Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction

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ABSTRACT

Background: To investigate the clinical outcome two years after intracoronary administration of autologous progenitor cells in patients with acute myocardial infarction (AMI).

Methods and Results: Using a double-blind, placebo-controlled multicenter trial design, we randomized 204 patients with successfully reperfused acute myocardial infarction to receive intracoronary infusion of bone marrow–derived progenitor cells (BMC) or placebo medium into the infarct artery 3 to 7 days after successful infarct reperfusion therapy.

At 2 years, the cumulative endpoint of death, myocardial infarction or necessity for revascularization was significantly reduced in the BMC group compared to placebo (HR 0.58; 95%CI 0.36 – 0.94, p = 0.025). Likewise, the combined endpoint death, recurrence of myocardial infarction and rehospitalization for heart failure, reflecting progression towards heart failure, was significantly reduced in the BMC group (HR 0.26; 95%CI 0.085 – 0.77, p = 0.015). Intracoronary administration of BMC remained a significant predictor of a favorable clinical outcome by Cox regression analysis, when adjusted for classical predictors of poor outcome after AMI. There was no evidence of increased restenosis or atherosclerotic disease progression after BMC therapy, nor any evidence of increased ventricular arrhythmias or neoplasms. In addition, regional left ventricular contractility of infarcted segments, as assessed by MRI in a subgroup of patients at 2 years follow-up, was significantly higher in the BMC group compared to the placebo group (p<0.001).

Conclusions: Intracoronary administration of bone marrow–derived progenitor cells is associated with a significant reduction of the occurrence of major adverse cardiovascular events maintained for two years after acute myocardial infarction. Moreover, functional improvements following BMC therapy may persist for at least 2 years. Larger studies focusing on clinical event rates are warranted to confirm the effects of bone marrow-derived progenitor cell administration on mortality and progression of heart failure in patients with acute myocardial infarctions.

Clinical Trial Registration Information: www.clinicaltrials.gov, number NCT00279175
Key words: myocardial infarction ◆ prognosis ◆ stem cells ◆ heart failure
INTRODUCTION

Loss of contractile myocardium after acute myocardial infarction (AMI) may lead to an adverse left ventricular remodeling and subsequent clinically overt heart failure 1. Contemporary state-of-the-art therapy of AMI including acute revascularization of the infarct-related vessel has demonstrated to be able to rescue myocardium at risk 2. However, patients who do not immediately recover their contractile function despite acute PCI and optimal medical therapy are at risk for adverse left ventricular remodeling and, as a consequence, subsequent clinically overt heart failure.

A recent metaanalysis has demonstrated that intracoronary infusion of bone marrow – derived progenitor cells has the potential to recover contractile function and to counteract end-systolic volume expansion within 6 months after AMI in patients with reduced ejection fraction despite successfully revascularized acute myocardial infarction 3. The double-blind, placebo-controlled, randomized multicenter trial design, the REPAIR-AMI trial indicated, that beneficial effects of BMC therapy on left ventricular remodeling 4 may translate into reduced cardiovascular event rate, including a combined endpoint summarizing progression towards heart failure 5. So far, only one other study reported outcome after BMC therapy beyond 12 months follow-up, raising the question, whether BMC effects on clinical outcome will be sustained 6.

Therefore, we extended clinical follow-up in the REPAIR-AMI trial, in order to assess long-term safety and durability of the observed beneficial effects on cardiovascular event rate and cardiac function at 2 years.
METHODS

Study population and protocol

The study protocol has been described in detail previously 4, 5, 7. In brief, patients aged 18 to 80 years were eligible for inclusion into the study, if they had an acute ST elevation myocardial infarction successfully reperfused with stent implantation with a residual significant left ventricular regional wall motion abnormality (ejection fraction ≤ 45% by visual estimate). The ethics review board of each individual participating center approved the protocol and the study was conducted in accordance with the Declaration of Helsinki. The study is registered with clinicaltrials.gov, number NCT00279175.

