ± 3.4 | 26.3 ± 4.3 | 26.4 ± 2.4 | 0.92 |
| Risk factors for coronary artery disease | | | | |
| Diabetes mellitus | 1 (4) | 0 (0) | 0 (0) | 0.44 |
| Hypertension | 10 (44) | 0 (0) | 8 (42) | 0.004 |
| Family history of coronary heart disease | 13 (57) | 6 (33) | 10 (53) | 0.30 |
| Hypercholesterolemia | 5 (22) | 2 (11) | 3 (16) | 0.66 |
| Current smoking | 10 (44) | 11 (61) | 11 (58) | 0.47 |
| Angiography and infarct treatment | | | | |
| Symptom onset to balloon (h) | 3.0 (2.5–4.1) | 3.5 (2.1–4.9) | 3.0 (2.1–3.9) | 0.71 |
| Infarct-related artery | | | | 0.28 |
| Left anterior descending artery | 17 (74) | 10 (56) | 16 (84) | |
| Left circumflex artery | 2 (9) | 1 (6) | 1 (5) | |
| Right coronary artery | 4 (17) | 7 (39) | 2 (11) | |
| TIMI flow grade after primary PCI | | | | 0.03 |
| 2 | 4 (17) | 0 (0) | 0 (0) | |
| 3 | 19 (83) | 18 (100) | 19 (100) | |
| Cardiovascular magnetic resonance imaging | | | | |
| LV ejection fraction (%) | 44.1 ± 9.7 | 42.9 ± 7.9 | 41.3 ± 8.5 | 0.62 |
| LV end-diastolic volume (ml/m$^2$) | 94.4 ± 13.5 | 95.3 ± 13.0 | 100.4 ± 17.0 | 0.40 |
| LV end-systolic volume (ml/m$^2$) | 53.3 ± 13.6 | 54.7 ± 12.0 | 59.3 ± 14.8 | 0.38 |
| Infarct mass (g/m$^2$) | 14.5 ± 7.4 | 10.9 ± 4.6 | 14.1 ± 7.4 | 0.22 |
| Presence of microvascular obstruction | 15 (65) | 11 (61) | 13 (68) | 0.60 |
| Cell infusion | | | | |
| Days after primary PCI | 6 (4–7) | 5 (4–7) | — | |
| Number of injected cells ($\times 10^6$) | 291 ± 173 | 288 ± 91 | — | |
| Absolute number of CD34$^+$ cells ($\times 10^6$) | 6.8 ± 5.1 | 0.3 ± 0.1 | — | |
| Absolute number of CD14$^+$ cells ($\times 10^6$) | 17.9 ± 9.4 | 63.5 ± 30.1 | — | |
| Medication at discharge | | | | |
| Aspirin | 23 (100) | 18 (100) | 19 (100) | — |
| Clopidogrel | 23 (100) | 18 (100) | 19 (100) | — |
| Beta-blockers | 22 (96) | 18 (100) | 19 (100) | 0.44 |
| ACE inhibitor | 22 (96) | 14 (78) | 18 (95) | 0.12 |
| ATII-receptor blocker | 0 (0) | 1 (6) | 1 (5) | 0.53 |
| Nitrates | 0 (0) | 0 (0) | 0 (0) | — |
| Calcium-channel antagonists | 0 (0) | 1 (6) | 1 (5) | 0.53 |
| Medication at 4-month follow-up | | | | |
| Aspirin | 23 (100) | 18 (100) | 18 (95) | 0.33 |
| Clopidogrel | 18 (78) | 16 (89) | 18 (95) | 0.28 |
| Beta-blockers | 19 (83) | 17 (94) | 19 (100) | 0.11 |
| ACE inhibitor | 20 (87) | 13 (72) | 18 (95) | 0.15 |
| ATII-receptor blocker | 2 (9) | 1 (6) | 2 (11) | 0.86 |
| Nitrates | 1 (4) | 0 (0) | 2 (11) | 0.34 |
| Calcium-channel antagonists | 0 (0) | 0 (0) | 1 (5) | 0.53 |

Values are mean ± SD, n (%), or median (25th to 75th percentile).

