Clinical Outcome 2 Years After Intracoronary Administration of Bone Marrow–Derived Progenitor Cells in Acute Myocardial Infarction

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Background—The aim of this study was to investigate the clinical outcome 2 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 AMI 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 end point of death, myocardial infarction, or necessity for revascularization was significantly reduced in the BMC group compared with placebo (hazard ratio, 0.58; 95% CI, 0.36 to 0.94; \(P<0.025\)). Likewise, the combined end point death and recurrence of myocardial infarction and rehospitalization for heart failure, reflecting progression toward heart failure, was significantly reduced in the BMC group (hazard ratio, 0.26; 95% CI, 0.085 to 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-year follow-up, was significantly higher in the BMC group compared with the placebo group (\(P<0.001\)).

Conclusions—Intracoronary administration of BMC is associated with a significant reduction of the occurrence of major adverse cardiovascular events maintained for 2 years after AMI. Moreover, functional improvements after BMC therapy may persist for at least 2 years. Larger studies focusing on clinical event rates are warranted to confirm the effects of BMC administration on mortality and progression of heart failure in patients with AMIs.

Clinical Trial Registration—clinicaltrials.gov. Identifier: NCT00279175.

Key Words: myocardial infarction ■ prognosis ■ stem cells ■ heart failure
the potential to recover contractile function and to counteract end-systolic volume expansion within 6 months after AMI in patients with reduced ejection fraction (EF), despite successfully revascularized AML. The double-blind, placebo-controlled, randomized multicenter trial design, the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial, indicated that beneficial effects of BMC therapy on LV remodeling may translate into reduced cardiovascular event rate, including a combined end point summarizing progression toward heart failure. 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.

Therefore, we extended clinical follow-up in the REPAIR-AMI trial, 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. In brief, patients aged 18 to 80 years were eligible for inclusion into the study if they had an acute ST-elevation MI successfully reperfused with stent implantation with a residual significant LV regional wall motion abnormality (EF ≤ 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.

In this double-blind, placebo-controlled, randomized trial performed in 17 centers at a median of 4 days after AMI 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 BMC-receiving groups. Cell processing has been described in detail elsewhere. 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 end point, change of left ventricular ejection fraction (LVEF) by LV angiography as a covariate. Statistical significance was assumed for P values < 0.05. All reported probability values are 2-sided. Statistical analyses were performed using SPSS (version 15, SPSS Inc, Chicago, Ill).

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 men. There were no significant differences in baseline characteristics (a detailed list of baseline characteristics are available in references). 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. Two-year 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-Year Follow-Up**

A total of 11 deaths (5.4%) occurred during 2 years of follow-up, 8 in the placebo group and 3 in the BMC group (Table 1). There was a significant difference in recurring MIs between the 2 groups (P=0.014): none of the patients in the BMC group experienced a myocardial reinfarction, whereas 7 patients in the placebo group suffered a total of 12 MIs during follow-up. Of those, 10 were located to the target vessel supplying the index infarct area, whereas 2 were located to a nontarget vessel. There was a trend, albeit statistically not significant, toward less revascularizations in the BMC group (P=0.061; Table 1).

There were no statistically significant differences between the 2 groups with respect to ventricular arrhythmia or syncope, stroke, or cancer during follow-up (Table 1). The combined end point death, recurrence of MI or revascularization procedures was significantly reduced in the BMC group compared with the placebo group (P=0.025). Likewise, the combined end point death, recurrence of MI, 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 end point analyses in Table 1 include myocardial reinfarction as a major end point, 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 End Point of Death, MI, or Rehospitalization for Heart Failure**

By univariable Cox regression analysis, age (HR, 1.07; 95% CI, 1.02 to 1.12; P=0.004) and EF by quantitative LV angiography (HR, 0.95; 95% CI, 0.91 to 0.99; P=0.023) were independent predictors of adverse outcome with respect to the combined end point death, MI, 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 HRs of BMC infusion therapy with respect to death, recurrence of MI, 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 end point death, recurrence of MI, 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 LV function was performed after 24 months. Baseline LVEF, as measured only by LV angiography did not differ between the 2 groups (BMC 45.4±9.4% versus placebo 48.7±10.4%, P=0.21). At 2 years, MRI-derived LVEF tended to be higher, although statistically nonsignificant, in the BMC-treated patients compared with the placebo group (50.1% [95% CI, 46.5 to 53.7] versus 43.6% [95% CI, 40.4 to 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 2 groups at 2 years. LV volumes did not show significant differences between the 2 groups, although there was a trend toward 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 with the placebo group (Figure 4).
Table 1. Clinical Events During 2 Years of Follow-Up

<table>
<thead>
<tr>
<th>No. of Patients With Events</th>
<th>Placebo* (n=103)</th>
<th>BMC (n=101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<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>MI</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*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>2†</td>
<td>0</td>
<td></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>Nontarget 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 or syncope</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>
</tr>
<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>
<tr>
<td>Combined events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined death or MI</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>

Values are presented as n (%).
*Stroke.
†Cancer and suicide.
‡Lung, colon, and sigma cancer.
§Prostate cancer.

