The TIME Randomized Trial: Effect of Timing of Intracoronary Delivery of Autologous Bone Marrow Mononuclear Cells on Left Ventricular Function Following STEMI

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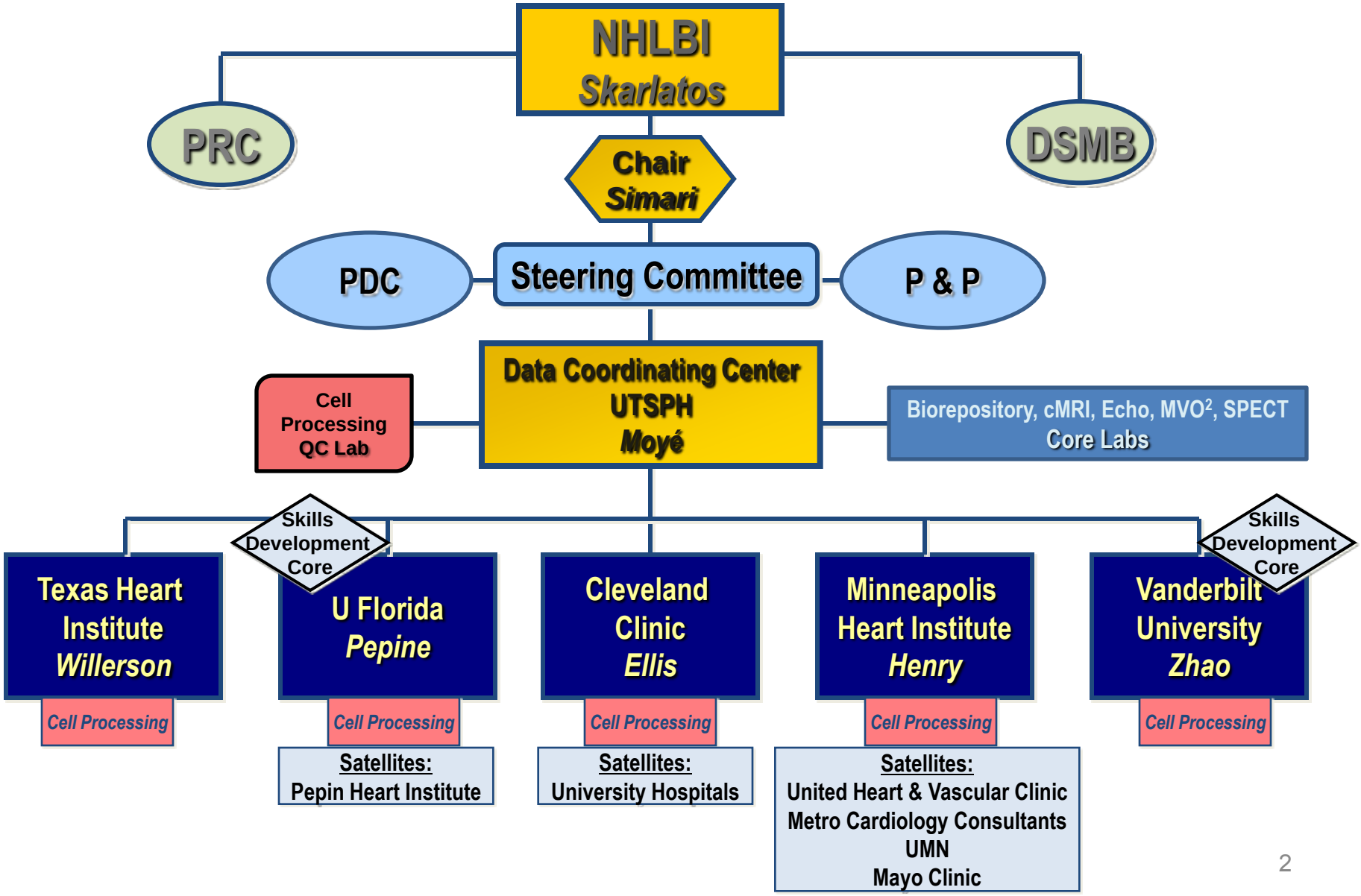
Organizational Structure: NHLBI Cardiovascular Cell Therapy Research Network (CCTRN)



