Mobilization of bone marrow-derived stem cells after myocardial infarction and left ventricular function

Antonio Maria Leone1*, Sergio Rutella2, Giuseppina Bonanno2, Antonio Abbate1, Antonio G. Rebuzzi1, Silvia Giovannini1, Mariaelena Lombardi1, Leonarda Galiuto1, Giovanna Liuzzo1, Felicita Andreotti1, Gaetano A. Lanza1, Anna Maria Contemi2, Giuseppe Leone2, and Filippo Crea1

1 Institute of Cardiology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy
2 Institute of Haematology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy

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Aims Recent data suggest that the administration of bone marrow-derived stem cells (BMSC) might improve myocardial perfusion and left ventricular (LV) function after acute myocardial infarction (AMI). The aim of this study was to assess spontaneous mobilization of BMSC expressing the haematopoietic and endothelial progenitor cell-associated antigen CD34+ after AMI and its relation to post-infarction remodelling.

Methods and results Peripheral blood concentration of CD34+ BMSC was measured by flow cytometry in 54 patients with AMI, 26 patients with chronic stable angina (CSA), and 43 normal healthy subjects. In patients with AMI, LV function was measured by 2D-echocardiography. Eighteen AMI patients were reassessed at 1 year. BMSC concentration was higher in patients with AMI (mean peak value: 7.04 ± 6.27 cells/μL), than in patients with CSA (3.80 ± 2.12 cells/μL, P = 0.036) and in healthy controls (1.87 ± 1.52 cells/μL, P < 0.001). At multivariable analysis statin use (P < 0.001), primary percutaneous intervention (P = 0.048) and anterior AMI (P = 0.05) were the only independent predictors of increased BMSC mobilization after AMI. In the 28 patients without subsequent acute coronary events reassessed at 1 year follow-up, CD34+ cell concentration was an independent predictor of global and regional improvement of LV function (r = 0.52, P = 0.004 and r = −0.41, P = 0.03, respectively).

Conclusion AMI is followed by enhanced spontaneous mobilization of BMSC, in particular, in patients on statin therapy and following a primary percutaneous intervention. More importantly persistent spontaneous mobilization of BMSC might contribute to determine a more favourable post-AMI remodelling.
Introduction

The dogma that the heart is a post-mitotic organ has recently been challenged by Beltrami et al., who identified a subpopulation of cardiomyocytes that were not terminally differentiated and had the ability to re-enter the cell cycle and undergo nuclear mitotic division in the infarcted human heart. The same group and others, subsequently, described the presence of cardiomyocytes of extracardiac origin in human hearts. An impressive repair of infarcted hearts in experimental models of acute myocardial infarction (AMI), with improvement of myocardial function and survival, was obtained in mice by local and intravenous administration of bone marrow-derived stem cells (BMSC) or by intravenous administration of mobilizing cytokines, thus suggesting myocardial regeneration by administered or mobilized BMSC. Recent studies, however, failed to find evidence of transdifferentiation of BMSC into cardiomyocytes.

Accordingly, early data from clinical studies suggest that intracoronary or intramyocardial injection of autologous progenitor cells may beneficially affect post-infarction remodelling and perfusion.

In spite of the growing number of experimental and clinical studies on the effects of BMSC and mobilizing cytokines in AMI, very little is known about the spontaneous release of BMSC after AMI and its impact on left ventricular (LV) remodelling in man. To address this issue we measured BMSC expressing the haematopoietic and endothelial progenitor cell-associated antigen CD34 in patients with AMI, in patients with chronic stable angina (CSA), and in healthy controls.

Methods

Patients

From October 2002 to December 2003, 54 consecutive patients with AMI, 26 consecutive patients with CSA, and 43 healthy controls were enrolled in the present study (Table 1). All patients with AMI exhibited typical chest pain, cardiac enzyme elevation, and persistent ST segment elevation. Exclusion criteria were cardiogenic shock, in-hospital death, or conditions potentially influencing white blood cell count, such as cancer, haematological diseases, and infections.

