Intracoronary infusion of bone marrow-derived selected CD34\(^{+}\)CXCR4\(^{+}\) cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial

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Received 3 November 2008; revised 12 January 2009; accepted 30 January 2009; online publish-ahead-of-print 10 February 2009

See page 1310 for the editorial comment on this article (doi:10.1093/eurheartj/ehp073)

**Aims**

Comparison of intracoronary infusion of bone marrow (BM)-derived unselected mononuclear cells (UNSEL) and selected CD34\(^{+}\)CXCR4\(^{+}\) cells (SEL) in patients with acute myocardial infarction (AMI) and reduced <40% left ventricular ejection fraction (LVEF).

**Methods and results**

Two hundred patients were randomized to intracoronary infusion of UNSEL (n = 80) or SEL (n = 80) BM cells or to the control (CTRL) group without BM cell treatment. Primary endpoint: change of LVEF and volumes measured by magnetic resonance imaging before and 6 months after the procedure. After 6 months, LVEF increased by 3% (P = 0.01) in patients treated with UNSEL, 3% in patients receiving SEL (P = 0.04) and remained unchanged in CTRL group (P = 0.73). There were no significant differences in absolute changes of LVEF between the groups. Absolute changes of left ventricular end-systolic volume and left ventricular end-diastolic volume were not significantly different in all groups. Significant increase of LVEF was observed only in patients treated with BM cells who had baseline LVEF < median (37%). Baseline LVEF < median and time from the onset of symptoms to primary percutaneous coronary intervention ≥ median were predictors of LVEF improvement in patients receiving BM cells. There were no differences in major cardiovascular event (death, re-infarction, stroke, target vessel revascularization) between groups.
**Conclusion**

In patients with AMI and impaired LVEF, treatment with BM cells does not lead to a significant improvement of LVEF or volumes. There was however a trend in favour of cell therapy in patients with most severely impaired LVEF and longer delay between the symptoms and revascularization.

**Keywords**

Bone marrow progenitor cells • Myocardial infarction • CXCR4$^+$ cells • Intracoronary infusion

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**Introduction**

Despite widespread use of primary percutaneous coronary intervention (PCI) for prompt reperfusion of the infarcted myocardium, acute myocardial infarction (AMI) is a major cause of chronic heart failure (CHF). In patients with reduced left ventricular ejection fraction (LVEF) after AMI, the risk of CHF as well as mortality and morbidity are significantly increased. The recovery of left ventricular (LV) function if often poor even in patients treated successfully with primary PCI and aggressive anti-thrombotic regimen. Intracoronary infusion of bone marrow (BM)-derived cells (BMC) has been envisioned as a novel approach, which on top of the state-of-the-art interventional and medical treatment might improve functional myocardial recovery and reduce the risk of CHF as well as improve clinical outcomes.

BM harbours heterogenous population of cells, consisting of committed cell lineages such as granulocytes, lymphocytes, and monocytes, but also rare subpopulations of mono- and multipotent cells, which may play a role in cardiac and endothelial repair. Results of studies using BMC in animal models of myocardial infarction suggest that they may play a role in structural and functional repair of the myocardium.$^2$–$^4$

Data from randomized placebo controlled REPAIR-AMI trial showed that intracoronary infusion of BMC is safe, feasible and leads to a significant but modest improvement of LVEF in patients with AMI.$^5$ Contradictory findings came from ASTAMI trial, which did not show any significant benefit of such therapy, and BOOST trial which showed that the initial improvement of LVEF after BMC treatment was not sustained in long-term follow-up.$^6$–$^7$ Also, large randomized clinical trials powered to show the impact of BMC infusion on clinical outcomes are still missing. So far most of the studies used non-selected BM-derived mononuclear cells (MNC) for intracoronary infusion and no study demonstrated which particular type of cells within this population might have the highest potential for myocardial repair in patients with AMI.

