TIME Trial: Effect of Timing of Stem Cell Delivery Following ST-Elevation Myocardial Infarction on the Recovery of Global and Regional Left Ventricular Function

Final 2-Year Analysis

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Rationale: **The TIME trial (Timing in Myocardial Infarction Evaluation) was the first cell therapy trial sufficiently powered to determine if timing of cell delivery after ST-segment–elevation myocardial infarction affects recovery of left ventricular (LV) function.**

Objective: **To report the 2-year clinical and cardiac magnetic resonance imaging results and their modification by microvascular obstruction.**

Methods and Results: **TIME was a randomized, double-blind, placebo-controlled trial comparing 150 million bone marrow mononuclear cells versus placebo in 120 patients with anterior ST-segment–elevation myocardial infarctions resulting in LV dysfunction. Primary end points included changes in global (LV ejection fraction) and regional (infarct and border zone) function. Secondary end points included changes in LV volumes, infarct size, and major adverse cardiac events. Here, we analyzed the continued trajectory of these measures out to 2 years and the influence of microvascular obstruction present at baseline on these long-term outcomes. At 2 years (n=85), LV ejection fraction was similar in the bone marrow mononuclear cells (48.7%) and placebo groups (51.6%) with no difference in regional LV function. Infarct size and LV mass decreased ≥30% in each group at 6 months and declined gradually to 2 years. LV volumes increased ≈10% at 6 months and remained stable to 2 years. Microvascular obstruction was present in 48 patients at baseline and was associated with significantly larger infarct size (56.5 versus 36.2 g), greater adverse LV remodeling, and marked reduction in LV ejection fraction recovery (0.2% versus 6.2%).**

Conclusions: **In one of the longest serial cardiac magnetic resonance imaging analyses of patients with large anterior ST-segment–elevation myocardial infarctions, bone marrow mononuclear cells administration did not improve recovery of LV function over 2 years. Microvascular obstruction was associated with reduced recovery of LV function, greater adverse LV remodeling, and more device implantations. The use of cardiac magnetic resonance imaging leads to greater dropout of patients over time because of device implantation in patients with more severe LV dysfunction resulting in overestimation of clinical stability of the cohort.**

Clinical Trial Registration: **URL: http://www.clinicaltrials.gov. Unique identifier: NCT00684021.**

(*Circ Res*. 2018;122:479-488. DOI: 10.1161/CIRCRESAHA.117.311466.)

Key Words: bone marrow ■ magnetic resonance imaging ■ myocardial infarction ■ stem cell

Original received June 6, 2017; revision received November 29, 2017; accepted December 1, 2017. In November 2017, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 11.99 days.

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This manuscript was sent to Gerd Heusch, Consulting Editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at http://circres.ahajournals.org/lookup/suppl/doi:10.1161/CIRCRESAHA.117.311466/-/DC1.

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Novelty and Significance

What Is Known?

- Microvascular obstruction observed on cardiac magnetic resonance imaging (cMRI) after ST-segment–elevation myocardial infarction is associated with adverse left ventricular (LV) remodeling and poor clinical outcomes.
- The long-term effects of microvascular obstruction on cMRI of LV function and infarct size in response to cell therapy with bone marrow mononuclear cells (BMCs) have not been previously described.

What New Information Does This Article Contribute?

- Cell therapy with BMCs did not improve global or regional LV function compared with placebo in patients with anterior ST-segment–elevation myocardial infarctions and moderate-to-severe LV dysfunction over 2 years of follow-up.
- The presence of microvascular obstruction on baseline (day 3) cMRI was associated with a significant reduction in the recovery of LV function and adverse LV remodeling and increased need for implantable cardioverter-defibrillator placement at 2 years of follow-up.
- The use of cMRI for end point analysis in cell therapy trials is adversely affected by patient dropout because of clinical events such as device implantation that occurs more frequently in patients with more severe LV dysfunction.

The TIME trial (Timing in Myocardial Infarction Evaluation) was developed by the Cardiovascular Cell Therapy Research Network to investigate the effect of timing (day 3 versus day 7) of BMC delivery on the recovery of global and regional LV function in 120 patients after anterior ST-segment–elevation myocardial infarction. Prespecified cMRI measurements of LV function were performed at baseline, 6 months, 1 year, and 2 years. In one of the longest serial cMRI imaging analyses of patients with large anterior ST-segment–elevation myocardial infarctions, BMCs had no effect on the recovery of LV function, volumes, or infarct size compared with placebo at any time point over 2 years of follow-up. No effect of timing of BMC administration was observed. Microvascular obstruction was observed in half the cohort on baseline cMRI and was associated with reduced recovery of LV function, greater adverse LV remodeling, and more implantable cardioverter-defibrillator implantations. The use of cMRI results in greater patient loss over time because of device implantation and occurred in patients with more severe LV dysfunction resulting in overestimation of clinical stability of the cohort.