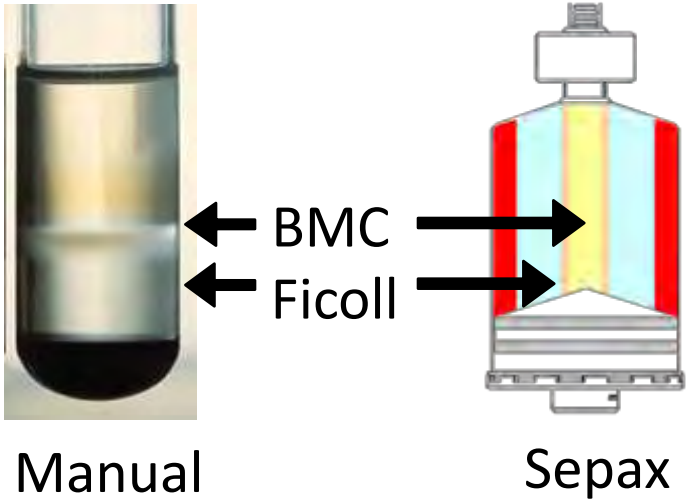
Rationale for TIME

- Optimal timing for cell delivery post-AMI is unknown and has not been directly tested in a prospective clinical trial.
- Biochemical and structural changes in myocardium and bone marrow in first week (cytokines, inflammation, ROS) may create optimal window for cell delivery.
- Almost all BMC trials delivered cells ≤7 days post-AMI.
  - REPAIR-AMI subgroup suggested later delivery preferable to earlier
- LateTIME showed no benefit when BMCs delivered 2-3 weeks post-MI.

TIME Study Design

- **Study Aim:** assess the effect of autologous BMCs and timing of delivery at Day3 vs. Day7 post MI on measures of LV function
- **Target Population:** 120 patients w/first anterior MI, reperfused by PCI + stent, with residual LV dysfunction (EF≤45%)
- **Treatment:** 150 x 10^6 autologous BMCs or placebo delivered by intracoronary infusion (Stop Flow)
- **Primary Endpoints:** change in global and regional LV function from baseline to 6 months by cardiac MRI
- **Secondary Endpoints:** change in infarct size and LV volumes
- **Subgroups:** age, LVEF

Cell Processing



- Local, automated
- Sepax System
  - Automated processing
  - Includes cell washing
  - Closed system
  - Sterile disposable set
- Validated by extensive pre-clinical testing

Sepax vs. Manual Ficoll

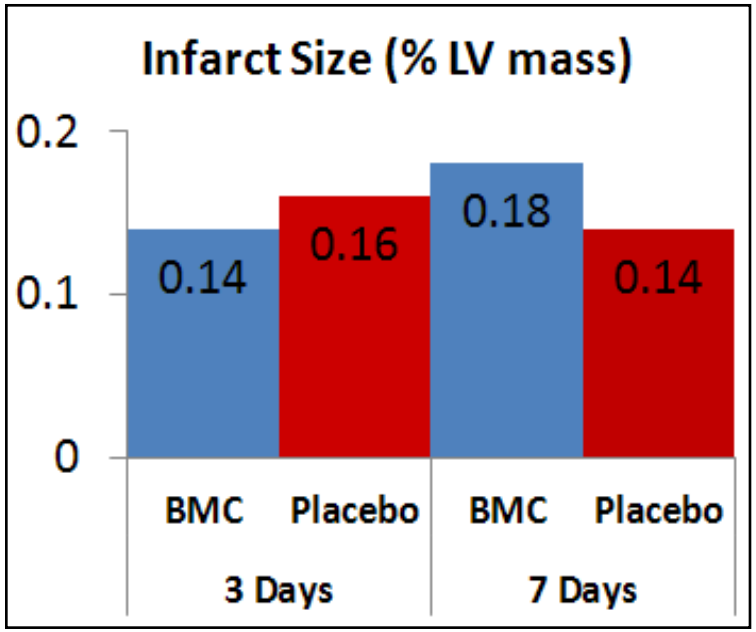
- No difference in cell recovery, migration or CFU ability
- Equivalent perfusion in hindlimb ischemia model

