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A Critical Analysis of Clinical Outcomes Reported in Stem Cell Trials for Acute Myocardial Infarction: Some Thoughts for Design of Future Trials

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Abstract

The purpose of stem cell therapy for myocardial infarction (MI) is to improve clinical outcomes, and detailed information on clinical outcomes is critical to appropriate planning of phase III trials. We examined data from select phase II trials using autologous bone marrow-derived stem cells (BMCs) in patients with acute MI. We extracted available definitions and outcome data, and generated standardized estimates of events to permit summary comparisons. Nine trials (1040 patients) with results for 6 months to 5 years were evaluated. Adverse outcomes varied widely, and there was a general lack of details in the definitions of these outcomes. Heart failure related hospitalizations occurred in only 16 (1.5%) and death in only 43 (4.1%) of all patients. Ischemia-related outcomes outnumbered heart failure outcomes more than 10-fold. Uniform criteria need to be developed to better define clinical outcomes of interest. Furthermore, a refocus from heart failure to ischemia-related outcomes seems appropriate.

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Conflict of Interest

Anita D. Szady, Carl J. Pepine, Shreela V. Sharma, Christopher R. Cogle, and Lemuel A. Moyé declare no conflict of interest. Emerson C. Perin has been a consultant to Amorcyte, Biologics Delivery System, Celgene, Cytori, TEVA, St. Jude Medical, and Viromed.

Stephen G. Ellis has been a consultant to Juventas and Athersys.

Human and Animal Rights and Informed Consent

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Keywords

stem cells; acute myocardial infarction; clinical outcomes; secondary outcomes; phase II trials

Introduction

In recent years, stem cell therapy to improve left ventricular (LV) function after acute myocardial infarction (MI) has become an area of increasing interest. But much additional investigation is required if cell therapy is to become an effective treatment strategy toward improving clinical outcomes. Indeed, most of the focus to date has been directed toward effects on LV function, perfusion, and cell fate in this ischemic population [1–23]. However, the goal is not just the demonstration of increased LV function, but to decrease adverse outcomes in this at-risk, post-MI population. Additionally, the literature suggests that information on objective clinical outcomes such as death, MI, arrhythmias, and hospitalization for heart failure and other cardiac reasons has not been emphasized [1–23]. The investigation of cell therapy has been confined to phase I and early phase II studies, as required for evaluation of new procedures for which the safety profile is unknown. Because little is known about possible risks and benefits, these trials include relatively small numbers of patients. Yet information about clinical events is critical to adequately design appropriately powered phase III trials.

The purpose of this manuscript is to critically examine and summarize reported phase II clinical trial results with respect to secondary clinical outcomes. A specific focus will be placed on the definitions used, as well as the incidence of these clinical outcomes in order to better design future trials assessing the influence of cell-based therapy on clinical adverse outcomes.

Methods

We conducted a search of the English literature for randomized trials that used autologous bone marrow-derived stem cells (BMCs) in patients with acute MI. In order to assure sufficient research team experience, we limited the search to trials reporting 50 patients with clinical outcomes after at least 6 months of follow-up. Additional selection criteria included BMCs delivered into an infarct-related artery after reperfusion by percutaneous intervention. For trials with multiple reports, we used only the report with the longest follow-up duration that contained clinical outcomes data. We extracted the reported definitions for each event when this information was provided and tabulated the reported event rates. Event rates are recorded per patient, and patients with multiple events in a single category were recorded only once (Table I).

To account for differences in trial follow-up duration we generated standardized estimates of event rates to permit comparison of event rates for the different clinical outcomes across all trials. By employing a weighted general linear model, using the cumulative total of the study sample as the standard population, we estimated the event rates per year per 1000 for each outcome among the cell intervention and control groups for each study identified. Standardized event rates were calculated for death, MI, coronary artery bypass graft (CABG), overall coronary revascularization, target vessel revascularization (TVR), and heart failure hospitalizations as the clinical outcomes of most interest (Table II).

