Monocytes in ischemic heart disease
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Chapter 3

Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood after acute myocardial infarction in patients: the 2-year results from the randomized controlled HEBE trial


In preparation
ABSTRACT

Aims The HEBE study is a multicenter trial that randomized 200 patients with large first acute myocardial infarction (AMI) treated with primary percutaneous coronary intervention (PCI) to either intracoronary infusion of bone marrow mononuclear cells (BMMC) \( n=69 \), peripheral blood mononuclear cells (PBMC) \( n=66 \), or standard therapy \( n=65 \). At 4-months of follow-up, regional and global systolic myocardial function improved in all three groups, with no significant differences between groups. Here, we report the 2-year cardiac magnetic resonance imaging (CMR) follow-up data from the HEBE trial.

Methods In addition to 3 [2-4] days and 4 months after AMI, all patients underwent CMR at 2 years after AMI. CMR analyses were performed in a core laboratory using a standardized cine protocol and blinded for treatment assignment.

Results Improvement of left ventricular ejection fraction (LVEF) from baseline to 2 years of follow-up was 4.2±8.6% in the BMMC group and 3.0±8.3% in the PBMC group, compared to 4.0±8.6% in the control group \( P=0.91 \) and \( P=0.53 \), respectively. The percentage of dysfunctional left ventricular (LV) segments that improved during 2 years of follow-up did not differ between the BMMC and control group (45.0±26.3% versus 52.3±22.6%, \( P=0.14 \)). However, in the BMMC group, the increase in LV end-diastolic volume index was lower (3.5±16.9 mL/m\(^2\) versus 11.2±19.8 mL/m\(^2\), \( P=0.03 \)). Furthermore, there was significantly less improvement in dysfunctional segments in the PBMC group compared to controls (42.5±20.7% versus 52.3±22.6%, \( P=0.03 \)). Finally, the three groups did not differ in changes in LV systolic volume.

Conclusion Long-term follow-up from the HEBE trial showed no beneficial effect of intracoronary delivery of mononuclear cells from bone marrow or peripheral blood on regional and global systolic myocardial function following primary PCI in patients.
INTRODUCTION

The effect of intracoronary infusion of mononuclear bone marrow cells (BMMC) after acute myocardial infarction (AMI) in patients has been reviewed in the past, with a moderate positive effect of BMMC treatment on left ventricular (LV) function at short-term follow-up. Currently, intracoronary BMMC therapy is used in research setting only and a large randomized controlled trial with a primary clinical endpoint is awaited.

Few studies have investigated the long-term effects of BMMC therapy. Long-term follow-up data on global and regional LV function are important for further evaluation of the efficacy of BMMC therapy after AMI. In the present study, we investigated both the regional as well as the global systolic function in the HEBE trial, using cardiac magnetic resonance imaging (CMR).

METHODS

Study population and procedures
The HEBE trial was a multicenter, randomized, open trial with blinded evaluation of endpoints of which the details of the design and main results have been published previously. Briefly, 200 patients with first ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (PCI) were enrolled in this study. After CMR, on day 2 to 7, patients were randomly assigned in a 1:1:1 ratio to either intracoronary infusion of autologous mononuclear BMMCs \((n=69)\), intracoronary infusion of peripheral blood mononuclear cells (PBMC) \((n=66)\), or standard therapy (without placebo infusion) \((n=65)\).

In the BMMC and PBMC group, cell harvesting was performed within 8 days after primary PCI. Bone marrow (60 mL) was aspirated from the iliac crest under local anaesthesia (60 mL). In the PBMC group, 150 mL of venous blood was collected. BMMCs or PBMCs were isolated by density gradient centrifugation, and 15 mL of cell suspension was used for intracoronary infusion. In the BMMC group, 3 patients did not have intracoronary infusion, in the PBMC group 1 patient refused intracoronary infusion.

The three groups were comparable with respect to baseline characteristics (Table 1). Overall, the mean age was 56±9 years and 85% of the patients were males. At discharge, 95% were treated with β-blockers and 93% with angiotensin-converting-enzyme or angiotensin inhibitors. There was no significant difference between the two treatment groups and the control group regarding the primary end point, namely the change in regional myocardial function in dysfunctional segments at 4 months of follow-up relative to baseline, based on segmental analysis as measured by CMR. Also, no significant differences in the secondary endpoints of change in LV ejection fraction (EF), LV volumes, LV mass, and infarct size were observed. Furthermore, the three groups had similar rates of clinical events at 4 months of follow-up. We now performed a 2-year follow-up of patients from the HEBE trial to evaluate long-term effects on regional and global LV function.
Cardiac magnetic resonance imaging

Patients who were alive at 24 months were invited for a CMR scan. Patients were studied on a clinical 1.5 Tesla scanner (Siemens, Erlangen, Germany; Philips, Best, the Netherlands; GE Healthcare, Buckinghamshire, UK). The CMR protocol at 2-years was similar to the CMR protocol at baseline and 4 months, with the exception that no contrast medium was administrated. In short, contiguous short axis slices were acquired every 10 mm covering the whole left ventricle using a cine retrospectively ECG-gated segmented steady state free precession pulse sequence, with image parameters identical to the baseline and 4-month follow-up scan. LV volumes were measured on the cine images and indexed for body-surface area, and LVEF was calculated.