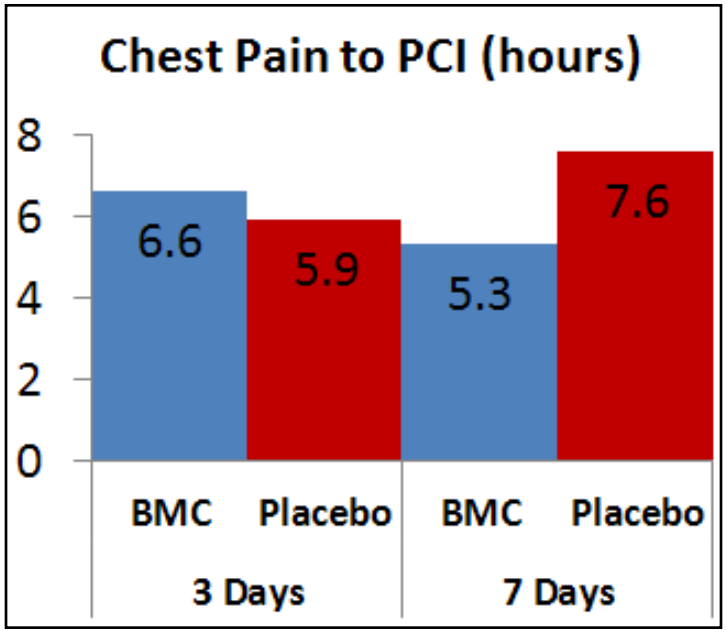
Baseline Characteristics

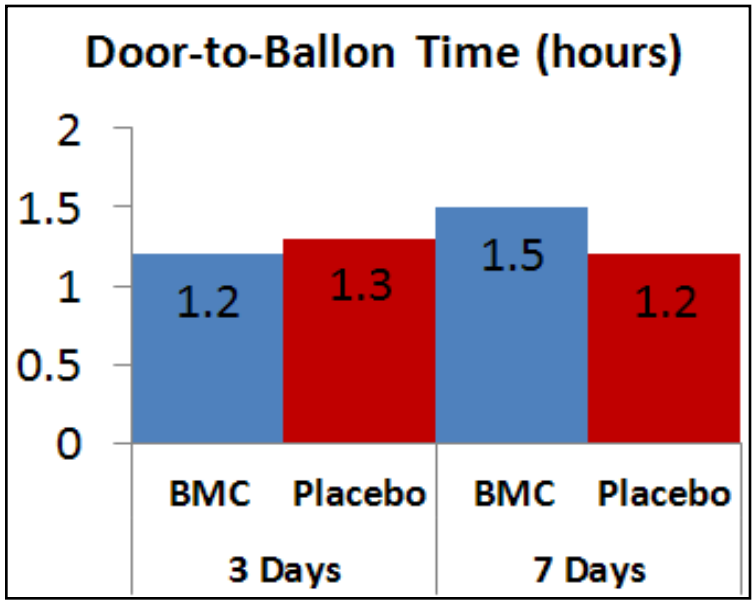
	3 Day		7 Day		
	BMC N=43	Placebo N=24	BMC N=36	Placebo N=17	P-Value
Age in years, mean (SD)	55.6 (10.8)	57.0 (12.4)	58.2 (11.3)	57.0 (8.0)	0.766
Female	12%	13%	14%	12%	0.992
White	88%	83%	86%	88%	0.945
History of:					
Diabetes	23%	33%	11%	0%	0.007
High Blood Pressure	44%	63%	64%	77%	0.087
Hyperlipidemia	65%	63%	69%	77%	0.777
Smoking	65%	71%	53%	65%	0.510
Preinfarction Angina	23%	29%	31%	41%	0.606
Qualifying LVEF (echo), mean (SD)	36.1 (6.1)	37.8 (6.6)	36.5 (6.3)	36.6 (4.1)	0.763
Peak CKMB, mean (SD)‡	200.6 (179.8)	225.8 (206.6)	583.3 (1257.9)	251.6 (184.7)	0.179
Drug Eluting Stent	77%	88%	81%	82%	0.745
Infarct Artery:					
LAD	86%	96%	97%	100%	

