

# Letters

## 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<sup>1,2</sup> 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]  $\leq$ 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 <sup>a</sup>
	BMC Group (n = 65)	Placebo Group (n = 30)			
<b>LVEF, %</b>					
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
<b>Regional infarct zone, mm</b>					
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
<b>Regional border zone, mm</b>					
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
<b>Infarct size, g<sup>b</sup></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
<b>LV mass, g<sup>b</sup></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
<b>LVEDVI, mL/m<sup>2</sup></b>					
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
<b>LVESVI, mL/m<sup>2</sup></b>					
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.

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

<sup>b</sup> There were only 63 patients in the BMC group for this variable.

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

	No. of Patients <sup>a</sup>	
	BMC Group (n=79)	Placebo Group (n = 41)
Had any event	18	9
Death	1	0
Reinfarction <sup>b</sup>	2	3
Repeat revascularization <sup>c</sup>	9	6
Target vessel	4	4
Nontarget vessel	5	2
Heart failure during hospitalization	4	1
ICD placement <sup>d</sup>	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.

<sup>a</sup> Unless otherwise indicated.

<sup>b</sup> There were 2 reinfarctions after 6 months (1 in the BMC group and 1 in the placebo group).

<sup>c</sup> There were 4 repeat revascularizations after 6 months (2 in the BMC group and 2 in the placebo group).

<sup>d</sup> 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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*Study concept and design:* Traverse, Henry, Willerson, Ellis.

*Acquisition of data:* Traverse, Henry, Pepine, Willerson.

*Analysis and interpretation of data:* Traverse, Henry, Willerson.

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