Results

From a total of 33 trials identified, 10 met the preset criteria summarized above (Figure 1). One trial (66 patients) was excluded since patients were not followed after early events that

influenced LV function. A total of 9 randomized, controlled phase II trials [1–20, 22, 23] published from 2002 to present were identified that included 1040 patients with more than 275 clinical events (Table I). A tenth trial published in 2008 [21] comprised 66 patients randomized to control, high dose BMCs, and low dose BMCs. This trial excluded patients once they experienced any event that affected LV function, and thus we did not include this trial in our analysis. In a 2012 Cochrane Review [24], the majority of the trials listed did not meet our selection criteria. In the remaining 9 trials we found that definitions and numbers of events reported varied greatly across trials while the primary measures of interest centered on LV function, size, perfusion, and infarct size in this post MI population. While definitions of the primary outcome measures have been clearly stated, only limited information was provided to define the clinical outcomes reported. Some trials also reported the numbers of patients experiencing a “first event” among a cluster of events (Table III—see Appendix). A complete summary of each trial’s clinical outcomes and definitions of these outcomes are listed in the Appendix.

Overall, a total of 1040 patients were described from these 9 trials, and the patients were followed for up to 5 years in some of the trials. The major clinical events of each trial are reported in Table I. In total, 43 patients died, 22 had an MI, and another 5 had a stroke. Repeat revascularization procedures were done in 179 patients: 127 TVRs, 33 non-TVRs, 6 CABG surgeries, and 24 unspecified revascularizations were performed. A total of 16 patients were hospitalized for heart failure reasons, and 15 patients had ventricular arrhythmias. Cancers were detected in 6 patients, but in some cases the authors commented that evidence for cancer predated the cell-based treatments. Unfortunately, very few of these 9 trials commented on specific prospective criteria for these clinical events. Over half of the trials (ASTAMI [9], FINCELL [8], BALANCE [20], REGENT [18], LateTIME [22]) provided no definitions for the clinical events they reported, accounting for 109 (47%) of the 233 definable events (death needing no definition) reported by all 9 studies. Two trials [6, 10, 11, 19] defined in-stent restenosis, and 1 trial [1, 3, 14] defined recurrent MI (Appendix). These 3 trials otherwise provided no definitions of their clinical outcomes, accounting for another 32 of the reported clinical events that were not defined. REPAIR AMI [2, 7, 15–17, 23] provided the most complete account of their clinical outcomes, defining recurrent MI, rehospitalization for congestive heart failure, ventricular arrhythmia, syncope, cerebrovascular accident, and cancer (Appendix). Of the 90 definable events reported by REPAIR AMI, 74 were not defined [2, 7, 15–17, 23]. Thus, in total 215 (92%) of the 233 definable events reported in Table I were not defined.

Although all of these trials mentioned heart failure prevention in the post MI patient with LV dysfunction as the primary rationale for treatment, we observed that hospitalization for heart failure reasons occurred infrequently (in 16/1040 or only 1.5%). When standardized per 1000 patients, heart failure hospitalizations occurred in 5.3/1000 of controls and only 1.9/1000 of BMC patients. Not surprisingly, repeat revascularization procedures were the most frequent events, occurring in 17% (or 179/1040) of patients treated. When standardized per 1000 patients, total repeat revascularizations were similar in both groups, occurring in 27.1/1000 of controls and 27.5/1000 of BMC patients. There were less target vessel revascularizations in the BMC group, 12.7/1000 vs. 16.6/1000 in the controls. The standardized event rates per 1000 for MI and death were also lower in the BMC group (Table II). Thus, even though BMCs did not affect the overall need for revascularization, they may have had an impact on the most important events, TVR, MI, and death. When compared with a similar population of acute coronary syndrome (ACS) patients with a 5-year follow-up (GRACE UK-Belgian Study [25]), the death rate was significantly lower in the BMC group (43/1040 or 4.1% over 5 years) vs. in the GRACE UK Belgian Study (736/3721 or 19.7% over 5 years). Similarly, the incidence of MI was significantly lower than in the UK cohort (22/1040 or 2.1% over 5 years vs. 320/2065 or 15.4% over 5 years).

[25]. Of course, it is difficult to compare ischemic events between these trials because there are several variables that are not uniform, including time to percutaneous coronary intervention (PCI) and type of stent used (drug eluting vs. bare metal). Nonetheless, these findings suggest that more emphasis should be placed on defining, in a uniform fashion, the outcomes that are likely ischemia-related. To this end, criteria used for recurrent MI could be critical as well as those used for need for repeat revascularization. Given the importance of defining recurrent MI, perhaps the definition set forth by the ESC/ACCF/AHA/WHF expert consensus document [26] for recurrent MI post PCI should be used. Recurrent MI is defined as a troponin T increase >3 times the 99th percentile of the upper limit of normal. Similarly, the standard of 50% narrowing of the luminal diameter should be used as the definition for in-stent restenosis [27].