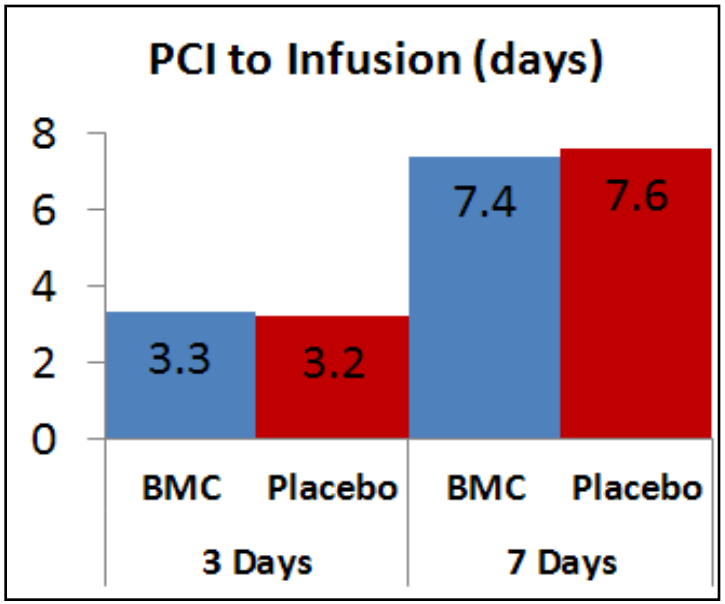
‡N=29 BMC 3 day, N=19 Placebo 3 day; N=31 BMC 7 day, N=15 Placebo 7 day

Infarct Size and Treatment Times









3 Days

BMC (N=43)

Placebo (N=24)

7 Days

BMC (N=36)

Placebo (N=17)

Cell Characteristics

	3 Day BMC N=43	7 Day BMC N=36
Total nucleated cells/product (x10^6), median	150	150
% Viability by Trypan Blue Exclusion,		
Mean (SD)	98.1 (1.7)	98.1 (1.4)
Median (interquartile range)	99 (98-99)	98 (97-99)
% CD34 cells/product, mean (SD)*	2.4 (1.3)	1.6 (0.8)
% CD34+/CD133+ cells/product, mean (SD)*	1.1 (0.7)	0.9 (0.6)
Colony-forming units-Hill/product, mean (SD)‡	300.0 (537.2)	204.0 (216.2)
Endothelial colony-forming cells/product, mean (SD)§	327.9 (575.2)	676.2 (2220.3)

