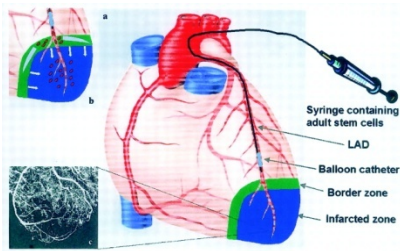


Progenitor cell therapy in acute MI



Jacob George
Kaplan Medical Center

The Endothelial cells as a paracrine factory

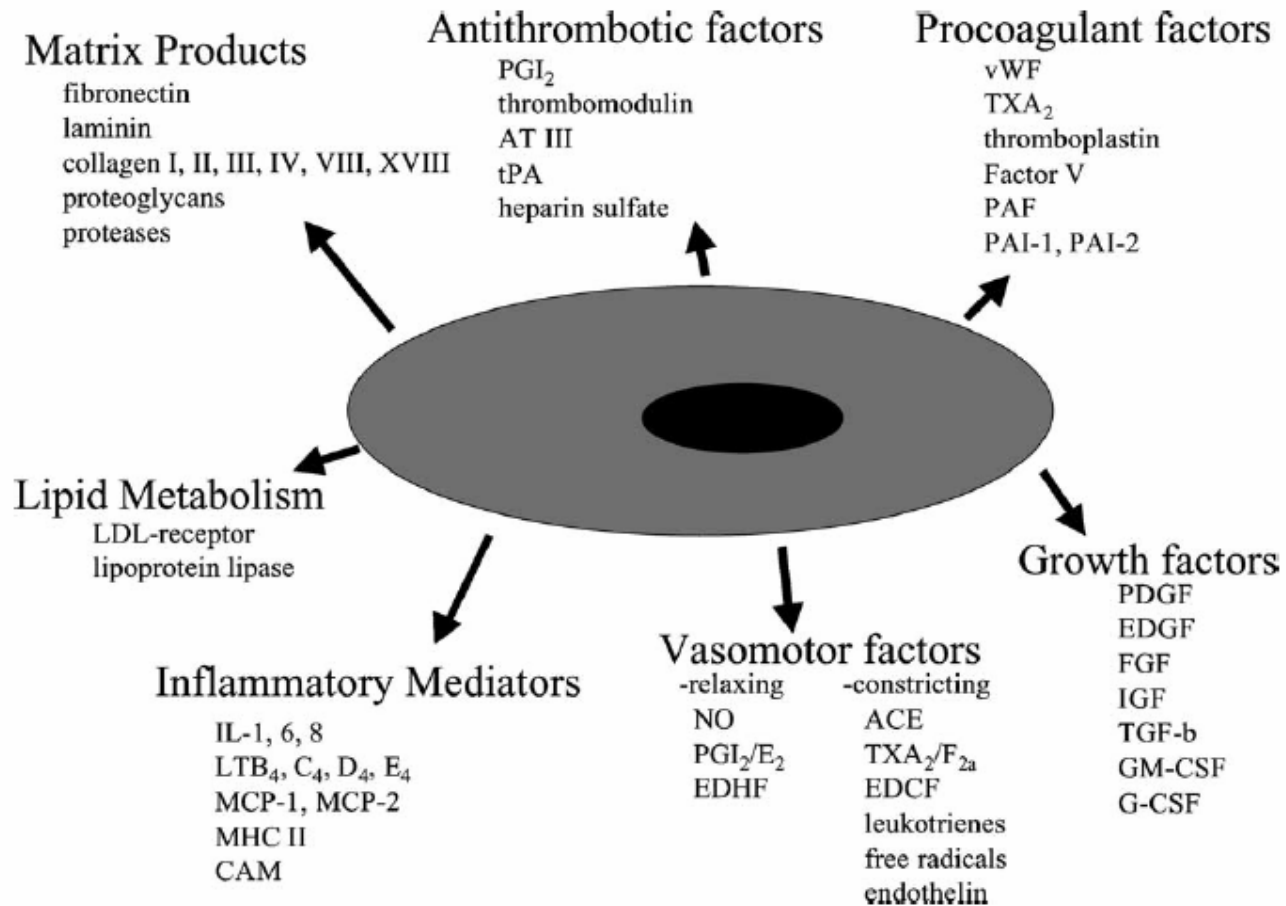
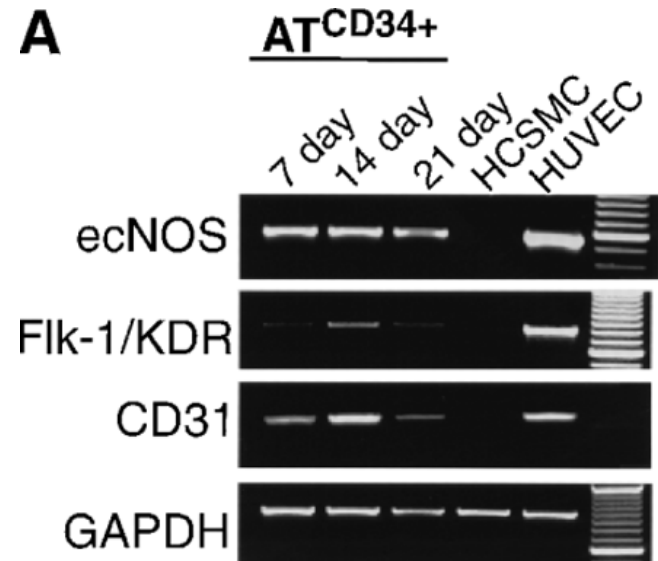
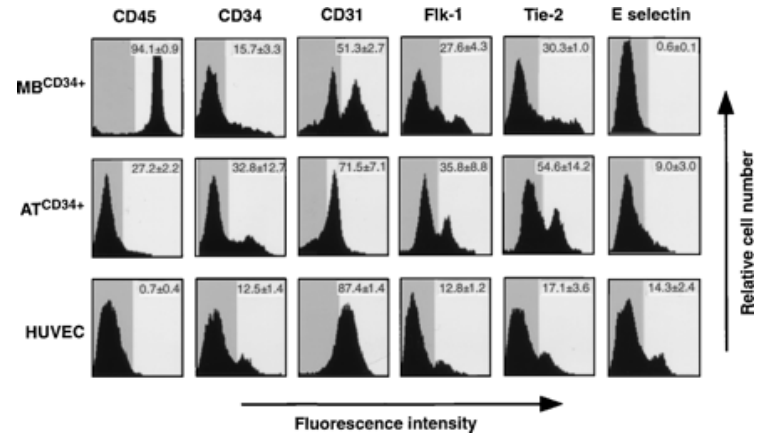
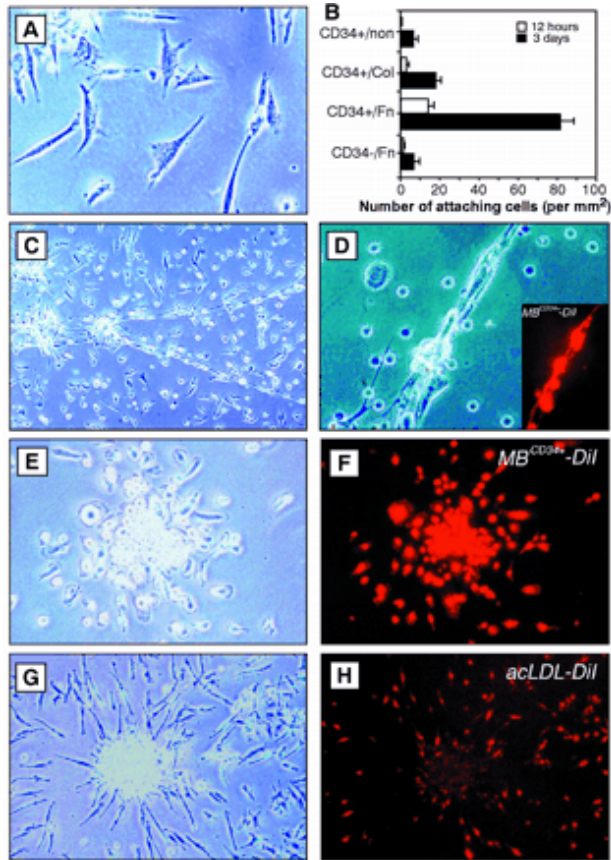


Fig. 1. Known secretory/expression products of endothelial cells relating to vessel physiology.

