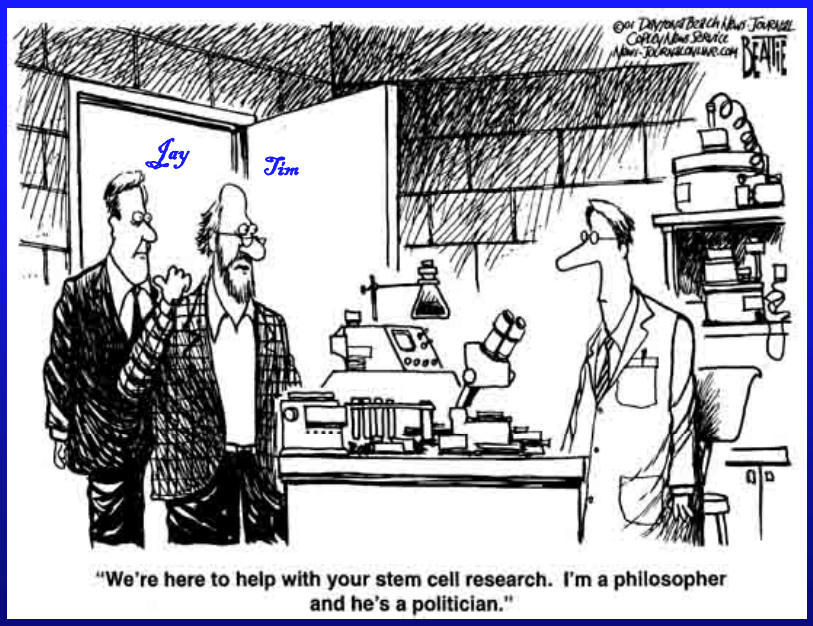
Stem Cells:
The Dawn of a New Era

Tim Henry, MD
Director of Research
Minneapolis Heart Institute Foundation

Minneapolis Heart Institute Foundation™
Creating a world without heart disease™



"We're here to help with your stem cell research. I'm a philosopher and he's a politician."

Too Much Controversy!

Too Much Hype!

Which Cell is the BEST Cell?

Cell Therapy

- Embryonic stem cells
- Cord blood stem cells
- Adult stem cells
  - Circulating
  - Bone marrow
    - Hematopoietic
    - Mesenchymal
  - Tissue specific
    - Fat, Muscle, etc

Cardiovascular Disease Targets

- Refractory angina
- Acute myocardial infarction
- Congestive heart failure
  - Ongoing ischemia
  - Previous MI
  - Nonischemic
- Peripheral arterial disease
  - CLI
  - Claudication

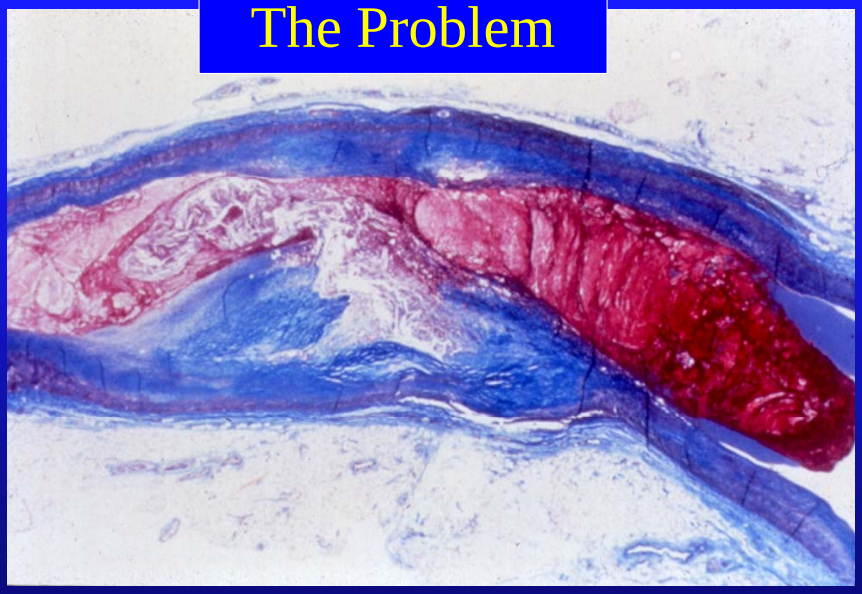
How do Cells Work?

- Cell as a *cell*
- Cell as a *factory*
- Cell as a *courier*

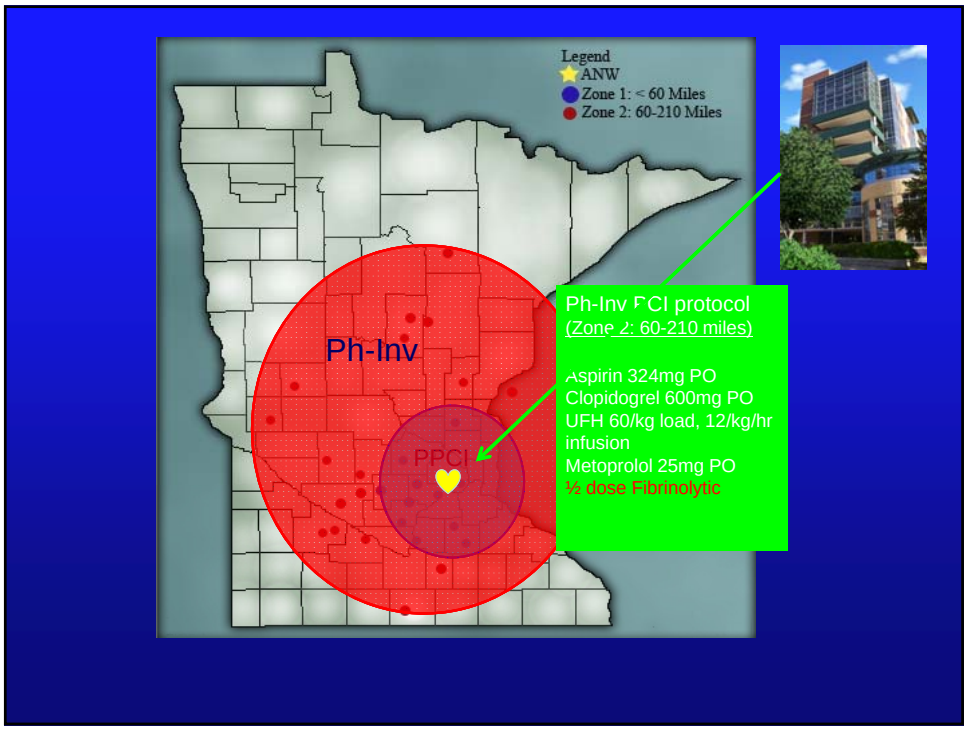
Will Stem Cell therapy play a key role in the Prevention and Treatment of CHF post-MI?