Among patients with AMI, at discretion of the caring physician, 16 underwent a primary percutaneous coronary intervention (PCI) (time from beginning of symptoms and PCI was 262 ± 213 min), 26 thrombolysis with r-tPA according to GUSTO protocol, and 12 did not undergo either thrombolysis or primary PCI for prolonged time from the beginning of symptoms (from 12 to 24 h). Rescue PCI was performed after unsuccessful thrombolysis in six patients. Twenty-seven patients (18 initially treated with thrombolysis and 9 not submitted to reperfusion therapy) underwent elective angiography within 5 ± 2 days of admission because of spontaneous or inducible ischemia; PCI or coronary artery by-pass grafting were, respectively, performed in 18 and in 3 of these patients. Statin treatment was at the discretion of the caring physician. It was started within 3 days of admission in 32 patients, and at discharge in the remaining 22 patients. Twenty-one AMI patients received simvastatin, the

Table 1 Characteristics of patients

<table>
<thead>
<tr>
<th>n (%)</th>
<th>AMI</th>
<th>CSA</th>
<th>Healthy controls</th>
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<tbody>
<tr>
<td>Males</td>
<td>37 (68.5)</td>
<td>19 (73)</td>
<td>29 (67)</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>28 (51.8)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>16 (29.6)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>26 (48.1)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>20 (37.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>25 (46.3)</td>
<td>20 (76.9)</td>
<td>0 (0)</td>
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<tr>
<td>Diabetes</td>
<td>7 (13.0)</td>
<td>10 (38.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (55.5)</td>
<td>17 (65.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>36 (66.6)</td>
<td>11 (42.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18 (33.3)</td>
<td>17 (65.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>14 (25.9)</td>
<td>9 (34.6)</td>
<td>0 (0)</td>
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<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>AMI</th>
<th>CSA</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61 ± 14</td>
<td>67 ± 5</td>
<td>39 ± 11</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>44 ± 11</td>
<td>65 ± 5</td>
<td>Normal</td>
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<tr>
<td>WMSI</td>
<td>1.97 ± 0.39</td>
<td>1</td>
<td>Normal</td>
</tr>
<tr>
<td>CPK (UI/L)</td>
<td>3221 ± 3596</td>
<td>102 ± 70</td>
<td>85 ± 46</td>
</tr>
<tr>
<td>TnT (ng/mL)</td>
<td>8.9 ± 7.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>332 ± 152</td>
<td>293 ± 62</td>
<td>253 ± 68</td>
</tr>
<tr>
<td>CRP (mg/mL)</td>
<td>40 ± 59</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>WBC (cells/µL)</td>
<td>11662 ± 3370</td>
<td>7421 ± 1379</td>
<td>6066 ± 1409</td>
</tr>
</tbody>
</table>
others atorvastatin. All patients with CSA had evidence of inducible ischaemia at non-invasive stress test and significant stenoses at coronary angiography (≥70% lumen reduction in at least one major coronary artery branch), but no history of previous acute coronary syndromes. All patients with CSA were on statin treatment. Among CSA patients 14 were on simvastatin, 9 on atorvastatin, and the others on pravastatin. We selected a control group of 43 healthy blood donors (mean age 39 ± 11 years, 29 males) without overt heart disease and/or major cardiovascular risk factors (diabetes, smoking, hypertension, hypercholesterolaemia, and familial history). Hypercholesterolaemia, diabetes mellitus, and hypertension were considered present if they were diagnosed during hospitalization or if drugs for these conditions had been prescribed prior to admission. Hypercholesterolaemia was diagnosed by a total serum cholesterol concentration >200 mg/dL, diabetes by fasting glycaemia >126 mg/dL on more than two occasions, and hypertension by blood pressure values >140/90 on more than two occasions. Smokers were defined as smokers of >1 cigarette/day at the time of admission. Patients were defined as having a familial history of ischaemic heart disease in the case of a documented acute coronary syndrome before 60 years of age in at least one first-degree relative.