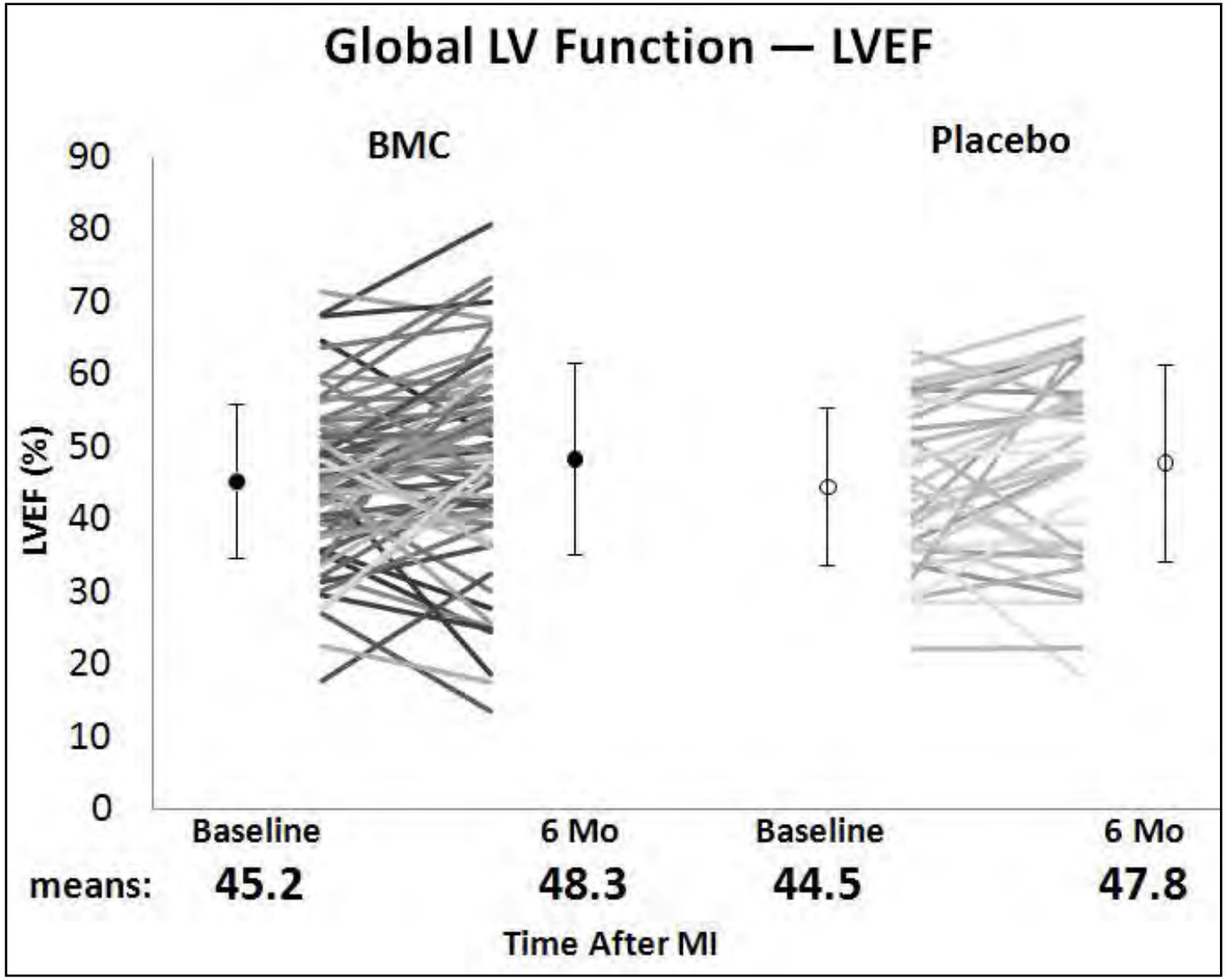
*N=41 BMC 3 day, N=23 Placebo 3 day; N=28 BMC 7 day, N=16 Placebo 7 day