Nonstandard Abbreviations and Acronyms

BMC	bone marrow mononuclear cells
CCTRN	Cardiovascular Cell Therapy Research Network
cMRI	cardiac magnetic resonance imaging
LV	left ventricular
LVEDVI	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
LVESVI	left ventricular end-systolic volume index
MVO	microvascular obstruction
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction
TIME	Timing in Myocardial Infarction Evaluation

The Cardiovascular Cell Therapy Research Network (CCTRN) was established by the National Heart, Lung and Blood Institute to foster the development of adult stem cell–based trials in the United States.[1] An initial focus of the Network was the use of bone marrow mononuclear cells (BMCs) in the setting of ST-segment–elevation myocardial infarction (STEMI) based on results suggesting benefit in left ventricular ejection fraction (LVEF) from several European trials.[2,3] An important question not addressed in these early trials was whether timing of cell delivery after reperfusion by primary percutaneous coronary intervention (PCI) with stenting influenced recovery of LV function because temporal changes in the myocardium known to occur shortly after reperfusion could either promote or inhibit cell survival and engraftment.[4,5]

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Accordingly, the CCTRN developed 2 trials, TIME (Timing in Myocardial Infarction Evaluation) and LateTIME, to investigate the role of timing of cell delivery after STEMI. Specifically, the TIME trial[6] examined cell delivery on day 3 versus day 7 after primary PCI with stenting, whereas LateTIME[7] examined whether cell delivery 2 to 3 weeks post-STEMI could enhance the recovery of LV function. Although TIME found that BMCs did not improve the recovery of global or regional LV function compared with placebo at its 6-month primary end point, we prespecified that patients were to be followed for 2 years with additional serial cardiac magnetic resonance imaging (cMRI) at 1 and 2 years. Here, we report the final 2-year results for TIME that provides one of the largest serial cMRI measurements of patients with moderate-to-large anterior infarctions and demonstrates the powerful predictive effects of microvascular obstruction (MVO) on LV function when observed on the baseline cMRI scans.

Methods

Result data at the 6-month primary end point are available at clinicaltrials.gov, and additional data from later time points can be requested from CCTRN Data Coordinating Center (L.M.).

Eligibility criteria of the TIME trial have been previously described in detail.[8] In brief, TIME was a randomized, placebo-controlled trial of patients with anterior STEMI who underwent successful primary PCI with stenting and who had at least moderate LV dysfunction (LVEF≤45%) by screening echocardiography 1 to 2 days post-PCI. All patients provided informed written consent. The study was approved by the Institutional Review Boards of each participating center. Patients were randomized (1:1) to study product delivery on day 3 or day 7 post-PCI. On the day of delivery, patients underwent measurement of global and regional LV function and infarct size with a 1.5-T cMRI scanner using protocols developed by the MRI Core Laboratory (University of Florida). Those patients randomized to day 7 also had a cMRI performed on day 3 to establish the same baseline between all patients. For the purposes of this article, day 3 images are heretofore referenced as baseline. All patients were prescribed standard postmyocardial infarction medications including β-blockers and ACE inhibitors (Table 1) that were recommended to be continued over the 2 years of follow-up. However, follow-up medications were not recorded. Data are given in Table 1.

Table 1. Baseline and Cell Characteristics for TIME (Timing in Myocardial Infarction Evaluation) 2-Year Cohort (n=85)

	BMC n=58	Placebo n=27	*P* Value
Patient characteristics			
Age, mean (SD)	55.9 (11.0)	56.4 (10.4)	0.845
Female, n (%)	7 (12)	4 (14)	0.737
Race			
White, n (%)	51 (87)	23 (85)	0.737
Nonwhite, n (%)	7 (12)	4 (14)	
Hispanic, n (%)	2 (3)	1 (3)	1.000
History, n (%)			
Diabetes mellitus	7 (12)	5 (18)	0.508
Hypertension	26 (44)	22 (81)	0.002
Hyperlipidemia	41 (70)	20 (74)	0.802
Angina	8 (13)	5 (18)	0.747
Smoking	33 (56)	16 (59)	1.000
Physical, mean (SD)			
BMI	30.6 (5.6)	31.1 (5.4)	0.732
EF			
Echo screening	37.1 (6.3)	37.7 (4.8)	0.654
cMRI core (3 d) EF	45.9 (9.4)	46.9 (8.7)	0.657
Medications, n (%)			
ACE inhibitor	52 (89)	21 (77)	0.184
Plavix/Prasugrel	55 (94)	27 (100)	0.548
Aspirin	55 (94)	27 (100)	0.548
β-blockers	56 (96)	27 (100)	1.000
Statins	52 (89)	26 (96)	0.423
Diuretics	12 (20)	6 (22)	1.000
Coumadin/ Warfarin/ Lovenox	14 (24)	2 (7)	0.080
Laboratories, [n] mean (SD)			
Hemoglobin	[50] 14.2 (1.5)	[21] 13.2 (2.1)	0.031
hsCRP	[53] 38.7 (48.8)	[25] 38.4 (29.6)	0.976
Peak CK	[48] 3210.2 (2178.6)	[25] 2027.1 (1820.4)	0.023
Peak CKMB	[44] 258.3 (175.9)	[23] 185.8 (170.8)	0.111
BNP reg	[48] 293.3 (613.7)	[24] 286.9 (330.5)	0.962
BNP pro	[8] 1537.2 (1518.7)	[3] 2123.3 (3030.9)	0.669
Myocardial Infarction treatment			
Ischemic time, h, mean (SD)	6.4 (9.6)	7.2 (7.4)	0.726
Time from aspirate to infusion, h, mean (SD)	8.9 (3.3)	8.4 (1.1)	0.450
Drug-eluting stent n (%)	46 (79)	23 (85)	0.766
Cell processing, [n] mean×10^6 (SD)			
Final cell dose	[58] 146.1 (20.1)	[27] 148.9 (3.2)	0.471
Viability [n] % mean (SD)	[58] 98.1 (1.6)	[27] 98.2 (1.5)	0.862
$CD34^+$ ISHAGE	[53] 2.0 (1.1)	[26] 2.4 (1.0)	0.184
$CD133^+$ ISHAGE	[53] 1.0 (0.6)	[26] 1.3 (0.8)	0.088
CFUec per dose	[41] 303.7 (479.6)	[18] 381.5 (812.3)	0.647
ECFC per dose	[41] 615.4 (1806.7)	[16] 163.5 (262.5)	0.326
MSC per dose	[40] 511.9 (556.8)	[18] 364.6 (459.9)	0.331

ACE indicates angiotensin-converting enzyme; BMC, bone mononuclear cells; BMI, body mass index; BNP=brain natriuretic peptide; CFU, colony-forming units; CK, creatine kinase; CKMB, creatine kinase-myocardial band; cMRI, cardiac magnetic resonance imaging; ECFC, endothelial colony–forming cells; EF, ejection fraction; hsCRP, high-sensitivity C-reactive protein; ISHAGE, International Society for Hematotherapy and Graft; and MSC, mesenchymal stem cells.