The first 28 AMI patients enrolled in the study without subsequent ischaemic events (death, myocardial infarction, and acute coronary syndrome) underwent repeat blood sampling and 2D-echocardiography at 1 year follow-up. Clinical features of these patients are reported in Table 2. All these patients were on therapy with statins, aspirin, and angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers; 26 patients were on beta-blockers also.

Each participant to the study gave informed consent. The study protocol was approved by the Ethics Committee.

Assessment of LV function

In all patients, with AMI within the first 5 days of admission to coronary care unit, and then in 28 of these patients, at 1 year follow-up, regional and global LV function were measured by 2D-echocardiography by two independent cardiologists blinded to BMSC concentration and patient’s clinical history according to the recommendations of the American Society of Echocardiography. LV ejection fraction (LVEF) was measured from the end-diastolic and end-systolic volumes calculated with the Simpson method from two orthogonal apical views. LV regional wall motion analysis was based on grading the contractility of individual segments. Left ventricle was divided into three levels (basal, mid, and apical) and 16 segments. The basal and mid levels are subdivided into six segments and the apical level is subdivided into four segments. A numerical scoring was adopted on the basis of contractility of the individual segments. In this scoring system, higher scores indicate more severe wall motion abnormality: (i) normokinesis, (ii) hypokinesis, (iii) akinesis, (iv) dyskinesis, and (v) aneurysm. The regional wall motion score index (WMSI) was derived by dividing the sum of wall motion score by the number of visualized segments; a normal WMSI was 1.

Assessment of BMSC

In AMI patients, blood samples to measure CD34+ and CD45+ cells were collected on day 1 after the acute event and then on days 3, 5, 7, and at the 1 year follow-up. A single sample was obtained in CSA patients and in healthy controls. Aliquots of EDTA-anticoagulated peripheral blood were incubated with saturating amounts of the following: fluorescein isothiocyanate (FITC), phycocerythrin (PE), or peridinin chlorophyll (PerCP)-conjugated monoclonal antibodies (mAb); CD34 (BG12 clone, IgG1) and CD45 (H30 clone, IgG1; Caltag Laboratories, Burlingame, CA, USA). In five patients, on day 5 after AMI, an aliquot of purified CD34+ BMSC was obtained from peripheral blood using an immunomagnetic device for a phenotypic characterization of CD34+ cells. The following mAbs were used to this end: CD34, CD45, CXC chemokine receptor 4 (CXCR4; 12G5 clone, IgG2a), CD38 (HB7 clone, IgG1), CD33 (WM3 clone, IgG1; Becton Dickinson (BD), Mountain View, CA, USA), HLA-DR (TU3 clone, IgG1), CD11b (CR3 Bear-1 clone, IgG1), CD13 (TU1 clone, IgG1), CD45 (H30 clone, IgG1; Caltag Laboratories), CD133 (AC133 clone, IgG1; Miltenyi Biotec, Bergisch Gladbach, Germany), or VEGF R2 (KDR; R&D Systems, Abingdon, Oxon, UK). Appropriate fluorochrome-conjugated isotype-matched mAb purchased from the different manufacturers were used as control for background staining. After extensive washings with PBS-1% BSA, cells were kept on ice until flow cytometric analysis. Cells were run through a FACSscan flow cytometer (BD), equipped with an argon laser emitting at 488 nm. Details on instrument requirements and settings were published elsewhere. FITC, PE, and PerCP signals were collected at 530, 575, and 670 nm, respectively; spectral overlap was minimized by electronic compensation with CalibrBeads (BD) before each determination series. A minimum of 10,000 events was collected and acquired in list mode using the CellQuest software (BD).

