Left ventricular systolic and diastolic function improve after acute myocardial infarction treated with acute percutaneous coronary intervention, but are not influenced by intracoronary injection of autologous mononuclear bone marrow cells: a 3 year serial echocardiographic sub-study of the randomized-controlled ASTAMI study

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Aims
To clarify long-term changes in global, regional, and diastolic left ventricular (LV) function after intracoronary injection of autologous mononuclear bone marrow cells (mBMCs) in acute myocardial infarction (AMI).

Methods and results
In the Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) study, 100 patients with anterior ST-elevation myocardial infarction and percutaneous coronary intervention on the left anterior descending artery (LAD) were randomized to receive intracoronary injection of mBMCs or not. Transthoracic echocardiography was performed at baseline, 3, 6, 12 months, and 3 years. Regional LV function was assessed by two-dimensional speckle-tracking echocardiography. From baseline to 3 years, LV ejection fraction changed from 45.7 to 47.5% in the mBMC group, and from 46.9 to 46.8% in the control group (P = 0.87 for difference in change over time between groups). Longitudinal strain in the LAD territory improved from 2 -9.7 to -12.2% in the mBMC group and from -9.9 to -12.8% in the control group (P = 0.45). E/e′ decreased from 14.7 to 12.9 in the mBMC group and from 14.8 to 11.9 in the control group (P = 0.31). There were no significant differences between groups in change of LV volumes, global systolic function, regional function, or diastolic function during 3 years follow-up.

Conclusion
No differences between groups indicating beneficial effect of intracoronary mBMC injection could be identified. Both groups in ASTAMI experienced improvement of global, regional, and diastolic LV function after 3–6 months, with effects sustained at 3 years.

Keywords
Cell therapy • Stem cells • Echocardiography • Diastolic function • Speckle-tracking • Acute myocardial infarction

Background
Cell therapy has been introduced as a novel treatment modality in acute myocardial infarction (AMI), aiming to promote recovery or repair of the infarcted myocardium.¹ Meta-analyses of numerous small and medium sized trials have confirmed feasibility and short-term safety.²–⁴ A modest beneficial effect on left ventricular ejection fraction (LVEF) has been reported, but trial-designs and results

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on efficacy are heterogeneous. Long-term follow-up data on global, regional, and diastolic LV function are important for further evaluation of safety, and for understanding the process of repair and remodelling after AMI and mBMC therapy. In the Autologous Stem Cell Transplantation in Acute Myocardial Infarction (ASTAMI) study, 100 patients with ST-elevation AMI were randomized to intracoronary injection of autologous mononuclear bone marrow cells (mBMCs) or control. Here, we present a comprehensive analysis of both regional and global systolic function, including strain parameters, as well as diastolic function based on repeated echocardiograms during 3 years follow-up.

**Methods**

The study design, primary endpoints, and long-term clinical outcome in ASTAMI have been described previously. Briefly, patients presenting with their first ST-elevation AMI and successful percutaneous coronary intervention (PCI) with stent on the left anterior descending artery (LAD), were randomized to intracoronary injection of autologous mBMCs 4–8 days after the acute event (n = 50), or control (n = 50). The study was open-label, randomized controlled without sham bone marrow aspiration or sham PCI performed in the control group. All imaging analyses were performed blinded to treatment allocation. In the mBMC group, 50 mL bone marrow was harvested from the iliac crest and the mononucleated cell fraction was isolated by Isopaque-Ficoll gradient centrifugation. Median cell viability was 95% and median number of injected viable cells was \(68 \times 10^6\) (interquartile range \(54 \times 10^6\) to \(130 \times 10^6\)). Ten millilitres of cell suspension was injected by PCI on LAD with the stop flow technique 5–8 days after the acute event. Patients in both groups received post-infarction surveillance and medical treatment according to current guidelines. The study complies with the Declaration of Helsinki, and the protocol was approved by the regional committee for research ethics. All patients gave written, informed consent. The study is registered at www.clinicaltrials.gov NCT 00199823. The authors had full access to the data and take responsibility for its integrity. All authors have read the manuscript and agree to it as written.