Discussion

This 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 BMC. The 2-year follow-up clearly demonstrates, first, that 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 LV function in the BMC group is maintained for at least 2 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.9–11 This 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 2 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 4 month follow-up—indicated a significantly greater recovery of coronary blood flow reserve in the BMC-treated infarct artery compared with infarct vessels receiving placebo infusion.12 Given the well-established inverse association between coronary flow reserve and atherosclerotic disease progression,13 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 MI may also represent play of chance.

In addition, there was no evidence of malignant ventricular arrhythmias or synapses within 2 years after intracoronary infusion of BMC.

Although <20% of the intracoronary infused cells actually are retained in the heart,14 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 meta-analyses comprising >1000 patients, which did not provide any hints for an increase in tumor formation in patients undergoing intracoronary BMC administration in AMI.3,15

The most important finding of this analysis is the observation, that there is a persistent reduction of the combined end point of death, recurrent MI, and rehospitalization for heart failure throughout the course of the 2-year follow-up period.

Thus, the beneficial effects on this end point, reflecting progression of ischemic heart disease toward heart failure, indicate that increased recovery of EF 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-year follow-up still demonstrates a beneficial effect on regional LV contractility of the infarct area. However, global LV function was only significantly different between the BMC and the placebo group at 2-year follow-up after adjustment for baseline LVEF. These results are in contrast to the 18 months results from the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration trial, where no significant differences in EF could be detected between the BMC and the control group.6 However, lack of statistically significant differences in the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration trial may be due to sample size because EF did not decline in the BMC group.

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

This clinical study obviously cannot disclose the pathophysiological mechanisms related to improved cardiovascular outcome. Nevertheless, because reduced LVEF and enlarged end-systolic volume are important predictors of mortality\textsuperscript{16} and reflect the pathophysiological substrate of postinfarction heart failure,\textsuperscript{1} it is likely, that the observed beneficial effects of BMC therapy on LV 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

Figure 2. HRs 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.
the microvasculature after AMI is associated with lack of recovery of LV contractile function and further predicts clinical event rate. In experimental studies, progenitor cell therapy was shown to increase vascular density, indicating neovascularization induced by application of progenitor cells. In the clinical setting, the Doppler substudy of the REPAIR-AMI trial demonstrated that coronary flow reserve, blunted after AMI, 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 after BMC therapy, which may be a link to the beneficial effects of BMC therapy on LVEF, because elevated vascular resistance after AMI predicts a lack of contractile recovery within the subsequent months. 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 BMC 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.

### Clinical Implications

This analysis indicates that intracoronary infusion of BMC after AMI beneficially affects LV contractile function and modifies cardiovascular event rates and progression toward heart failure within 2 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, this analysis should be viewed as hypothesis generating.

As such, this analysis provides the rationale to design a larger clinical outcome trial addressing the clinical end points death, MI, or rehospitalization for heart failure.

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**Table 2. Unadjusted and Adjusted HRs for BMC Infusion Therapy and Multivariable Cox Regression Analyses of BMC Infusion Therapy, With Respect to Death, Recurrence of MI, or Rehospitalization for Heart Failure**

<table>
<thead>
<tr>
<th>Analysis of BMC Infusion</th>
<th>Unadjusted</th>
<th>Adjusted HRs of BMC Infusion</th>
<th>Multivariable Cox Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR 95% CI P</strong></td>
<td><strong>HR 95% CI P</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization to BMC</td>
<td>0.26 0.09 to 0.8 0.015</td>
<td>0.24 0.07 to 0.89 0.032</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.27 0.09 to 0.81 0.019</td>
<td>1.05 1.00 to 1.11 0.045</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.25 0.08 to 0.76 0.014</td>
<td>0.56 0.12 to 2.6 0.46</td>
<td></td>
</tr>
<tr>
<td>Days to infusion†</td>
<td>0.28 0.09 to 0.84 0.023</td>
<td>1.09 0.69 to 1.74 0.71</td>
<td></td>
</tr>
<tr>
<td>Baseline ejection fraction‡</td>
<td>0.32 0.10 to 0.97 0.004</td>
<td>0.98 0.92 to 1.05 0.55</td>
<td></td>
</tr>
<tr>
<td>Baseline end-systolic volume‡</td>
<td>0.32 0.10 to 0.98 0.046</td>
<td>1.008 0.99 to 1.03 0.43</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist at hospital discharge§</td>
<td>0.21 0.06 to 0.75 0.016</td>
<td>1.61 0.33 to 7.9 0.56</td>
<td></td>
</tr>
</tbody>
</table>

*Analysis includes 15 events in 197 patients with all variables available.
†Less than or equal to 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.