The frequency of CD34+ events in the peripheral blood was expressed as the percentage of CD34+ cells among all leukocytes, after electronic gating on viable cells. The number of CD34+ per microlitre of cells was calculated by multiplying the frequency of CD34+ events by the total leukocyte count.
Cell cultures

Colonies forming cells (CFU-granulocyte macrophage, CFU-GM and
burst forming unit erythroid, BFU-E) from isolated CD34+ cells from
the first five patients with AMI were generated in 14 day
methylcellulose semisolid cultures in the presence of 25%
serum substitute to avoid interference from serum factors (Bit
9500, Stem Cell Technologies, Vancouver, Canada) and
supplemented with stem cell factor, interleukin 3, granulocyte-
colonies stimulating factor (GM-CSF), granulocyte
colonies stimulating factor (G-CSF), Flt3-ligand, and
erythropoietin. Cloning activity was expressed as cumulative colony
efficiency (CFU-GM + BFU-E).

Statistical methods

Normal distribution was tested by the Kolmogorov–Smirnov test.
Continuous variables were compared by t-test, Mann–Whitney,
ANOVA, or Kruskal–Wallis test, as appropriate. For multiple
comparison between groups, t-test or Mann–Whitney U-test
with Bonferroni’s correction (P × number of groups) was used.
Correlations were evaluated by Spearman or Pearson r tests.
Categorical variables were compared with the use of χ2 or
Fisher’s exact test. Multivariable analysis was performed using
a forward stepwise linear regression analysis with an F to enter
more than one (Statistica 5.5, Stat Soft Inc., Tulsa, OK, USA).
We evaluated the following clinical variables: age, sex, anterior
AMI, primary PCI, multivessel disease, major cardiovascular risk
factors (diabetes mellitus, smoking, hypertension, hyper-
cholesterolemia, and familial history), statin use, creatine-
phosphokinase (CPK) and troponin T (TnT) peak serum
levels, fibrinogen, C-reactive protein (CRP) serum levels, and
white blood cell count on admission. Continuous data are
presented as mean ± SD. For the calculation of the sample we
hypothesized that CD34+ cells could not differ significantly in
CSA patients and healthy controls, as no data were available in
patients with coronary artery disease at the time of the study.
According to the previous data in healthy subjects,17 we expected
an average number of 2.0 ± 2.8 CD34+ blood cells/μL; thus, we
calculated that, to have an 80% power to detect an increase of at
least 2 cells/μL, at a significance level of P < 0.05, in AMI
patients, compared with CSA patients, we needed to enrol 50
patients in the AMI group and 25 in the CSA group. Differences
of P < 0.05 were considered significant.

Results

Mobilization of BMSC

In AMI patients, the number of circulating CD34+ cells
was similar on days 1, 3, 5, and 7 (5.95 ± 6.23,
3.78 ± 3.08, 4.76 ± 3.74, and 5.03 ± 3.74 cells/μL,
respectively; P = 0.20) (Figure 1). Most of the patients
had the peak concentration on day 5. In fact the peak
number was reached on day 1 in 11 patients, on day 3
in 14, on day 5 in 19, and on day 7 in 10. A marked varia-
bility in the peak number of CD34+ cells ranging from
0.84 to 33.4 CD34+ cells/μL was noted among patients.
The peak number of circulating CD34+ cells in AMI
patients (7.04 ± 6.27 cells/μL) was higher than that
observed in patients with CSA (3.80 ± 2.12 cells/μL,
P = 0.039) or in healthy controls (1.87 ± 1.52 cells/μL,
P < 0.001). Furthermore, the number of CD34+ cells
in patients with CSA was higher than in controls
(P < 0.001) (Figure 2). Among the 28 AMI patients reas-
sessed at 1 year follow-up, CD34+ cell concentration at
follow-up was significantly lower than that observed
early after AMI (3.34 ± 2.70 vs. 6.99 ± 5.41 cells/μL,
P < 0.01).