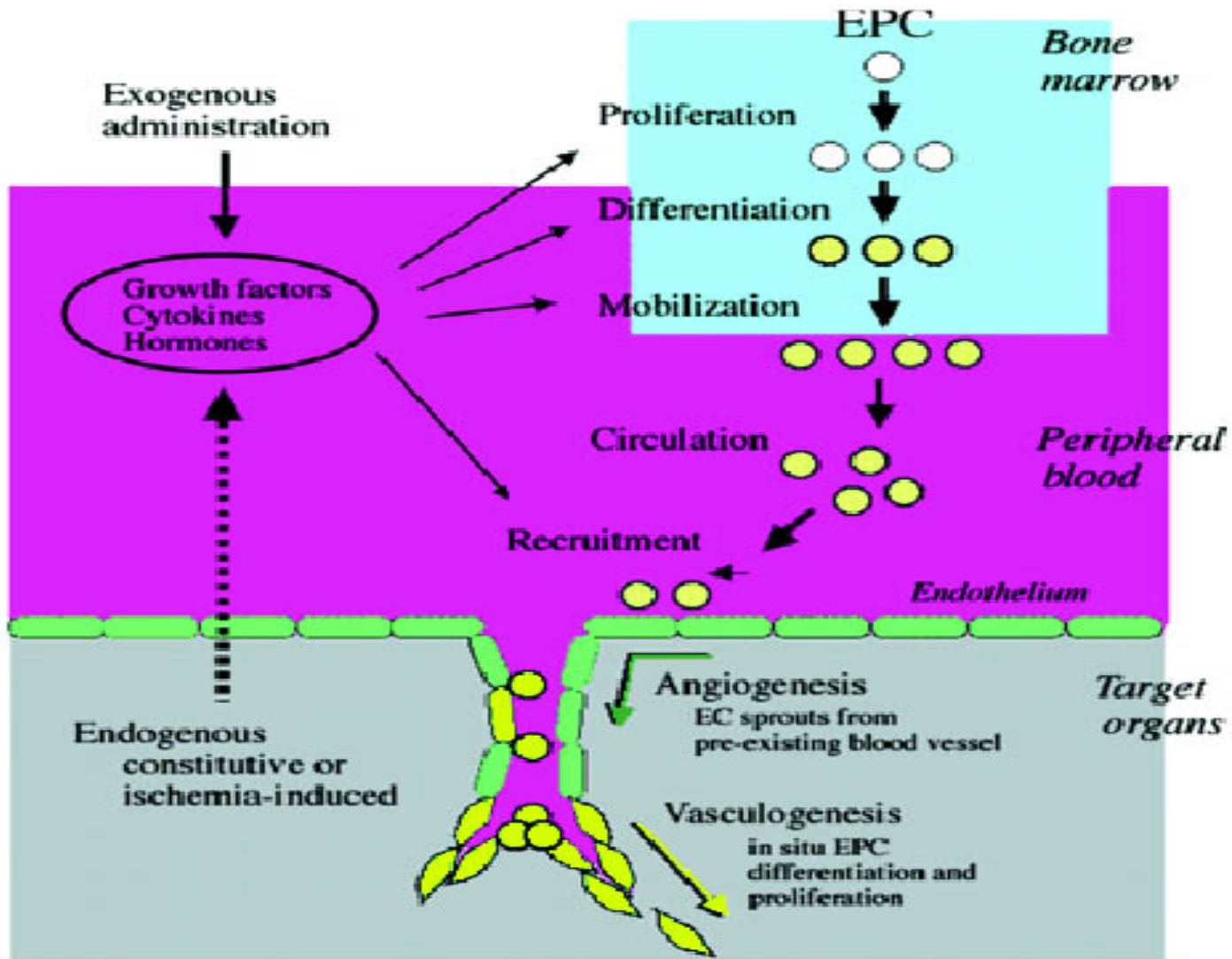
Isolation of putative progenitor endothelial cells for angiogenesis.

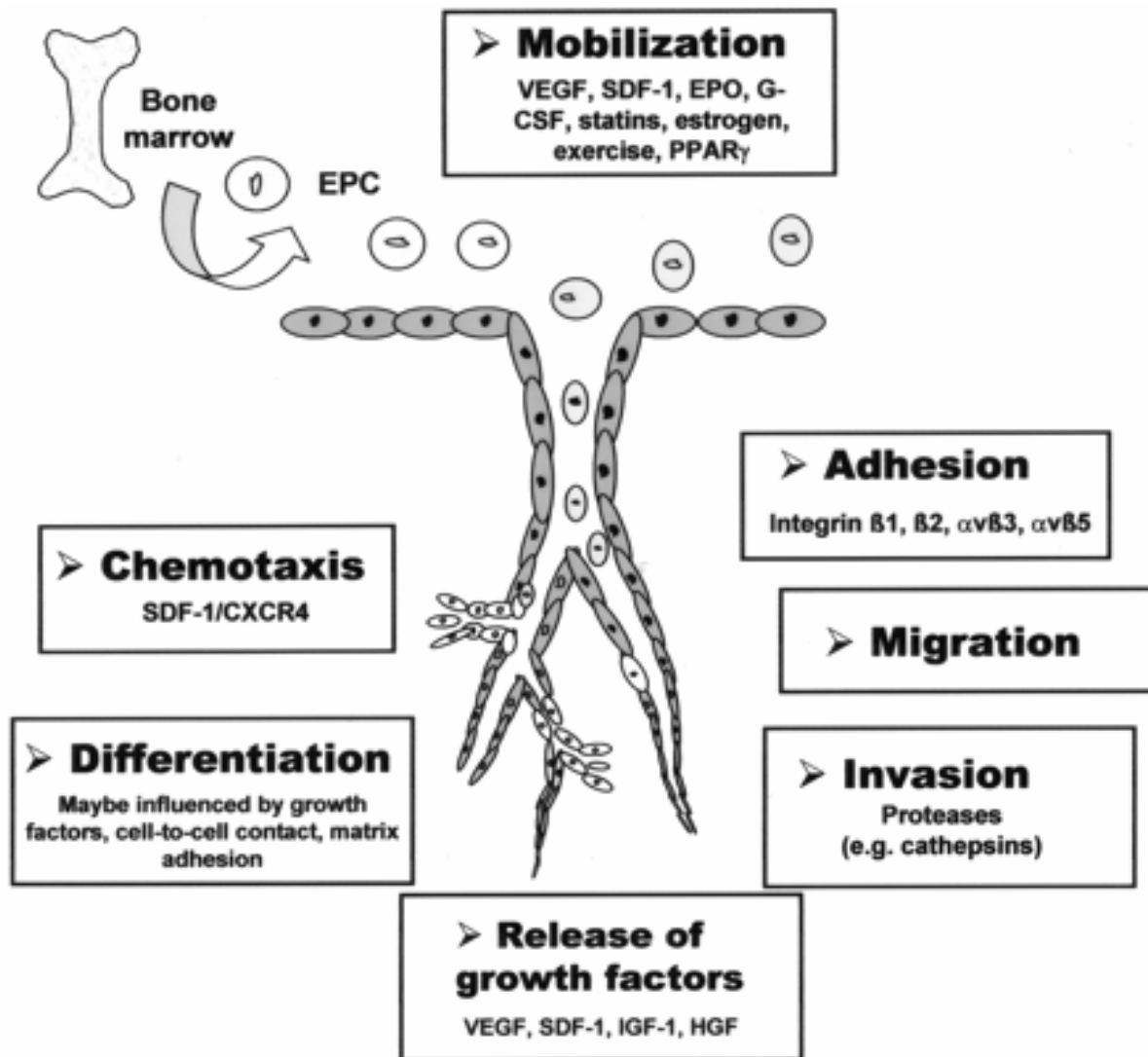
Asahara et al. *Science* 1997



Attachment, cluster formation, and capillary network development by progenitor ECs in vitro

