PreSERVE-AMI: A Randomized, Double-Blind, Placebo Controlled Clinical Trial of Intracoronary Infusion of Autologous CD34+ Cells (NBS10) in Patients with Left Ventricular Dysfunction Post STEMI

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The PreSERVE AMI Study: Funding Sources and Disclosures

Conflict of Interest Disclosures

- Quyyumi: NeoStem Advisory Board member

Funding Source

- Study funded by NeoStem, Inc.

Background

- **>2600 AMI patients have received intracoronary Infusion of Bone Marrow MNC (BMNC) Post AMI and have had significant improvements in:[1]**
  - Modest improvement in ejection fraction (EF 3 to 4%)
  - Reduction in infarct size and end-systolic volume
  - Reduction in MACE (recurrent AMI, new onset CHF and death)
- **Significant Improvement in cardiac function and reduction in MACE dependent on:[2,3]**
  - Infusion of BMNC 5 or more days post STEMI
  - IRA infusion of higher numbers of CD34+ cells.

1. Rendon E.M. et al Eur Heart J. 2008; 29: 1807-1818. 2. Huikuri H.V. et al Eur Heart J. 2008 29: 2723-2732. 3. Schachinger V. N Eng J Med 2006; 355: 1210-1221. 4. Cao F. et al Eur Heart J 2009: 30: 1986-1994. 5. Jeevanantham V et al. Circulation 2012;126:551-568

CD34+ cell infusion after ST elevation myocardial infarction is associated with improved perfusion and is dose dependent

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- Phase I study
- Patients: Randomized to autologous bone marrow harvest (n=16) or placebo (n=15).
- $CD34^+$ cells infused intracoronary at a median of 8.3 days after coronary stenting for STEMI
- 3 dose levels (5, 10 and 15 x 10^6 cells)

The phase I study provided initial evidence of feasibility and safety and suggested a threshold dose of 10 million CD34 cells for bioactivity

Quyyumi AA et al; Am Heart J. 2011 Jan;161(1):98-105.

PreSERVE Study Design

Phase II, double-blind, randomized, placebo-controlled

Safety and Efficacy Trial of CD34 cells (NBS10) following Acute STEMI

- NBS10 is a formulation of autologous CD34+ cells which enhances and preserves functional CXCR4 expression
- 160 subjects randomized 1:1 to receive intracoronary autologous CD34+ cells (NBS10) or matching placebo (cell diluent) 6 and 11 days after stent placement

PreSERVE Sites

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Alejandro Vasquez	Heart Center Research
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Barry Bertolet	Cardiology Associates Research LLC
Majid Qazi	Detroit Clinical Reseach Center PC
Paul Huang	Swedish Medical Center

PreSERVE: Eligibility

INCLUSION CRITERIA

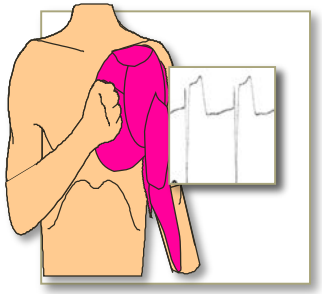
- Acute ST elevation myocardial infarction.
- Stenting within 3 days of chest pain
- LVEF ≤48% by CMR or≤45% by SPECT after 4 days
- Wall motion abnormality associated with the target lesion
- NYHA heart failure class I, II or III.

EXCLUSION CRITERIA

- STEMI > 4 days before stenting.
- Cardiogenic shock
- Severe aortic stenosis.
- Re-occlusion of the infarct related artery (IRA) prior to the infusion.
- Planned revascularization during the next 6 months.