For analysis of regional myocardial function, each short axis slice was divided in 12 equi-angular segments to calculate wall thickening (in mm) of each segment by subtracting end-diastolic from end-systolic wall thickness. Myocardial segments were considered dysfunctional if segmental wall thickening was <3 mm, based on the mean wall thickening of 4.4±0.7 mm (mean ±2 SD) in a group of 10 healthy volunteers (age 50 to 75 years). Improved wall thickening of a segment at follow-up was defined as >1.5 mm improvement in segmental wall thickening as compared to baseline and complete recovery was defined as segmental wall thickening ≥3.0 mm improvement.

All CMR analyses were performed in a core laboratory using a standardized protocol. Both baseline and 4-month follow-up scan were used to match all three studies for slice position using anatomic landmarks, such as papillary muscles and right ventricular insertion sites.

Table 1 Baseline characteristics of the HEBE trial

<table>
<thead>
<tr>
<th></th>
<th>BMMC group (n=69)</th>
<th>PBMC group (n=66)</th>
<th>Control Group (n=65)</th>
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<tr>
<td>Age (years)</td>
<td>56±9</td>
<td>57±9</td>
<td>55±10</td>
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<tr>
<td>Male gender</td>
<td>58 (84)</td>
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<td>56 (86)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3 (4)</td>
<td>7 (11)</td>
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<td>Known hypertension</td>
<td>27 (39)</td>
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<td>Family history of coronary heart disease</td>
<td>33 (48)</td>
<td>30 (45)</td>
<td>33 (51)</td>
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<td>Hypercholesterolemia</td>
<td>17 (25)</td>
<td>14 (21)</td>
<td>15 (23)</td>
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<td>Current cigarette smoking</td>
<td>37 (54)</td>
<td>31 (47)</td>
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<td>Infarct related artery</td>
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<tr>
<td>Left anterior descending artery</td>
<td>42 (61)</td>
<td>46 (70)</td>
<td>40 (62)</td>
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<tr>
<td>Left circumflex artery</td>
<td>14 (20)</td>
<td>5 (8)</td>
<td>5 (8)</td>
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<tr>
<td>Right coronary artery</td>
<td>13 (19)</td>
<td>15 (23)</td>
<td>20 (31)</td>
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<tr>
<td>Multivessel disease</td>
<td>12 (17)</td>
<td>21 (32)</td>
<td>16 (25)</td>
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</table>

Values are expressed as number (%) or mean±SD. BMMC denotes bone marrow mononuclear cells; PBMC, peripheral blood mononuclear cells.
Statistical analysis
All analyses were performed on the basis of the intention-to-treat principle. The analyses consisted of separate comparisons of the CMR endpoints between the two treatment groups and the control group, using the Student’s t test. All P-values are two-sided and statistical significance was set at P<0.05. Statistical analysis was done with the Statistical Package for Social Sciences software (SPSS 19.0 for Windows).

RESULTS
Patients
Of the 200 patients originally enrolled in the HEBE study, 3 patients had died and 7 were lost to follow-up. Nineteen patients did not undergo CMR because of implantable cardioverter-defibrillator implantation (n=8), pacemaker implantation (n=1) or because they refused (n=10). In 12 patients the CMR scan was of poor quality due to breathing or triggering artefacts, or it was not possible to match with the baseline and 4 months studies. Therefore these studies were excluded from the analysis by the core lab (see Figure 1).

Figure 1 Study flow chart. BMMC denotes bone marrow mononuclear cells; CMR, cardiac magnetic resonance imaging; PBMC, peripheral blood mononuclear cells; STEMI, ST-segment elevation myocardial infarction.
Left ventricular function and volumes

Paired cine CMR images for functional analyses were available for 59 patients in the BMMC group, 48 in the PBMC group, and 52 in the control group. At 2-years of follow-up, 45.0±26.3% of the dysfunctional segments showed improved segmental wall thickening in patients treated with BMMCs, compared to 52.3±22.6% in the control group ($P=0.14$). Patients treated with PBMCs showed less improvement of dysfunctional segments at 2-years of follow-up, compared to the control group (42.5±22.6%, $P=0.03$; Table 2).

Improvement of LVEF was 4.2±8.6% in the BMMC group and 3.0±8.3% in the PBMC group as compared with 4.0±8.6% in the control group ($P=0.91$ and $P=0.53$, respectively). Patients treated with intracoronary BMMC therapy had less increase in LV end-diastolic volume index (3.5±16.9 mL/m$^2$) as compared to controls (11.2±19.8 mL/m$^2$, $P=0.03$). There were no other significant differences in the changes in LV volumes between the BMMC, PBMC and control group (Table 2).