ACE = angiotensin-converting-enzyme; AT = angiotensin; BMMC = bone marrow mononuclear cell; LV = left ventricular; PBMC = peripheral blood mononuclear cell; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Furthermore, there are differences in methodology with regard to the BMMC processing protocol that might affect the therapeutic potential of the BMMCs. This issue has been extensively addressed by van Beem et al. (14), who compared the cell processing protocol as applied in the Hebe trial with the protocol of the REPAIR-AMI trial. It

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**Table 2. Effect of BMMC and PBMC Therapy on Coronary Flow**

| | BMMC Group (n = 23) | | | PBMC Group (n = 18) | | | Control Group (n = 19) | | | p Value of Change | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow-Up | Change | Baseline | Follow-Up | Change | Baseline | Follow-Up | Change | BMMS vs. Control* | PBMS vs. Control* |
| Heart rate (beats/min) | 75 ± 14 | 63 ± 15 | −13 ± 11 | 69 ± 10 | 66 ± 9 | −3 ± 10 | 73 ± 7 | 63 ± 8 | −10 ± 7 | 0.49 | 0.046 |
| Systolic BP (mm Hg) | 112 ± 23 | 120 ± 18 | 8 ± 19 | 110 ± 24 | 120 ± 23 | 9 ± 16 | 111 ± 17 | 125 ± 22 | 15 ± 22 | 0.25 | 0.37 |
| Diastolic BP (mm Hg) | 68 ± 10 | 69 ± 8 | 1 ± 12 | 66 ± 9 | 69 ± 11 | 3 ± 11 | 70 ± 7 | 74 ± 11 | 5 ± 12 | 0.09 | 0.30 |
| Infarct-related artery | | | | | | | | | | | |
| Baseline APV (cm/s) | 23 ± 10 | 17 ± 7 | −6 ± 10 | 22 ± 11 | 18 ± 13 | −5 ± 7 | 24 ± 10 | 17 ± 8 | −7 ± 5 | 0.70 | 0.23 |
| Hyperemic APV (cm/s) | 42 ± 13 | 51 ± 19 | 8 ± 22 | 46 ± 19 | 52 ± 26 | 6 ± 20 | 45 ± 16 | 53 ± 14 | 8 ± 13 | 0.77 | 0.72 |
| CFVR | 2.0 ± 0.5 | 3.1 ± 0.7 | 1.1 ± 0.7 | 2.2 ± 0.6 | 3.2 ± 0.8 | 1.0 ± 0.8 | 2.0 ± 0.5 | 3.4 ± 0.9 | 1.4 ± 0.8 | 0.20 | 0.21 |
| BMRI (mm Hg s/cm) | 4.1 ± 1.6 | 5.8 ± 2.3 | 1.7 ± 2.4 | 4.2 ± 1.8 | 6.1 ± 2.8 | 1.8 ± 2.2 | 3.9 ± 1.2 | 6.2 ± 2.1 | 2.3 ± 1.4 | 0.39 | 0.36 |
| HMRI (mm Hg s/cm) | 2.0 ± 0.5 | 1.8 ± 0.6 | −0.2 ± 0.8 | 1.9 ± 0.8 | 1.8 ± 0.6 | −0.1 ± 0.8 | 1.9 ± 0.5 | 1.7 ± 0.5 | −0.2 ± 0.4 | 0.73 | 0.54 |
| Reference vessel | | | | | | | | | | | |
| Baseline APV (cm/s) | 20 ± 6 | 16 ± 5 | −4 ± 7 | 19 ± 8 | 16 ± 7 | −3 ± 6 | 18 ± 6 | 18 ± 6 | 0 ± 9 | 0.23 | 0.28 |
| Hyperemic APV (cm/s) | 50 ± 13 | 50 ± 16 | 1 ± 16 | 53 ± 22 | 54 ± 14 | 1 ± 20 | 47 ± 10 | 61 ± 22 | 14 ± 24 | 0.06 | 0.16 |
| CFVR | 2.6 ± 0.6 | 3.2 ± 0.6 | 0.5 ± 0.6 | 2.8 ± 0.5 | 3.5 ± 0.8 | 0.7 ± 0.7 | 2.8 ± 0.5 | 3.4 ± 0.7 | 0.7 ± 0.6 | 0.39 | 0.74 |
| BMRI (mm Hg s/cm) | 4.6 ± 1.7 | 5.7 ± 1.9 | 1.1 ± 2.1 | 4.7 ± 1.6 | 5.9 ± 2.2 | 1.2 ± 2.3 | 5.1 ± 1.4 | 5.5 ± 1.7 | 0.3 ± 1.8 | 0.41 | 0.34 |
| HMRI (mm Hg s/cm) | 1.7 ± 0.6 | 1.7 ± 0.5 | 0.0 ± 0.5 | 1.7 ± 0.6 | 1.6 ± 0.4 | −0.1 ± 0.6 | 1.8 ± 0.4 | 1.5 ± 0.5 | −0.3 ± 0.4 | 0.07 | 0.49 |
| Relative CFVR | 0.8 ± 0.2 | 1.0 ± 0.3 | 0.2 ± 0.2 | 0.8 ± 0.2 | 0.9 ± 0.2 | 0.1 ± 0.2 | 0.7 ± 0.2 | 1.0 ± 0.3 | 0.3 ± 0.3 | 0.70 | 0.19 |