Assessment of MVO

The presence of MVO (late) was identified using delayed gadolinium imaging in the baseline images. Images were acquired 15 to 20 minutes after the administration of gadolinium-DTPA (diethylenetriaminepentacetate; 0.20 mmol/kg). Quantification of infarct tissue and MVO was performed using cvi42 postprocessing software (Version 5.1; Calgary, AB, Canada). MVO was defined as an area of hypointensity within subendocardial hyperintensities. MRI analyses were performed at the Core Laboratory, and readers were blinded to patient data and treatment assignment.

Cell Processing and Delivery

After baseline cMRI, patients underwent a bone marrow aspiration and BMCs were isolated at each center using an automated, Ficoll-based cell separation device previously validated by the CCTRN for BMCs (Sepax; Biosafe Inc).[9]

All patients randomized to BMCs received 150 million nucleated cells containing 70% to 80% BMCs. Patients randomized to placebo received a cell-free product of 5% albumin in normal saline with the addition of 100 µL of whole blood to maintain similar appearance to the BMC product.

Patients underwent intracoronary infusion of BMCs or placebo in the cardiac catheterization laboratory, within 12 hours of bone marrow aspiration, using the stop-flow technique.

Primary End Points

The primary end points were changes in global LVEF and regional (infarct and border zone) LV function measured at 6 months by cMRI compared with baseline and whether day of treatment (day 3 versus day 7) affected these results. Secondary end points were major adverse cardiac events and changes in LV volumes and infarct size.

Statistical Methods

Baseline comparisons were conducted using 2-sample unpaired *t* tests for continuous variables and Fisher exact test for dichotomous indicator (0–1) variables. Comparisons between the time

trajectories (from baseline to 2 years) for LVEF, infarct zone wall motion, border zone wall motion, infarct size, LV mass, and LV end-diastolic volume index (LVEDVI), and LV end-systolic volume index (LVESVI) were performed using a repeated-measure general linear model. These models included terms for trajectories, treatment effect (BMC versus placebo), and trajectory–treatment interactions. To assess the ability of MVO to explain differences in LVEF from baseline to 6 months, a multiple regression model was performed. The change in LVEF was the dependent variable, and baseline MVO was the explainer variable of interest. Additional explainer variables included sex, baseline LVEF, baseline LVEDVI, baseline LVESVI, and baseline infarct size. Clinical events were evaluated using a χ^2 test for proportion. Any P value <0.05 was considered statistically significant with no adjustment for multiplicity.

Results

Cohort Sizes for cMRI Data

Between July 2008 and November 2011, 120 patients were enrolled and randomized (BMC=79, placebo=41) of which cMRI analysis was completed in 110 patients at 6 months. Expanding out to 2 years, 85 patients completed baseline, 6-month, 1-year, and 2-year cMRI; these patients comprise the 2-year cohort (BMC=58, placebo=27) (Figure 1).[10] This 2-year cohort represents 71% of all randomized participants (n= 85/120). Loss of analyzable MRIs over 2 years was because of the following reasons: implantable cardioverter-defibrillator (ICD) implants (n=10), death (n=3), lost to follow-up (n=7), and refused or other MRI contraindication (n=15).

Baseline Characteristics

Baseline characteristics of the 2-year cohort appear in Table 1. Cardiac risk factors were uniformly distributed between the 2 groups with the exception of hypertension history that was more prevalent in the placebo group (P=0.002).

Global and Regional LV Function

Overall, for the 2-year cohort, there was a nonsignificant absolute increase in global LVEF in both groups: from 45.9±9.4% to 48.7±11.2% in the BMC group and from 46.9±8.7% to 51.6±11.7% in the placebo group from baseline to 2 years (Table 2).

In the 2-year cohort, mean wall motion in the infarct zone increased in both groups: from 3.9±4.8 to 6.0±6.3 mm in the BMC group (P<0.001) and from 4.7±4.7 to 7.0±6.0 mm in the placebo group (P=0.009; Table 2). Similarly, in the infarct border zone, mean wall motion increased from 16.3±10.4 to 21.3±12.1 mm in the BMC group (P<0.001) and from 14.9±10.1 to 20.4±13.3 mm in the placebo group (P<0.001). The greatest increase in LV function occurred between baseline and 6 months with minimal change between 6 months and 2 years.

Infarct Size and LV Mass

In the 2-year cohort, from baseline to 2 years, infarct size significantly decreased in both groups: from 44.1±23.1 to 25.0±14.4 g in the BMC group and from 48.4±27.9 to 22.6±12.1 g in the placebo group; both P<0.001. Infarct size declined at a greater rate in the placebo group than the treatment group (P=0.042). In addition, LV mass decreased in both groups: from 179.2±48.8 to 143.0±38.2 g in the BMC group (P=0.001) and from 180.4±47.1 g to 149.9±44.1 g in the placebo group (P=0.092; Table 2).