In this double-blind, placebo-controlled randomized trial, performed in 17 centers, at a median of 4 days after acute myocardial infarction reperfusion therapy, bone marrow aspiration was performed in 204 patients and the aspirate was sent to a central cell processing laboratory (Institute for Transfusion Medicine, Frankfurt, Germany), where patients were randomized to placebo medium or bone marrow-derived progenitor cell (BMC) receiving groups. Cell processing has been described in detail elsewhere 4, 7. BMC or placebo was infused using a stop-flow technique via an over-the-wire balloon, positioned in the infarct-related coronary artery within the segment of the previously implanted stent.

The results for the primary endpoint, change of left ventricular ejection fraction by LV angiography assessed at 4 months, as well as the 12 months clinical outcome have been previously reported 4, 5. For analysis of the primary endpoint, the study analyzing center had been unblinded after all 4 months data had been collected and finally analyzed. However, patients, study centers, investigators and those entering the data into the database still remained blinded until 12 months follow-up had been completed and clinical events had been finally categorized. Thereafter, patients and investigators were unblinded. However, data base entry and categorization of events were performed unaware of the randomization status.

End points
Results and assessment of the primary endpoint, defined as the absolute improvement in global left ventricular ejection fraction from baseline to 4 months, have been published previously.

Two year clinical event analyses were performed according to a study protocol amendment filed on May 30th, 2006. The following events were assessed, as described previously in detail:

- Death of any cause and type of death (cardiac, cardiovascular or non-cardiovascular),
- Repeated myocardial infarction,
- Revascularization procedures (PCI or CABG),
- Stent thrombosis,
- Syncope,
- Ventricular arrhythmias,
- Stroke or cancer.

Rehospitalization due to heart failure was defined as hospitalization with typical clinical findings of heart failure requiring the addition of medication for the treatment of heart failure.

Combined clinical endpoints included death, repeated myocardial infarction or any revascularization procedure, an endpoint reflecting progression of vascular disease, as well as death, myocardial infarction or rehospitalization for heart failure, reflecting progression of disease towards heart failure. For analysis per patient, including Cox regression analysis and Kaplan Meier analysis, only the first event of each patient was included into the analysis.

It is important to state that the sample size of the REPAIR-AMI trial was not powered to definitely answer the question whether BMC administration is capable to modify mortality and morbidity after AMI. Likewise, the relatively small sample size might limit the detection of infrequent safety events.

MRI protocol

In a subgroup of 59 patients, MRI imaging at 2 year follow-up was available. Details of MRI protocols and imaging analysis have been described previously, and were performed in identical fashion. Although MRI analysis at the offline work station in the MRI core lab was preformed by blinded investigators, the statistical analysis was performed by investigators being aware of the treatment assignment of the patients. Baseline and one year MRI follow-up of 27 of those patients have been reported previously. However, of the 59 patients undergoing 2 years follow-up MRI imaging, only 27 patients had baseline MRI.
Statistics

All data were analyzed according to the intention-to-treat design. Continuous variables are presented as mean ± SD (if not stated otherwise). Categorical variables were compared with the Chi-square-test or Fisher’s exact test, as appropriate. Time-dependent event rates were estimated by Kaplan Meier survival curves for the randomization status and p values were determined by use of log rank statistics. Kaplan-Meier curves include only the first event per patient (= subsequent censored events were excluded). Plotting log-minus-log function for each randomization group with respect to the combined clinical endpoint death, recurrent myocardial infarction and revascularization procedures indicated proportional hazard. Therefore, Cox regression analysis was used to assess the hazard ratios of the randomization status - unadjusted and, furthermore, after adjustment of additional single or multiple other variables potentially related to the clinical endpoint to be assessed. As such variables, we selected predictors commonly known to be associated with a poor clinical outcome after an acute myocardial infarction, namely age, diabetes mellitus, baseline ejection fraction, baseline end-systolic volume and the use of aldosterone antagonist at hospital discharge as well as variables demonstrating an interaction with the treatment effect of bone marrow-derived progenitor cells on the primary endpoint (improvement of left ventricular function), namely days to intracoronary infusion and, once again, baseline ejection fraction. For MRI functional analysis, between-group differences in ejection fraction, end-systolic and end-diastolic volumes, wall thickening and relative infarct size at 2 years were computed using an ANCOVA with baseline values derived from LV angiography as covariate. Statistical significance was assumed, if p < 0.05. All reported p-values are 2-sided. Statistical analyses were performed using SPSS (Version 15, SPSS Inc.).
RESULTS