Discussion

As expected with all early phase clinical studies primarily focused on safety and feasibility, clinical outcomes and efficacy measures were secondary interests in these initial cardiovascular cell therapy clinical trials. In all 9 trials identified in our search for further examination, a clinical surrogate, in most cases LV ejection fraction, was the primary measure of interest. This is interesting, given the fact that these trials were conducted in acute MI patients and a marker such as need for repeat revascularization or recurrent MI would seem more appropriate. Clinical outcomes were relatively infrequent in these small studies, and their low occurrence rate all but assured that enough clinical events would not have occurred for precise and reliable detection of a treatment effect generalizable to the population. For example, a clinical trial with a single treatment arm and control group arm requires as many as 3300 patients in order to detect a 20% reduction in the event rate if the control group event rate is 18% (with a two-sided type I error level of 0.05 and 80% power). Therefore, in a standard analysis setting, phase II clinical trials are relegated to measuring clinical endpoints as secondary outcomes where they can at least provide some useful information about how to best design future phase III trials.

The primary end points of these trials focused on LV function and heart failure in this acute MI population. Surprisingly, the incidence of hospitalization for CHF was low (1.5%) across all of the trials. One explanation for this could be that this was an acute MI population of patients who presumably had normal LV function prior to their acute MI, who were revascularized quickly thus decreasing the incidence of lasting LV dysfunction. The data suggest a trend in decreased hospitalizations for heart failure in the BMC group (1.9/1000 vs. 5.3/1000 in the control group). The difference between the groups is 3.4 patients/1000, and thus is not likely significant. The overall need for repeat revascularization between the BMC and control groups was similar, but the incidence of TVR, MI, and death were all lower in the BMC group, indicating an effect on ischemia-related outcomes.

Several recommendations can be made to the scientific community for design of studies to examine these secondary clinical outcomes. First, uniform criteria should be developed to better define the clinical outcomes of interest in these trials. We must understand how treatment may influence these outcomes and thus provide direction for the design of future trials. For example, if a cell therapy graft is designed to revascularize myocardial tissue, then efficacy outcome measures should focus on quantifying myocardial perfusion and clinical outcomes related to improved perfusion (e.g., less ischemia-related events). Second, prospective study designs such as cohort and experimental studies can illuminate the incidence of these events in a target population. It is important to know the incidence of these events in a population to determine sample size estimates for future studies. In addition, in the design of phase I/II clinical trials, targeting a population that is at high risk for these outcomes would provide the incidence rates (and power) necessary to adequately

examine these events. For example, if MI were one of the events of interest, targeting a population at high risk for developing MI such as those with unstable angina would provide the necessary sample size to examine these outcomes of interest [28, 29].

Limitations

This is a retrospective analysis of previously published BMC trials that were neither designed nor powered to focus on secondary clinical outcomes. Nevertheless the events comprising these outcomes, and their frequencies, are critically important for proper planning of more definitive trials. The event rates observed may have been influenced by the design of each of the trials. Also, the time to initial revascularization, type of revascularization (bare metal vs. drug eluting stent), time to injection of BMCs, and type of BMCs used varied greatly between the studies. Each of these variables may have influenced the capture of the secondary outcomes reported, thus limiting any statistical analysis of these events.

Conclusion

In summary, even with the above limitations, there appears to be an increased incidence of ischemia-related events compared with heart failure events in this population over the intermediate term follow-up. These findings suggest the need to focus on ischemia-related outcomes in future cell therapy trials. The purpose of this investigation was to examine the criteria used for these clinical outcomes in phase II trials; it is clear that there is a need for standard definitions of these outcomes in order to better design future phase III trials.

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Appendix

TOPCARE AMI [1, 3, 14] randomized 59 patients to receive either BMC or circulating progenitor cells. Investigators reported an increase in global LV ejection fraction (LVEF) and regional wall motion from baseline, and reduced LV end systolic volume at 4 months, in both the BMC and circulating progenitor cell groups. At 1 year, magnetic resonance imaging (MRI) data noted an increase in global LVEF and reduction in infarct size [1, 14]. Another recent abstract reporting 5-year data noted a significant decrease in levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) from baseline, 4 months and 5 years in the cell therapy group [1]. Several clinical outcomes were reported in 1-year follow-up data (Table I). In addition, troponin T was measured after cell therapy and was normalized 14 days post injection; therefore, it was concluded that cell injection did not induce myocardial damage. Recurrent MI was defined as total creatinine kinase elevation two times the upper limit of normal. There were no ventricular arrhythmias, episodes of syncope, or cancers detected at 1 year [14]. There was one patient with bowel cancer reported at 5-years [1]. The 1-year data also report the number of patients experiencing some different “combined clinical outcomes” (Table II) of interest. Other than criteria for recurrent MI, no definitions of the other clinical outcomes are listed [14].