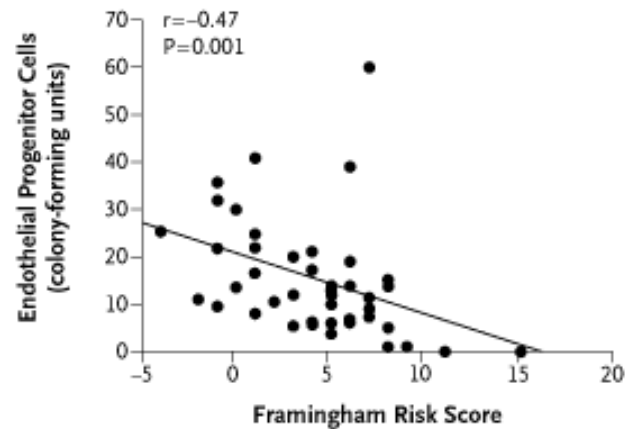
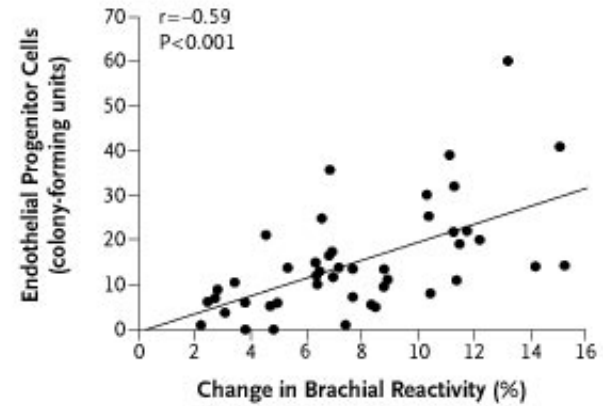
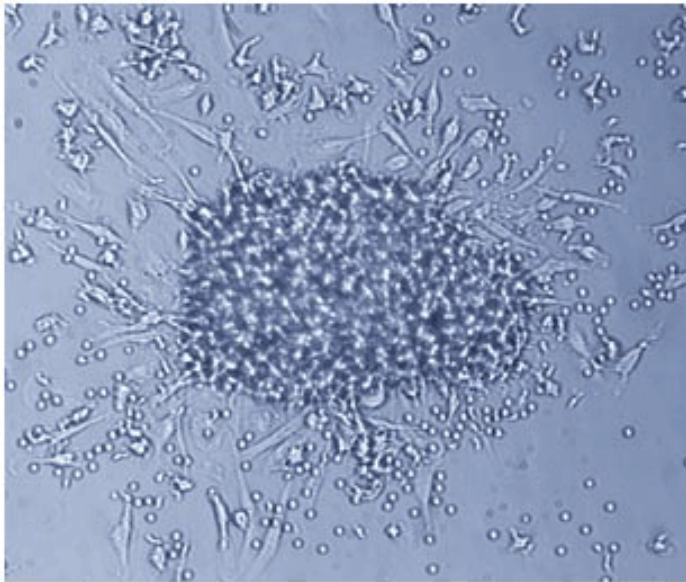
Endothelial progenitor cell hemostasis

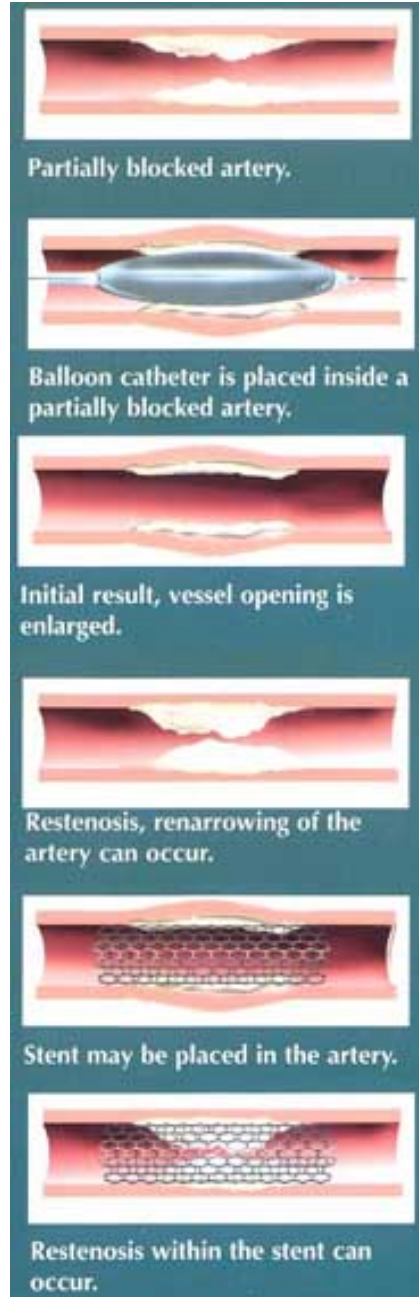




Circulating endothelial progenitor cells, vascular function, and cardiovascular risk.

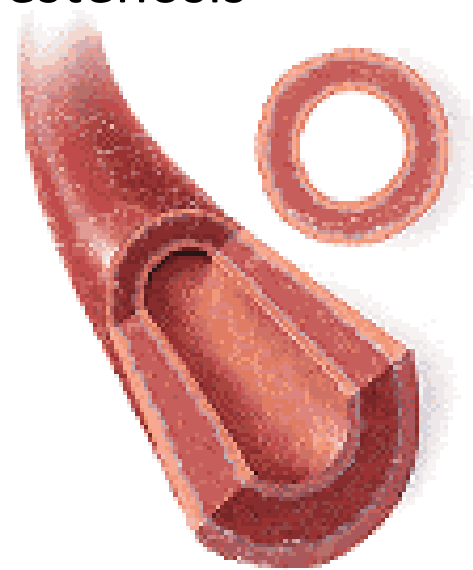
Hill et al NEJM, 2003



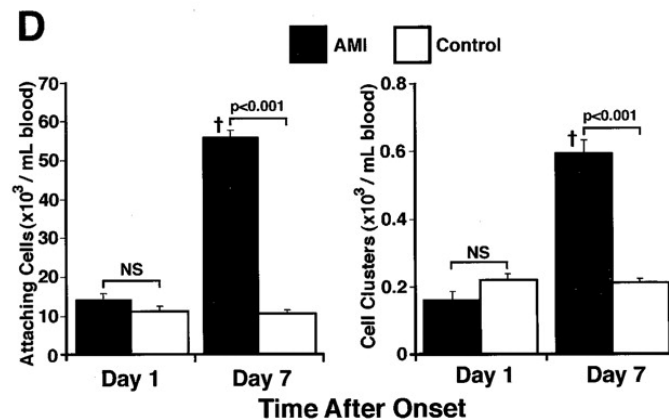
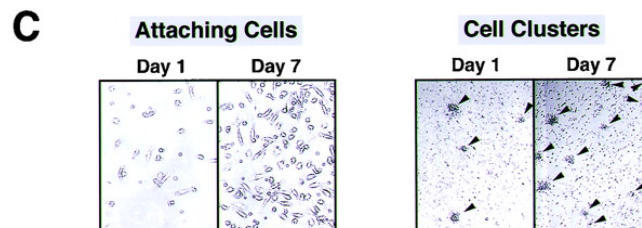
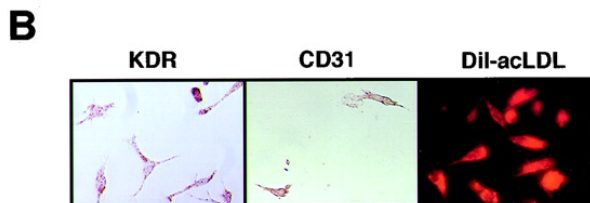
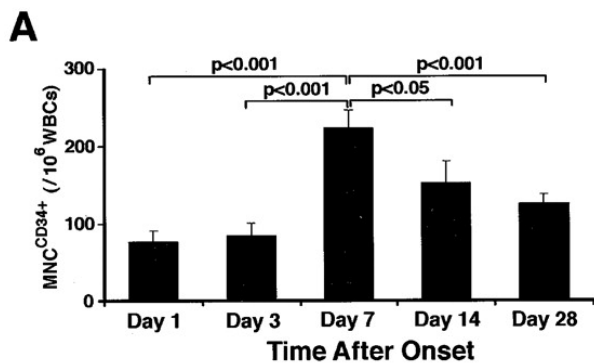