**Transthoracic echocardiography**

Transthoracic echocardiography was performed at baseline (4.5 ± 1.1 days after the acute event) and thereafter at 3, 6, and 12 months, and finally at 3 years using a high-end cardiac ultrasound scanner (Vivid 7 with the M3S transducer, GE Vingmed, Horten, Norway). The recordings and analyses were performed according to general recommendations. Briefly, minimum three cardiac cycles were recorded during a brief apnoea. LV volumes and ejection fraction (LVEF) were calculated by the modified Simpson method on apical four-chamber and apical long-axis images. When two-chamber images were of clearly better quality than the long-axis images, these were used. Tissue Doppler recordings were obtained from the apical four-chamber view. High frame rate (>100 Hz) and correctly angled ultrasound beam were pursued. Peak early diastolic (\(e'\)) velocities were registered in the septal and lateral mitral annulus, and mean values used for further calculations. Wall motion score index (WMSI) was assessed by use of a segmental LV model, excluding the apical cap. Two-dimensional speckle-tracking echocardiography (2D-STE) was performed in the standard three image planes acquired from the apex. Longitudinal (peak negative systolic) strain was measured to assess regional and global myocardial function in a 16 segment model of the left ventricle, as illustrated in Figures 1 and 2. The infarct zone was defined as the six segments schematically
supplied by LAD\textsuperscript{16} as all patients had LAD related infarcts. All other segments (supplied by left circumflex and right coronary arteries) were defined as remote. Regional and global strain were calculated as the average of all analysed corresponding segmental strain values\textsuperscript{17}.

Peak E- and A-wave velocities, E-wave velocity deceleration time (DT), and A-wave duration were measured from mitral flow recordings by pulsed Doppler. Flow signals in the right upper pulmonary vein (pv) were obtained by low pulse repetition frequency (LPRF) Doppler from the four-chamber apical view. Peak systolic (pvS)-, diastolic (pvD)-, and atrial reverse (pvA)-wave velocities, and pvA duration were recorded.

\(E/e'\)-ratio was calculated from peak early mitral inflow velocity (\(E\)) and the mean value of the septal and the lateral peak early mitral annulus velocity (\(e'\)).

All analyses were performed offline on GE Echopac software, blinded to patient identity and treatment allocation.

**Statistics**

Continuous data with approximated normal distribution are presented as mean ± standard deviation (SD). Independent sample t-tests were used to compare the groups at baseline. For analysis of continuous data measured at ≥3 points of time, we used mixed model linear regression. Time and the interaction between time and treatment (treatment effect), were fixed variables. No random variables were included in the model\textsuperscript{19} Data from all available time points were included in the analyses. Intragroup changes from baseline were evaluated by paired sample t-tests. Categorical data are presented as frequency (percentage) and \(\chi^2\) or Fisher’s exact tests were used as appropriate. EpiData entry software version 3.1 and SPSS version 15.0 were utilized. All analyses were performed according to the intention-to-treat principle, tested two-sided and \(P\)-values of <0.05 were considered statistically significant.

**Results**

All 100 patients were investigated at all time points, except at 3 years when two patients (one in each group) were dead, and one patient (in the mBMC group) had withdrawn from further follow-up. Clinical characteristics and medication were similar in the two groups (Table 1), except a higher proportion of patients in the mBMC group on diuretics, mainly thiazides prescribed for hypertension before inclusion. All patients were in sinus rhythm, except one patient in the mBMC group with atrial fibrillation during the baseline recording. One patient in the control group had right bundle-branch block, while one patient in the mBMC
Left ventricular systolic and diastolic function