Population of BMCs expressing CD34 and CXCR4 markers can be isolated from the human BM. Presence of these surface markers identifies subpopulation of cells, which undergo rapid mobilization during AMI in response to chemokine stromal cell-derived factor-1 (SDF-1) secreted by the cardiac muscle. In addition, CD34$^+$CXCR4$^+$ cells express cardiac and endothelial lineage markers, therefore this population is likely to contribute to myocardial repair or regeneration following the acute ischaemic injury.$^2$–$^8$–$^9$

The objective of Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENER) study was to determine the effect of intracoronary infusion of selected population of autologous BM-derived CD34$^+$CXCR4$^+$ progenitor cells in comparison with non-selected BM MNC on LV function in patients with acute ST-segment elevation MI and reduced LVEF.

**Methods**

**Patient population**

Study population consisted of 200 patients with AMI treated with primary percutaneous coronary intervention (PCI). Patients were enrolled in five centres in Poland between March 2005 and September 2007, and 6-month follow-up was completed in March 2008. Inclusion criteria were as follows: anterior AMI, successful PCI with stent implantation in the infarct-related left anterior descending (LAD) artery within 12 h after the symptoms onset, reduced LVEF ≤ 40% in qualifying echocardiogram, and age 18–75 years. Exclusion criteria were: prior MI, presence of significant stenoses in other coronary vessels requiring revascularization, cardiogenic shock, renal failure, past or present malignancy, pregnancy, lactation and contraindications for magnetic resonance imaging (MRI). All patients received medications, as recommended by current guidelines.

**Study design and protocol**

REGENT was a multicentre, randomized, prospective study. The study design is shown in Figure 1. Eligible patients were randomized by centre in 2:2:1 fashion into three parallel groups: actively treated by infusion of either selected CD34$^+$CXCR4$^+$ cells ($n = 80$) or non-selected MNCs ($n = 80$) and the control group, receiving no cell therapy ($n = 40$). No BM aspiration was performed in patients of control group. Echocardiography was used to qualify the patients with reduced LVEF and MRI was done 1–3 days after the cell transfer. Both were repeated after 6 months in active treatment groups and patients in control group.
Isolation of bone marrow-derived cells

In patients from actively treated groups BM (100–120 mL in patients receiving selected cells and 50–70 mL in patients receiving MNC) was aspirated from the posterior superior iliac spine under short intravenous general anaesthesia. BM aspiration was done 7 (3–12) [median (range)] days after the primary PCI. Non-selected BMCs were isolated using the Ficoll density gradient centrifugation technique as previously described. Median cell yield was 1.78 × 10^6 cells. In patients receiving selected CD34+CXCR4+ cells, following Ficoll isolation, the cell population was isolated using two-step immunomagnetic selection with monoclonal antibodies coupled with magnetic beads and MidMACS System (Miltenyi Biotec GmbH). The median number of CD34+CXCR4+ cells was 1.90 × 10^6. Cells were enumerated by FACS (FACS-Calibur, Beckton Dickinson) according to ISHAGE guidelines (see Supplementary material online, Figure S1 A and B). BMCs were resuspended in phosphate-buffered saline (final volume of 10 mL) and transferred on the same day to the catheterization lab for intracoronary infusion. (More details are available in the Data Supplement.)

Intracoronary infusion of bone marrow-derived cells

Intracoronary BMC transfer was done using the ‘stop-flow technique’ as previously described (more details are available in the Data Supplement).

Cardiac imaging

Cardiac magnetic resonance imaging

Cardiac MRI was performed for evaluation of LVEF, end-systolic (ESV), and end-diastolic volumes (EDV). (More details are available in the Data Supplement.)

Left ventricular angiography

In patients assigned to the active treatment arms LV-angiograms were recorded in right anterior oblique projections prior to the infusion of BMC and repeated in the same projections after 6 months as previously described. (More details are available in the Data Supplement.)