- Acute:
  - STEMI
- Chronic:
  - Ischemic Cardiomyopathy
    - With ongoing Ischemia: Hibernating Myocardium
    - Without Ischemia: SCAR

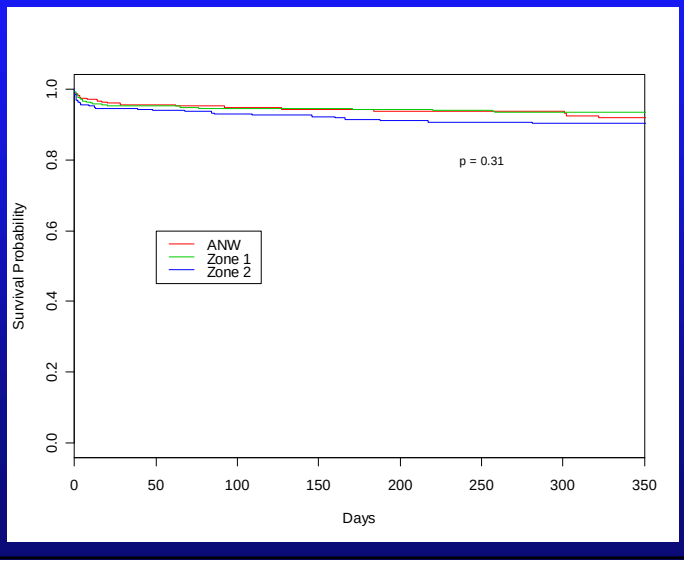
The Problem




The Solution
Artery
CLEANERS
1
HOUR


Legend
ANW
Zone 1: < 60 Miles
Zone 2: 60-210 Miles
Ph-Inv
PPCI
Ph-Inv PCI protocol
(Zone 2: 60-210 miles)
Aspirin 324mg PO
Clopidogrel 600mg PO
UFH 60/kg load, 12/kg/hr infusion
Metoprolol 25mg PO
½ dose Fibrinolytic

Kaplan-Meier Survival Curve



MHI Level 1 STEMI results

1 year cardiovascular mortality < 6%

- Early 1/3 card shock, anoxic brain injury, arrythmia
- Late mortality noncardiac, CHF rare

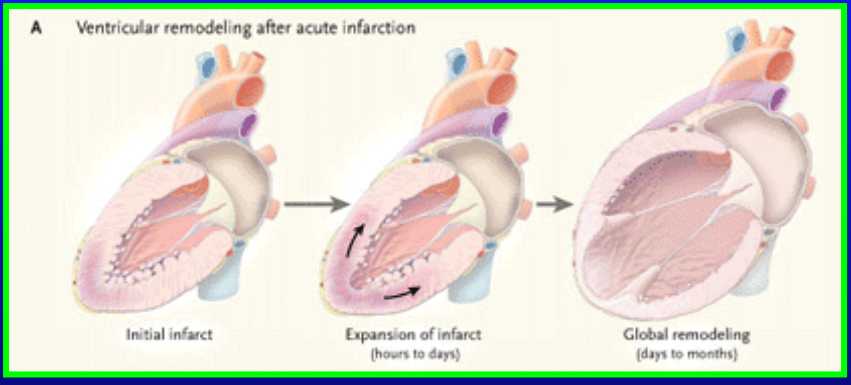
Persistent LV dysfunction/need for AICD < 3% at 1 year

Readmission rate at 1 year 10% majority elective, CHF admissions <2%

STEMI:
Is there a role for stem cells?

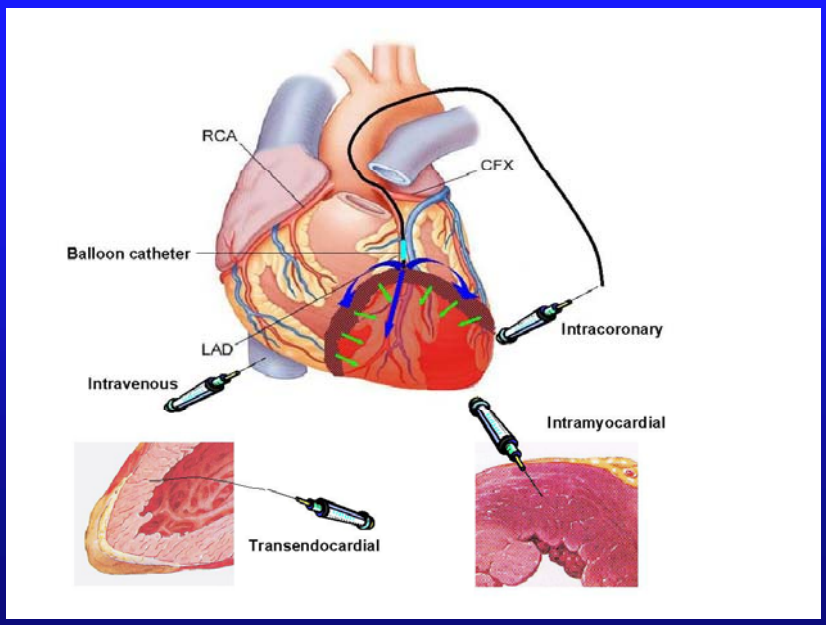
Yes, when the Horse is out of the Barn!!

Ventricular Remodeling After Myocardial Infarction



NEJM 2003;348(20):2011

Transplantation Pathways of Bone Marrow Cells



Strauer & Kornowski, Circulation 2003;107:929-934

REPAIR-AMI Team

Hamburg
Mathey

Bad Oeynhausen
Horstkotte / Farr

Lippe-Detmold
Tebbe / Cueno

Bochum
Mügge / Germing
☆ **Echo Core Lab**

Giessen
Hölschermann

Bad Nauheim
Hamm / Elsässer
Dill
☆ **MRT Core Lab**

Mainz
Münzel / Horstick

Homburg / Saar
Böhm / Nickenig

Ludwigshafen
Senges / Mark

Mannheim
Haase / Süsselbeck

Zürich
Lüscher / Corti

Berlin
Rutsch

Suhl
Haberbosch

Bad Berka
Lauer

Leipzig
Hambrecht / Schuler / Erbs
☆ **Doppler Core Lab**

Frankfurt / Rotes Kreuz
Haase

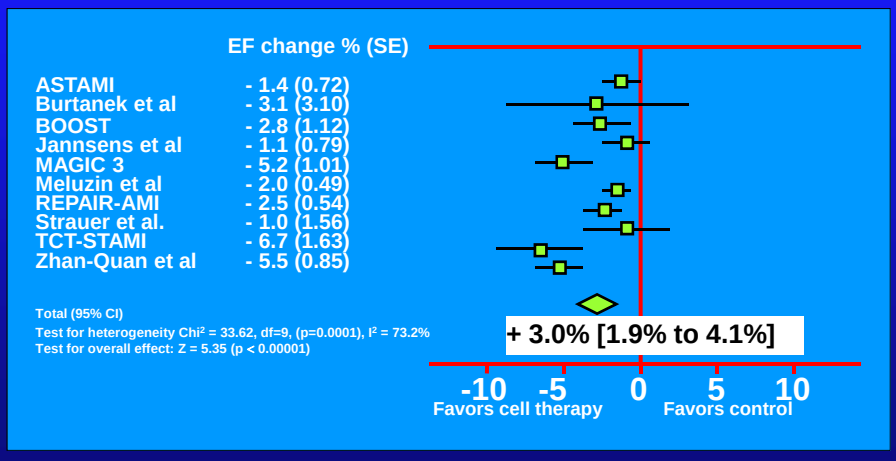
Frankfurt / J. W. Goethe Uni
Zeiher / Schächinger
Dimmeler / Martin
☆ **Coordination / Angio Core Lab**

BSD Hessen
Tonn / Krzossok / Seifried
☆ **Cell Processing Center**

Outcomes	Placebo	BM Cell	p
Change EF			
Overall	3.0 +/- .7	5.5+/- .7	0.014
EF <49%	2.5	7.5	0.002
EF >49%	3.7	4.0	0.81
≥ 5 days	1.9	7.0	0.004
<5 days	3.9	4.5	0.62
Death	2	0	
MI	5	0	
CHF	2	0	
Revasc	28	19	
Death/MI/revasc	30	21	0.17
Death/MI/CHF	9	2	0.03