LV Volumes

In the in the 2-year cohort, LVEDVI and LVESVI increased from baseline to 1 year and then stabilized through 2 years in both groups. In the BMC group, over 2 years, LVEDVI increased from 76.7±17.7 to 85.2±25.3 mL/m^2 (P=0.050) and from 69.4±17.6 to 78.2±22.7 mL/m^2 in the placebo group (P=0.272), whereas LVESVI had very little change in either group (Table 2).

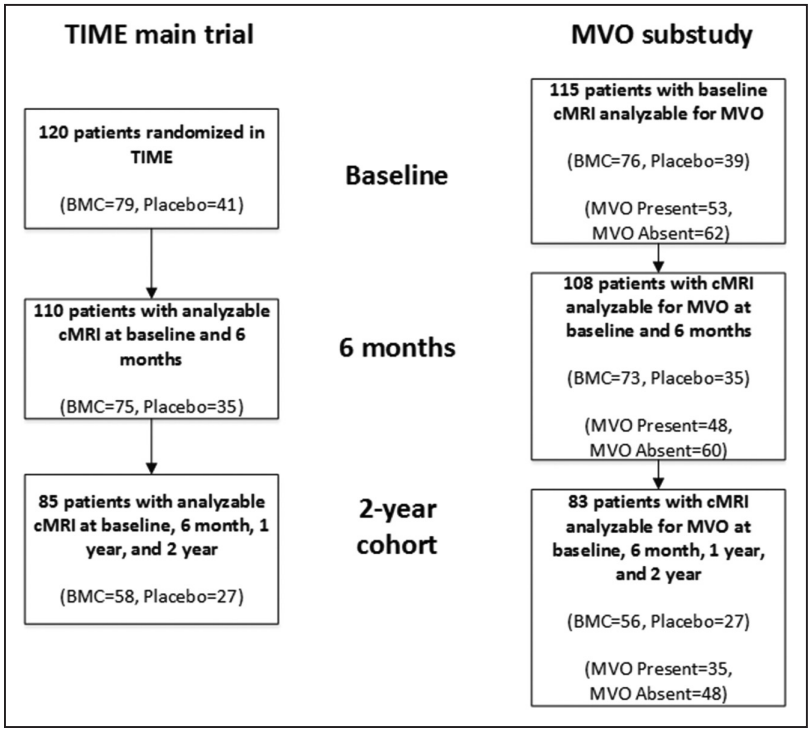

Figure 1. Patient flowchart for TIME (Timing in Myocardial Infarction Evaluation) main trial and microvascular obstruction (MVO) substudy. BMC indicates bone marrow mononuclear cells; cMRI, cardiac magnetic resonance imaging.

Table 2. Magnetic Resonance Imaging Analysis for TIME (Timing in Myocardial Infarction Evaluation) 2-Year Cohort

	BMC Change From 3 d						Placebo Change From 3 d						
	n	Mean	SD	Mean	SD	*P* Value*	n	Mean	SD	Mean	SD	*P* Value*	*P* Value†
LVEF													
Baseline	58	45.9	9.4				27	46.9	8.7				
6 mo	58	50.3	11.1	4.4	9.4		27	51.6	11.2	4.7	11.8		
1 y	58	49.8	11.8	3.9	9.2		27	50.0	10.8	3.2	11.4		
2 y	58	48.7	11.2	2.8	9.4	0.381	27	51.6	11.7	4.7	12.0	0.324	0.302
Wall motion IZ, mm													
Baseline	58	3.9	4.8				27	4.7	4.7				
6 mo	58	6.1	6.6	2.2	6.0		27	8.2	6.0	3.6	5.5		
1 y	58	6.5	5.8	2.6	4.7		27	6.6	5.4	2.0	6.1		
2 y	58	6.0	6.3	2.1	5.4	<0.0001	27	7.0	6.0	2.4	6.6	0.009	0.175
Wall motion BZ, mm													
Baseline	58	16.3	10.4				27	14.9	10.1				
6 mo	58	20.7	11.2	4.4	7.6		27	21.6	13.2	6.7	10.2		
1 y	58	21.7	11.5	5.3	7.3		27	22.1	13.0	7.2	11.1		
2 y	58	21.3	12.1	5.0	7.6	<0.0001	27	20.4	13.3	5.5	10.8	<0.0001	0.394
Infarct size, g													
Baseline	56	44.1	23.1				27	48.4	27.9				
6 mo	56	29.8	15.1	−14.2	17.5		27	31.5	20.9	−16.9	24.0		
1 y	56	28.2	15.3	−15.8	16.9		27	28.1	17.9	−20.4	26.6		
2 y	56	25.0	14.4	−19.1	15.7	<0.0001	27	22.6	12.1	−25.9	21.6	<0.0001	0.042
LV mass, g													
Baseline	56	179.2	48.8				27	180.4	47.1				
6 mo	56	155.1	42.2	−24.1	23.0		27	163.6	43.9	−16.8	27.0		
1 y	56	148.1	43.8	−31.0	21.8		27	153.6	45.2	−26.8	24.2		
2 y	56	143.0	38.2	−36.2	25.4	0.001	27	149.9	44.1	−30.5	21.5	0.092	0.500
LVEDVI, mL/m^2													
Baseline	58	76.7	17.7				27	69.4	17.6				
6 mo	58	87.7	25.2	11.0	15.5		27	77.5	22.0	8.2	18.3		
1 y	58	90.1	24.6	13.4	16.0		27	80.9	21.9	11.5	18.4		
2 y	58	85.2	25.3	8.5	20.0	0.050	27	78.2	22.7	8.8	18.6	0.272	0.652
LVESVI, mL/m^2													
Baseline	58	42.0	13.7				27	37.0	11.8				
6 mo	58	45.0	20.5	3.0	12.8		27	38.6	17.3	1.6	15.2		
1 y	58	46.9	21.7	4.9	13.6		27	41.7	18.1	4.7	15.2		
2 y	58	45.3	21.6	3.3	15.5	0.302	27	38.6	16.6	1.5	12.7	0.969	0.696

BMC indicates bone marrow mononuclear cells; BZ, border zone; IZ, infarct zone; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; and LVESVI, left ventricular end-systolic volume index.