Table 1  Patient characteristics and medication

<table>
<thead>
<tr>
<th></th>
<th>mBMC Baseline (n = 50)</th>
<th>mBMC 3 years (n = 48)</th>
<th>Control Baseline (n = 50)</th>
<th>Control 3 years (n = 49)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.1 ± 8.5</td>
<td>61.2 ± 8.4</td>
<td>56.7 ± 9.6</td>
<td>59.7 ± 9.8</td>
<td>0.34</td>
</tr>
<tr>
<td>Female gender</td>
<td>8 (16%)</td>
<td>7 (15%)</td>
<td>8 (16%)</td>
<td>7 (14%)</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 ± 3.8</td>
<td>27.0 ± 4.0</td>
<td>27.1 ± 3.5</td>
<td>26.6 ± 5.0</td>
<td>0.88</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>66 ± 13</td>
<td>63 ± 15</td>
<td>66 ± 10</td>
<td>61 ± 9</td>
<td>0.44</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132 ± 21</td>
<td>129 ± 18</td>
<td>132 ± 23</td>
<td>126 ± 17</td>
<td>0.32</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82 ± 14</td>
<td>79 ± 9</td>
<td>83 ± 17</td>
<td>79 ± 9</td>
<td>0.96</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>49 (98%)</td>
<td>46 (96%)</td>
<td>50 (100%)</td>
<td>45 (92%)</td>
<td>0.68</td>
</tr>
<tr>
<td>ACE-inhibitors/ARBs</td>
<td>50 (100%)</td>
<td>46 (96%)</td>
<td>50 (100%)</td>
<td>46 (94%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diuretics</td>
<td>21 (42%)</td>
<td>17 (35%)</td>
<td>16 (32%)</td>
<td>8 (16%)</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA I/II/III/IV</td>
<td>28/18/4/0a</td>
<td>30/16/2/0</td>
<td>27/22/1/0a</td>
<td>31/15/3/0</td>
<td>0.89</td>
</tr>
<tr>
<td>CCS 0/II/III/IV</td>
<td>43/7/0/0/0a</td>
<td>43/5/0/0/0</td>
<td>44/6/0/0/0a</td>
<td>47/1/0/1/0</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Medication at primary discharge.

†Data obtained 2–3 weeks after AMI.

‡P-value for difference between groups at 3 years.

NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society.

diastolic function during 3 years follow-up (Figure 4, Table 4). In both groups, there was a significant decrease in E-wave velocity, increased A-wave velocity, decreased E/A-ratio, and increased DT from baseline to 3 years. E/e′ decreased from 14.7 to 12.9 in the mBMC group and from 14.8 to 11.9 in the control group during the study period (P = 0.31 for treatment effect). There were only minor changes in mean isovolumetric relaxation time (IVRT), pvA-velocities, and pv S/D-ratio.

Intra- and interobserver variability

Intra- and interobserver variability were assessed in a random subset of 25 patients. Intraobserver variability (mean ± SD) was 2 ± 13 mL for left ventricular end-diastolic volume (LVEDV) and 2.5 ± 4.1% for LVEF. Interobserver variability was 0.22 ± 14 mL for LVEDV, 0.22 ± 8 mL for left ventricular end-systolic volume (LVESV), 0.04 ± 0.13 for WMSI, and 1.1 ± 4.9% for LVEF. For global strain, interobserver variability was 0.75 ± 0.22%.

Regional systolic function

The infarct zone had significantly lower peak negative systolic strain values compared with remote segments at baseline (−9.8 ± 3.7% in LAD segments vs. −14.9 ± 2.8% in remote segments, P < 0.001), with similar values in both groups (Figure 3, Table 3). The improvement in regional longitudinal strain from baseline to 3 years did not differ between groups in the infarct zone (improvement: 2.6 ± 3.4% in the mBMC group vs. 3.0 ± 3.3% in the control group, P = 0.45) or in the remote segments (2.2 ± 2.8% in the mBMC group vs. 2.3 ± 2.8% in the control group, P = 0.93). In the entire population, strain improved from baseline to 3 years both in the infarct zone (from −9.8 ± 3.7 to −12.5 ± 4.2%, P < 0.001) and in the remote segments (from −14.9 ± 2.8 to −17.0 ± 3.2%, P < 0.001).