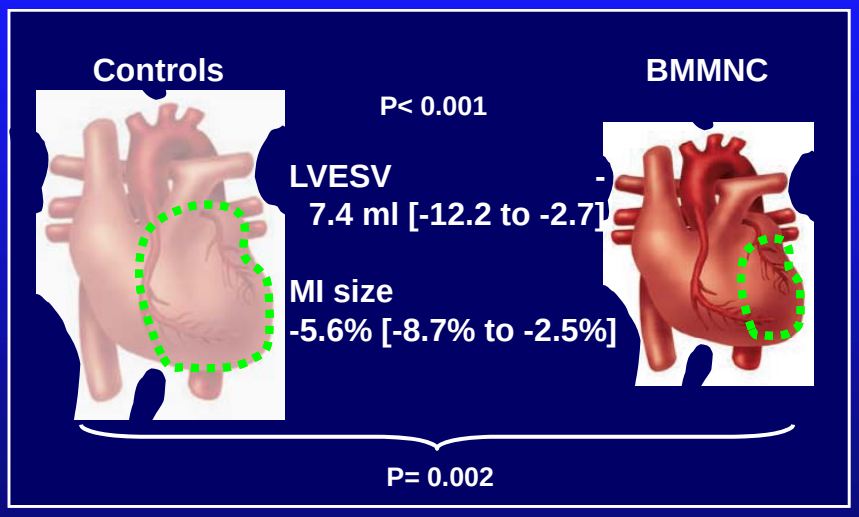
Schachinger NEJM 2006;355:1210-1221

Ejection fraction change



Lipinski, JACC 2007;50:1761

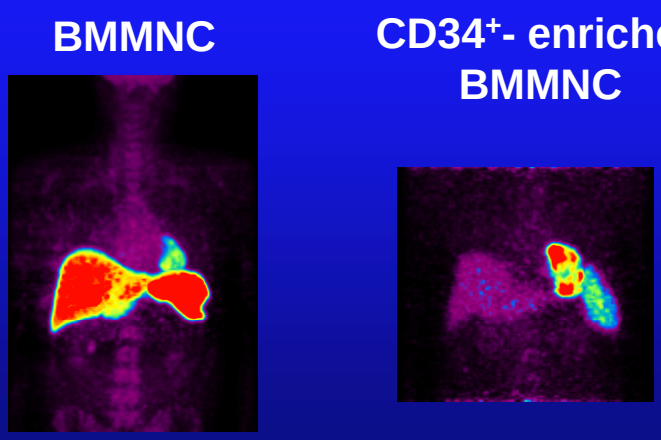
LVESV and MI size



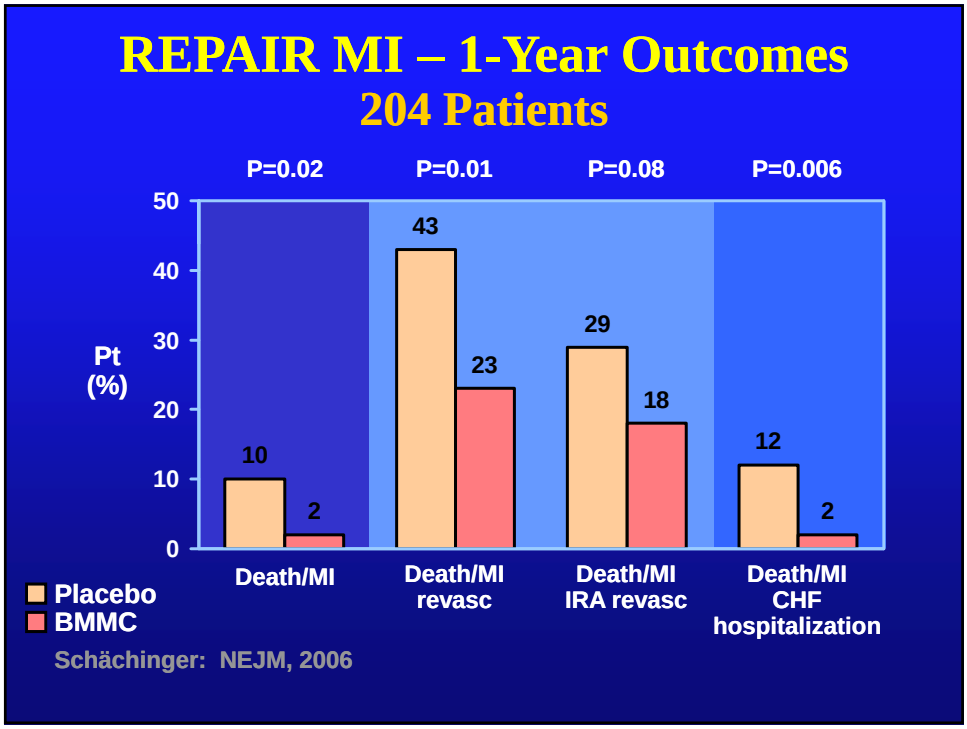
Lipinski, JACC 2007;50:1761

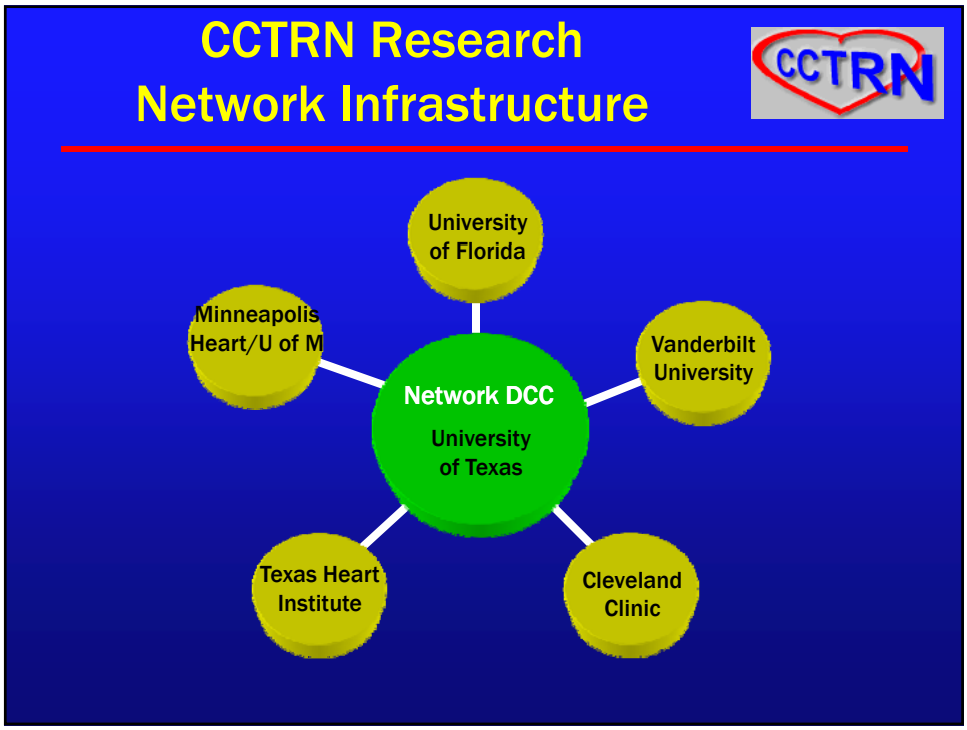
Cells labeled with ^{18}F-FDG

3d-PET imaging 75 minutes post injection



Circulation 2005;111:2198


REPAIR MI – 1-Year Outcomes
204 Patients
P=0.02
P=0.01
P=0.08
P=0.006
Pt (%)
50
40
30
20
10
0
10
2
43
23
29
18
12
2
Death/MI
Death/MI revasc
Death/MI IRA revasc
Death/MI CHF hospitalization
Placebo
BMMC
Schächinger: NEJM, 2006