Phenotypic characterization of CD34+ cells

In all patients we measured the co-expression of the leu-
kocyte common antigen (CD45). More than 95% of CD34+ cells
co-expressed CD45 antigen, thus suggesting that
these cells originated from bone marrow and were not
circulating endothelial cells. To better define the
surface phenotype, CD34+ cells obtained from the first
five patients on day 5 after AMI were purified from
enriched peripheral blood mononuclear cell preparations,
as previously reported,18 and a subcharacterization was
performed by flow cytometry. CD34+ cells, in addition
to the CD45 antigen, homogeneously co-expressed the myeloid-associated antigens CD33 and CD13, in conjunction with high levels of MHC class II, CD133, CD38, and the chemokine receptor CXCR4. Notably, only ~1% of CD34+ cells were positive for the KDR (the VEGFR-2), the typical endothelial progenitor cell marker (Figure 3). In summary, this phenotype was virtually identical to that of the G-CSF-mobilized transplantable cells (Figure 4). Accordingly isolated CD34+ cells, plated in semisolid culture medium under permissive conditions, were able to differentiate along the granulocyte macrophage (CFU-GM) as well as the erythroid lineage (BFU-E).

Predictors of circulating CD34+ cells early after AMI

A significantly higher concentration of CD34+ cells was found in AMI patients with an anterior AMI (8.81 ± 7.76 vs. 5.19 ± 3.35, P = 0.03), who underwent a primary PCI (9.92 ± 9.00 vs. 5.88 ± 4.31, P = 0.03) and who were on statin therapy (8.81 ± 7.76 vs. 5.19 ± 3.35, P = 0.004). These results were confirmed at the multivariable analysis (β = 0.48, P < 0.001; β = 0.24, P = 0.048; β = 0.24, P = 0.05, for statin use, primary PCI, and anterior AMI, respectively) (Table 3).

No correlation was found between peak number of circulating CD34+ cells and markers of myonecrosis or inflammation.

Multivariable model, however, explained only 27% of the whole variability of the CD34+ cell count, suggesting a marked inter-individual variability not explained by the clinical variables taken into account in the model. Accordingly, in the homogenous group of AMI patients on statins and not undergoing primary PCI, and thus similar to CSA patients with regard to treatment, age, sex, risk factors, and severity of coronary artery disease, BMSC count was significantly higher compared with the latter group (7.47 ± 4.75 vs. 3.80 ± 2.12 CD34+ cells/μL, P < 0.001).

Predictors of LV function early after AMI

At the multivariable analysis, LVEF early after AMI was significantly predicted by CPK peak (β = −0.49, P < 0.001), anterior AMI (β = −0.26, P = 0.021), fibrinogen concentration (β = −0.23, P = 0.037), primary PCI (β = 0.21, P = 0.044), and smoking (β = 0.21, P = 0.044), but not by CD34+ cell concentration (Table 4). This model explained 57% of the whole variability of LVEF. Similar results were obtained using WMSI as the dependent variable.

Predictors of LV function change at follow-up

Changes of LVEF, WMSI, left ventricular end-diastolic volume (LVEDV)-, and left ventricular end-systolic volume (LVESV)- were assessed at 1 year in the first 28 AMI patients available for follow up without new acute coronary events potentially modifying post-infarction remodelling. Of note, all 28 patients had been on statin treatment after discharge. CD34+ cell concentration at follow-up was significantly and favourably correlated to variations of LV function in terms of LVEF, WMSI, and LVESV (r = 0.52, P = 0.004; r = −0.41, P = 0.003; and r = −0.42, P = 0.02, respectively) (Figure 5A–C) and with a borderline significance for variations of LVEDV (r = −0.38, P = 0.06) (Figure 5D). Moreover, after dividing the patients into four groups according to the concentration of CD34+ cells greater than or less than the median value early after AMI and at follow-up, the greatest improvement of LVEF, WMSI, LVESV, and LVEDV was found in patients with persistent mobilization (Figure 6A–D).

Discussion

Our study shows that circulating BMSC count is higher in patients with AMI than in patients with CSA or in control subjects, in particular in those on statin therapy.
or treated by primary PCI. More importantly, our study shows that among patients with AMI, a greater mobilization of BMSC, in particular if sustained at follow-up, could be associated to a more favourable remodelling.