Patient population and baseline characteristics
A total of 204 patients have been randomized (103 to placebo and 101 to BMC). Mean age was 56±11 years, 82% of patients were male. There were no significant differences in baseline characteristics (a detailed list of baseline characteristics are available in references 4, 5). Likewise, study medication did not significantly differ between placebo and BMC at hospital discharge and up to 2 years follow-up, with the exception of aldosterone antagonists, which were significantly less frequently used in the BMC group at hospital discharge and at 12 months follow-up 5. 2 years follow-up of clinical events was completed in 99% of the patients (2 patients in the placebo group and 1 patient in the BMC group were lost follow-up; Figure 1).

Clinical events at 2 years follow-up
A total of 11 deaths (5.4 %) occurred during 2 years follow-up – 8 in the placebo group and 3 in the BMC group (Table 1). There was a significant difference in recurring myocardial infarctions between the two groups (p = 0.014): none of the patients in the BMC group experienced a myocardial re-infarction, whereas 7 patients in the placebo group suffered a total of 12 myocardial infarctions during follow-up. Of those, 10 were located to the target vessel supplying the index infarct area, whereas 2 were located to a non-target vessel. There was a trend, albeit statistically not significant, towards less revascularizations in the BMC group (p = 0.061) (table 1).

There were no statistically significant differences between the two groups with respect to ventricular arrhythmia or syncope, stroke or cancer during follow up (table 1).

The combined end point death, recurrence of myocardial infarction or revascularization procedures was significantly reduced in the BMC group compared to the placebo group (p = 0.025). Likewise, the combined endpoint death, recurrence of myocardial infarction and rehospitalization for heart failure was significantly reduced (p = 0.015). These findings are corroborated by-time dependent analyses such as Cox regression analysis (Figure 2) and Kaplan Meier analyses (Figure 3).
However, it has to be acknowledged that all combined endpoint analyses in table 1 include myocardial reinfarction as a major endpoint, and, thus, the observed effects may be intensified by the significantly different frequencies of reinfarction between the BMC and the placebo group.

**Predictors of combined endpoint of death, myocardial infarction or rehospitalization for heart failure**

By univariable Cox regression analysis, age (Hazard ratio 1.07; 95% CI 1.02 – 1.12, p = 0.004) and ejection fraction by quantitative LV angiography (Hazard ratio 0.95; 95% CI 0.91 – 0.99, p = 0.023) were independent predictors of adverse outcome with respect to the combined endpoint death, myocardial infarction or revascularization for heart failure. In contrast, diabetes mellitus, timing of BMC infusion, end-systolic volume at baseline or aldosterone therapy at discharge were not associated with outcome. However, randomization to BMC therapy remained a significant predictor of a reduced cardiovascular event rate, when adjusted for each of these variables. Unadjusted and adjusted hazard ratios of BMC infusion therapy with respect to death, recurrence of myocardial infarction or rehospitalization for heart failure are summarized in table 2.

Importantly, multivariable Cox regression analysis revealed that randomization to the BMC group (p = 0.032) and age (p = 0.045) remained the only significant independent predictors of an improved clinical outcome as assessed by the combined endpoint death, recurrence of myocardial infarction or rehospitalization for heart failure (table 2).