CCTRN Research
Network Infrastructure
CCTRN
University of Florida
Minneapolis Heart/U of M
Vanderbilt University
Network DCC
University of Texas
Texas Heart Institute
Cleveland Clinic

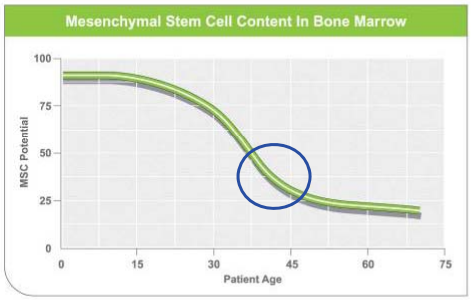
AMI Cell therapy

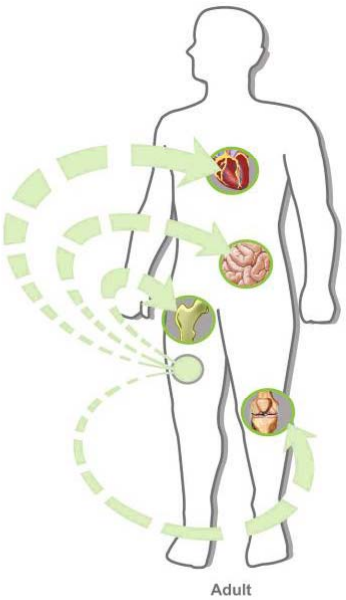
- Alternative cells
- Allogeneic cells
- Alternative methods of delivery

The Mesenchymal Stem Cell

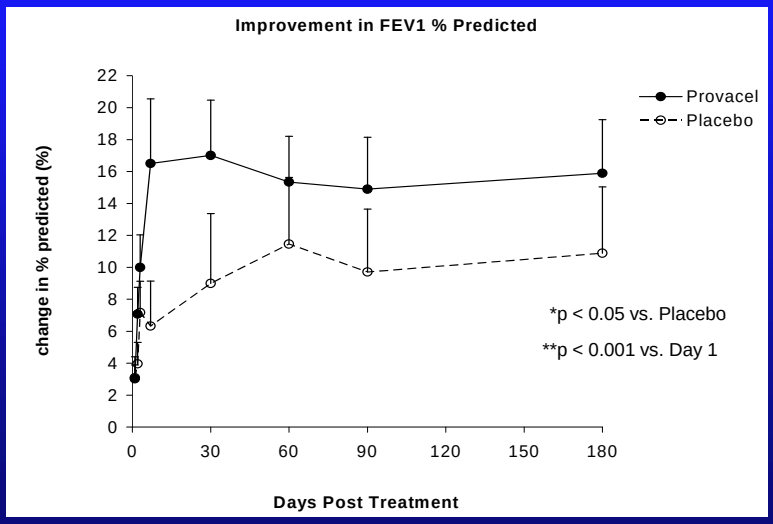
As we age, the number declines.

Older people do not heal as well.

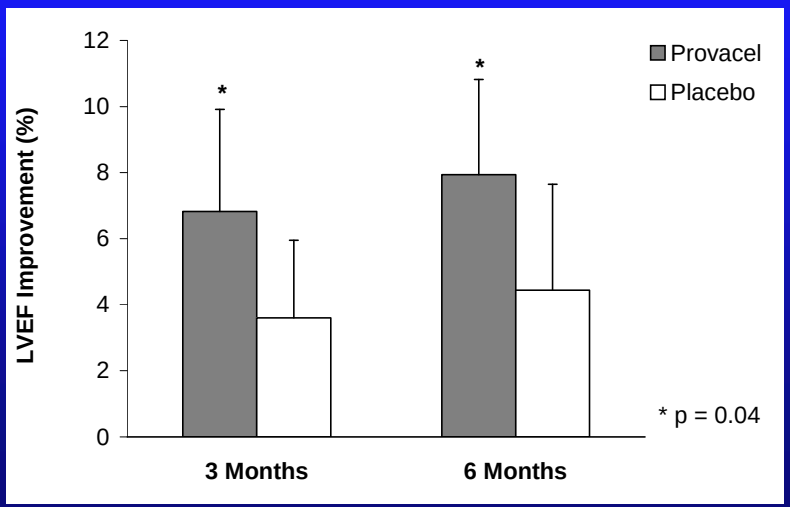




Pulmonary Improvement



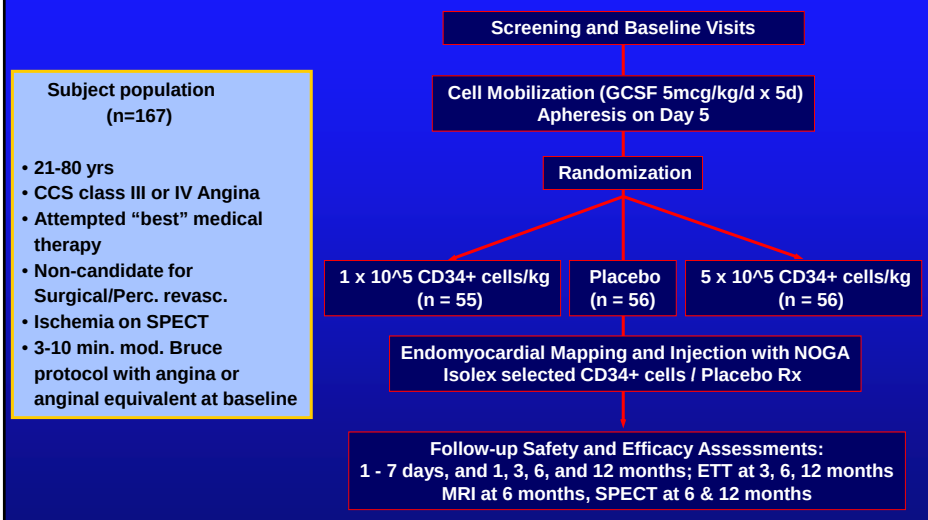
LV Ejection Fraction: Anterior MI's



CHF with Ongoing Ischemia

When the Horse is out of the barn and thirsty!