Number and adhesive properties of circulating endothelial progenitor cells in patients with in-stent restenosis. *George et al. Arterioscler Thromb Vasc Biol 2003*

Impaired endothelialization and in stent restenosis

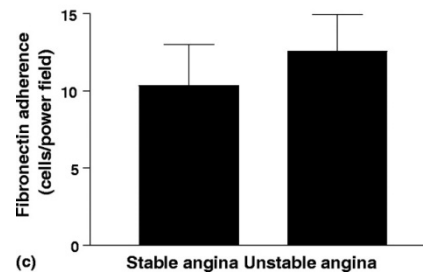
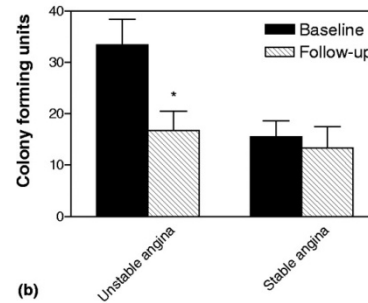
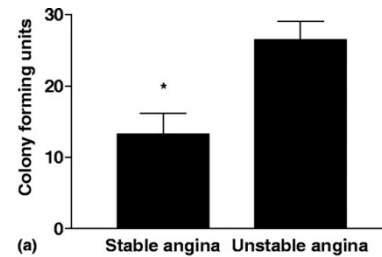
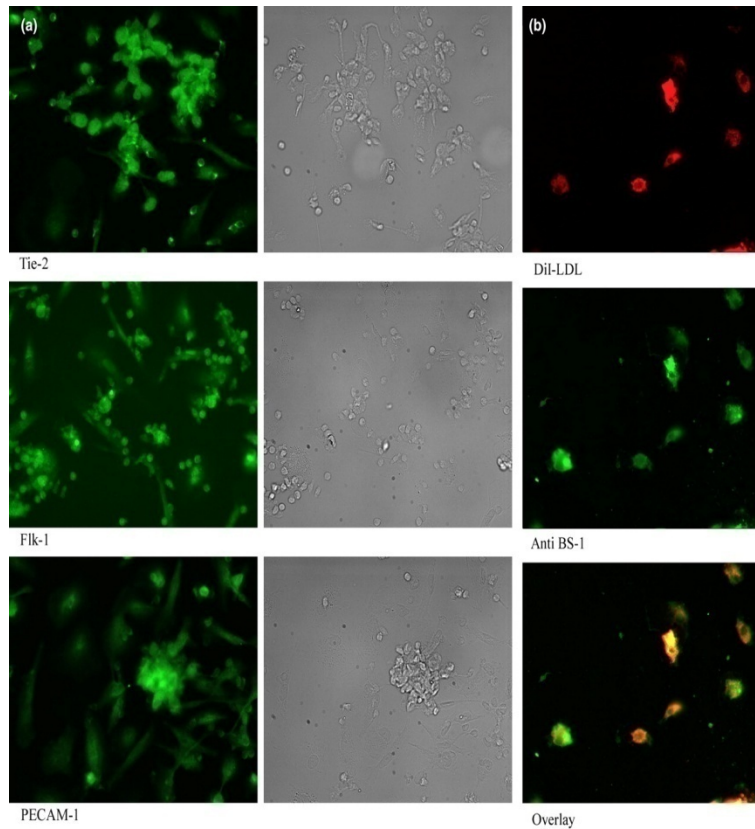


Circulating progenitors after AMI



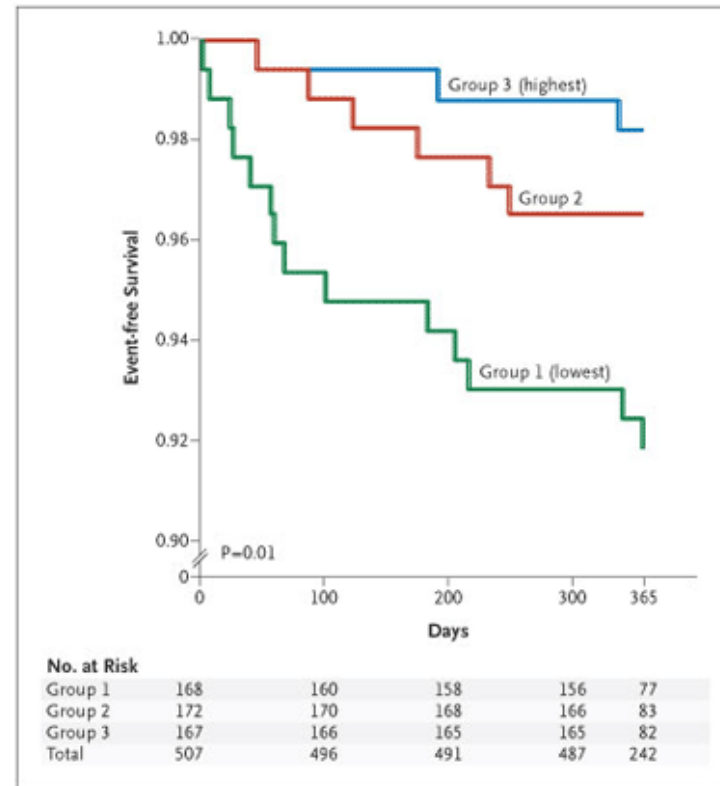
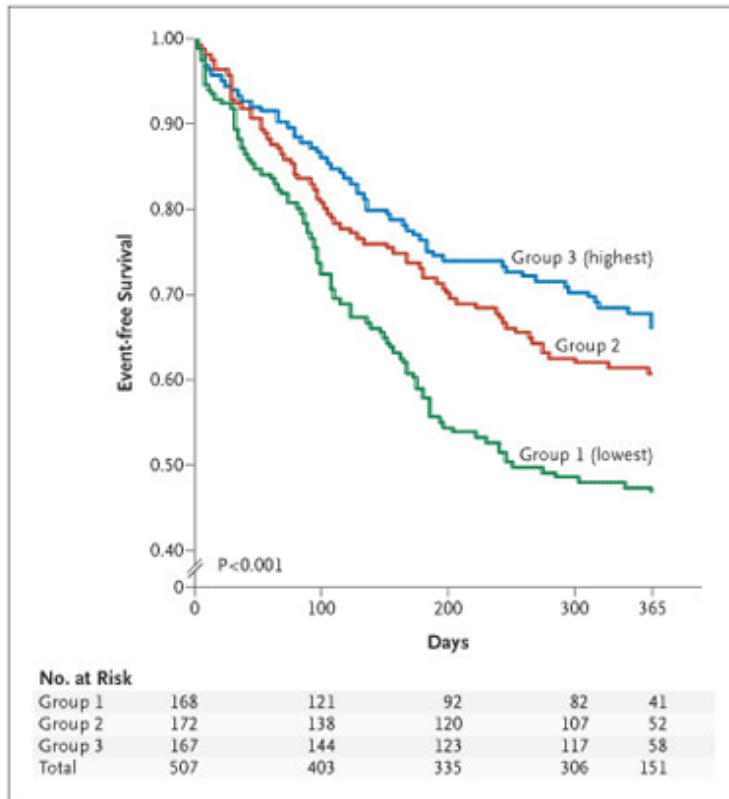
Shintani, S. et al. *Circulation* 2001;103:2776-2779

