RESEARCH LETTER

One-Year Follow-up of Intracoronary Stem Cell Delivery on Left Ventricular Function Following ST-Elevation Myocardial Infarction

The Timing In Myocardial Infarction Evaluation (TIME) trial[1,2] assessed whether the timing of stem cell delivery affects the recovery of left ventricular (LV) function following myocardial infarction (MI). Patients with anterior ST-elevation MI (STEMI) who were reperfused with primary percutaneous coronary intervention and stenting and had at least moderate LV dysfunction (LV ejection fraction [LVEF] ≤45%) were randomized (2:1) to 150 million autologous bone marrow mononuclear cells (BMCs) or placebo with intracoronary delivery performed on day 3 (n = 67) or day 7 (n = 53). At 6 months, no benefit of cell therapy was observed compared with placebo following cell delivery at either time. We now report outcomes at 1 year. The collection of clinical end point and cardiac magnetic resonance imaging (MRI) data was prespecified but the analysis plan was post hoc.

Methods | TIME was approved by each center's institutional review board with written informed consent collected from all participants. Ninety-five patients (65 in BMC group, 30 in placebo group) of the original 112 analyzed at 6 months (75 in BMC group, 37 in placebo group) had analyzable MRI data through 1 year. Baseline characteristics of those analyzed at 6 months and 1 year were not different. Reasons for the drop-off between 6 months and 1 year included 3 implantable cardioverter-defibrillator placements, 1 death, 12 lost to follow-up or refused to participate, and 1 MRI not performed. Follow-up was completed by November 12, 2012.

The primary analyses were changes in LVEF and regional (infarct and border zone) LV function between baseline and 6 months by cardiac MRI. Primary and secondary outcomes at 1 year appear in **Table 1**. Safety outcomes appear in **Table 2**. Because an effect of timing was not observed, data are presented as the aggregate of the means of day 3 and day 7 delivery. Differences in the changes in primary and secondary end points between therapy groups and trajectories over time were assessed using repeated-measures analysis of variance. Worst-case imputation (substituting worst value in the cohort for the missing value) was also conducted. All

Table 1. Cardiac Magnetic Resonance Imaging Results From the Timing In Myocardial Infarction Evaluation Trial

	Mean (95% CI) [SD]		*P* Value vs Baseline	*P* Value: 6 mo vs 1 y	*P* Value[a]
	BMC Group (n = 65)	Placebo Group (n = 30)			
LVEF, %					
Baseline	46.2 (43.9-48.5) [9.6]	46.3 (43.3-49.3) [8.5]			
6 mo	50.1 (47.2-53.0) [11.8]	51.5 (47.5-55.5) [11.2]	<.001	.20	
1 y	49.5 (46.5-52.5) [12.3]	49.6 (45.8-53.4) [10.7]	<.001		.30
Regional infarct zone, mm					
Baseline	3.8 (2.6-5.0) [4.9]	4.6 (3.0-6.2) [4.6]			
6 mo	5.8 (4.2-7.4) [6.6]	8.1 (5.8-10.4) [6.4]	<.001	.58	
1 y	6.2 (4.8-7.6) [5.9]	6.4 (4.3-8.5) [5.8]	<.001		.67
Regional border zone, mm					
Baseline	16.4 (13.9-18.9) [10.2]	14.4 (10.9-17.9) [9.8]			
6 mo	20.6 (17.8-23.4) [11.6]	21.1 (16.3-25.9) [13.4]	<.001	.49	
1 y	21.2 (18.3-24.1) [12.0]	21.2 (16.5-25.9) [13.2]	<.001		<.001
Infarct size, g[b]					
Baseline	44.7 (39.0-50.4) [23.1]	46.3 (36.5-56.1) [27.4]			
6 mo	30.7 (26.9-34.5) [15.4]	31.7 (24.5-38.9) [20.2]	<.001	.04	
1 y	28.8 (25.0-32.6) [15.4]	27.7 (21.5-33.9) [17.2]	<.001		<.001
LV mass, g[b]					
Baseline	180.4 (168.6-192.2) [47.6]	177.3 (160.8-193.8) [46.1]			
6 mo	156.8 (146.7-166.9) [41.0]	161.3 (146.1-176.5) [42.6]	<.001	<.001	
1 y	148.9 (138.6-159.2) [41.8]	151.0 (135.3-166.7) [44.0]	<.001		<.001
LVEDVI, mL/m^2					
Baseline	77.1 (72.7-81.5) [18.0]	70.5 (64.4-76.6) [17.1]			
6 mo	86.7 (80.6-92.8) [25.0]	80.3 (72.1-88.5) [22.8]	<.001	.14	
1 y	88.7 (82.6-94.8) [25.0]	82.6 (74.6-90.6) [22.4]	<.001		<.001
LVESVI, mL/m^2					
Baseline	41.9 (38.6-45.2) [13.5]	38.0 (33.8-42.2) [11.7]			
6 mo	44.7 (39.8-49.6) [20.3]	40.0 (33.7-46.3) [17.6]	.08	.02	
1 y	46.3 (41.1-51.5) [21.3]	42.9 (36.3-49.5) [18.4]	<.001		.02

Abbreviations: BMC, bone marrow mononuclear cells; LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESI, LV end-systolic volume index.