Our findings confirm the results previously published by Shintani et al. only partially. Indeed, these authors found an increased concentration of CD34+ cells after AMI with a peak on the seventh day after the acute event. In contrast, we found similar concentrations of CD34+ cells on days 1, 3, 5, and 7. This difference is probably explained by the inclusion of patients who underwent PCI only in the study by Shintani et al., whereas in our study we enrolled a continuous series of patients with AMI undergoing PCI, thrombolysis, or no reperfusion treatment, at the discretion of the caring physician. In this more heterogeneous population, the peak level of circulating CD34+ cells was probably achieved at different times after the acute coronary event, thus explaining why the average CD34+ count was similar in blood samples obtained on different days. Primary PCI was an independent predictor of CD34+ mobilization. This might be related to an early and abrupt release of mobilizing factors from the infarcted myocardial region. Statin use also was an independent predictor of CD34+ mobilization. This is in agreement with previous findings suggesting that statins

![Figure 4 Immunophenotype of purified CD34+ cells in one patient.](https://academic.oup.com/eurheartj/article-abstract/26/12/1196/524874)
expand the subset of circulating CD34+ cells with the ability to differentiate in endothelial cells.\textsuperscript{20} On the other hand, in our study, age failed to predict CD34+ mobilization after AMI; this is in agreement with previous data of Vasa \textit{et al.}\textsuperscript{21} who found no correlation between CD34/CD45 double positive cells and age in stable patients. In our study, peak CPK serum level also failed to predict CD34+ cell count and age in stable patients. The main emphasis of our study, however, was on patients, and the comparison between patients and controls yields results simply confirmatory of previous studies.\textsuperscript{19} With regard to the statistical analysis, despite the fact that univariable and correlation analysis carried out in our study provide interesting new data about CD34+ cells’ mobilization and LV function after AMI, multivariable analysis is a hypothesis generating approach and independent predictors of mobilization have to be validated in prospective

Limitations of the study

Several limitations of our study have to be acknowledged. First, we compared patients with AMI and CSA with healthy blood donors without coronary risk factors who were younger. The main emphasis of our study, however, was on patients, and the comparison between patients and controls yields results simply confirmatory of previous studies.\textsuperscript{19} With regard to the statistical analysis, despite the fact that univariable and correlation analysis carried out in our study provide interesting new data about CD34+ cells’ mobilization and LV function after AMI, multivariable analysis is a hypothesis generating approach and independent predictors of mobilization have to be validated in prospective...
Mobilization of BMSC after myocardial infarction and LV function

Figure 5  Correlation between CD34+ cell concentration at follow-up and variations of LVEF (A), WMSI (B), LVESV (C), and LVEDV (D) in the 28 AMI patients reassessed at 1 year follow-up.

Figure 6  Variations of LVEF (A), WMSI (B), LVESV (C), and LVEDV (D) among patients allocated to four different groups according to the concentration of CD34+ cells greater than or less than the median value early after AMI and at follow-up (Group 1: early and late CD34+ less than median; Group 2: early CD34+ greater than median and late CD34+ less than median; Group 3: early CD34+ less than median and late CD34+ greater than median; Group 4: early and late CD34+ greater than median).
studies. Moreover, even if we chose to exclude patients with recurrent coronary events, potentially influencing LV function, at the 1 year follow-up to avoid a possible confounding factor this selection bias could have affected the correlation between CD34+ cells and LV function changes. Finally, another possible limitation is represented by the fact that we compared the peak value of CD34+ cells in AMI patients with single measurements in the other groups, although CD34+ cell count has been found considerably stable in stable patients and in controls in previous studies.17, 31

Conclusions
This study shows for the first time that spontaneous mobilization of CD34+ cells after AMI is associated to favourable LV remodelling. It is tempting to speculate that this association might be due to the favourable action of CD34+ cells on myocardial repair process. If this will be confirmed in further studies, it might open the way to new forms of treatment aimed to transform ‘poor’ post-AMI ‘mobilizers’ of CD34+ cells into ‘good mobilizers’.

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