Circulating endothelial progenitors in patients with ACS

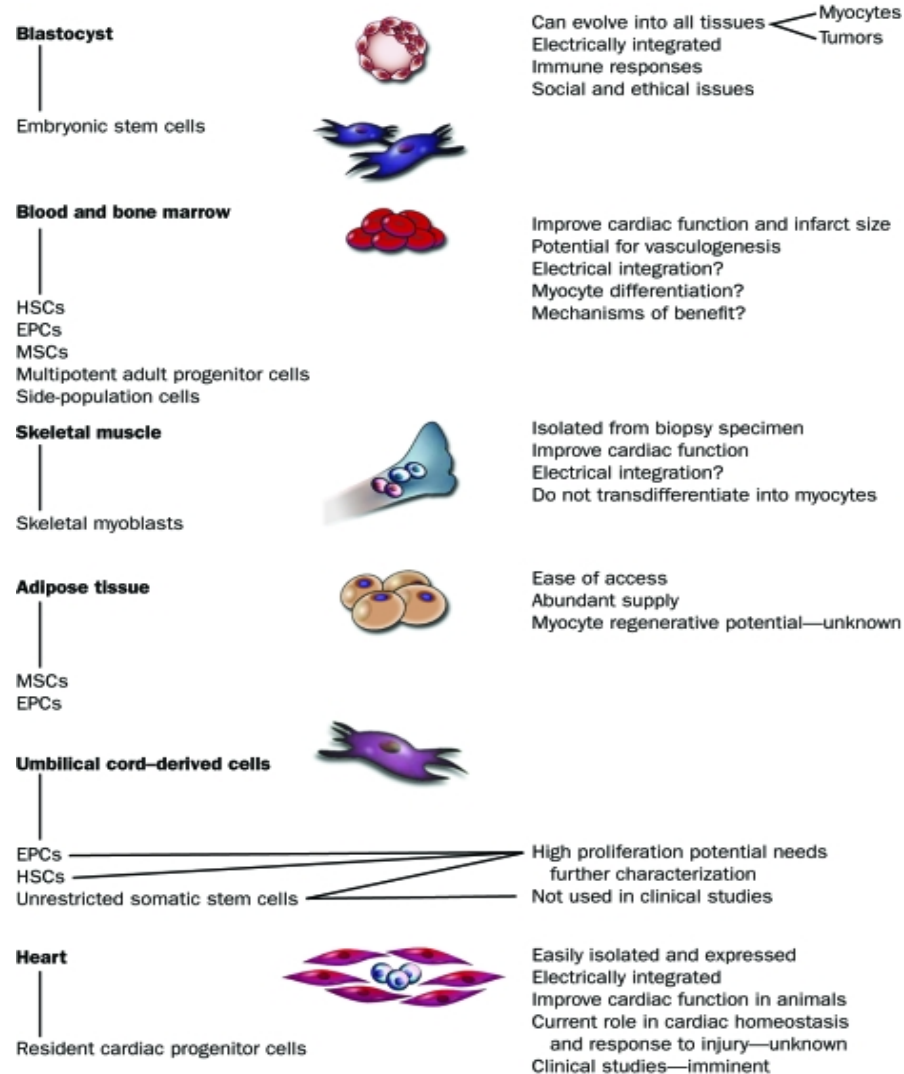


George, J. et al. Eur Heart J 2004 25:1003-1008; doi:10.1016/j.ehj.2004.03.026

Circulating Endothelial Progenitor Cells and Cardiovascular Outcomes (Werner et al. NEJM. September, 2005



Which cell to be used for myocardial cell therapy



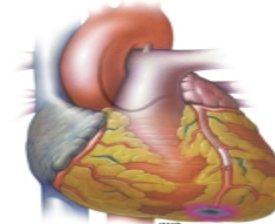
Potential delivery modes of cells

Intravenous



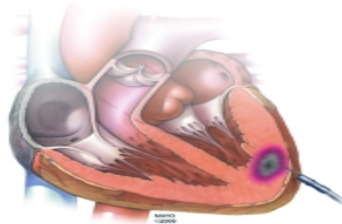
A

Intracoronary



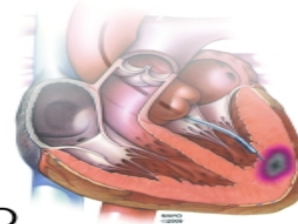
B

Direct epicardial



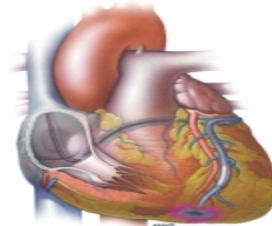
C

Direct endocardial



D

Coronary sinus injection

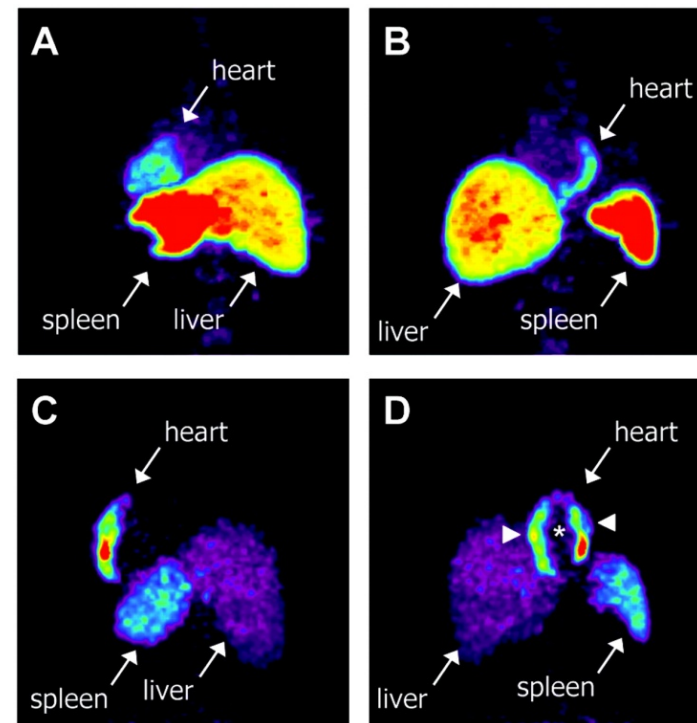


E

Potential mechanisms of benefit by progenitor cells in acute MI

- Paracrine effects (reduced cm apoptosis, modulation of inflammation)
- Increased angiogenesis
- Transdifferentiation

Myocardial homing and biodistribution of ^{18}F -FDG-labeled BMCs



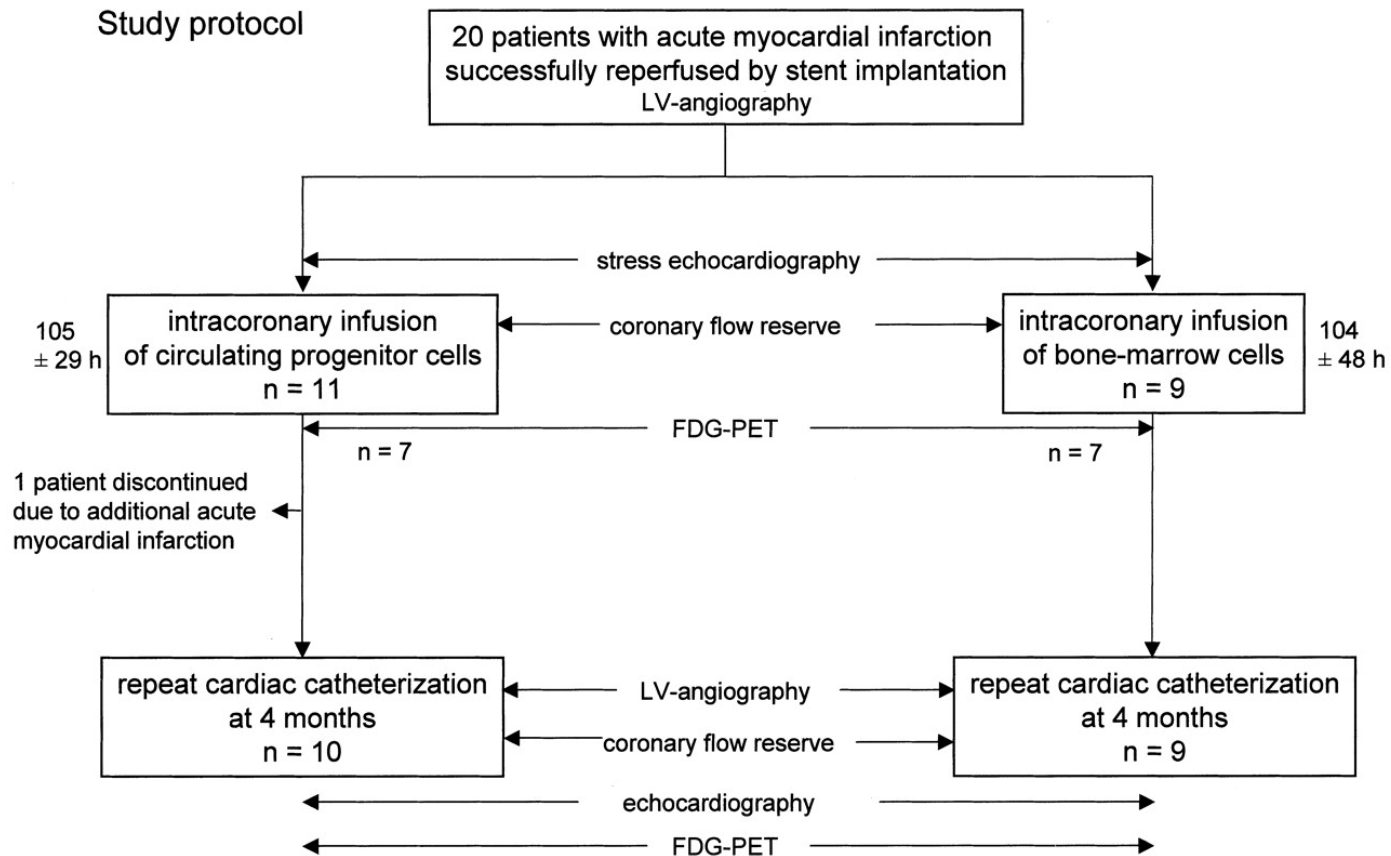
Hofmann, M. et al. *Circulation* 2005;111:2198-2202