ASTAMI randomized 100 patients to a BMC (50 patients) or to control (50 patients) group [9]. The investigators found no statistically significant differences from baseline to 6 months in LVEF, end-diastolic volume, or infarct size [9]. In a 3-year echocardiographic sub-study, they report no differences between the BMC group and the control group with regards to LVEF, LV volumes, regional function, and LV diastolic function [4]. They do report a statistically significant increase in exercise time at 2–3 weeks and at 3 years in the BMC group, but no difference in peak VO₂ [5]. Their 3-year reported clinical outcomes are noted in Table I. In addition to the outcomes reported in Table I, they also report 3 episodes of

sustained ventricular arrhythmias and no detected cancers. None of the clinical outcomes are defined [5].

FINCELL [8] randomized 80 patients to BMC (40 patients) or control (40 patients) groups after thrombolytic therapy prior to PCI. The investigators reported in their 6-month data that the absolute change in global EF measured by both LV angiography and echocardiogram was significantly greater in the BMC group when compared with controls. No significant differences were found between the control group and the BMC group with regard to intravascular ultrasound measurements or arrhythmia risk variables [8]. They reported several clinical outcomes as well (Table I). Prior to initial hospital discharge, 1 episode of no reflow in the infarct-related artery after PCI occurred in the BMC group. There were 4 episodes of major bleeding—1 in the BMC group and 3 in the control group. Major bleeding was not defined. They also reported 4 episodes of sub-acute stent thrombosis prior to hospital discharge—1 in the BMC group and 3 in the control [8]. None of these clinical endpoints were defined.

The *FINCELL* investigators reported two additional sub-studies on inflammatory markers and their relation to LVEF [12, 13]. They first looked at the relationship between baseline LVEF and inflammatory markers including NT-proBNP [12]. They found that patients in the BMC group who had an initial LVEF below the median (62.5%) had a significantly greater improvement in LVEF at 6 months when compared with the control group or those patients in the BMC group with an LVEF above the median. They also found a significant correlation between baseline NT-proBNP and improvement in 6-month LVEF in the BMC group [12]. Unfortunately, in a second sub-study they found an overall decline in NT-proBNP from baseline to 6 months, but there was no statistical difference between the BMC group and the control group. They also found no statistically significant differences in NT-proBNP, interleukin-6, high resolution C-reactive protein, or tumor necrosis factor between the BMC group and the control group at 6 months [13].

BALANCE [20] randomized 124 patients to BMC (62 patients) or control (62 patients). They reported improvements in LVEF, LV volumes, and contractility in their 5-year data. The investigators commented on a limited amount of clinical outcomes (Table I). In addition to the data shown in Table I, they reported no statistical difference in unplanned hospitalizations (14.5 BMC, 12.9 control). They also reported a statistical difference in mortality favoring the BMC group [20]. No clinical outcomes are defined.

Cao et al. [6] randomized a total of 86 patients to receive BMCs (41 patients) or to a control group (45 patients). They reported 4-year follow-up data which noted statistically significant improvements in LVEF, LV end systolic volume, and LV wall motion index at 6 months, 1 year, and 4 years when compared with controls [6]. A limited amount of data on clinical outcomes were reported (Table I). In addition to data shown in Table I, one case of “transient heart failure” occurred in the BMC group. They reported no arrhythmias, cancers, or intramyocardial calcifications [6]. In-stent restenosis was defined as more than 50% loss of luminal diameter within a stent. Other than this, no other clinical outcomes were defined.

BOOST [10, 11, 19] randomized 100 patients to either a BMC (50 patients) or control (50 patients) group. Although there were early differences, no significant difference in LVEF between the BMC and control groups at 5 years was observed. However, in a sub-study analysis, patients in the BMC group who experienced a transmural infarct greater than the median did show a statistically significant improvement in LVEF at 5 years when compared with those patients with a transmural infarct less than the median [10]. Several clinical outcomes were reported in their 5-year follow-up (Table I). In addition to the information noted in Table I, they also reported 2 cases of either ventricular tachycardia or syncope, one

in each group. The distinction between ventricular tachycardia and syncope was not made. One case of cancer was detected in the control group as well. NYHA class was also commented on with no statistical significance between the groups. The BOOST investigators also commented on one composite outcome (Table II). They defined in-stent restenosis as at least 50% narrowing of the luminal diameter [10]. No other clinical outcomes were defined.