Discussion

The present study provides a comprehensive assessment of long-term changes in LV systolic and diastolic function in patients with acute AMI treated with PCI and intracoronary injection of mBMCs. There were no significant effects of mBMC therapy on LV global systolic function, remodelling, regional systolic function, or diastolic function during 3 years follow-up. Most randomized-controlled studies on mBMC treatment after AMI have used change in LVEF as the primary endpoint. Although some studies report significant treatment effects after 4–6 months, others are negative. Sample size is important. In ASTAMI, 100 patients were included to provide 80% power to detect a 5% treatment effect on LVEF by SPECT. In the Cochrane-report by Martin-Rendon...
Table 2 Left ventricular dimensions and systolic function by echocardiography

<table>
<thead>
<tr>
<th></th>
<th>mBMC treated patients</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=50</td>
<td>n=50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>6 months</td>
<td>3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDd (cm)</td>
<td>5.2±0.6</td>
<td>5.4±0.8</td>
<td>0.27</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>156±31</td>
<td>145±43</td>
<td>0.39</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>212±46</td>
<td>207±42</td>
<td>0.99</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>47±9.0</td>
<td>50±10.2</td>
<td>0.32</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.7±0.2</td>
<td>1.5±0.3</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*P < 0.05 for subgroup change from baseline, †P < 0.05 for difference between groups.

ET al.2 an average improvement in LVEF of 3.0% was found in mBMC treated patients compared with controls. Thus, ASTAMI was not powered to detect the moderate effect on LVEF indicated by this meta-analysis. In this long-term follow-up by echocardiography, we have used LVEF, WMSI and the more sensitive global strain to assess systolic global LV function, and the results are concordantly neutral throughout all these methods, and also with the results obtained by MRI at 2–3 weeks, 6 months, and 3 years. Thus, the neutral result is more likely due to but little effect of the intervention rather than a type II error. To date, only the REPAIR-AMI20-, REGENT11-, and Hebe12-trials have included more patients than ASTAMI to investigate this therapy, but complete long-term results from these trials have not been published.

Long-term follow-up on systolic and diastolic LV function have, till now, only been published from 60 patients in the BOOST trial.23,24 Significant improvement in LVEF by MRI was observed from baseline to 6 months in the mBMC group vs. controls, but after 5 years LVEF was similar in both groups. Thus, neither ASTAMI nor BOOST support a long-term benefit of mBMC therapy on LVEF. Experimental studies have suggested beneficial effects of cell therapy on diastolic function.25-26 In humans, serial invasive haemodynamics have been reported only from a cohort of five patients with post-infarction heart failure receiving skeletal myoblasts by catheter-based transendocardial injections.27 Significant improvement in LV systolic function was found after 6 and 12 months, whereas indices on diastolic function were not significantly changed, although Tau and LV end-diastolic pressure trended to increase. In the BOOST trial, E/A-ratio decreased in the control group when compared with the mBMC group at 6 and 18 months, with the overall effect still significant after 5 years. This was interpreted by the authors as improved diastolic function related to mBMC. In our study, reduced E/A-ratio, increased DT, and reduced E/e′ were observed in both groups, probably reflecting a decrease in filling pressure during recovery after AMI. E/A-ratio, DT, and IVRT have a biphasic relation to LV diastolic properties and filling pressure. Patents with AMI may have pseudonormal or restrictive mitral flow patterns at baseline due to high filling pressure. Changes in mean E/A should therefore be interpreted with caution. E/e′ has a more linear relation to LV filling pressure and is recommended for the evaluation of LV diastolic function.13 In BOOST, E/e′ was similar between groups during the entire study. Herbots et al.28 did not find differences in diastolic function between groups, including E/e′ during 4 months follow-up after injection of bone marrow cells. Plewka et al.29 reported improved E/e′ after 6 months in mBMC treated patients, but the change in E/e′ was not compared statistically between groups.