American Heart Association® 

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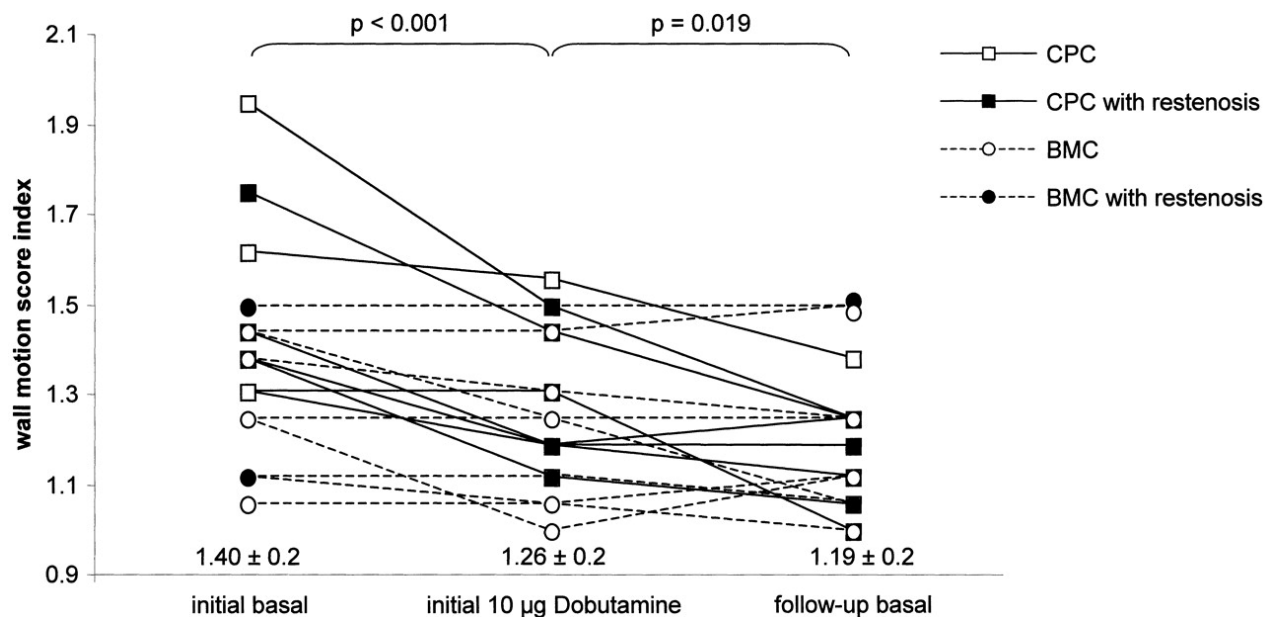
Learn and LiveSM

TOPCARE-AMI *Assmus, et al, Circ 2002*



Assmus, B. et al. *Circulation* 2002;106:3009-3017

Echocardiographic wall motion score index at rest (initial basal) and during low-dose dobutamine stimulation (initial 10 {micro}g dobutamine) at baseline before progenitor cell therapy and at rest at 4-month follow-up (follow-up basal)

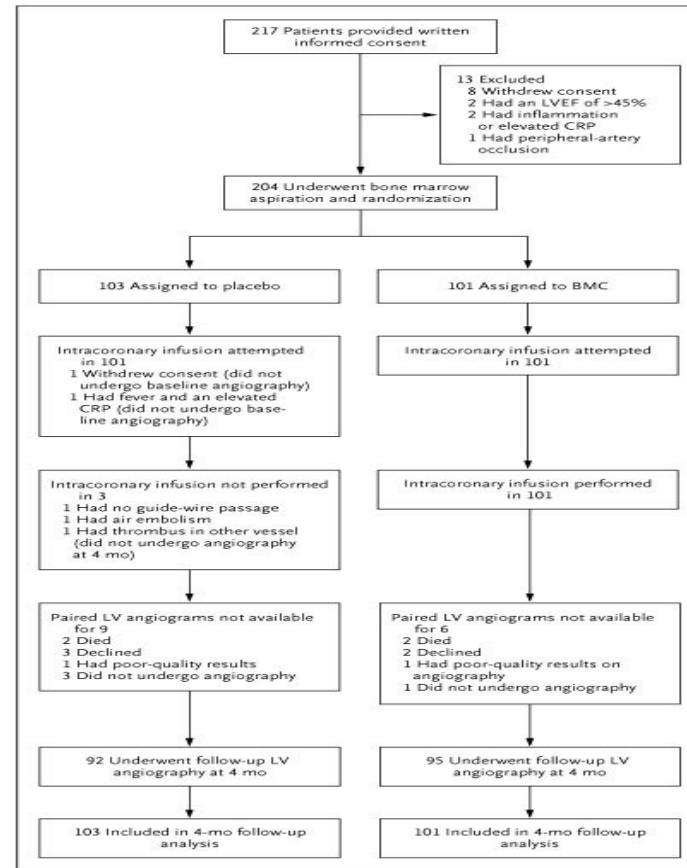


Assmus, B. et al. *Circulation* 2002;106:3009-3017

In patients with AMI, intracoronary infusion of autologous progenitor cells appears to be feasible and safe and may beneficially affect postinfarction remodeling processes.

REPAIR-AMI, *NEJM*, 2006

- BM cells versus medium.
- Recruited: 204 pts.
- 3-7 days post revascularization
- 4 month follow up quantitative LV angiogram
- Primary endpoint: change in LVEF
- Secondary: change in LVEDV, LVESV, regional wall motion



Intracoronary Bone Marrow–Derived Progenitor Cells in Acute Myocardial Infarction

REPAIR-AMI. NEJM, 2006

Table 2. Quantitative Measures of Left Ventricular Function.*

Variable	Placebo (N=92)	BMC (N=95)	P Value
Global LVEF (%)			
Baseline			
Mean	46.9±10.4	48.3±9.2	0.31
Median	47.5	50.6	
4 Mo			
Mean	49.9±13.0	53.8±10.2	0.02†
Median	53.2	54.7	
Absolute difference			
Mean	3.0±6.5	5.5±7.3	0.01‡
Median	4.0	5.0	
P value (baseline vs. 4 mo)	<0.001	<0.001	
End-diastolic volume (ml)			
Baseline			
Mean	139±46	128±38	0.09
Median	132	121	
4 Mo			
Mean	153±57	141±43	0.09
Median	138	134	
Difference			
Mean	14±33	12±31	0.64
Median	12	13	
P value (baseline vs. 4 mo)	<0.001	<0.001	
End-systolic volume (ml)			
Baseline			
Mean	75±32	67±26	0.09
Median	69	62	
4 Mo			
Mean	80±45	67±30	0.01§
Median	66	59	
Difference			
Mean	5.6±22	-0.6±19	0.04¶
Median	1.5	-2.6	
P value (baseline vs. 4 mo)	0.02	0.76	
Regional wall-motion analysis in infarcted zone			
Contractility in infarcted zone (SD from normal/chord)**			
Baseline			
Mean	-1.54±0.42	-1.54±0.42	0.27
Median	-1.53	-1.49	
4 Mo			
Mean	1.27±0.60	-1.17±0.60	<0.001
Median	-1.29	-1.20	
Difference			
Mean	0.28±0.52	0.37±0.53	<0.001
Median	0.23	0.28	
P value (baseline vs. 4 mo)	<0.001	<0.001	

* Plus-minus values are means ±SD. P values were determined by analysis of variance.