**Cardiac function after 2 years as assessed by MRI**

In a subgroup of 59 patients, 33 patients of the Placebo group and 26 patients of the BMC group, MRI analysis of left ventricular function was performed after 24 months. Baseline left ventricular ejection fraction, as measured only by LV angiography did not differ between the two groups (BMC 45.4 ± 9.4% vs. Placebo 48.7 ± 10.4%, p = 0.21). At 2 years, MRI-derived left ventricular ejection fraction (LVEF) tended to be higher, although statistically non-
significant, in the BMC treated patients compared to the placebo group (50.1% [95% CI: 46.5; 53.7] vs. 43.6% [95% CI: 40.4; 46.8], p = 0.14). However, the difference between the 2 groups was only statistically significant after adjustment for baseline, angiography-derived LVEF (p=0.009). The mean absolute difference in LVEF was 6.5±2.4% between the two groups at 2 years. Left ventricular volumes did not show significant differences between the two groups, although there was a trend towards smaller end-systolic volumes in the BMC group. However, relative infarct size and regional contractility as assessed by percent wall thickening of infarcted segments were significantly improved in the BMC treated patients compared to the Placebo group (figure 4).
DISCUSSION

The present analysis of the REPAIR-AMI trial, up to date, is the longest follow-up of clinical event rates available from a randomized, double-blind trial investigating the effects of intracoronary infusion of bone marrow-derived progenitor cells. The two years follow-up clearly demonstrates that first, there are no late hazards associated with BMC therapy, and second, that the beneficial effects of BMC therapy on cardiovascular outcome are preserved beyond the first months up to the end of the present observation period. Moreover, the better regional recovery of left ventricular function in the BMC group is maintained for at least two years.

It has been questioned whether infusion of progenitor cells may alter the process of restenosis development and / or atherosclerotic disease progression, either adversely by incorporation of inflammatory progenitor cells into the epicardial vascular wall, or beneficially via enhanced reendothelialization and potential vascular repair. The present data point against an adverse effect of BMC administration on atherosclerosis progression or restenosis development. If anything, revascularization rates, which were significantly reduced in the BMC group within the first year, still tend to be lower in the BMC group compared to placebo at two years follow-up. Indeed, a substudy of REPAIR-AMI – assessing the effect of intracoronary BMC administration on coronary flow dynamics using intracoronary Doppler flow velocity measurements at baseline and at four months follow-up – indicated a significantly greater recovery of coronary blood flow reserve in the BMC – treated infarct artery compared to infarct vessels receiving placebo infusion. Given the well established inverse association between coronary flow reserve and atherosclerotic disease progression, the improved coronary vascular conductance capacity of the infarcted artery treated with BMC administration might have contributed to the reduced incidence of revascularization procedures in the BMC group. However, given the rather small sample size of patients experiencing epicardial artery disease progression, the higher rate of recurrent myocardial infarction may also represent play of chance.
In addition, there was no evidence of malignant ventricular arrhythmias or syncopes within 2 years after intracoronary infusion of bone marrow-derived progenitor cells. Although less than 20% of the intracoronary infused cells actually are retained in the heart, with the remaining cells distributing throughout the body including lung, liver and spleen, there is no signal of an increased rate of neoplasms within 2 years after intracoronary BMC therapy. These data are in line with recent metaanalyses comprising more than 1000 patients, which did not provide any hints for an increase in tumor formation in patients undergoing intracoronary BMC administration in AMI.