Endpoints

The primary endpoint was the absolute change of the LVEF measured by MRI at baseline and after 6 months following the cell infusion. The secondary endpoints were: change of LV volumes measured by MRI, and change of LVEF measured by LV-angiography. Safety outcome measure was the composite endpoint which included major cardiovascular adverse events (MACE) [death, re-infarction, stroke, and target vessel revascularization (TVR)]. Prespecified subgroup analyses were carried out to identify the interaction between baseline LVEF, time from the onset of symptoms to primary PCI, time from the primary PCI to cell infusion, and number of infused cells with the change of LVEF as well as the factors associated with clinically significant improvement of LVEF, which was defined as the absolute increase of LVEF by ≥5%.

Statistical analysis

As distribution of the variables was different from normal (Kolmogorov–Smirnov test), non-parametric tests were used for statistical analysis. Comparison of baseline characteristics of the groups was done using χ² test and Mann–Whitney U test. Changes of LVEF, LVEDV, and LVESD in groups were analysed using Wilcoxon test. Relative changes of the above parameters were compared among groups using Mann–Whitney U test, while rates of patients who achieved ≥5% increase of EF were compared using Fisher’s exact test. Prognostic value of factors influencing a chance to achieve ≥5% increase of EF was evaluated by logistic regression. In a multivariate analysis backward stepwise procedure was used. All tests were two-sided. Values of P < 0.05 were considered statistically significant. For within group comparison, the Bonferroni correction was applied and P < 0.0167 was considered statistically significant. Statistica 6.0 software (StatSoft Inc., Tulsa, OK, USA) was used.

Results

Patients enrolment and procedural feasibility

There were no significant differences between the groups with regard to gender, age, and major clinical and laboratory variables (Table 1). The intracoronary BMC transfer was successfully carried out in all patients randomized to active treatment arms without complications. One patient developed arteriovenous fistula of the femoral artery after the procedure and required surgical treatment.

Left ventricular ejection fraction and volumes

The paired results of LV imaging by MRI were available in 117 patients (20 from control group, 46 receiving non-selected, and 51 selected cells). Paired LV-angiography results were available in 152 patients from BMC treatment arms only (75 from non-selected and 77 from selected cells groups). There were no significant differences in baseline values of LVEF and volumes between the groups (see Supplementary material online, Table S1). MRI studies revealed that after 6 months there was an increase of LVEF in patients receiving BMC in comparison with baseline values. LVEF increased from 37 to 40% in patients treated with non-selected MNC and from 35 to 38% in those receiving CD34+CXCR4+ cells. However, after applying the Bonferroni correction for within-group comparison the absolute increase of LVEF was significant for non-selected cells group only. There was no significant change of LVEF in the control group. Comparison of the absolute changes between the groups showed no significant differences between active treatment and the controls (Figures 2 and 3, see Supplementary material online, Table S1). As the control group had no LV-angiography performed, only the results of active treatment arms were compared and similarly for the results obtained with MRI, the LVEF values measured by LV-angiography increased after 6 months in both groups receiving BMC. The differences in absolute changes of LVEF between the groups were not significant (see Supplementary material online, Figure S2). After 6 months there were no significant changes in ESV in treatment and control arms. EDV did not change significantly in control group and in patients receiving BMC. The comparison of absolute changes in ESV and EDV between the groups did not show significant differences (Figure 4, see Supplementary material online, Table S1).
Factors associated with left ventricular ejection fraction improvement

Prespecified analyses were carried out to identify factors predictive of clinically significant improvement of LVEF ($\Delta \geq 5\%$). There was a significant inverse correlation between the baseline LVEF and its change after BMC therapy ($R = -0.5; P = 0.0008$) in patients treated with selected BMC, but not in the non-selected BMC ($R = -0.26; P = 0.13$) and in the control group ($R = -0.11; P = 0.7$). Patients were divided according to the baseline values of LVEF below and above the median value of 37%. There was a significant improvement in LVEF in patients receiving both types of BMC therapy.
BMC who had baseline LVEF below the median [absolute change, median 6 (−6.37) for non-selected cells and 7 (−9.26) for selected cells], but not in patients with baseline LVEF ≥ median (Figure 5). No such interaction was found in the control group. Univariate analysis revealed that baseline LVEF < median was predictive of significant improvement of LVEF after 6 months in both groups treated with BMC, but not in the control group. In this model the number of infused CD34+CXCR4+ cells, leukocyte count, and time from PCI to infusion of cells were not significant predictors of LVEF improvement. In multivariate logistic regression only two variables—baseline LVEF value below median and time from the onset of symptoms to primary PCI ≥ median remained significant predictors of LVEF improvement in both groups receiving BMC (Figure 6).