† P=0.05 by nonparametric testing.

‡ P=0.04 by nonparametric testing.

§ P=0.07 by nonparametric testing.

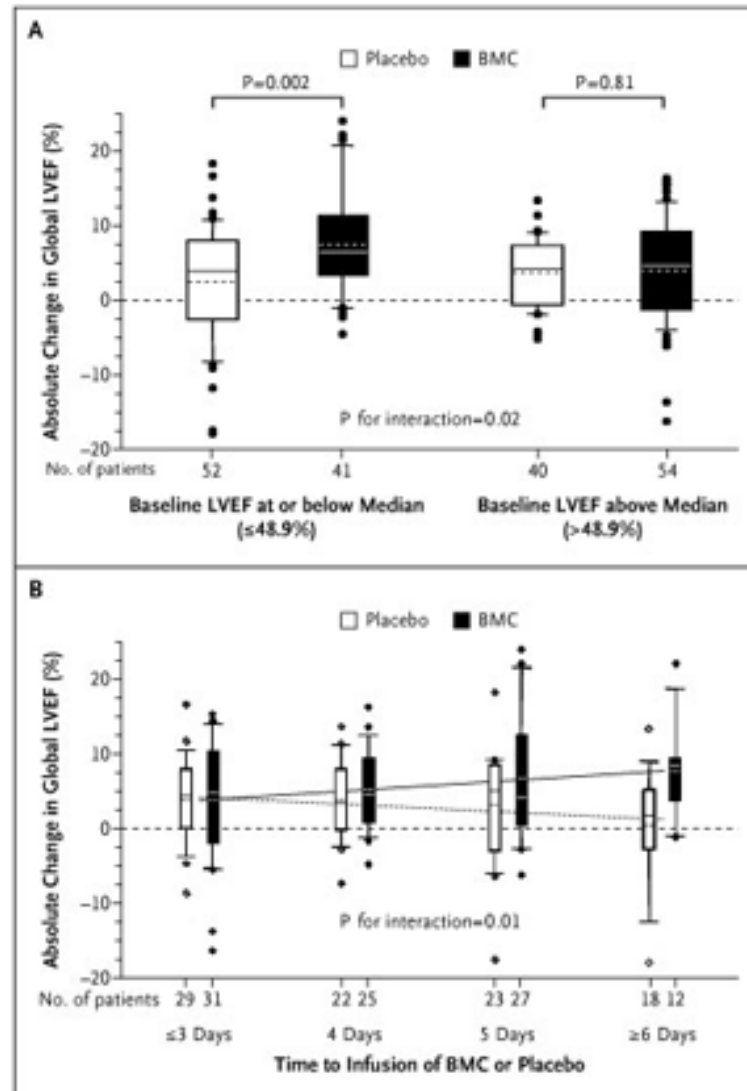
¶ P=0.06 by nonparametric testing.

|| P=0.09 by nonparametric testing.

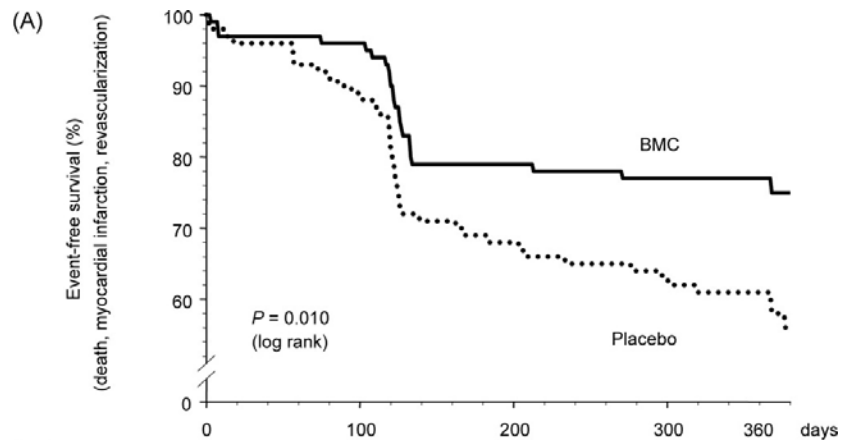
** Values represent the cumulative analysis of all chords in the infarct area.

Interaction between Change in LVEF and Both Baseline LVEF and Time to Infusion. *REPAIR AMI, NEJM, 2006*

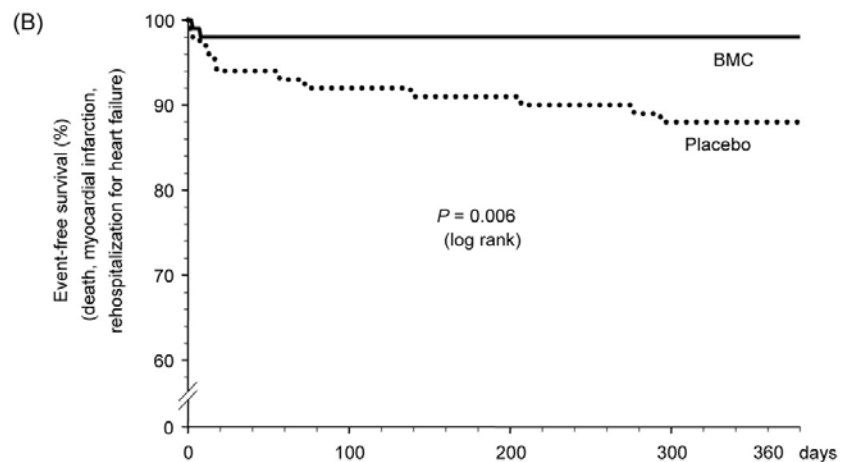
The beneficial effects of BMC infusion on the recovery of contractile function were confined to patients who were treated more than 4 days after infarct reperfusion.



Kaplan-Meier event-free survival analysis



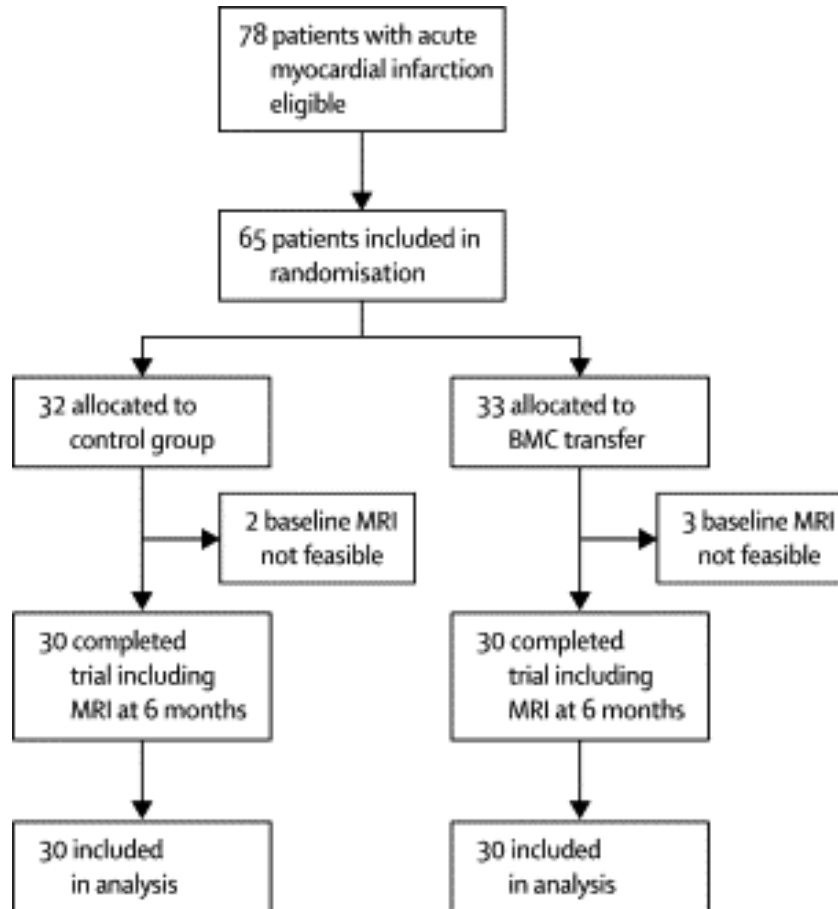
Number exposed to risk	Placebo	103	91	68	63	55
BMC	101	97	80	77	66	