Phase II ACT34–CMI Study Design

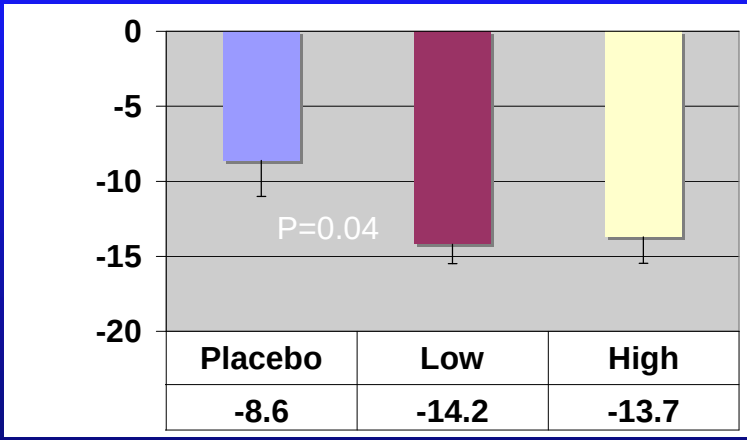


Subject population (n=167)

- 21-80 yrs
- CCS class III or IV Angina
- Attempted "best" medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia on SPECT
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline

ACT-34 CMI: Reduction in Angina

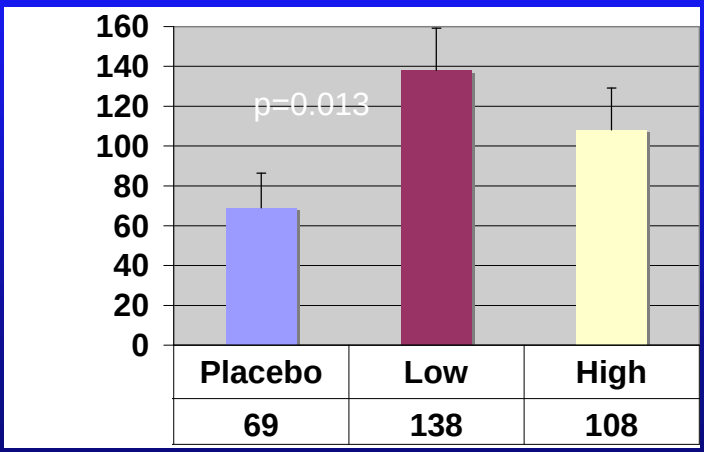
Anginal Episodes per Week
Change from baseline at 6 months



Analysis of Variance (ANOVA)

ACT-34 CMI: Exercise Time

Total ETT Time
Change from baseline at 6 months



Study Design

- **DESIGN:** Single-blinded, dose-escalation, randomized, multicenter clinical trial
- **PRIMARY ENDPOINTS:** To evaluate the feasibility and safety of transendocardial injection of MPCs
- **SECONDARY ENDPOINTS:**
  - NYHA class
  - MLWHF
  - SF36
  - 6 minute walk test
  - EF: Echo, MUGA
  - Spect Perfusion
  - MACE, Mortality

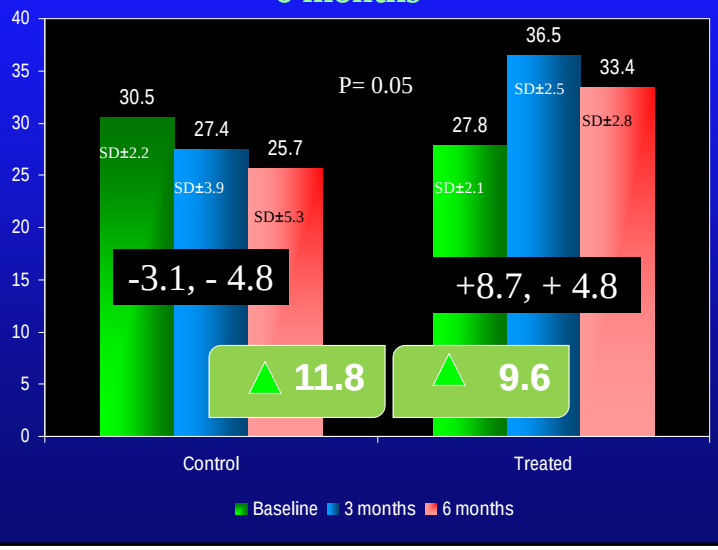
60 Patients

Cohort A	Cohort B	Cohort C
Low Dose	Med Dose	High Dose
25 M	75 M	150 M
15 Treated	15 Treated	15 Treated
5 Placebo	5 Placebo	5 Placebo

Time Points
Safety:
1, 2, 30, 90, 180, & 360 days
Efficacy:
3,6, & 12 months

Increase In EF Relative To Controls EF < 40%

6 months

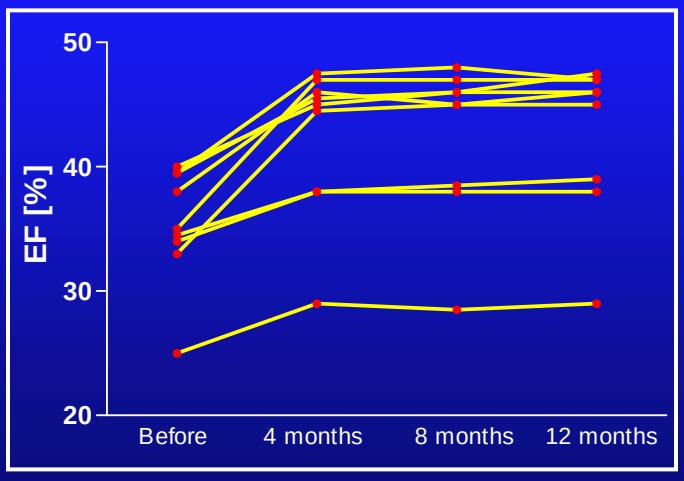


CHF with Scar

When the Horse is not only out of the barn;

Its DEAD!!

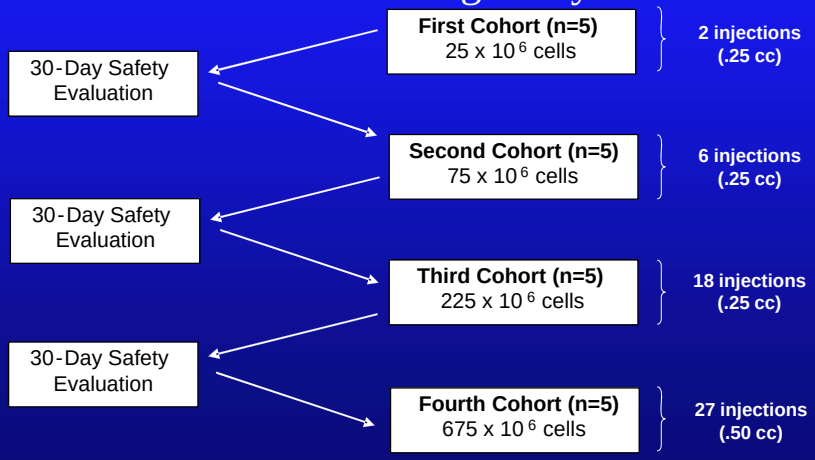
LV ejection fraction after autologous myoblast transplantation – 12 months follow up



Dr. Tomasz Siminiak, University School of Medical Sciences related study as presented at the AHA meeting November 2003. Surgical (epicardial) study.