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**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.

- **Relative infarct size**
  - Placebo: 14 ± 2%
  - BMC: 12 ± 2%
  - P = 0.049

- **Wall thickening of infarcted segments**
  - Placebo: 30 ± 16%
  - BMC: 40 ± 18%
  - P < 0.001

- **Aldosterone antagonist at hospital discharge**
  - Placebo: 0.21 ± 0.06 to 0.75
  - BMC: 1.61 ± 0.33 to 7.9
  - P = 0.016

- **Baseline ejection fraction**
  - Placebo: 50 ± 10%
  - BMC: 55 ± 10%
  - P = 0.009

- **Baseline end-systolic volume**
  - Placebo: 150 ± 10 ml
  - BMC: 170 ± 10 ml
  - P = 0.98

- **Baseline end-diastolic volume**
  - Placebo: 90 ± 10 ml
  - BMC: 100 ± 10 ml
  - P = 0.16

- **Baseline LV ejection fraction**
  - Placebo: 55 ± 10%
  - BMC: 50 ± 10%
  - P = 0.049

- **Baseline LV end-diastolic volume**
  - Placebo: 110 ± 10 ml
  - BMC: 120 ± 10 ml
  - P = 0.016
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 EF below the median of 49% did derive the most benefit with respect to parameters of LV remodeling, namely recovery of EF 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 LV remodeling. Two-year MRI follow-up confirms these results, and still demonstrates a better regional contractility of the infarcted segments in patients treated with BMC compared with 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 this analysis is too small to further subdivide between patients with an EF above or below the median. Nevertheless, given the significant morbidity and mortality of patients with failed recovery of contractile function early after AMI, despite successful reperfusion and optimal medical therapy, intracoronary infusion of BMC seems to be an attractive therapeutic concept to counteract the development of heart failure specifically in patients at highest risk for adverse LV remodeling.

Acknowledgments
We thank Heike Braun, Beate Mantz, Isabel Geweyer, Liane Ziska, and Heike Wagner for excellent trial organization and expert assistance. We also thank Hans Martin (Department of Hematology) for expert advice, Tina Rasper and Nicola Krzossok for technical assistance in cell processing, Wilhelm Sauermann (Datamap) for statistical advice, and Florian Seeger and Jörg Honold for logistic support. In addition, we thank the following nonprofit research organizations, which have supported the Honold for logistic support. In addition, we thank the following nonprofit research organizations, which have supported the Honold for logistic support. In addition, we thank the following nonprofit research organizations, which have supported the Honold for logistic support. In addition, we thank the following nonprofit research organizations, which have supported the

Sources of Funding
This work was supported by an unrestricted research grant from Guidant, Inc. Guidant provided balloon catheters, and Eli Lilly provided the abxicimab.

Disclosures
Dr Schächinger reports having received consulting fees from Guidant and t2cure GmbH. 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 co-founders of t2cure, a for-profit company focused on regenerative therapies for cardiovascular disease. They serve as scientific advisers and are shareholders.

References
Intracoronary infusion of bone marrow–derived progenitor cells (BMC) after acute myocardial infarction may provide an attractive approach to improve left ventricular function and remodeling in addition to interventional and medical therapy. The randomized, placebo-controlled, double-blind REPAIR-AMI trial has demonstrated a significant greater contractile recovery and improvement of microvascular function in the BMC treated patients compared to the Placebo-group after 4 months. The current analysis with extended 2-year follow-up confirms the excellent safety profile of intracoronary BMC administration compared with placebo, demonstrating a significant reduction in the cumulative end points of death, myocardial infarction, and revascularization as well as death, recurrence of acute myocardial infarction, and rehospitalization for heart failure. In parallel, 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, in a subgroup of patients undergoing MRI imaging, regional left ventricular contractility of the infarcted segments was significantly better in the BMC group compared with the placebo group, suggesting that beneficial interference of BMC therapy with remodeling processes may contribute to improved clinical outcome. These findings make it intriguing to speculate that intracoronary application of BMC may be associated with improved regional contractility, leading to a better clinical outcome at 2-year follow-up. However, larger randomized, adequately powered outcome trials are urgently needed to assess the effects of progenitor cell therapy on prognosis in patients with acute myocardial infarction.
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_Circ Heart Fail._ 2010;3:89-96; originally published online December 8, 2009; doi: 10.1161/CIRCHEARTFAILURE.108.843243

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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