The most important finding of the present analysis is the observation, that there is a persistent reduction of the combined end point of death, recurrent myocardial infarction and rehospitalization for heart failure throughout the course of the two years follow-up period. Thus, the beneficial effects on this endpoint, reflecting progression of ischemic heart disease towards heart failure, indicate, that increased recovery of ejection fraction and abrogation of end-systolic volume expansion after BMC therapy may indeed translate into a more favorable clinical outcome and prevention of the development of overt heart failure. Indeed, MRI subgroup analysis at 2 years follow-up still demonstrates a beneficial effect on regional left ventricular contractility of the infarct area. However, global LV function was only significantly different between the BMC and the Placebo group at 2 years follow-up after adjustment for baseline LVEF. These results are in contrast to the 18 months results from the BOOST trial, where no significant differences in ejection fraction could be detected between the BMC and the control group. However, lack of statistically significant differences in the BOOST trial may be due to sample size, since ejection fraction did not decline in the BMC group.

Another limitation of the current analysis is the fact that investigators and patients were unblinded at 12 months follow-up, which may have caused some bias with respect to the 2 years follow-up data.

The present clinical study obviously cannot disclose the pathophysiological mechanisms related to improved cardiovascular outcome. Nevertheless, since reduced LV ejection...
fraction and enlarged end-systolic volume are important predictors of mortality \(^{16}\) and reflect the pathophysiological substrate of post-infarction heart failure \(^{1}\), it is likely, that the observed beneficial effects of BMC therapy on left ventricular function might have contributed to the improved clinical outcome. In fact, an important target of BMC therapy might be the coronary microcirculation. It has been suggested, that impairment of the microvasculature after AMI is associated with lack of recovery of left ventricular contractile function \(^{17}\) and further predicts clinical event rate \(^{18}\). In experimental studies, progenitor cell therapy was shown to increase vascular density, indicating neovascularization induced by application of progenitor cells \(^{19}\). In the clinical setting, the Doppler substudy of the REPAIR-AMI trial \(^{12}\) demonstrated that coronary flow reserve, blunted after acute myocardial infarction, completely recovered in the group treated with progenitor cells, whereas there was significantly less improvement in the placebo group. Likewise, minimal microvascular resistance during maximal hyperemia significantly decreased following BMC therapy \(^{12}\), which may be a link to the beneficial effects of BMC therapy on LV ejection fraction, since elevated vascular resistance after AMI predicts a lack of contractile recovery within the subsequent months \(^{17}\). Taken together, neovascularization induced by intracoronary infusion of BMC may be a key mechanism leading to recovery of contractile function and subsequent reduction of clinical event rate. Restoration of microvasculature function early after the AMI event induced by the infused bone marrow-derived progenitor cells may also explain the durability of the observed clinical benefits, regardless of the discussion of the existence and relevance of transdifferentiation of BMC into cardiac myocytes and long-term survival of injected cells \(^{20}\).

**CLINICAL IMPLICATIONS**

The present analysis indicates that intracoronary infusion of BMC after AMI beneficially affects left ventricular contractile function and modifies cardiovascular event rates and progression towards heart failure within two years after therapy. However, the REPAIR-AMI trial was not powered to definitely answer the question whether BMC administration is
capable to modify mortality and morbidity after AMI. Therefore, the present analysis should be viewed as hypothesis – generating.

As such, the present analysis provides the rationale to design a larger clinical outcome trial addressing the clinical endpoints death, myocardial infarction or rehospitalization for heart failure. However, such a trial may focus on those patients deriving the most benefit from intracoronary administration of BMC. Indeed, in the REPAIR-AMI trial, patients with an ejection fraction below the median of 49% did derive the most benefit with respect to parameters of left ventricular remodeling, namely recovery of ejection fraction and abrogation of end-systolic volume expansion. Moreover, cardiac MRI analyses at 1 year follow-up in a subpopulation of REPAIR-AMI revealed that the beneficial effects are entirely confined to patients at risk for adverse left ventricular remodeling. 2 years MRI follow-up confirms these results, and still demonstrates a better regional contractility of the infarcted segments in patients treated with BMC compared to placebo. Likewise, the majority of adverse cardiovascular events occurred in patients with an EF below the median at baseline (13 events versus 4 events in patients above the median of patients, in whom baseline EF was measurable). However, the sample size of the present analysis is too small to further subdivide between patients with an EF above or below the median. Nevertheless, given the significant mortality and morbidity of patients with failed recovery of contractile function early after AMI despite successful reperfusion and optimal medical therapy, intracoronary infusion of bone marrow-derived progenitor cells appears to be an attractive therapeutic concept to counteract the development of heart failure specifically in patients at highest risk for adverse left ventricular remodeling.
ACKNOWLEDGEMENT