Patients receiving both types of BMC more frequently achieved significant increase of LVEF than patients in control group (51% for selected BMC, 39% for non-selected cells, and 36% for control

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**Figure 4** Comparison of absolute changes of LVEDV (A) and LVESV (Panel B) measured by cMRI between the groups (control n = 20; non-selected cells n = 46, selected cells n = 51). Values are median (small boxes). Whiskers represent the minimum and maximum values and boxes represent the interquartile (25th–75th percentiles) range. Two-sided Mann–Whitney U test was used.

**Figure 5** Comparison of LVEF after 6 months in subgroups of patients stratified according to baseline LVEF equal and above (Panel A) or below (Panel B) median value of 37%. Values of LVEF are median (small boxes). Whiskers represent the minimum and maximum values and boxes represent the interquartile (25th–75th percentiles) range. Wilcoxon test was used.

**Figure 6** Factors predictive of significant ≥5% increase of left ventricular injection fraction after bone marrow-derived cells infusion in multivariate logistic regression.
group), however the differences between the groups did not reach statistical significance.

**Major cardiovascular adverse events**

MACE are summarized in Table 2. There were three deaths, one in each group. Two patients from control group and one from selected BMC group developed re-infarction. There were no significant differences in the frequency of MACE as well as the composite endpoint including death, re-infarction, stroke, and TVR between the groups. Seven patients from the control group, 13 from the group treated with non-selected BMC, and 12 receiving selected BMC underwent repeat PCI in the infarct-related artery.

**Discussion**

The main finding of the REGENT trial is that in patients with successfully reperfused anterior MI, the use of either selected BM-derived CD34+/CXCR4+ cells or non-selected MNCs did not significantly improve the LVEF after 6 months follow-up. Although within the groups there was a significant increase by 3% in LVEF in patients treated with non-selected cells in comparison with baseline and no increase in the control group, the differences in the absolute changes of LVEF between the active groups and the controls did not reach statistical significance. There was however a clear trend for better outcome in patients with severely reduced baseline LVEF (<37%) who did receive the cell therapy. No significant improvement in comparison with baseline was observed in patients with baseline LVEF equal or above the median value of 37%. In this study, the use of BMC had no effect on reduction of the LV volumes in comparison with the control. Above findings were however a result of post hoc analysis, so need to be interpreted with caution and further studies aiming specifically to investigate the relation of baseline LVEF impairment and the improvement caused by BMC should be carried out. The results of the MRI imaging and LV-angiography were consistent. All treated patients had anterior wall infarction, which was timely reperfused with stent implantation into the infarct-related LAD artery. In addition to PCI, the patients received currently recommended medications including glycoprotein IIb/IIIa inhibitors, clopidogrel, beta-blockers, and high-dose statins unless contraindicated. Despite successful reperfusion, the patients represented a high-risk population owing to significantly reduced LVEF.

**Table 2 Clinical follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 40)</th>
<th>Non-selected MNC (n = 80)</th>
<th>Selected CD34+/CXCR4+ cells (n = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>1 (2.5)</td>
<td>1 (1.25)</td>
<td>1 (1.25)</td>
<td>0.92</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>2 (5.0)</td>
<td>1 (1.25)</td>
<td>2 (2.5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TVR, n (%)</td>
<td>7 (17.5)</td>
<td>13 (16.2)</td>
<td>12 (15.0)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

MACE are summarized in Table 2. There were three deaths, one in each group. Two patients from control group and one from selected BMC group developed re-infarction. There were no significant differences in the frequency of MACE as well as the composite endpoint including death, re-infarction, stroke, and TVR between the groups. Seven patients from the control group, 13 from the group treated with non-selected BMC, and 12 receiving selected BMC underwent repeat PCI in the infarct-related artery.