PreSERVE: Study Protocol

1. Patient presents with chest pain + STEMI



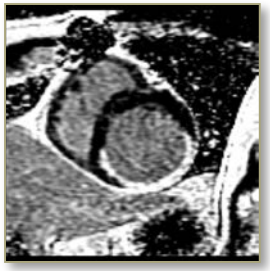
Day 1

2. Stenting and usual medical Rx

Day 1 - 3

3. Enrolled if EF ≤ 48%

CMR

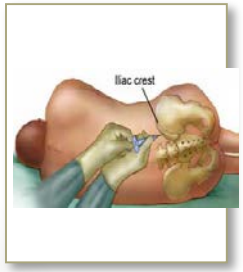


Day 4

4. Patient randomized to Treatment or Control

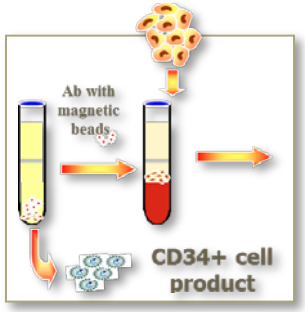
Day 4

5. Patient Bone Marrow Harvested



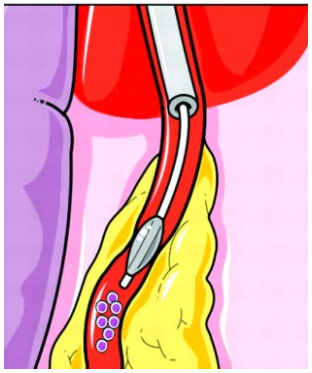
Day 4-9

6. $CD34^{+}CXCR4^{+}$ immunomagnetic separation



Day 5-10

7. Intracoronary injection: CD34+ Cells/Placebo



Day 6-11

8. MACE and Cardiac function measures by SPECT MPI, CMR

- SAE, MACE
- RTSS
- LVEF

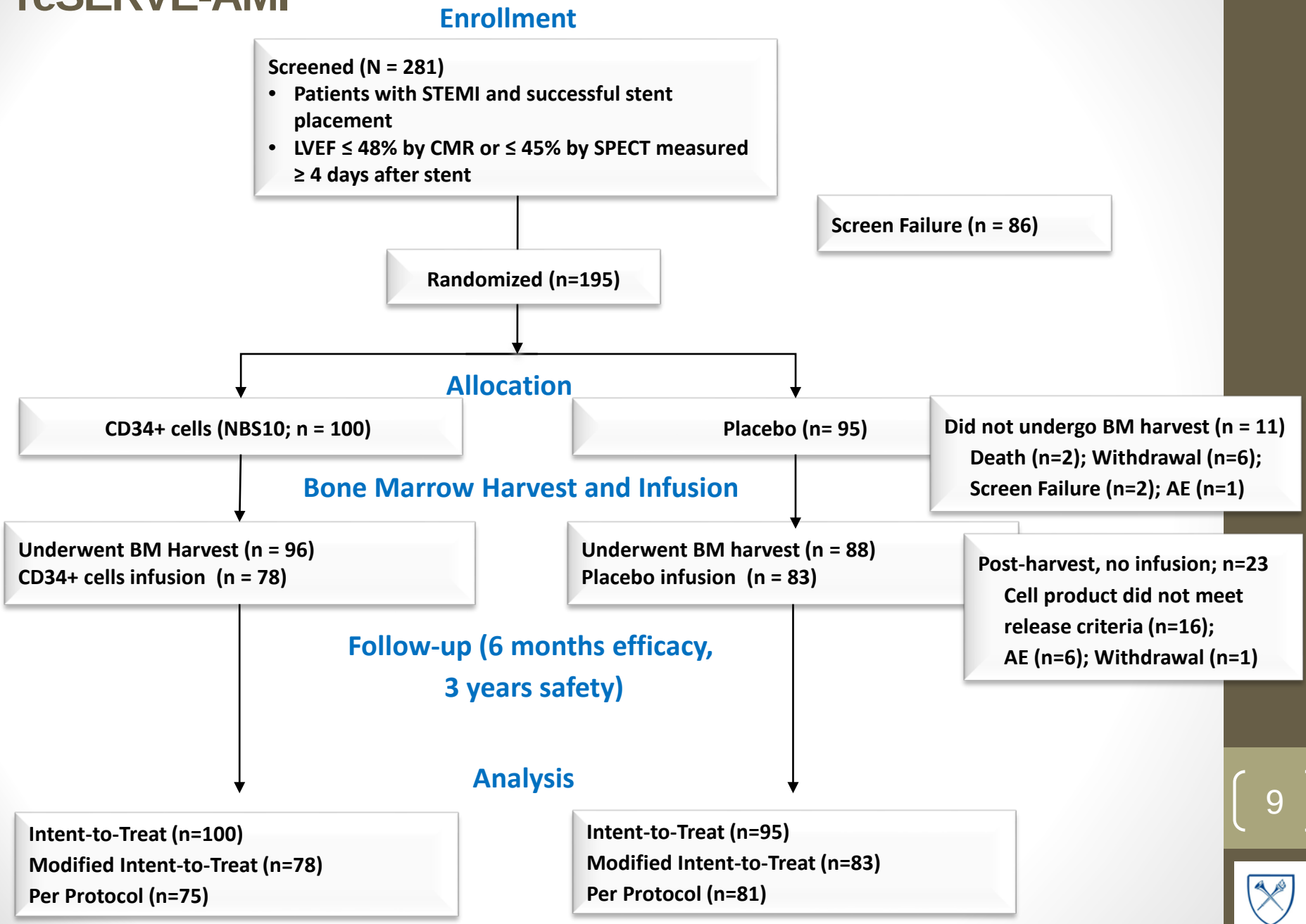
6 Months

9. MACE

- Mortality
- AMI
- Admission for CHF
- Vascular events

12, 18, 24, 36 Months

PreSERVE-AMI



Study Endpoints

- **Primary Endpoints**
  - MACE (cardiac death, recurrent MI, heart failure hospitalization, coronary revascularization) through 3 year follow-up
  - Serious Adverse Events (SAEs) through 3 year follow-up
  - 6 month change in myocardial perfusion (RTSS) measured quantitatively by gated SPECT MPI
- **Secondary Endpoint**
  - 6 month change in left ventricular ejection fraction (LVEF)

Baseline Characteristics

	Treated NBS10 (N=78)	Placebo (N=83)	P-value*
Demographics			
Age; mean ± SD	57.1 ± 10.1	56.4 ± 10.1	0.65
Female; n (%)	12 (15%)	17 (20%)	0.4
Race; White, n (%)	56 (72%)	62 (75%)	0.87