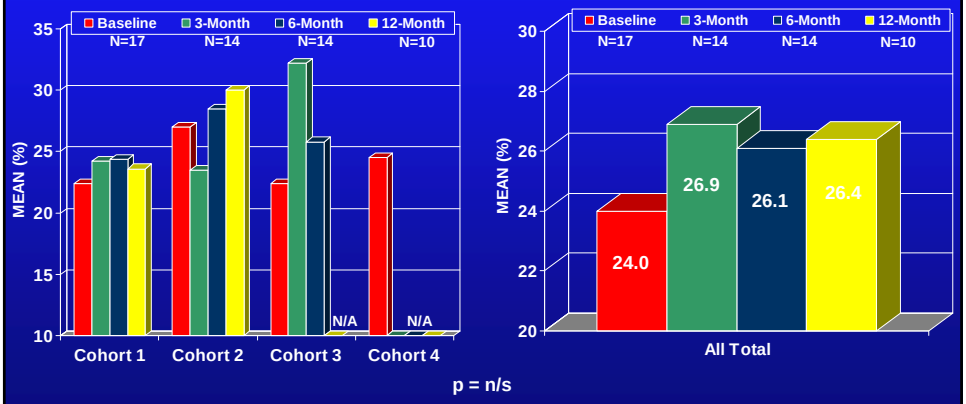
MYOHEART Study Design

A Phase 1, Multi-Center, Open Label, Dose Escalating Study



MYOHEART LVEF (MUGA)

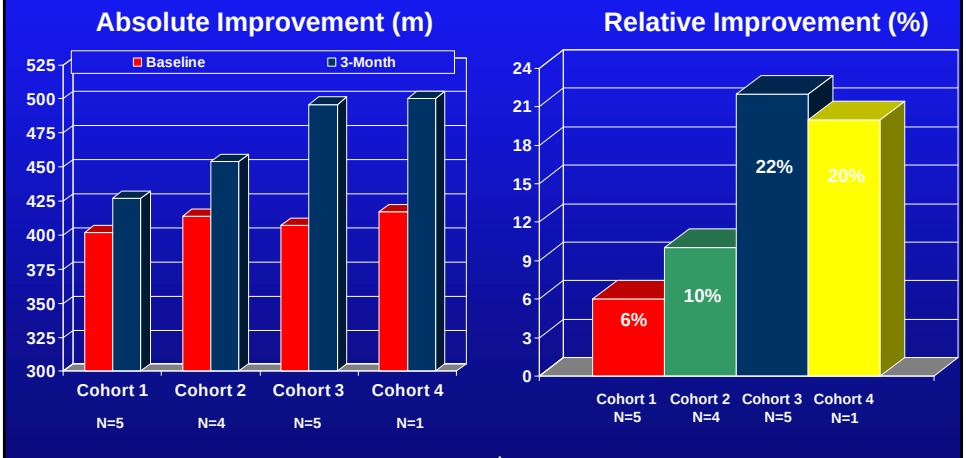
Interim Analysis



p = n/s

MYOHEART 6-Minute Walk

Interim Analysis



p = n/s

MARVEL Study Design

330 Patients with Ischemic Cardiomyopathy
EF ≤ 35%, Class II-III, Stable Medical Therapy, ICD Placement ≥ 2 mos.

Informed Consent Provided, Screening, 1:1:1 Randomization

Group A*	Group B*	Group C*
800 x 10^6 ASMs	400 x 10^6 ASMs	Sham Injection
N = 110	N = 110	N = 110

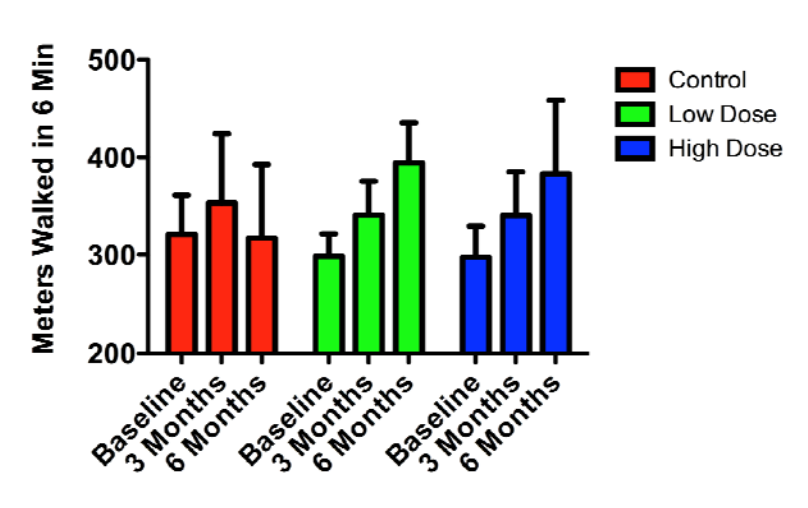
Muscle Biopsy

Cardiac Cath Lab Procedure

Post-Procedure, Week 1, Week 2, Week 3, 1-Month, 3-Month, 6-Month Follow-Up:
Medical Review, Haematology, ICD Interrogation, ECG, DSE / WMSI, MUGA / LVEF, 6MWT, QOL, NYHA Class

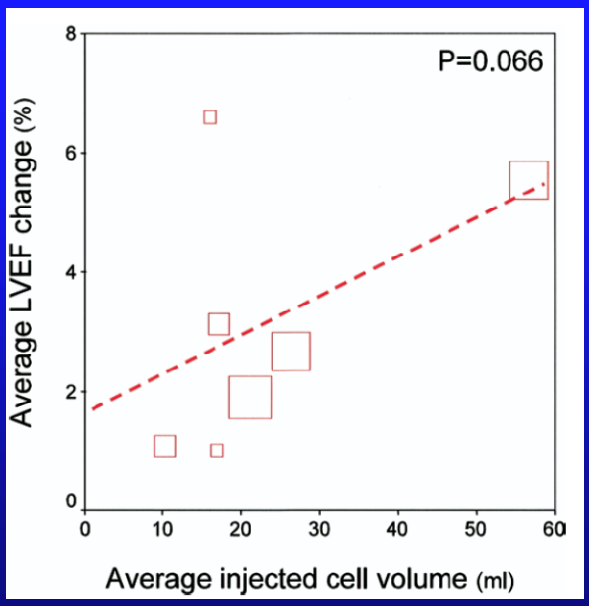
* All patients receive 16 injections of 0.25 mL over 20 seconds

MARVEL-1: Mean 6 Minute Walk Distance (meters)



Still not available at the florist yet….GETTING CLOSER!

- t



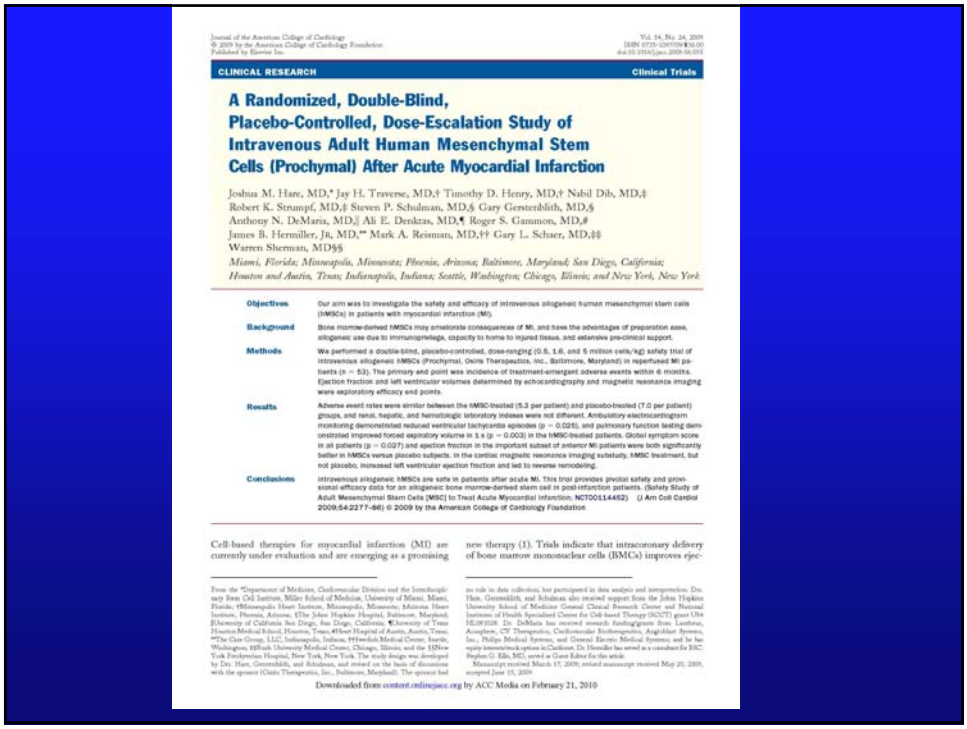
Lipinski, JACC 2007;50:1761

Overview: 10 studies, 698 patients

Table 4 Clinical Events at the Longest Available Follow-Up as Reported by Included Studies and Pooled With Peto Method*