The primary endpoint in ASTAMI trial can be explained by significant improvement of LVEF not only in patients treated with BMC but also in the control group, which was not the case in our study where the control group did not show an improvement at 6 months (Figure 3). Also the BOOST trial showed that despite the initial improvement of LVEF observed after 6 months following the cell infusion, the difference between the BMC treatment arm and control group was no longer significant after 18 months. Comparing with the REGENT trial, the BOOST trial showed a trend towards increase of EDV and no change of ESV during the 18-month follow-up. Conversely, REPAIR-AMI investigators have found that BMC transfer significantly improved the LVEF after 4-months follow-up. The absolute increase of LVEF in REPAIR-AMI was significantly increased by 2.5% in actively treated patients in comparison with control group. In the REPAIR-AMI trial EDV increased significantly in both groups in comparison with baseline and ESV increased only in the placebo group and the increase of LVEF was associated with a significant improvement of regional contractility in the segments located in the area of infarction. Similar conclusions were reached in the meta-analysis of Abdel-Latif, which included 999 patients enrolled into 18 studies and showed that stem/progenitor cell therapy significantly increased LVEF by 3.66% and reduced ESV in comparison with the control group. However, this data set included patients treated with various types of cells and different routes of their delivery were employed. Lipinski et al. performed meta-analysis and systematic review including only patients with AMI treated with BMC by intracoronary delivery and showed a 3% significant increase of LVEF coexisting with a significant reduction of ESV by 7.4 mL in comparison with control group. Similar results were obtained in the recent systematic review of trials enrolling patients with AMI, which showed benefits of BMC therapy (increase of LVEF by 2.9% and decrease of ESV by 4.74 mL) over standard reperfusion therapy. We identified two variables predictive of the improvement of LVEF following the BMC therapy—the baseline LVEF and time from the onset of symptoms to primary PCI. Subgroup analysis revealed that in patients with severely reduced LVEF (<37%), the use of a relatively small number of selected CD34+/CXCR4+ cells is associated with similar trend for improvement of LVEF as the use of 100 times higher number of non-selected MNC (1.78 x 10^8 vs. 1.90 x 10^9). When patients were subdivided according to the baseline EF below and above the median, the improvement in LVEF in those with worse systolic function was significant, and similar for the selected and non-selected BMC. Baseline EF below median was
The mechanisms of improvement of LV function after BMC therapy are not clear. There is no convincing data that transdifferentiation of BMC into cardiac myocytes plays a significant role in myocardial repair after acute MI in humans. Also, it is highly unlikely that physiologically relevant amount of cardiac tissue can be derived from small number of BM cells that engraft within the necrotic area after intracoronary delivery.\textsuperscript{23} Most likely, implantation of BMC improves the perfusion of peri-infarct area by inducing neovascularization, as shown in the substudy of REPAIR-AMI using the intracoronary Doppler-wire measurements.\textsuperscript{21} In addition BMC may synthesize and secrete cytokines and growth factors, which reduce the apoptosis of cardiomyocytes and activate resident cardiac stem cells in a paracrine manner.\textsuperscript{2,3}

Adult bone marrow harbours various populations of cells, which can potentially contribute to myocardial and endothelial repair. The rationale of the REGENT trial was based on the data from the experimental models as well as patients with AMI who showed that in response to myocardial ischaemia population of BM-derived cells expressing CD34\textsuperscript{+} and CXCR4\textsuperscript{+} markers but also significantly enriched in early cardiac (Nkx2.5, GATA-4) and endothelial (VE-cadherin, von Willebrand factor) markers is rapidly mobilized into peripheral blood.\textsuperscript{9} At the same time there is a significant upregulation of SDF-1 in the myocardium. This chemokine ligand of the CXCR4 receptor is a pivotal factor in mobilization, homing, and engraftment of the CXCR4\textsuperscript{+} cells to the ischaemic myocardium.\textsuperscript{8} In addition, the number of circulating CD34\textsuperscript{+}CXCR4\textsuperscript{+} cells is correlated with the improvement of LVEF and LV remodelling after the MI. On the other hand patients with acute MI and reduced LVEF have also significantly impaired mobilization of CD34\textsuperscript{+}CXCR4\textsuperscript{+} cells.\textsuperscript{24,25} Since the subpopulation of CD34\textsuperscript{+}CXCR4\textsuperscript{+} cells enriched in potential cardiac-committed progenitor cells is rapidly mobilized into the blood following the acute ischaemia, the use of these cells was likely to mimic the physiological reparatory mechanism of myocardial recovery.