CV Risk Factors			
Hypertension (%)	53 (68%)	56 (67%)	0.80
Diabetes (%)	27 (35%)	19 (23%)	0.1
Hyperlipidemia (%)	13 (17%)	17 (20%)	0.82
NYHA Class*; mean ± SD	1.8 ± 0.6	1.9 ± 0.7	0.59
CV Medical History			
Prior CABG; n(%)	2 (3%)	2 (2%)	0.95
Prior PCI; n(%)	15 (19%)	15 (18%)	0.85
Prior CHF; n(%)	11 (14%)	11 (13%)	0.88
Prior MI; n(%)	13 (17%)	15 (18%)	0.34
Index AMI/PCI			
Infarct size (grams); mean ± SD	33.8 ± 17.4	38.6 ± 19.5	0.16
Pre-discharge LVEF (%); mean ± SD	34.3 ± 7.3	34.1 ± 8.4	0.90
LVEDV index; mean ± SD	98.0 ± 25.6	91.9 ± 20.8	0.12
LVESV index; mean ± SD	61.2 ± 23.6	58.5 ± 19.9	0.46
Time from symptoms to stent (min); mean ± SD	**931 ± 1277**	**569 ± 864**	**0.041**
Time from stent to infusion (days); mean ± SD	9.3 ± 1.23	9.4 ± 1.43	0.60

*P-values for quantitative characteristics are based on a t-test. P-values for categorical characteristics are based on a Chi-square test.

PreSERVE-AMI: Bone Marrow Aspiration and Cell Product

- Bone marrow aspirated: 388±18 ml
- CD34+ cell yield: Range 20 to 100 million
- $CD34^{+}$ cells infused: mean 14.9±8 (range 8 to 40) million

Overall Safety
Bone Marrow Harvest and Infusion

Harvest (n=184)	**Treated**	**Placebo**	**Total**	**P-value***
Serious Adverse Event	5 (5.2%)	3 (3.4%)	8 (4.3%)	0.42

Infusion (n=161)	**Treated**	**Placebo**	**Total**	**P-value***
Serious Adverse Event	7 (9%)	7 (8%)	14 (9%)	0.90