[a] Comparison is for the change in the mean value from baseline through 6 months to 1 year using a repeated-measures mixed model.

[b] There were only 63 patients in the BMC group for this variable.

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Table 2. Clinical and Safety Outcomes From Baseline to 1 Year

	No. of Patients[a]	
	BMC Group (n=79)	Placebo Group (n = 41)
Had any event	18	9
Death	1	0
Reinfarction[b]	2	3
Repeat revascularization[c]	9	6
Target vessel	4	4
Nontarget vessel	5	2
Heart failure during hospitalization	4	1
ICD placement[d]	4	5
Stroke	2	2
Total	22	17
Proportion of patients with events	0.228	0.220

Abbreviations: BMC, bone marrow mononuclear cell; ICD, implantable cardioverter-defibrillator.

[a] Unless otherwise indicated.

[b] There were 2 reinfarctions after 6 months (1 in the BMC group and 1 in the placebo group).

[c] There were 4 repeat revascularizations after 6 months (2 in the BMC group and 2 in the placebo group).

[d] There were 3 ICD placements after 6 months (1 in the BMC group and 2 in the placebo group).

hypothesis testing was 2-tailed. Results with $P < .05$ were considered statistically significant. Analyses were performed with SAS version 9.3 (SAS Institute Inc).

Results | Levels of LVEF increased from baseline to 6 months in both the BMC (46.2% [95% CI, 43.9%-48.5%] to 50.1% [95% CI, 47.2%-53.0%]) and the placebo groups (46.3% [95% CI, 43.3%-49.3%] to 51.5% [95% CI, 47.5%-55.5%]) ($P < .001$) but did not improve further between 6 months and 1 year in either group (BMC, 49.5% [95% CI, 46.5%-52.5%]; placebo, 49.6% [95% CI, 45.8%-53.4%]). Regional LV function increased in infarct and border zones between baseline and 6 months in both groups with no further increase between 6 months and 1 year (Table 1). There were no differences at any time between the BMC and placebo groups.

Between baseline and 1 year, there were increases in LV volumes in both the BMC and placebo groups, with no significant differences between groups (Table 1). The results were unchanged in the worst-case imputation analysis.

Infarct size decreased in the BMC and placebo groups between baseline and 6 months with a smaller reduction between 6 months and 1 year. The reduction in infarct size was accompanied by a similarly significant reduction in LV mass through 1 year (Table 1). There were no differences in the reduction in infarct size and LV mass between the BMC and placebo groups at any time.

Between 6 months and 1 year, there were 2 more infarctions, 4 repeat revascularizations, and 3 implantable cardioverter-defibrillator placements (Table 2).

Conclusion | In this post hoc analysis, the administration of BMCs following moderate to large anterior STEMIs was not associated with improved recovery of global and regional LV function at 1 year, irrespective of cell delivery at 3 or 7 days. The recovery of LV function following STEMI appeared complete by 6 months because no additional improvement in LV function was observed in either group between 6 months and 1 year. Our results do not support the administration of BMCs following MI. However, because we were unable to obtain 1-year MRIs on all patients, the precision of our estimates for change in LV function was reduced.

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Published Online: November 18, 2013. doi:10.1001/jama.2013.282674.

Author Contributions: Dr Traverse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Traverse, Willerson.
Obtained funding: Traverse, Pepine, Willerson.
Administrative, technical, or material support: Pepine, Willerson.
Study supervision: Traverse, Ellis.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Henry reported serving as a consultant for Capricor and Johnson & Johnson; and receiving grant support from Capricor and OSIRIS. Dr Pepine reported receiving funding for writing assistance, medicine, equipment, or administrative support from the National Heart, Lung, and Blood Institute, BDS Cordis Corp, and Biosafe; and receiving several institutional grants from several pharmaceutical companies and government institutions. Dr Willerson reported receiving funding from the National Heart, Lung, and Blood Institute for participation in review activities. Dr Ellis reported receiving travel support from Abbott Vascular and Boston Scientific. No other disclosures were reported.

Funding/Support: Funding for this trial was provided by the National Heart, Lung, and Blood Institute under cooperative agreement 5 UO1 HL087318-04. Support for cell processing (Sepax) was provided by Biosafe SA Inc. Angioplasty catheters were provided by Boston Scientific Corporation.

Role of the Sponsor: The National Heart, Lung, and Blood Institute had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We acknowledge all the contributions by the Investigators of the Cardiovascular Cell Therapy Research Network and the leadership and vision of the late Sonia Skarlatos, PhD (formerly with the National Heart, Lung, and Blood Institute).

Trial Registration: clinicaltrials.gov Identifier: NCT00684021

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