We also analysed regional systolic LV function by 2D-STE. There was significant recovery in systolic longitudinal strain after AMI, but no significant difference between groups. To our knowledge, Plewka et al.29 is the only other group reporting results with a 2D-STE analysis in this setting. The main finding in their study was a 10% increase in LVEF from baseline to 6 months in mBMC treated patients (n=40), compared with a 5% increase in the control group (n=20, P=0.04). 2D-strain was significantly improved in both infarcted (2%) and remote (1%) segments in the mBMC group, whereas no improvement was observed in the control group (1 and 0%, respectively). The 0–2% increase in
Global and regional longitudinal strain by two-dimensional speckle tracking echocardiography

<table>
<thead>
<tr>
<th></th>
<th>mBMC</th>
<th>Control</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 50)</td>
<td>(n = 50)</td>
<td></td>
</tr>
<tr>
<td>Peak negative $\varepsilon$ (global)</td>
<td>$-13.9 \pm 3.1$</td>
<td>$-16.0 \pm 2.9^*$</td>
<td>0.75</td>
</tr>
<tr>
<td>Peak negative $\varepsilon_s$ (global)</td>
<td>$-13.0 \pm 3.1$</td>
<td>$-15.0 \pm 3.2^*$</td>
<td>0.81</td>
</tr>
<tr>
<td>Peak negative $\varepsilon_s$ (LAD segments)</td>
<td>$-9.7 \pm 3.9$</td>
<td>$-12.3 \pm 3.7^*$</td>
<td>0.45</td>
</tr>
<tr>
<td>Peak negative $\varepsilon_s$ (remote segments)</td>
<td>$-14.9 \pm 3.1$</td>
<td>$-16.4 \pm 3.2^*$</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*P < 0.05 for change from baseline within group (t-test).
†P-value for difference between groups by mixed model regression analysis.
$\varepsilon$: peak negative strain; $\varepsilon_s$: peak negative systolic strain.

Figure 3 Markers and bars are mean $\pm$ SD. P-values by mixed model linear regression analysis. mBMC group: Black solid squares and lines. Control group: Grey solid circles and lines.

Left ventricular systolic and diastolic function

strain was small compared with the 5–10% change in LVEF seen in the two groups, and the treatment effect on change in strain is difficult to interpret as no statistical comparison was presented.

Herbots et al. reported significant beneficial effects of mBMC therapy on mitral annulus excursion, strain, and strain-rate in regions supplied by the target vessel in their study on 67 patients after mBMC therapy. A significant decline in blood pressure from baseline to 4 months in the mBMC group when compared with the control group may account for some of the difference between groups, since strain and strain-rate are dependent on changes in afterload. Their study did not show significant effect on diastolic function nor the primary endpoint, change in LVEF. Herbots et al. measured strain and strain-rate by tissue Doppler imaging (TDI). TDI is highly sensitive to sample volume position, angle, and translation. We used 2D-STE since 2D-STE is angle independent, comprises deformation data from a larger myocardial area, and carries a lower intra- and interobserver variability compared with TDI. Of notice, both Herbots et al. and our study reveal highly significant recovery of regional LV function assessed by longitudinal strain, despite only modest recovery in LVEF. Global strain by 2D-STE has recently demonstrated a superior sensitivity for assessment of systolic LV function compared with LVEF in patients with myocardial infarction, suggesting usefulness in detection of smaller therapeutic effects. In our study, there was significant improvement in LV global, regional, and diastolic function in both groups during the first 3–6 months after AMI, and the effect is sustained at 3 years, despite no significant effect of cell therapy. Baseline LVEF in ASTAMI was only 42% by SPECT, indicating significant myocardial infarctions, and an adequate patient population to study effects on LV recovery. Despite significant infarct size, the rate of clinical events is lower than in the contemporary trials HORIZONS-AMI and CADILLAC. When compared with these studies, patients in ASTAMI study had fewer previous myocardial infarctions, fewer prior revascularizations, and patients with kidney failure were not included. Furthermore, compliance with the guidelines in use of aspirine, thienopyridines, betablockers, ACE-inhibitors/ARBs, and statins was 100%, supporting a favourable outcome for these patients. As previously reported, one of our patients in the control group had early re-infarction with cardiogenic shock and received a heart transplant. Thus, the patient was ineligible for follow-up on the primary endpoint LVEF and was excluded from the study on day 11. Two patients (one in each group) were successfully resuscitated from in-hospital cardiac arrest during protocolled extended hospitalization (day 7–10). The significant recovery in LVEF in both groups is concordant with other studies, confirming the favourable impact of acute PCI and optimal medication in patients with larger myocardial infarcts. To date, only the BOOST and ASTAMI studies have reported complete long-term results on the primary endpoint, with no sustained positive effect on LVEF. With numerous human studies on mBMCs and other cells ongoing, it is...
Figure 4  Markers and bars are mean ± SD. P-values by mixed model linear regression analysis. mBMC group: Black solid squares and lines. Control group: Grey solid circles and lines.