**P-value reflects a chi-square test*

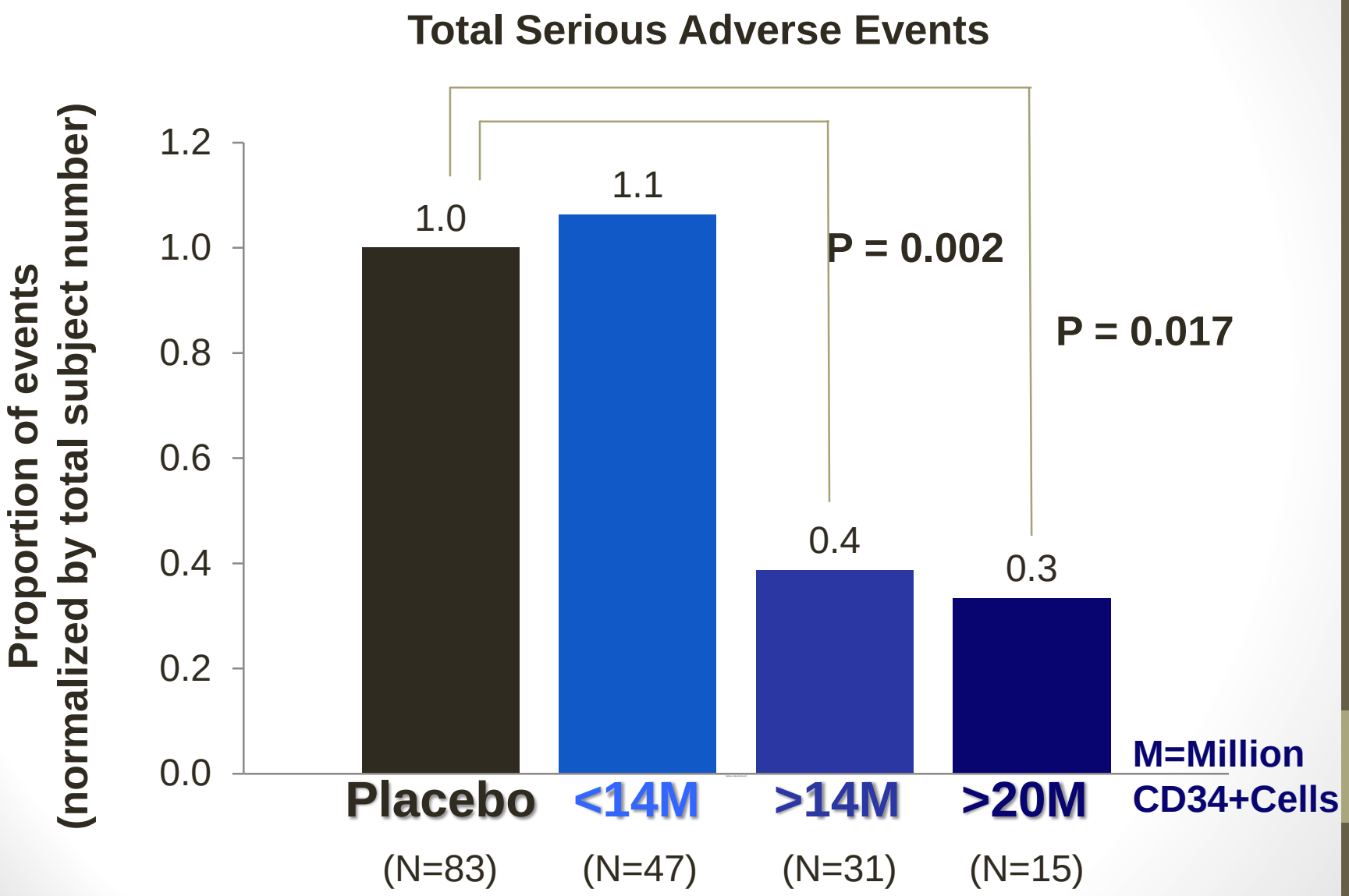
Primary Endpoint: Adverse Events

Follow-up period
(median 12 months)

	Treated (N=78)	Placebo (N=83)	Total (N=161)	P-value*
Adverse Event	49 (63%)	53 (64%)	102 (63%)	0.89
Serious Adverse Event	28 (36%)	30 (36%)	58 (36%)	0.97

**P-value reflects a chi-square test*

Primary Endpoint: Serious Adverse Events CD34+ Cell Dose-Dependent Reduction



P-values comparing groups of NBS 10 treated subjects to placebo subjects is based on a Poisson regression model