The primary goal of REGENT trial was to compare the effects of two different populations of BMCs on the improvement of LV contractility, but obviously the primary limitation of this study is the lack of placebo arm and its open-label design, which was partially responsible for the low retention of patients, particularly in the control group. Dropout rate was higher than that reported in other BMC trials (0–18%), especially in comparison with placebo-controlled trials.\textsuperscript{18} The major limitation of the study is a low number of patients having MRI imaging both at baseline and follow-up. This in our opinion is likely to be responsible for the failure to achieve the statistical significance for the primary endpoint analysis, which included <60% of the total population of patients. In both treatment arms, the absolute LVEF increase approximates 3%, so it is comparable with the results of REPAIR-MI study in which absolute increase of 2.5% was highly significant. Therefore, interpretation of the data should be careful given the fact that low retention of patients is probably the cause of the negative result. Therefore, a placebo-controlled study targeting the population of patients who might derive greatest benefit from this approach will be needed to validate the hypothesis.

**Conclusion**

In patients with AMI who despite timely and successful treatment with primary PCI developed impairment of the LVEF, treatment...
with either selected or non-selected BMCs does not lead to a significant improvement of LVEF. There was however a trend in favour of cell therapy, particularly in patients with most severely impaired LVEF and longer delay between the symptoms and revascularization, which is considered the high-risk group. Use of selected CD34+/CXCR4+ cells in patients with significantly reduced LV function is safe, feasible, and warrants further investigation.

Supplementary material

Supplementary Material is available at European Heart Journal online.

Funding

Polish Ministry of Science and Higher Education (grants number PBZ-KBN-099/P05/2003, 0651/P01/2007/32, 2422/P01/2007/32).

Conflict of interest: none declared.

Appendix

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References

Coronary artery embolism from native mitral valve thrombus

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An 80-year-old lady with hypertension, diabetes, and permanent pacemaker presented with presyncope but no other cardiovascular symptoms. Electrocardiogram showed a paced rhythm and troponin I was 0.16. Pacemaker check was normal, and angiography showed unobstructed coronary arteries. Transthoracic echocardiography (TTE) revealed a heavily calcified mitral valve (MV) and a hypermobile mass on the posterior MV leaflet consistent with thrombus (Panel A). Vegetation could not be excluded; however, she was afebrile, with normal inflammatory markers and negative blood cultures. She was discharged fully anticoagulated. Within a week the patient re-presented with chest pain and troponin I of 38. Her INR on presentation was 3.2. On TTE, the MV mass had disappeared except for a residual stump (Panel B). Attempts to retrieve the mass using a thrombus removal device and inflations using compliant and cutting balloons proved unsuccessful. After a prolonged procedure, treatment with abciximab was commenced. At re-study after 48 h, the mass remained unchanged. Successful removal was finally achieved with a distal protection device (Panels D and E). Histology (Panel F) confirmed calcified thrombus with no inflammatory infiltrate and microbiology was negative. Coronary artery embolism as a rare cause of myocardial infarction has been described from prosthetic valve thrombus in the context of subtherapeutic anticoagulation as well as in infective endocarditis. Here, we describe large coronary embolism from a native MV thrombus in a fully anticoagulated patient.

Panels A and B. TTE on first presentation: calcified MV with hypermobile mass on posterior MV leaflet (Panel A). TTE on second presentation: calcified MV with mass stump visible on posterior MV leaflet (Panel B).


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