**P* value for trend.

†*P* value for treatment effect.

Cohort Sizes for cMRI and MVO

At baseline, there were 115 patients who had analyzable MVO data; however, of these, only 108 patients also had 6-month cMRI data. Thus, this MVO analysis was conducted solely in patients with 6-month follow-up cMRI data. Of these 108 patients, 60 patients had no MVO on their baseline cMRI scans, whereas 48 patients or 44% had MVO present, a finding similar to that observed in a recent MVO meta-analysis of STEMI patients treated with primary PCI.[11]

MVO Findings

Patients with MVO tended to have lower baseline LVEF (MVO present=42.8±10.3 versus MVO absent=46.5±9.8%; *P*=0.057) and greater LVEDVI (MVO present=80.7±18.4 versus MVO absent=71.2±16.4 mL/m^2; *P*=0.007), LVESVI volumes (MVO present=46.1±13.2 versus MVO absent=38.5±12.5 mL/m^2; *P*=0.003), and infarct size (MVO present=56.5±27.9 versus MVO absent=36.2±19.0 g; *P*<0.001; Online Table I). There was also a marked disparity in the sex of patients with MVO. Only 1 of 11 women had MVO versus 47 of 97 men. MVO was independently associated (*P*=0.003) with the change in LVEF from baseline to 6 months, after adjusting in a multiple regression model for the simultaneous influences of sex (*P*=0.350), baseline LVEF (*P*=0.022), LVEDVI (*P*=0.184), LVESVI (*P*=0.086), and infarct size (*P*=0.279).

Patients with MVO at baseline (n=48) experienced an increase in LVEF at 6 months of only 0.2 versus 6.2 among those without MVO (n=60; *P*=0.003). In addition, patients with MVO present were associated with significantly greater adverse LV remodeling at 6 months versus patients without MVO (Figure 2).

In the 2-year cohort (patients with cMRI at baseline, 6 months, 1 year, and 2 years), 83 patients had analyzable MVO at baseline. At 2 years, patients with MVO (n=35) continued to have reduced LVEF and greater LV volumes and infarct size compared with those patients without MVO (n=48; Table 3). However, the disparity between the groups lessened as patients with larger infarcts had more associated severe LV dysfunction and were not included because of ICD implantation (Figure 3). To our knowledge, this represents the longest cMRI imaging follow-up of patients with MVO in the literature.

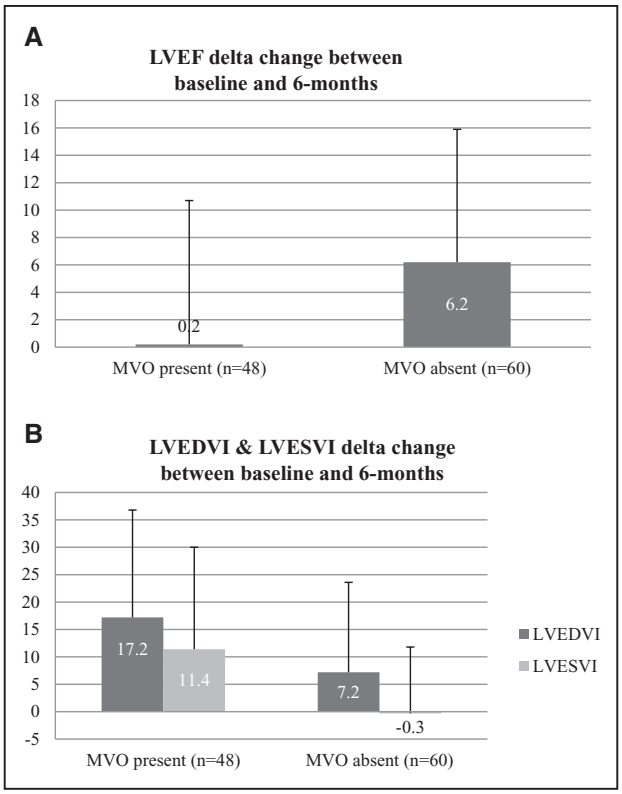

Figure 2. Change in left ventricular (LV) function between baseline and 6 mo stratified by the presence or absence of microvascular obstruction (MVO) at baseline. A, The presence of MVO was associated with little improvement in LV ejection fraction (EF) at 6 mo (0.2 absolute EF units) compared with those patients without MVO (6.2 absolute EF units). **B**, Change in LV end-diastolic volume index (EDVI) and LV end-systolic volume index (ESVI) showed patients with MVO had much greater adverse LV remodeling compared with patients without MVO at 6 mo.