Mortality and Overall MACE

MACE= Death, MI, CHF Hospitalization, Revascularization

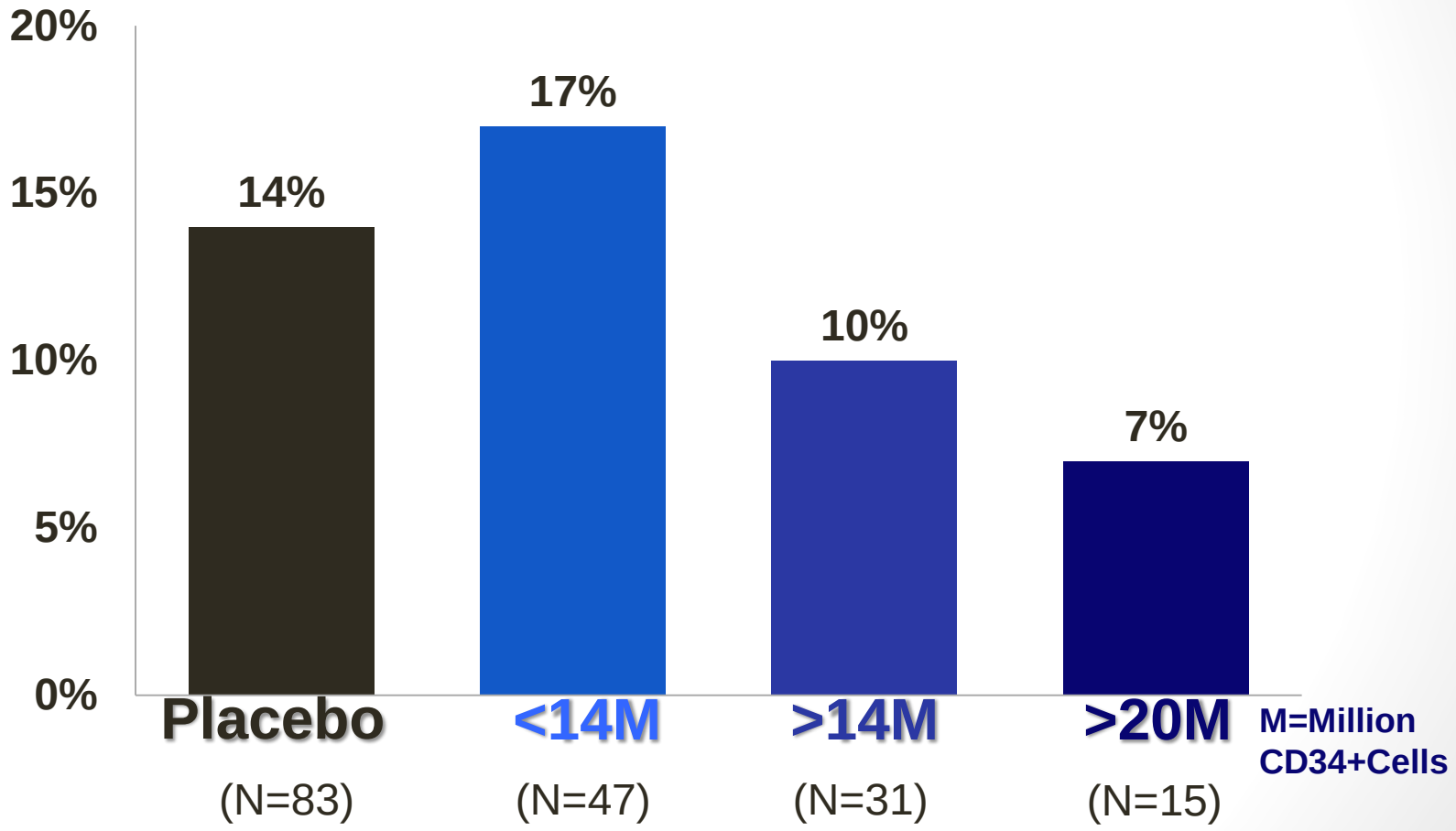
Infusion through last follow-up visit

	Placebo	Treated (NBS10)	p-value*
Death	**3 (3.6%)**	**0 (%)**	**0.04**
Total MACE	**14 (16.9%)**	**15 (19.2%)**	**0.66**

Subjects with MACE through 6 month follow up of last patient; P-value reflects a z-test **P-value reflects a z-test of the null hypothesis of no difference in mean number of total events against the alternative that treatment group subjects experience fewer total events on average compared to controls.