DISCUSSION

The present study confirms and extends our previous reports,5,8 as we could not demonstrate a strong beneficial effect of intracoronary delivery of mononuclear cells from bone marrow or peripheral blood on the regional and global systolic myocardial function at 2-year follow-up in patients treated with primary PCI. Nevertheless, we observed that the increase in LV end-diastolic volume index was lower in the BMMC group.

Of the 22 randomized controlled trials1-3 assessing intracoronary bone marrow cell therapy after AMI, only 7 trials included long term follow-up, defined as follow-up longer than 1 year after AMI. The REPAIR AMI trial9 and 2 other studies, conducted by Cao et al.10 and Plewka et al.11, demonstrated a larger increase of LV function after intracoronary BMMC therapy at the time of primary endpoint assessment, between 3 and 6 months after AMI. In these 3 studies, this effect remained significant in favour of intracoronary cell therapy at 25 months,12 48 months,10 and 24 months13 after AMI. The BOOST trial demonstrated a benefit for patients treated with intracoronary BMMC therapy compared to control patients at 4 months of follow-up.14 However, this positive effect was no longer significant after 18 months.15,16 This might be explained by a catch up phenomenon in the control group, suggesting that the effect of cell therapy is only transient. Although bone marrow cell therapy may accelerate functional recovery after AMI, the authors state that this mode of therapy is comparable with standard treatment. However, other trials did not observe any improvement in functional recovery by BMNCs over primary PCI alone. The study conducted by Penicka et al. was prematurely ended due to the lack of functional effects and serious adverse events in the BMMC group.17 In the ASTAMI trial18 and the study conducted by Wohrle et al.,19 intracoronary infusion of BMMCs did not improve global LV function at the primary endpoint, as well as after 3 years of observation.20,21 These data are in line with our observations in the HEBE trial.

Nevertheless, in the present study, we did find a lower increase in LV end-diastolic volume index in the BMMC group, suggesting a long-term beneficial effect
Table 2 Quantitative measures of regional and global left ventricular function and volumes by CMR

| Analysis at 4 months | BMMC group  
\( (n=67) \) | PBMC group  
\( (n=62) \) | Control group  
\( (n=60) \) | \( P \)-value:  
BMMC vs Control | \( P \)-value:  
PBMC vs Control |
<table>
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<tr>
<td>Analysis at 2 years</td>
<td>( (n=59) )</td>
<td>( (n=48) )</td>
<td>( (n=52) )</td>
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<tr>
<td>Dysfunctional segments (%)</td>
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<tr>
<td>Baseline</td>
<td>53.3±19.6</td>
<td>57.5±19.6</td>
<td>56.2±18.4</td>
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<td>0.71</td>
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<tr>
<td>Improvement during follow-up</td>
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<tr>
<td>4 months</td>
<td>38.6±24.7</td>
<td>36.8±20.9</td>
<td>42.4±18.7</td>
<td>0.33</td>
<td>0.14</td>
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<tr>
<td>2 years</td>
<td>45.0±26.3</td>
<td>42.5±20.7</td>
<td>52.3±22.6</td>
<td>0.14</td>
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<td>LV ejection fraction (%)</td>
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<tr>
<td>Baseline</td>
<td>43.7±9.0</td>
<td>41.7±9.1</td>
<td>42.4±8.3</td>
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<td>4 months</td>
<td>47.5±9.9</td>
<td>46.0±9.3</td>
<td>46.4±9.2</td>
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<td>2 years</td>
<td>49.2±8.1</td>
<td>44.9±10.3</td>
<td>47.7±9.4</td>
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<td>LV end-diastolic volume (mL/m²)</td>
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<tr>
<td>Baseline</td>
<td>97.3±14.0</td>
<td>98.0±15.4</td>
<td>100.0±16.9</td>
<td>0.32</td>
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<td>4 months</td>
<td>102.6±19.1</td>
<td>103.4±22.6</td>
<td>108.2±24.6</td>
<td>0.16</td>
<td>0.26</td>
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<td>2 years</td>
<td>99.9±20.2</td>
<td>108.0±28.1</td>
<td>110.3±28.3</td>
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<td>LV end-systolic volume (mL/m²)</td>
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<tr>
<td>Baseline</td>
<td>55.4±14.5</td>
<td>57.8±15.9</td>
<td>58.1±15.1</td>
<td>0.31</td>
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<td>4 months</td>
<td>54.9±19.5</td>
<td>57.1±21.6</td>
<td>59.3±21.7</td>
<td>0.23</td>
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<tr>
<td>2 years</td>
<td>51.8±17.4</td>
<td>61.3±26.4</td>
<td>59.1±23.8</td>
<td>0.07</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Values are expressed as number (%) or mean±SD. BMMC denotes bone marrow mononuclear cells; PBMC, peripheral blood mononuclear cells.
on the LV remodeling process following AMI. However, no differences in other CMR endpoints were observed in this study. Therefore, we cannot exclude that this finding is due to chance and multiple testing.

Conclusions
In the present study, we did not show a beneficial effect of intracoronary delivery of BMMCs or PBMCs on the regional and global systolic myocardial function at 2 years of follow-up in patients with first AMI treated with primary PCI.

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