Study	Death	Recurrent Myocardial Infarction	Target Vessel Revascularization	Rehospitalization for Heart Failure
Strauer et al. (10)	—	—	—	—
Bartunek et al. (11)	0/19 vs. 0/16	—	11/19 vs. 4/16	—
Jannsens et al. (8)	1/34 vs. 0/34	0/33 vs. 0/34	2/33 vs. 2/34	—
BOOST (7)	0/30 vs. 1/30	1/30 vs. 0/30	5/30 vs. 4/30	1/30 vs. 3/30
Zhan-Quan et al. (13)	0/35 vs. 0/23	0/35 vs. 0/23	0/35 vs. 0/23	0/35 vs. 0/23
MAGIC-CELL-3-DES (12)	1/27 vs. 1/29	0/27 vs. 1/29	0/27 vs. 1/29	—
TCT-STAMI (15)	0/10 vs. 0/10	0/10 vs. 0/10	0/10 vs. 0/10	0/10 vs. 0/10
ASTAMI (2,4)	0/50 vs. 0/50	—	11/50 vs. 11/50	1/50 vs. 1/50
REPAIR-AMI (5)	2/101 vs. 6/103	0/101 vs. 6/103	16/101 vs. 26/103	0/101 vs. 3/103
Meluzin et al. (16)	0/44 vs. 0/22	0/44 vs. 0/22	6/44 vs. 1/22	0/44 vs. 0/22
OR (95% CI)	0.52 (0.16–1.63)	0.22 (0.05–0.90)	0.97 (0.62–1.52)	0.32 (0.09–1.21)
p value	0.26	0.04	0.90	0.09

Lipinski, JACC 2007;50:1761



CLINICAL RESEARCH — Clinical Trials

A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (Prochymal) After Acute Myocardial Infarction

Joshua M. Hare, MD,* Jay H. Traverse, MD,† Timothy D. Henry, MD,† Nabil Dib, MD,‡ Robert K. Strumpf, MD,‡ Steven P. Schulman, MD,§ Gary Gerstenblith, MD,§ Anthony N. DeMaria, MD,‖ Ali E. Denktas, MD,¶ Roger S. Gammon, MD,# James B. Hermiller, Jr, MD,** Mark A. Reisman, MD,†† Gary L. Schaer, MD,‡‡ Warren Sherman, MD§§

Miami, Florida; Minneapolis, Minnesota; Phoenix, Arizona; Baltimore, Maryland; San Diego, California; Houston and Austin, Texas; Indianapolis, Indiana; Seattle, Washington; Chicago, Illinois; and New York, New York

Objectives Our aim was to investigate the safety and efficacy of intravenous allogeneic human mesenchymal stem cells (hMSCs) in patients with myocardial infarction (MI).

Background Bone marrow-derived hMSCs may ameliorate consequences of MI, and have the advantages of preparation ease, allogeneic use due to immunoprivilege, capacity to home to injured tissue, and extensive pre-clinical support.

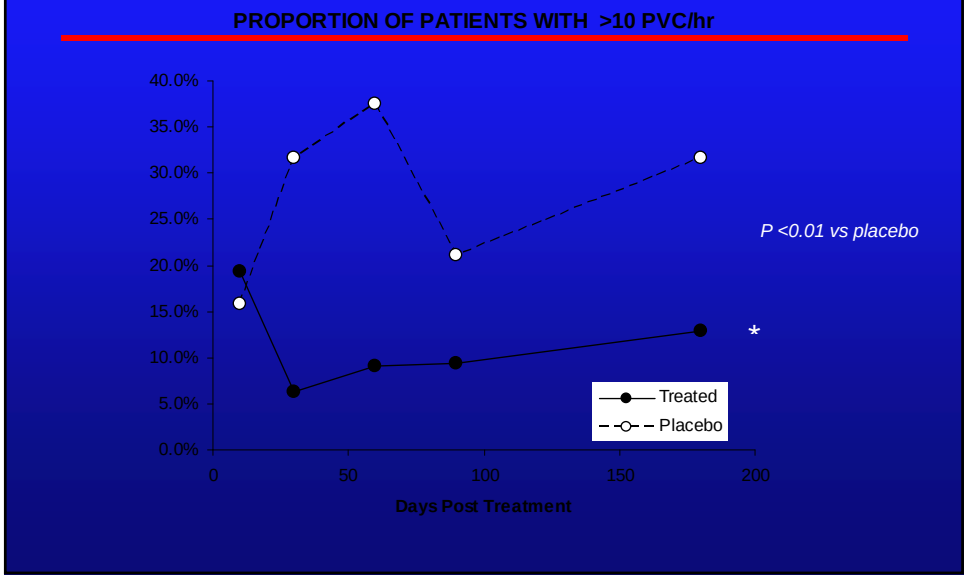
Methods We performed a double-blind, placebo-controlled, dose-ranging (0.5, 1.6, and 5 million cells/kg) safety trial of intravenous allogeneic hMSCs (Prochymal, Osiris Therapeutics, Inc., Baltimore, Maryland) in reperfused MI patients (n = 53). The primary end point was incidence of treatment-emergent adverse events within 6 months. Ejection fraction and left ventricular volumes determined by echocardiography and magnetic resonance imaging were exploratory efficacy end points.