CD34+ Cell Dose-Dependent Reduction in MACE Incidence

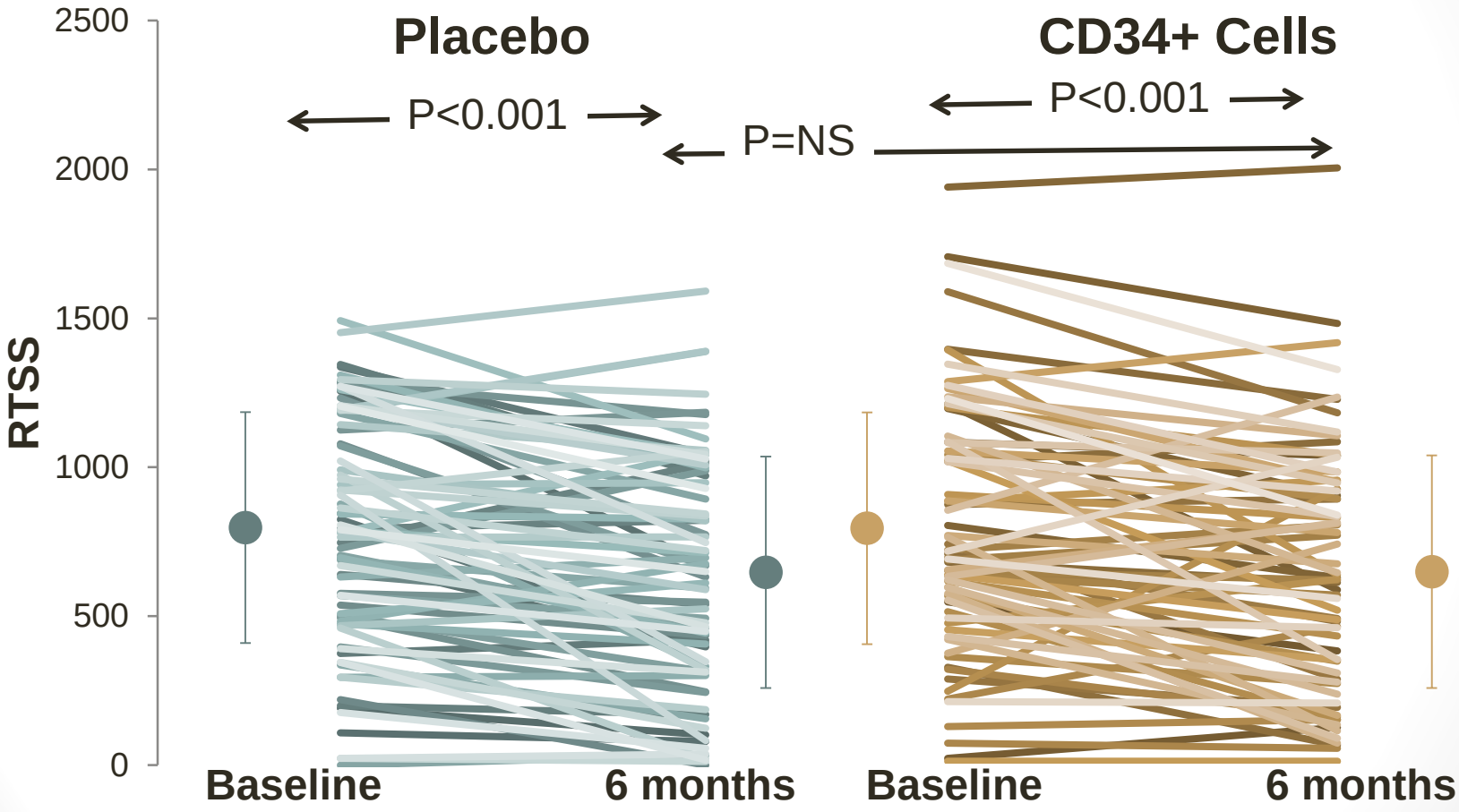
MACE= Death, MI, CHF Hospitalization, Revascularization



1 week post-infusion through last f/u visit.