Major Adverse Cardiac Events

Looking at the TIME main trial cohort, at 2 years, a total of 21 patients in the BMC group experienced 28 major adverse cardiac events (protocol-designated major adverse cardiac events), whereas 10 patients in the placebo group had 18 major adverse cardiac events (p=not significant; Online Table II). There were 3 deaths in the BMC group and none in the placebo group; 1 death caused by motor vehicle accident, another because of intracerebral bleed from an intracranial aneurysm before stem cell infusion and a presumed sudden cardiac death in a third patient who was found unresponsive in a parking lot. There were 17 repeat revascularizations (BMC=11; placebo=6) and 7 hospitalizations for heart failure (BMC=5; placebo=2). Notably, of the 10 patients receiving ICDs, 8 had underlying MVO (Online Table III).

Discussion

TIME was the first cell therapy trial sufficiently powered to examine the effect of timing of cell delivery on the recovery of LV function and the first trial to administer the same dose of cells in a network setting using a local, automated cell processing device.[8] TIME[6] was developed in parallel with LateTIME,[7] which investigated whether delayed delivery of cell therapy (2–3 weeks) in a similar STEMI population would also enhance the recovery of LV function. However, both trials individually and combined (ΔLVEF=−1.4±9.5%; *P*=0.967)[12] were notable for the failure of BMCs to improve LV function when measured at 6 months over the improvement observed in patients receiving cell-free placebo. SWISS-AMI (Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction)[13] also independently examined the role of timing of cell delivery in a similar STEMI population. In SWISS-AMI, patients were randomized (1:1:1) to cell delivery on days 5 to 7 versus 3 to 4 weeks compared with a control group. Similar to TIME and LateTIME results, no treatment effect of BMCs on LV functional recovery was detected at 4-month or at 1-year follow-up by cMRI.[13] Our 2-year cMRI follow-up of patients with moderate-to-large anterior STEMIs represents one of the longest serial MRI studies in the literature.

TIME was developed after the findings of REPAIR-AMI (Intracoronary Progenitor Cells in Acute Myocardial Infarction)[2] and BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration)[3] that demonstrated intracoronary delivery of autologous BMCs improved LV function after STEMI. However, since these publications, the results of BMC trials have been mixed. Although several meta-analyses have found a small treatment effect (3%) of BMCs on the recovery of LV function post-STEMI,[14,15] it is notable that this treatment effect seems to disappear when cMRI imaging is used[15,16] or when individual patient data are analyzed.[17]

Table 3. Magnetic Resonance Imaging Analysis of TIME (Timing in Myocardial Infarction Evaluation) 2-Year Cohort Stratified by Presence or Absence of Microvascular Obstruction at Baseline

	MVO Present			MVO Absent			Mean Difference	SE	*P* Value
	n	Mean	SD	n	Mean	SD			*t* test
LVEF to 6 mo									
Baseline	35	44.9	7.8	48	47.3	10.1			
6 mo	35	46.7	9.9	48	54.3	10.6			
Change	35	1.8	9.7	48	7.0	9.5	5.2	9.6	0.018
LVEF to 2 y									
Baseline	35	44.9	7.8	48	47.3	10.1			
2 y	35	46.7	10.4	48	52.1	11.7			
Change	35	1.8	10.7	48	4.8	10.0	3.0	10.3	0.192
LVEDVI to 6 mo									
Baseline	35	80.1	16.8	48	70.2	17.9			
6 mo	35	95.8	23.3	48	76.8	22.8			
Change	35	15.8	15.4	48	6.6	16.0	−9.1	15.8	0.011
LVEDVI to 2 y									
Baseline	35	80.1	16.8	48	70.2	17.9			
2 y	35	91.8	24.8	48	77.5	22.8			
Change	35	11.7	19.9	48	7.3	18.8	−4.5	19.3	0.305
LVESVI to 6 mo									
Baseline	35	44.3	12.4	48	37.5	13.4			
6 mo	35	52.3	20.3	48	36.1	16.6			
Change	35	8.0	13.9	48	−1.4	11.8	−9.4	12.8	0.002
LVESVI to 2 yr									
Baseline	35	44.3	12.4	48	37.5	13.4			
2 y	35	49.6	18.5	48	38.7	20.7			
Change	35	5.3	12.3	48	1.2	16.2	−4.1	14.7	0.191
Infarct size to 6 mo									
Baseline	33	57.4	27.8	48	37.3	19.2			
6 mo	33	38.1	18.2	48	25.2	14.6			
Change	33	−19.3	21.3	48	−12.1	18.7	7.2	19.8	0.121
Infarct size to 2 y									
Baseline	33	57.4	27.8	48	37.3	19.2			
2 y	33	30.8	13.6	48	19.6	12.2			
Change	33	−26.6	19.7	48	−17.7	16.3	8.9	17.8	0.037

LVEDVI indicates left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; and LVESVI, left ventricular end-systolic volume index.

LV Function and Volumes

Both global LVEF and regional LV function in the infarct and border zones increased similarly in the BMC and placebo groups from baseline to 6 months and then remained relatively stable out to 2 years of follow-up with no difference between groups. Much of the initial improvement in LV function could be attributed to the resolution of myocardial stunning that occurs days to weeks after reperfusion. In support of this, in LateTIME, the increase in LVEF between baseline (2–3 weeks) and 6 months was much less than in TIME because of the stipulated difference in the timing of the baseline LVEF (3.2% versus 1.4%). These early changes in LV function after reperfusion highlight one of the limitations of using the change in LVEF as a primary end point in STEMI trials.