Table 4  Left ventricular diastolic function by echocardiography

<table>
<thead>
<tr>
<th></th>
<th>mBMC</th>
<th>Control</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>3 years</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.2*</td>
<td>0.6 ± 0.1*</td>
</tr>
<tr>
<td>A (m/s)</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.2*</td>
</tr>
<tr>
<td>E/A-ratio</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.8</td>
<td>1.0 ± 0.3*</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>161 ± 43</td>
<td>194 ± 49†</td>
<td>194 ± 43*</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>104 ± 22</td>
<td>114 ± 27*</td>
<td>99 ± 13</td>
</tr>
<tr>
<td>pv S/D-ratio</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>pvA (m/s)</td>
<td>0.30 ± 0.06</td>
<td>0.27 ± 0.06*</td>
<td>0.33 ± 0.07*</td>
</tr>
<tr>
<td>pvA-mvA (ms)</td>
<td>8 ± 32</td>
<td>−10 ± 42*</td>
<td>−5 ± 33*</td>
</tr>
<tr>
<td>e′ (cm/s)</td>
<td>5.1 ± 1.6</td>
<td>5.2 ± 1.6</td>
<td>5.1 ± 1.6</td>
</tr>
<tr>
<td>E/e′-ratio</td>
<td>14.7 ± 4.7</td>
<td>13.4 ± 5.7</td>
<td>12.9 ± 3.8*</td>
</tr>
</tbody>
</table>

*P < 0.05 for change from baseline within group (paired t-test).
†P-value for difference between groups by mixed model regression analysis.
important to realize that long-term follow-up have not revealed data on clinical events, systolic-, diastolic-, or regional LV function raising safety concerns. New echocardiographic methods, like strain by 2D-STE, may also apply in future studies, as they are more sensitive than LVEF to detect global and regional changes in LV function. However, sufficient validation of these parameters as surrogate endpoints in clinical trials is still missing. Thus, an adequately designed and powered clinical trial to clarify the effect of mBMC therapy on hard clinical endpoints is warranted.

Limitations
Assessment of long-term changes in regional and diastolic function were not predefined endpoints in ASTAMI. Procedures on cell processing have been discussed, after Seeger et al. reported different cell numbers and quality when comparing the REPAIR-AMI and ASTAMI cell isolation protocols. However, independent comparisons of cell-isolation with Lymphoprep and Ficoll-Paque have not found any significant differences. The median number of injected cells in ASTAMI ($68 \times 10^5$) was slightly lower than the median ($80 \times 10^5$) in studies reviewed by Abdel-Latif et al. Cell counts may be important, but the dose–response relationship in mBMC therapy is not clear; as positive effect has been reported with lower cell numbers, and subgroup analyses on cell-numbers have not been significant in two of the meta-analyses.

Conclusion
Acute PCI and optimal medical care improved global, regional, and diastolic LV function in both groups from baseline to 3 and 6 months, with sustained effects over the following 2.5 years. Intra-coronary injection of autologous mononuclear bone marrow cells did not provide significant additional beneficial effects during 3 years follow-up.

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