‡N=30 BMC 3 day, N=17 Placebo 3 day; N=25 BMC 7 day, N=11 Placebo 7 day

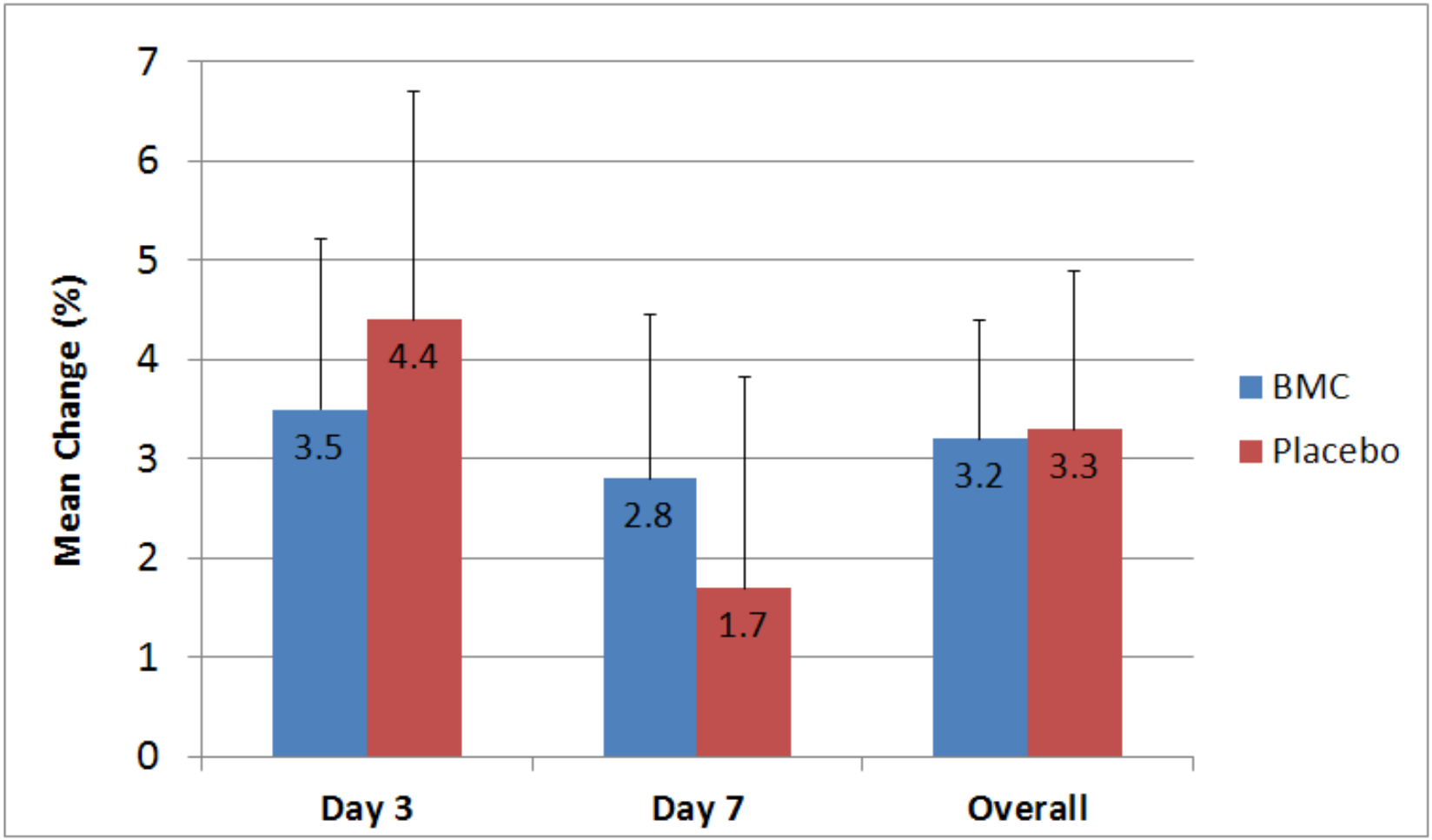
§N=29 BMC 3 day, N=16 Placebo 3 day; N=26 BMC 7 day, N=10 Placebo 7 day

Primary Endpoint: Global

No difference in the change in LVEF between BMC (n=75) and Placebo (n=37) groups from baseline to 6 months



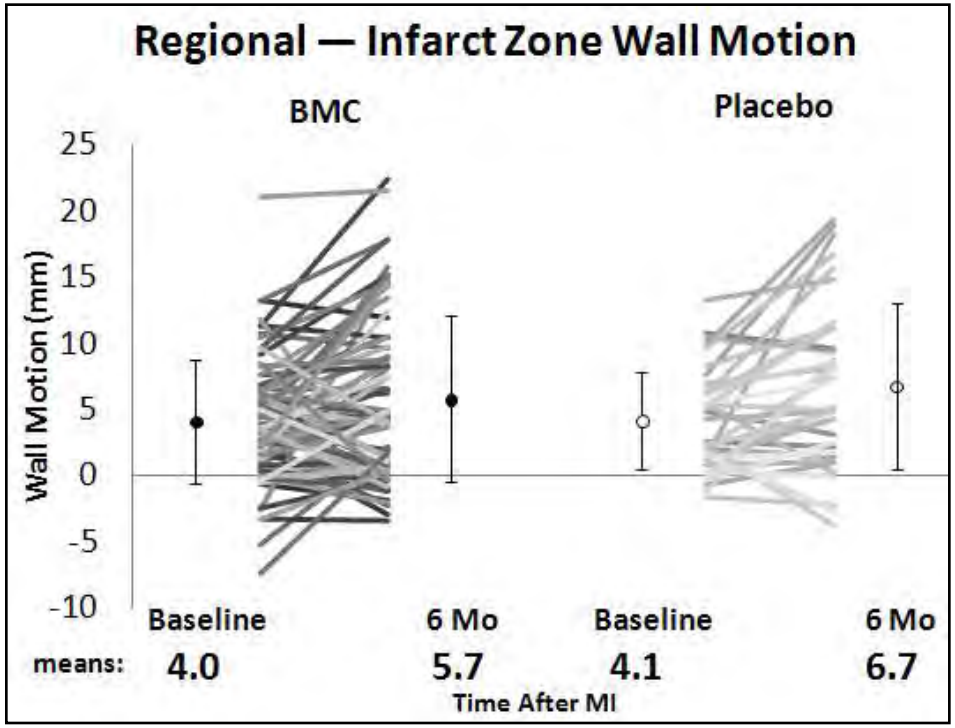
Effect of Delivery Timing on the Change from Baseline to Six Months for LVEF