The increase in LVEF observed at 6 months is consistent with previous serial imaging studies of STEMI in many noncell therapy trials. Ripa et al[18] performed serial cMRI imaging in 58 patients with STEMI and observed that LVEF increased from 52.9%

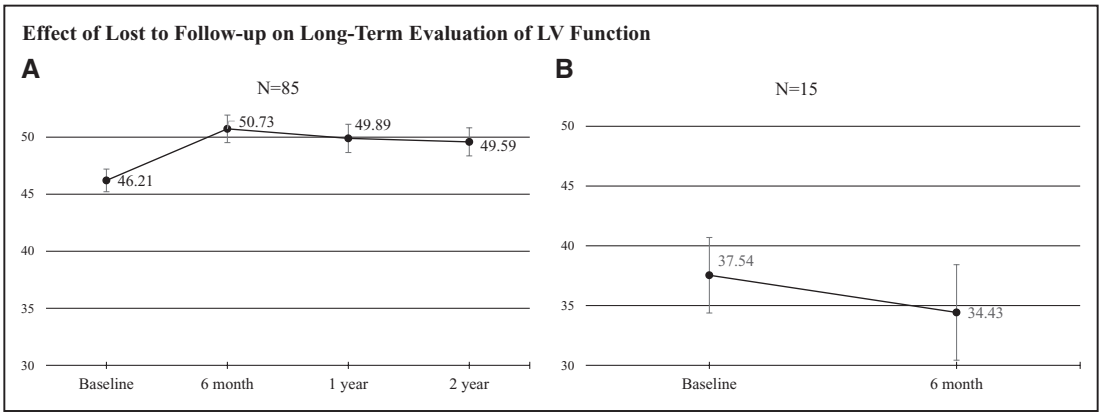

Figure 3. Effect of lost to follow-up on long-term evaluation of left ventricular (LV) function. A, Change in LV ejection fraction (EF) over 2 y in the 2-y cohort. **B**, Change in LVEF between baseline and 6 mo in those patients who completed only the 6-mo cardiac magnetic resonance imaging (cMRI) follow-up and then were lost to follow-up because of death, implantable cardioverter-defibrillator implantation, or MRI contraindication.

to 61.0% at 6 months with the greatest improvement occurring at 1 month (59.4%). Ndrepepa et al[19] measured the change in LVEF in 626 patients after primary PCI over 6 months using LV angiography and observed that LVEF increased from 51.6% to 57.4%. Those patients with the most depressed LVEF at baseline had the greatest recovery of LV function. Similar findings were also observed in the REPAIR-AMI trial[2] and in the combined TIME and LateTIME populations.[12] These modest improvements in LVEF over 6 months in the STEMI patient population could potentially obscure any treatment effect of cell therapy.

Patients in TIME were at risk of developing adverse LV remodeling and heart failure because of relatively large anterior infarctions.[20] However, the changes in LVEDVI and LVESVI were modest over the first year and actually declined slightly between years 1 and 2. This may have contributed to the relatively low incidence of heart failure in TIME (n=7) despite infarctions that averaged 25% of the LV and supports the benefit of the ongoing medical therapy and close observation that these patients received as part of a clinical trial. These small changes in LV volumes over several years were also observed by the ASTAMI (Autologous Stem Cell Transplantation in Acute Myocardial Infarction) investigators between 2 and 3 weeks post-PCI and 3 years by cMRI imaging.[21]

Although cMRI represents an ideal imaging modality for the serial follow-up of infarct size and LV function of STEMI patients in cell therapy trials, it is affected by patient dropout because of clinical events such as device (ICD or left ventricular assist device) implantation, heart transplantation, and death.[22] Because this occurs more frequently in patients with more severe LV dysfunction, it effectively acts to mitigate any decline in EF or adverse LV remodeling of the cohort over time. This may create an impression of overall stability of LV function in the follow-up period. This is reflected in our follow-up data demonstrating that patients who completed only 6 months of MRI follow-up (n=15) because of ICD implantation or other causes had significantly lower LVEFs than the overall cohort at baseline (37.5% versus 46.1%). Furthermore, this subgroup experienced an overall decline in LVEF at 6 months (−3.1%) compared with the improvement in the remainder of the cohort (+4.5%; Figure 3). This issue may arise more frequently as sicker populations of patients are enrolled in cell therapy trials.

Importantly, the CCTRN has recently developed cMRI protocols to permit imaging of patients with ICDs and pacemakers that should help to reduce losses in image acquisition over time.

Infarct Size and MVO

cMRI measurement of infarct size by late gadolinium enhancement has higher reproducibility and lower variability compared with SPECT (single-photon emission computed tomography)[23] and is a strong predictor of adverse outcomes and mortality.[24] Infarct size in TIME patients was large at baseline, averaging 25% of LV mass. However, a marked decline (>30%) was observed in infarct size over 6 months in both groups (Figure 4) with an ongoing small decline out to 2 years. In concert with the reduction in infarct size, a significant and parallel decrease in LV mass was observed. This reduction reflects the ongoing dynamic changes in infarct size that occur over time after reperfusion related to resorption of myocardial edema, adjacent wall thinning, and replacement fibrosis of necrotic myocardium.[25] These findings are similar to those of Ganame et al[25] who also noted a 40% decline in infarct size in patients after STEMI when measured by cMRI at 1 week and 4 months and the 14% decline in LV mass over 1 year in the study of O'Regan et al.[26] To the best of our knowledge, our 2-year MRI follow-up is unique in the literature for its duration of follow-up documenting this ongoing decline in infarct size and LV mass.