Values are mean ± SD. *p values were determined by analysis of covariance.

APV = average peak flow velocity; BMMC = bone marrow mononuclear cell; BMRI = baseline microvascular resistance index; BP = blood pressure; CFVR = coronary flow velocity reserve; HMRI = hyperemic microvascular resistance index; PBMC = peripheral blood mononuclear cell.

was concluded that the quantity and quality of the BMMCs was comparable in terms of BMMC recovery, migration, and clonogenic capacity. In the Hebe trial, no overnight storage of cells was included in the protocol, as applied in the REPAIR-AMI trial. Moreover, there might be small differences in cell handling between the 2 studies. Therefore, functional differences that are related to the preparation of cells cannot formally be excluded.

In the REPAIR-AMI study, Doppler flow measurements showed increased recovery of the CFVR in the infarct-related artery in patients treated with BMMCs, compared with the placebo group (7). Of relevance, the recovery of the CFVR in the placebo group of the REPAIR-AMI study (1.9 ± 0.5 months to 2.8 ± 1.0 at 4 months) was relatively low as compared with the control group of the present study (2.0 ± 0.5 months to 3.4 ± 0.9 at 4 months). Also, the study of Bax et al. (15)—investigating the natural course of coronary flow after primary PCI—reported a higher increase in CFVR (1.9 ± 0.5 at 1 week to 3.0 ± 0.8 at 6 months) as compared with the REPAIR-AMI study. It remains unclear whether the increased recovery of the CFVR in the BMMC group in the REPAIR-AMI study is the result of enhanced microvascular repair in the BMMC group or, alternatively, blunted repair in the placebo group.

**Study limitations.** First of all, our sample size might be too small to detect small differences in coronary flow parameters between groups. This study would have, considering the number of included patients, 80% power to pick up a mean difference of 0.6 in change of CFVR between the BMMC group and control group and a difference of 0.5 mm Hg s/cm in change of HMRI (assuming a 2-sided alpha of 0.05). Therefore, the present study was sufficiently powered to detect the difference in intracoronary Doppler flow measurements as reported in the REPAIR-AMI substudy (7). Second, intracoronary pressure measurements were not performed in this study. Combined Doppler flow and pressure measurements might provide more accurate information about changes in microvascular resistance (16). To minimize confounding effects of epicardial resistance, patients with ≥70% stenosis in the infarct-related artery were excluded. Third, baseline and follow-up intracoronary Doppler measurements were not performed on a fixed time point after primary PCI, which might have influenced the results. However, no differences in time between primary PCI and intracoronary Doppler measurements were observed among the 3 groups. Fourth, intracoronary Doppler measurements were performed only once at 4-month follow-up. Therefore, potential early or late effects on the coronary flow have not been evaluated.

## Conclusions

In STEMI patients treated with primary PCI, adjuvant therapy with BMMCs or PBMCs does not improve the recovery of microcirculation. Therefore, our data do not support the hypothesis of enhanced neovascularization after this mode of therapy.