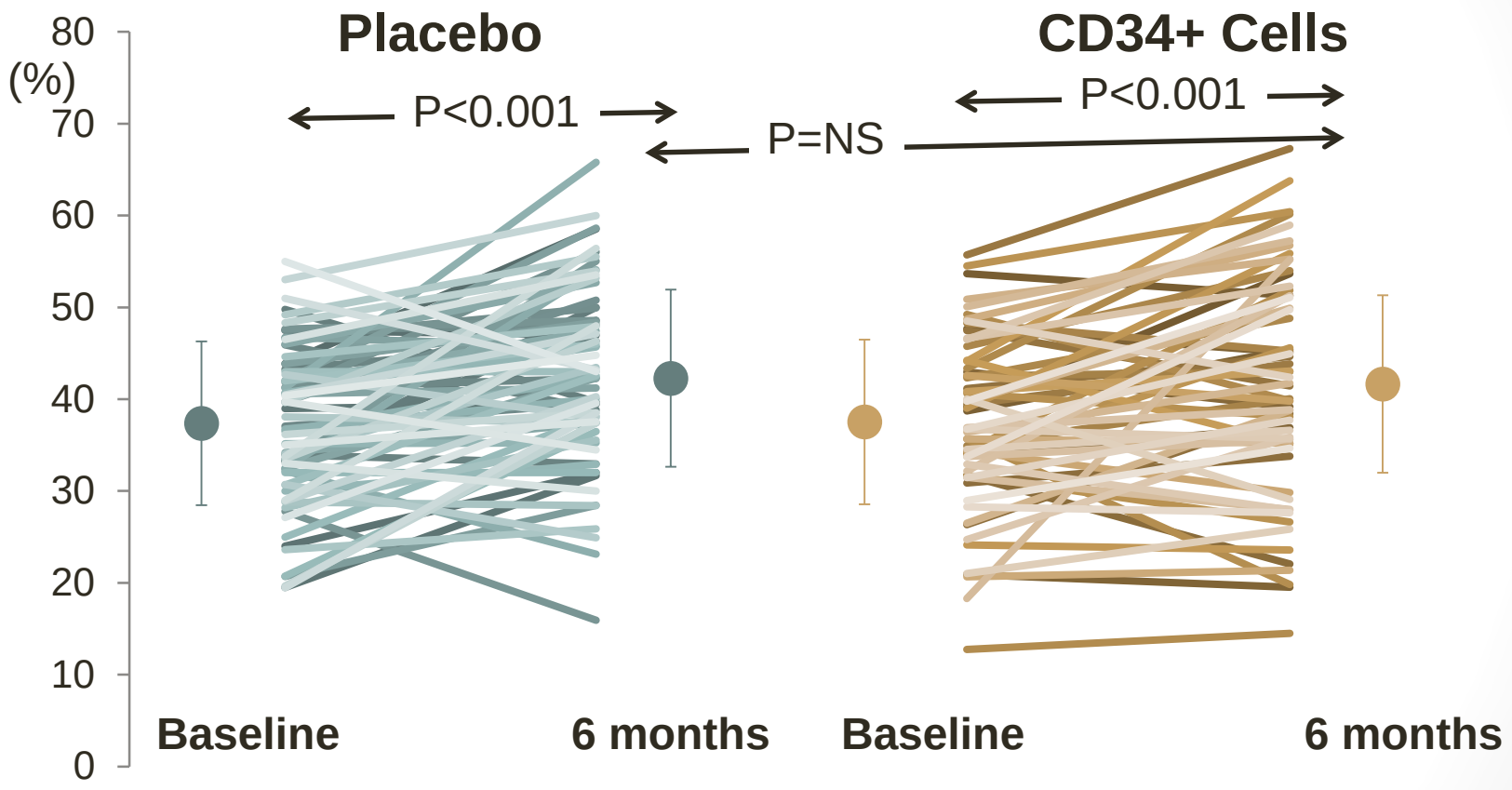
Perfusion:

SPECT Resting Total Severity Score (RTSS)