REGENT [18] enrolled 200 patients to receive either selected BMCs (80 patients) or unselected BMCs (80 patients) or to a control group (40 patients). Six-month follow-up data published in the literature noted no statistically significant improvements in LVEF or LV volumes measured by MRI between the BMC and the control groups. Four clinical outcomes were reported on in this study (Table I). No clinical outcomes were defined.

REPAIR AMI [2, 7, 15–17, 23] randomized 204 patients to BMCs (101 patients) or to control (103 patients). They reported at 1 year a significant decrease in the occurrence of death, recurrent MI, or need for revascularization. They also found a decrease in the occurrence of death, recurrent MI, or re-hospitalization for heart failure [16, 17]. The 2-year follow-up MRI data noted significant improvements in relative infarct size and regional contractility [2, 7]. A sub-study analysis also reported improvement in LV remodeling parameters at 4 months in the BMC group that were not present in the control group [15]. These investigators reported other numerous clinical outcomes as well in their 2-year data (Table I) and provided the most complete definitions of their clinical data. They reported a statistically significant difference in occurrence of MI between the BMC group and the control group. Recurrent MI was defined as a creatinine kinase 2 times upper limit of normal with a significant (>6%) MB fraction or new Q-waves on electrocardiogram (ECG). There was no significant difference in rates of re-hospitalization for heart failure between the groups. Re-hospitalization for heart failure was defined as hospitalization with clinical findings of heart failure requiring medication adjustment. There were no significant differences in need for TVR between the groups. They did not define the criteria for revascularization. There were a total of 10 patients with ventricular arrhythmias—5 in the control group and 5 in the BMC group. Ventricular arrhythmia was defined as any ventricular tachycardia or ventricular fibrillation on ECG, ambulatory ECG monitor, or pacemaker/implantable cardioverter defibrillator interrogation. Only 2 syncopal events occurred, both in the control group. Syncope was defined as any self-limiting or transient loss of consciousness. There was no statistical difference in the rate of strokes between the groups. Stroke was defined as any focal neurological deficit persisting for >24 hours and was confirmed by a neurologist or imaging study. Finally, 4 cancers were reported—3 in the control group and 1 in the BMC group. Cancer was defined as any new or recurrent disease confirmed by histology [2, 7, 15–17, 23]. Recently, 5 year follow-up data were presented at the 2011 Madrid cell therapy meetings. At that time, in the placebo group, death had occurred in 15 patients (of which 8 were cardiac deaths and 3 were sudden cardiac deaths). Among the BMC group, death occurred in 7 patients (of which 4 were cardiac deaths and 3 were sudden cardiac deaths). They also report no significant differences in the incidence of syncope and ventricular arrhythmia, with 7 instances in the placebo group and 6 in the BMC group; there was no distinction made between ventricular arrhythmia or syncope. The incidence of cancer was similar, with 7 occurrences in the placebo group and 4 in the BMC group. From this 5-year data abstract only the data on death are included in the analysis in this paper. The remaining data are from the 2-year report.

The REPAIR-AMI investigators also comment on four different combined outcomes (Table II). They reported a statistically significant difference in the combined outcomes of death or MI; death, MI or any revascularization; and death, MI, or re-hospitalization for heart failure,

all favoring the BMC group. They reported no difference for the outcome of death, MI, or infarct vessel revascularization [2, 17].

LateTIME [22] randomized 87 patients who were 2 to 3 weeks post anterior MI and had an LVEF $\leq$ 45% to BMCs (58 patients) or to control (29 patients). The primary outcomes were global and regional LVEF measured by cardiac MRI. The 6-month follow-up data noted no statistical significance in global or regional LVEF between the placebo and BMC groups. None of these clinical outcomes were defined.

Figure 1.

Table I

Clinical outcomes.