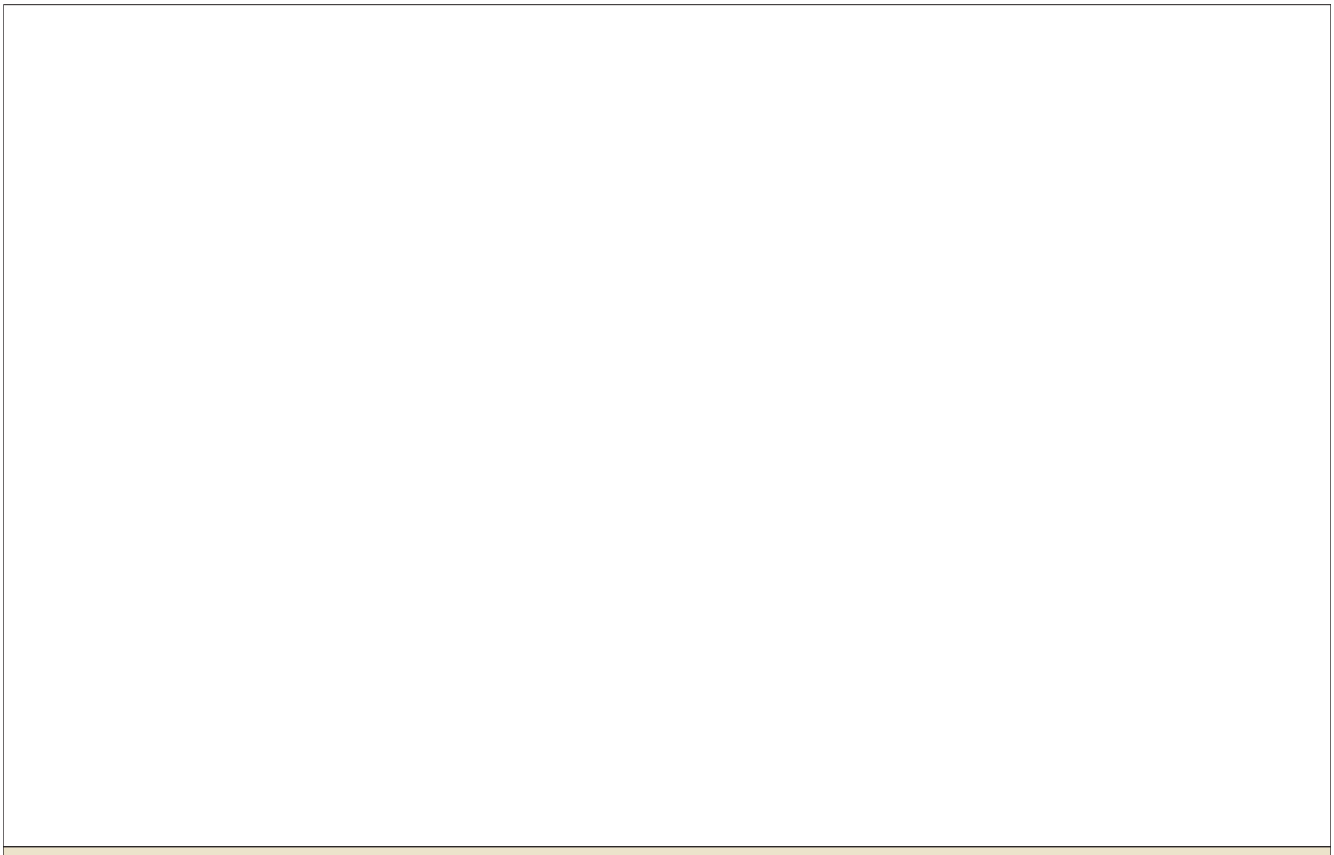

**Figure 2. Effect of BMMC and PBMC Therapy on Recovery of Infarct-Related CFVR and HMRI**

For each group, the individual change in coronary flow velocity reserve (CFVR) **(A)** and hyperemic microvascular resistance index (HMRI) **(B)** from baseline to 4-month follow-up is depicted. The p values for the change between baseline and follow-up within each group were calculated with paired Student *t* test. The mean change in CFVR **(C)** and HMRI **(D)** between baseline and 4-month follow-up is shown. Values are mean ± SD. The p values for the change between the treatment groups and the control group were determined by analysis of covariance. BMMC = bone marrow mononuclear cell; PBMC = peripheral blood mononuclear cell.

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