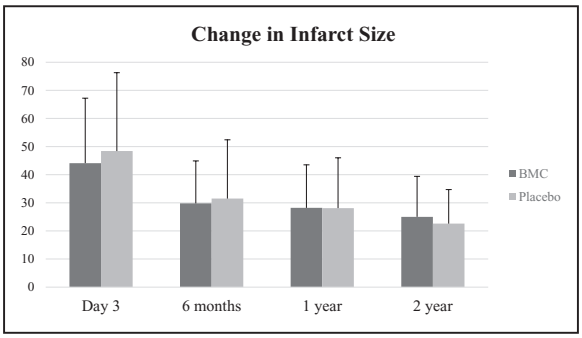

Figure 4. Serial measurement of infarct size (g) by cardiac magnetic resonance imaging **(cMRI) from baseline to 2 y in the bone marrow** mononuclear **cell (BMC) and placebo groups.** Serial measurement of infarct size (g) by cMRI from baseline to 2 y in the BMC and placebo groups.

In the acute period (days), infarct size may increase significantly because of the accumulation of myocardial edema and inflammatory cell infiltration that is accompanied by uptake of gadolinium resulting in an overestimation of irreversible injury. As a result, many LV segments with near transmural late gadolinium enhancement can recover contractile function over time as the transmural extent of late gadolinium enhancement is reduced.[27,28] In support of this concept, recovery of wall motion was observed in many segments in the stipulated infarct zone during the first 6 months of follow-up.

Although T2 imaging was not performed to measure myocardial edema, the baseline MRIs were performed during a period of maximal edema accumulation.[29] Over months, the gradual resorption of the infarct and edema contributes to the observed reduction in infarct size. Thus, cell therapy studies using change in infarct size as a primary end point must be cognizant of these dynamic changes in infarct size.

Late MVO was observed in ≈50% of patients. This is in agreement with other cMRI-based studies when measured several days after STEMI.[11] The presence of MVO was associated with marked reductions in the recovery of LVEF and larger LV volumes at 6 months and is consistent with the findings of a recent MRI-based meta-analysis after myocardial infarction.[30] Although the clinical consequences of MVO over several years measured by MRI have been well described in the literature, ours is the first study to show the long-term consequences of MVO on LV function and volumes by cMRI.[31] Presence or absence of MVO was the most powerful determinant of change in LV function at 6 months irrespective of therapy.

A noteworthy finding was the significant sex difference in MVO prevalence observed in <10% of women versus 50% of the men. A similar finding was observed by others where women had significantly less MVO and greater myocardial salvage than men despite similar ischemic times during STEMI.[32] The mechanism for this sex-related finding is unknown, but it presents an important knowledge gap and potential target for investigation into the cause and prevention of MVO given its adverse effects on LV function demonstrated in this study.

Conclusions

The initial lack of benefit of BMC administration on the recovery of global and regional LV function observed in patients with moderate-to-large anterior STEMI is maintained when measured at 2 years, regardless of day of cell delivery. Importantly, no concerns associated with the safety of using BMCs were observed in this high-risk cohort who demonstrate ongoing stability of LV function and volumes out to 2 years. The presence of MVO was observed in almost half the cohort at baseline and was associated with a significant reduction in the recovery of LV function and adverse LV remodeling and increased need for ICD placement.

Acknowledgments

R.F. Ebert is a staff member of the National Heart, Lung, and Blood Institute (NHLBI), the source of funding for the TIME trial (Timing in Myocardial Infarction Evaluation). The views expressed in this article are those of the authors and do not necessarily represent the views of the NHLBI, National Institutes of Health, or the United States Department of Health and Human Services.

Sources of Funding

This work was supported by grant number UM1 HL087318.

Disclosures

None.

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Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

TIME Trial: Effect of Timing of Stem Cell Delivery Following ST-Elevation Myocardial Infarction on the Recovery of Global and Regional Left Ventricular Function: Final 2-Year Analysis

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Circ Res. 2018;122:479-488; originally published online December 5, 2017;
doi: 10.1161/CIRCRESAHA.117.311466
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571

Supplemental Material

Online Table I. Baseline characteristics of patients stratified by presence or absence of MVO.

Baseline Value	MVO – Absent (N= 60)	MVO – Present (N = 48)	P-Value
Age (years)	58 ± 12	55 ± 10	0.126
Female Sex	10	1	0.021
LVEF (%)	46.5 ± 9.8	42.8 ± 10.3	0.057
LVEDVI (ml/m2)	71.2 ± 16.4	80.7 ± 18.4	0.007
LVESVI (ml/m2)	38.5 ± 12.5	46.1 ± 13.2	0.003
Infarct Size (g)	36.2 ± 19.0	56.5 ± 27.9	< 0.001
Peak CK (IU/ml)	2472 ± 2336	3766 ± 1995	0.005

MVO=microvascular obstruction; LVEF=left ventricular ejection fraction; LVEDVI=left ventricular end diastolic volume index; LVESVI=left ventricular end systolic volume index; CK=creatine kinase

Online Table II. Clinical and safety outcomes from baseline to 2-year follow-up by bone marrow cell (BMC) or placebo group.

Outcomes	Baseline - 2 years	
	BMC (n=79)	**Placebo (n=41)**
Patients	21	10
Deaths	3	
Reinfarctions	2	3
Repeat Revascularizations	11	6
Target Vessel	6	4
Non-Target Vessel	5	2
Hospitalization Heart Failure	5	2
ICD Placements	5	5
Stroke	2	2
Total	**28**	**18**

Online Table III. Clinical and safety outcomes from baseline to 2-year follow-up by presence or absence of MVO at baseline.

Outcomes	Baseline - 2 years	
	MVO Absent (n=60)	**MVO Present (n=48)**
Patients	15	16
Deaths	2	1
Reinfarctions	5	0
Repeat Revascularizations	10	7
Target Vessel	7	3
Non-Target Vessel	3	4
Hospitalization Heart Failure	4	3
ICD Placements	2	8
Stroke	3	1
Total	**26**	**20**