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Trial investigators and committee members see reference 4

FUNDING SOURCES

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DISCLOSURES

Dr. Schächinger reports having received consulting fees from Guidant and t2cure. Dr. Dimmeler reports having received consulting fees from Guidant and Genzyme. Dr. Zeiher reports having received consulting fees from Guidant. Drs. Dimmeler and Zeiher report that they are cofounders of t2cure, a for-profit company focused on regenerative therapies for cardiovascular disease. They serve as scientific advisers and are shareholders.
REFERENCES


FIGURE LEGENDS

Figure 1: Study flow diagram. * Two year follow-up was available in 1 patient lost to follow-up at 1 year.

Figure 2: Hazard ratios of BMC infusion therapy with respect to individual and combined clinical events (Cox Regression analysis)

Figure 3: Kaplan Meier event-free survival analysis: A = death, recurrence of myocardial infarction or revascularization procedures. B = death, recurrence of myocardial infarction or rehospitalization for heart failure.

Figure 4: MRI analysis of LV ejection fraction, end-diastolic and end-systolic volumes, relative infarct size and wall thickening of infarcted segments (* adjusted for baseline values derived from quantitative LV angiography, # adjusted for baseline LVEF derived from quantitative LV angiography).
**Table 1: Clinical events during 2 year follow-up.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo* (n=103)</th>
<th>BMC (n=101)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>8 (8)</td>
<td>3 (3)</td>
<td>0.13</td>
</tr>
<tr>
<td>- Cardiac death</td>
<td>5 (5)</td>
<td>3 (3)</td>
<td>0.72</td>
</tr>
<tr>
<td>- Myocardial rupture</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Myocardial infarction</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>- Sudden death</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- Heart failure</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>- Cardiovascular death</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>- Non-cardiovascular death</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (7)</td>
<td>0</td>
<td>0.014</td>
</tr>
<tr>
<td>Rehospitalization for heart failure</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Revascularization</td>
<td>38 (37)</td>
<td>25 (25)</td>
<td>0.061</td>
</tr>
<tr>
<td>- Target vessel revascularization</td>
<td>28 (27)</td>
<td>19 (19)</td>
<td>0.16</td>
</tr>
<tr>
<td>- Non-target vessel revascularization</td>
<td>16 (16)</td>
<td>11 (11)</td>
<td>0.33</td>
</tr>
<tr>
<td>Documented ventricular arrhythmia or syncope</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>0.97</td>
</tr>
<tr>
<td>- ventricular arrhythmia</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>0.73</td>
</tr>
<tr>
<td>- syncope</td>
<td>2 (2)</td>
<td>0</td>
<td>0.50</td>
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<tr>
<td>Stroke</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cancer</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>0.32</td>
</tr>
</tbody>
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### Table 1, continued