Trial	No. Pts	Follow-up	Death		MI		TVR		Non-TVIR		CABG		Reverse Unspec		CHF Hosp		CVA	
			C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B
ASTAMI [9]	100	3 yr	1	1	2	1	9	12	1	2	3	3	x	x	1	2	1	1
BALANCE [20]	124	5 yr	7	1	x	x	x	x	x	x	x	x	9.6	8	x	x	x	x
BOOST [10, 11, 19]	100	5 yr	2	2	1	1	4	6	x	x	x	x	x	x	3	2	x	x
Cao et al [6]	86	4 yr	1	0	x	x	1	x	x	x	x	x	x	x	x	x	x	x
FINCEL [8]	80	6 mo	1	0	2	0	x	x	x	x	x	x	3	3	1	0	x	x
REPAIR AMI [2, 7, 15–17, 23] *	204	5 yr	15	7	7	0	28	19	16	11	x	x	x	x	5	1	2	1
REGENT [18] †	200	6 mo	1	2	2	3	7	25	x	x	x	x	x	x	x	x	0	0
TOPCARE [1, 3, 14] ‡	59	5 yr	0	1	1	1	7	6	1	1	0	0	x	x	0	0	0	0
LateTIME [22]	87	6 mo	1	0	0	1	2	1	1	0	x	x	x	x	0	1	x	x
Total	1040		29	14	15	7	58	69	19	14	3	3	12.6	11	10	6	3	2

B, bone marrow derived stem cell (BMC) group; C, control group; CABG, coronary artery bypass graft; CHF Hosp, congestive heart failure hospitalization; CVA, cerebrovascular accident; MI, myocardial infarction; TVR, target vessel revascularization; X, not reported on in study.

* Repair AMI: 5-year data are reported for death, and remaining data are from 2 year data

† Regent: Selected and unselected BMC groups are combined.

‡ TOPCARE: Circulating progenitor group = control. 16 total TVRs reported in 5- year abstract, but not specified control vs BMC. Data in the table are from 1-year follow-up.

Table II

Standardized event rates for selected outcomes.

Trial	No. Pts.	Follow-up Duration (yrs)	MI		CABG		Death		Coronary Revascularization				CHF Hospitalization		TVR	
			Number of MI		Number of CABG		Number of Deaths		Event Rate per 1000 per year		Event Rate per 1000 per year		Number of CHF Hospitalization		Number of TVR	
			Control	BMC	Control	BMC	Control	BMC	Control	BMC	Control	BMC	Control	BMC	Control	BMC
ASTAMI [9]	100	3	2	1	6.7	3.3	1	1	10	10	46.7	3.3	1	2	9	12
BALANCE [20]	124	5	x	x	0.0	0.0	7	1			16.1	12.9	x	x	x	0
BOOST [10, 11, 19]	100	5	1	1	2.0	2.0	2	2			8.0	12.0	3	2	4	6
Cao et al [6]	86	4	x	x	0.0	0.0	1	0			0.0		x	x	1	x
FINCEL [8]	80	0.5	2	0	50.0	0.0	1	0			75.0		1	0	x	x
REPAIR AMI [2, 7, 15–17, 23] [‡]	204	5	7	0	6.9	0.0	15	7			37.3	24.5	5	1	28	19
REGENT [18] [‡]	200	0.5	2	3	20.0	30.0	1	2			70.0		x	x	7	25
TOPCARE [1, 3, 14] [‡]	59	5	1	1	3.4	3.4	0	1			23.7	20.3	0	0	7	6
LateTIME [22]	87	6	0	1	0.0	1.9	1	0			69.0	23.0	0	1	2	1
Totals	1040	0	15	7			29	14					10	6	10	6
Avg Rate					6.1	5.6			10	10	27.1	27.5		5.3		16.6

BMC, bone marrow derived stem cell group; CABG, coronary artery bypass graft; CHF, congestive heart failure; MI, myocardial infarction; TVR, target vessel revascularization; x, not reported on in study.

[‡] Repair AMI: 5-year data reported for death; remaining data are from 2-year data.

[‡] Regent: Selected and unselected BMC groups combined.

[‡] Topcare: Circulating progenitor group = control. 16 total TVRs reported in 5-year abstract, but not specified control vs BMC. Data in table are from 1-year follow-up.

Table III

Combined endpoints.

Study	Follow-Up	No. Pts.	Death, MI		Death, MI, CHF hosp		Death, MI, TVR		Death, MI, Any Revasc	
			B	C	B	C	B	C	B	C
TOPCARE [1, 3,14] *	5 yr	59	1	1	1	1	6	8	x	x
BOOST [10, 11, 19]	5 yr	100	x	x	5	6	x	x	x	x
REPAIR AMI [2, 7, 15–17, 23]	2 yr	204	3	12	4	15	22	34	28	44
Total		363	4	13	10	22	28	42	28	44

B, bone marrow derived stem cell group; *C*, Control group; *CHF*, congestive heart failure; *MI*, myocardial infarction; *TVR*, target vessel revascularization; *X*, not reported on in study.

* TOPCARE: Circulating progenitor group = control.