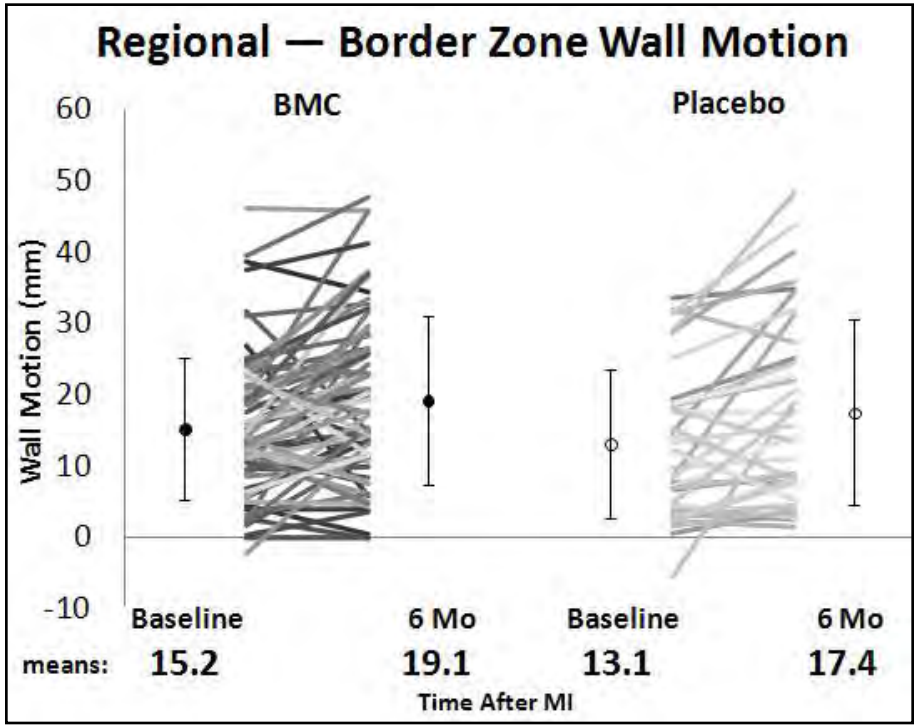


Results for both infarct zone and border zone wall motion were also not significant by therapy group for 3 days, 7 days, or overall.