#### Combined events

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Event Count</th>
<th>Event Count</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined death or myocardial infarction</td>
<td>12 (12)</td>
<td>3 (3)</td>
<td>0.018</td>
</tr>
<tr>
<td>Combined death, infarction or any revascularization</td>
<td>44 (43)</td>
<td>28 (28)</td>
<td>0.025</td>
</tr>
<tr>
<td>Combined death, infarction or infarct vessel revascularization</td>
<td>34 (33)</td>
<td>22 (22)</td>
<td>0.072</td>
</tr>
<tr>
<td>Combined death, infarction or rehospitalization for heart failure</td>
<td>15 (15)</td>
<td>4 (4)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* stroke, # cancer and suicide, ¶ lung, colon and sigma cancer; § prostate cancer.
Table 2: Unadjusted and adjusted Hazard ratios for BMC infusion therapy, and multivariable Cox regression analyses § of BMC infusion therapy, with respect to death, recurrence of myocardial infarction or rehospitalization for heart failure.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Hazard ratios of BMC infusion</th>
<th>Multivariable Cox regression analysis</th>
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<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.26</td>
<td>0.09 – 0.8</td>
</tr>
<tr>
<td>Randomization to BMC</td>
<td>0.24</td>
<td>0.07 – 0.89</td>
</tr>
<tr>
<td>Age</td>
<td>0.27</td>
<td>0.09 – 0.81</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.25</td>
<td>0.08 – 0.76</td>
</tr>
<tr>
<td>Days to infusion*</td>
<td>0.28</td>
<td>0.09 – 0.84</td>
</tr>
<tr>
<td>Baseline ejection fraction †</td>
<td>0.32</td>
<td>0.10 – 0.97</td>
</tr>
<tr>
<td>Baseline end-systolic volume †</td>
<td>0.32</td>
<td>0.10 – 0.98</td>
</tr>
<tr>
<td>Aldosterone antagonist at hospital discharge ‡</td>
<td>0.21</td>
<td>0.06 – 0.75</td>
</tr>
</tbody>
</table>

* ≤3, 4, 5 or ≥ 6 days, available in 202 patients with intracoronary infusion attempted; † available in 199 patients with baseline LV angiogram, ‡ available in 202 patients alive at hospital discharge, § analysis includes 15 events in 197 patients with all variables available.
Patients with acute MI (STEMI) successfully revascularized (stent PCI)

Bone marrow aspiration & Randomization

Intracoronary infusion (both groups)
- attempted (day 3-7)
- performed

Complete LV angio analysis at 4 months

4 months follow up

Lost to 12 months follow up

Lost to 2 years follow up

2 years follow up

Dead

Lost to 2 years follow up

Figure 1
Figure 2

- **Death**: p = 0.15
- **Myocardial infarction**: p = 0.18
- **Revascularization**: p = 0.052
- **Rehospitalization for heart failure**: p = 0.13

**Combined**

- **Death or MI**: p = 0.029
- **Death, MI or Rehospitalization for heart failure**: p = 0.015
- **Death, MI or Revascularization**: p = 0.025
Figure 3

A

Event-free survival (%)
(death, myocardial infarction, revascularization)

Placebo
BMC

p = 0.023
(log rank)

# exposed to risk

Placebo 103 72 60 58 58
BMC 101 80 76 72 71
Figure 3

B

Event-free survival (%) (death, myocardial infarction, rehospitalization f. heart failure)

Placebo

BMC

p = 0.009 (log rank)

# exposed to risk

Placebo 103 93 90 86 86
BMC 101 99 98 97 95
**Figure 4**

- **Absolute LV ejection fraction [\%]; (mean ± SEM)**
  - Placebo: P = 0.009 *
  - BMC: P = 0.16 *

- **Absolute enddiastolic volume [ml]; (mean ± SEM)**
  - Placebo: P = 0.98 *
  - BMC: P = 0.98 *

- **Absolute endsystolic volume [ml]; (mean ± SEM)**
  - Placebo: P = 0.16 *
  - BMC: P = 0.16 *

- **Relative infarct size [\%]; (mean ± SEM)**
  - Placebo: P = 0.049 *
  - BMC: P < 0.001

- **Wall thickening of infarcted segments [\%]; (mean ± SEM)**
  - BMC: P < 0.001

**Legend:**
- Placebo
- BMC
Clinical Outcome 2 Years After Intracoronary Administration of Bone Marrow-Derived Progenitor Cells in Acute Myocardial Infarction

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