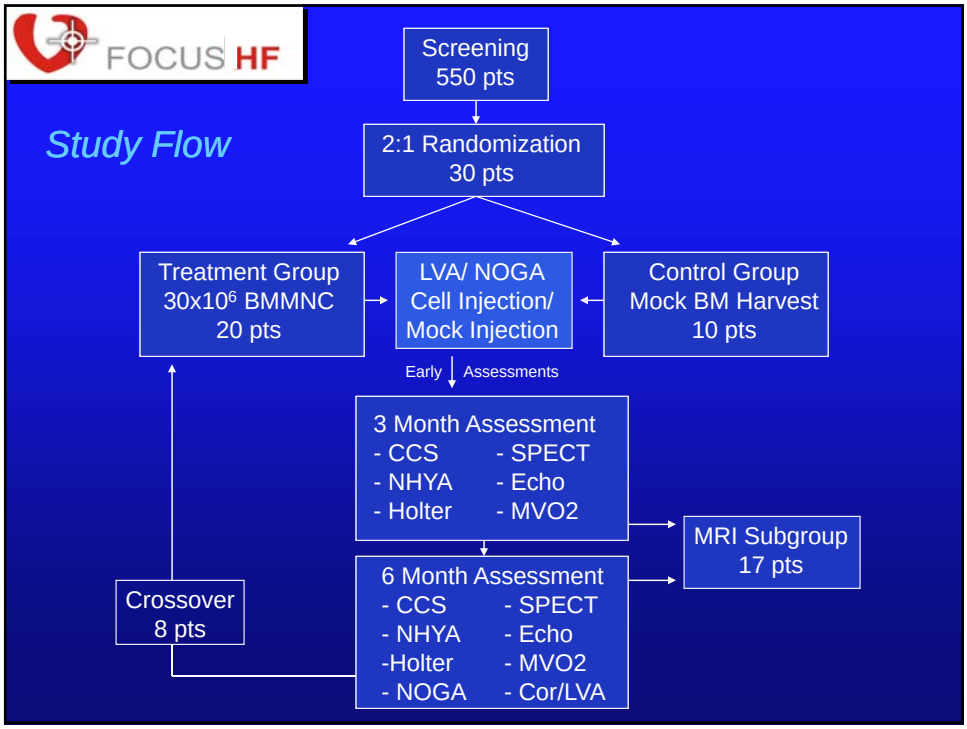
Results Adverse event rates were similar between the hMSC-treated (5.3 per patient) and placebo-treated (7.0 per patient) groups, and renal, hepatic, and hematologic laboratory indexes were not different. Ambulatory electrocardiogram monitoring demonstrated reduced ventricular tachycardia episodes (p = 0.025), and pulmonary function testing demonstrated improved forced expiratory volume in 1 s (p = 0.003) in the hMSC-treated patients. Global symptom score in all patients (p = 0.027) and ejection fraction in the important subset of anterior MI patients were both significantly better in hMSCs versus placebo subjects. In the cardiac magnetic resonance imaging substudy, hMSC treatment, but not placebo, increased left ventricular ejection fraction and led to reverse remodeling.

Conclusions Intravenous allogeneic hMSCs are safe in patients after acute MI. This trial provides pivotal safety and provisional efficacy data for an allogeneic bone marrow-derived stem cell in post-infarction patients. (Safety Study of Adult Mesenchymal Stem Cells [MSC] to Treat Acute Myocardial Infarction; NCT00114452) (J Am Coll Cardiol 2009;54:2277–86) © 2009 by the American College of Cardiology Foundation

Cell-based therapies for myocardial infarction (MI) are currently under evaluation and are emerging as a promising new therapy (1). Trials indicate that intracoronary delivery of bone marrow mononuclear cells (BMCs) improves ejec-

Premature Ventricular Contractions





Baseline and 3 Month Follow-up

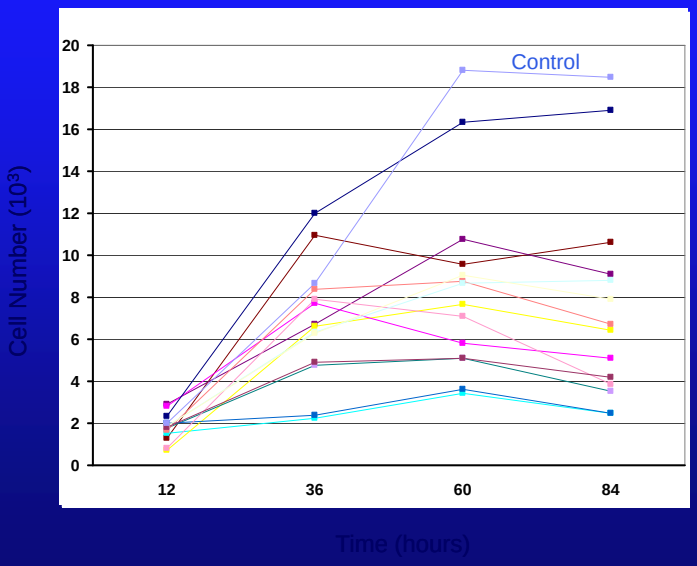
	Control			Treatment		
	Baseline	3 months	p	Baseline	3 months	p
Clinical Assessment						
CCS	3±0.8	2.2±0.8	0.08	3±0.8	2.1±1	0.01
NYHA	2.6±0.7	1.9±0.9	0.08	2.3±1.2	2±0.7	ns
Functional Assessment						
MVO2 (ml/Kg/min)	14.8±3	15.7±5	ns	14.7±4	15.5±4	ns
Echo EF (%)	39±9.1	41.1 ±8	ns	37.3±10.6	38.4±12	ns
SPECT % of reversibility	21.3±18	20.1±22	ns	16.8±9	11.7±11.7	0.005

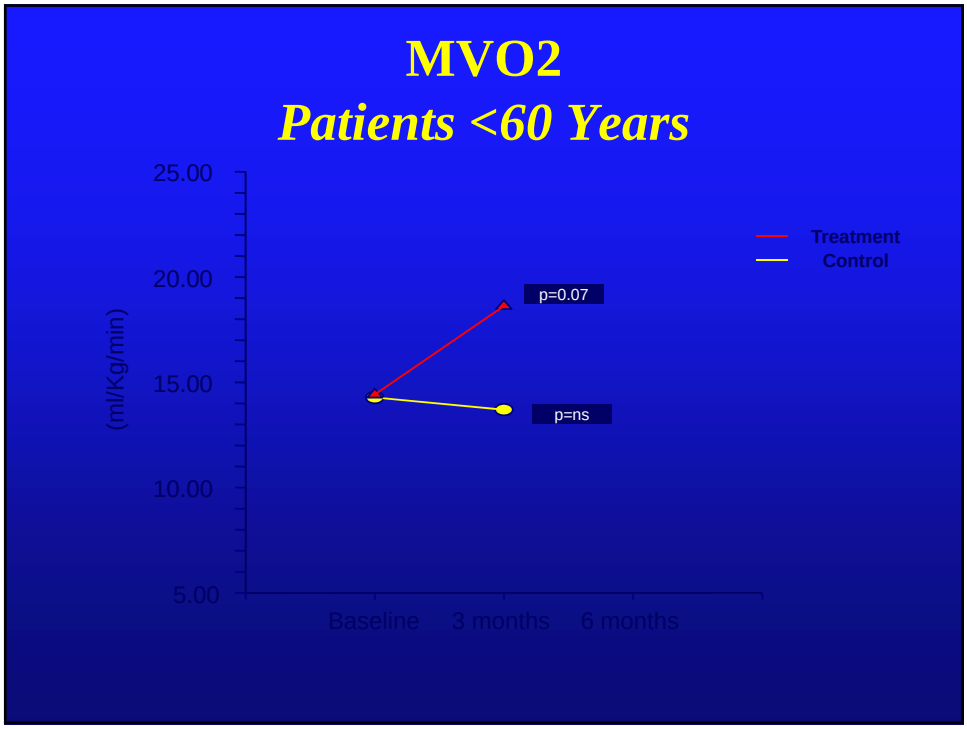
3 Month SPECT and MRI Results in the Injected Segments

	Baseline	Treatment	p
SPECT			
Rest perfusion	0.94±1.1	0.99±1.06	0.5
Stress Perfusion	1.48±1.1	1.46±1.1	0.63
Reversibility	0.57±0.7	0.41±0.6	0.01
MRI			
Rest Perfusion	0.08±0.34	0.02±0.14	0.08
Stress Perfusion	1.02±0.78	0.86±0.66	0.03

FOCUS HF

MSC Growth Kinetics




MVO2
Patients <60 Years
25.00
20.00
15.00
10.00
5.00
(ml/Kg/min)
Baseline
3 months
6 months
Treatment
Control
p=0.07
p=ns