Primary Endpoint: Regional

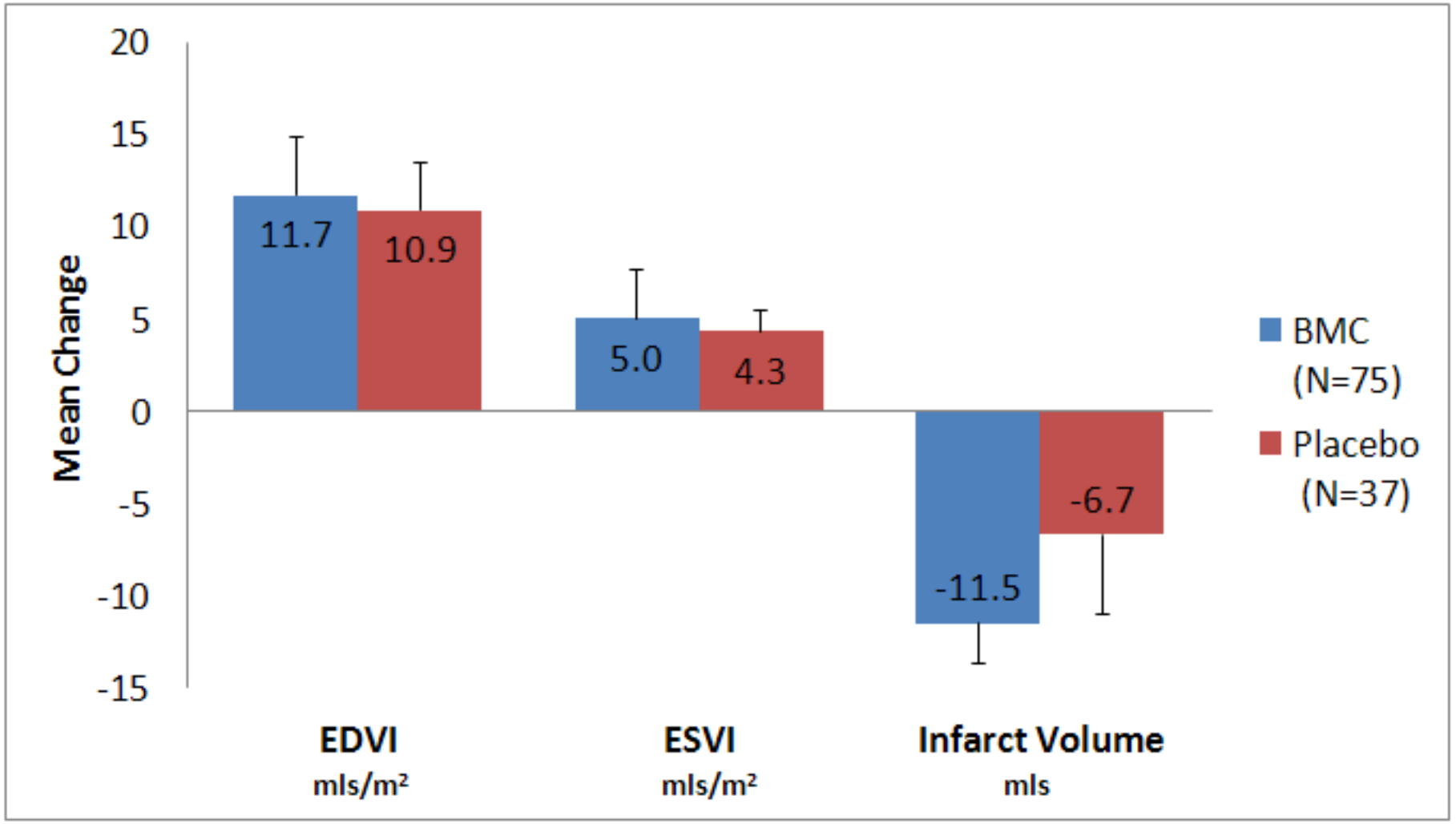
No difference in the change of regional wall motion in the infarct and border zone between baseline and 6 months





Secondary Endpoints:

Infarct Size and LV Volumes



Clinical/Safety Outcomes at 6-month Endpoint Window

	BMC (n=79)	Placebo (n=41)
Deaths	1	
Reinfarctions	1	2
Repeat Revascularizations	7	4
Target Vessel	2	3
Non-Target Vessel	5	1
Hospitalization Heart Failure	4	1
ICD Placements	3	3
Total Events	**16**	**10**
Patients	**13 (16%)**	**7 (17%)**

Conclusions

- Intracoronary delivery of autologous BMCs 3 or 7 days following primary PCI + stenting after moderate to large acute MIs is safe.

- No improvement in global and regional LV function is observed at 6 months by cMRI in response to intracoronary BMC delivery.

- Young patients at Day 7 randomized to BMCs had significant improvement with LVEF compared with placebo.

Acknowledgements

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