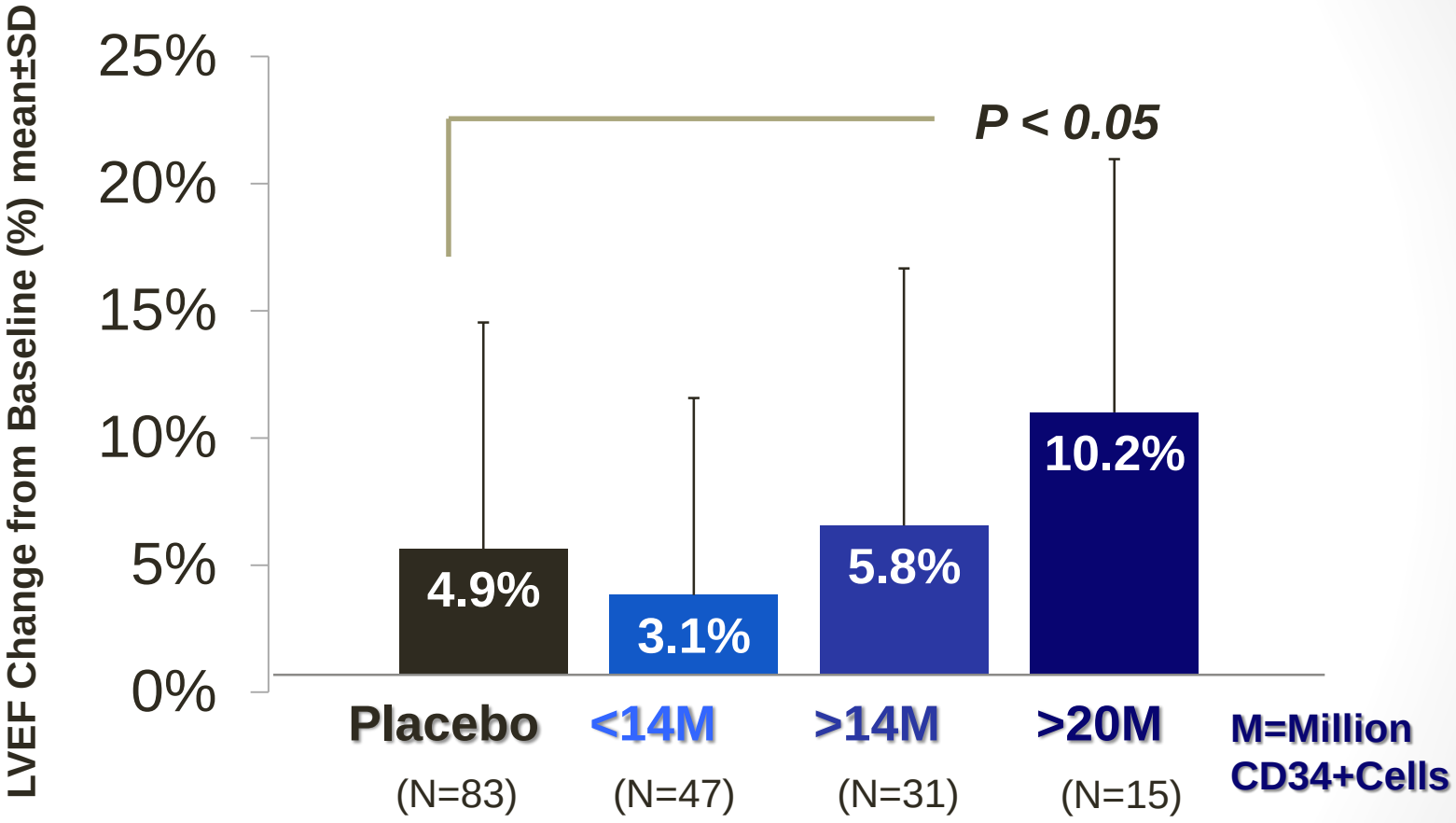
	Placebo	CD34+ cells	P Value
RTSS Mean Change from Baseline (±SD)	-149.6 ± 221.16	-142.7 ± 257.80	NS

Left Ventricular Ejection Fraction



	Placebo	CD34+ cells	P Value
LVEF Mean Change from Baseline (±SD)	4.9 ± 8.8	4.1 ± 8.7	NS

CD34+ Cell Dose-Dependent Increase in LVEF Change from Baseline



Multiple regression model with change in LVEF modeled as a function of time from pain to stent and infused CD34+ cell dose.

Parameter	Parameter Estimate (SE)*	P-Value*
Infused CD34+ Dose**	2.21 (1.084)	0.045

Conclusions

- Intracoronary administration of autologous CD34+ cells (NBS10) is
  - Safe and well tolerated
  - Associated with a statistically significant reduction in mortality
  - Associated with a statistically significant, dose-dependent reduction in SAE's
  - A dose dependent numerical reduction in MACE events
  - Associated with no change in myocardial perfusion
  - Associated with a statistically significant dose-dependent increase in LVEF

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