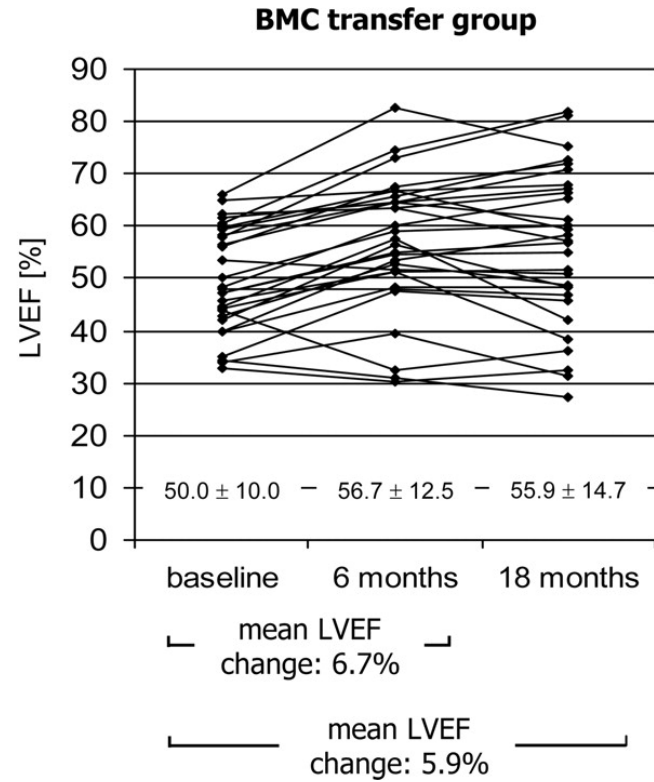
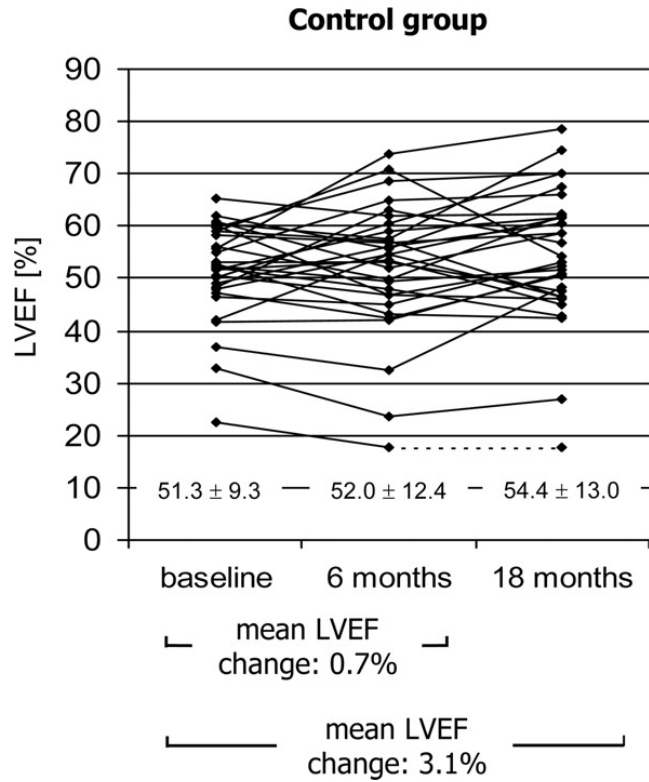
Number exposed to risk	Placebo	103	93	89	85	79
BMC	101	99	99	98	85	

Schachinger, V. et al. Eur Heart J 2006 27:2775-2783; doi:10.1093/eurheartj/ehl38

Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial . *Wollert et al. Lancet, 2004*

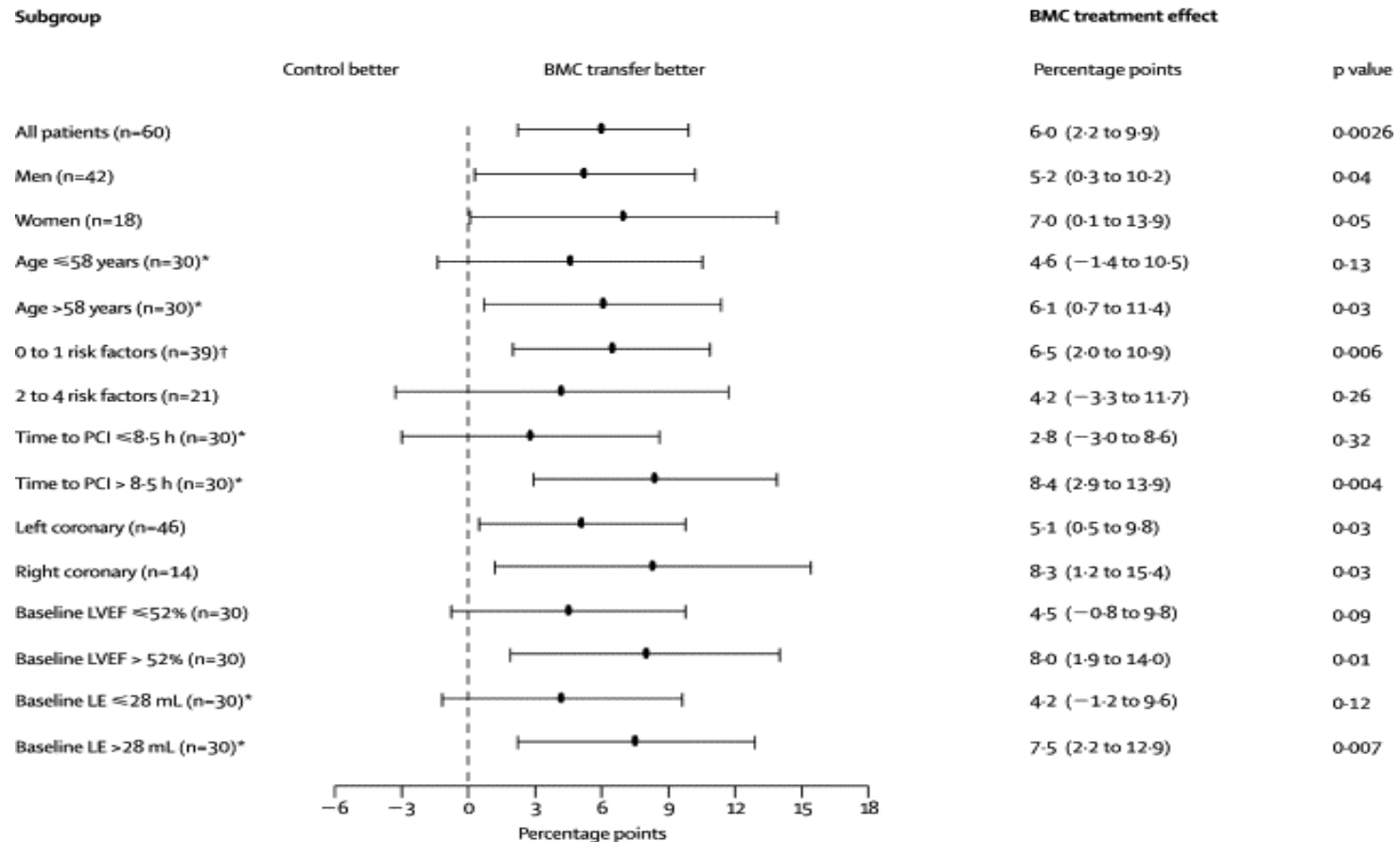


Global LVEF at baseline and at 6- and 18-month follow-up BOOST trial



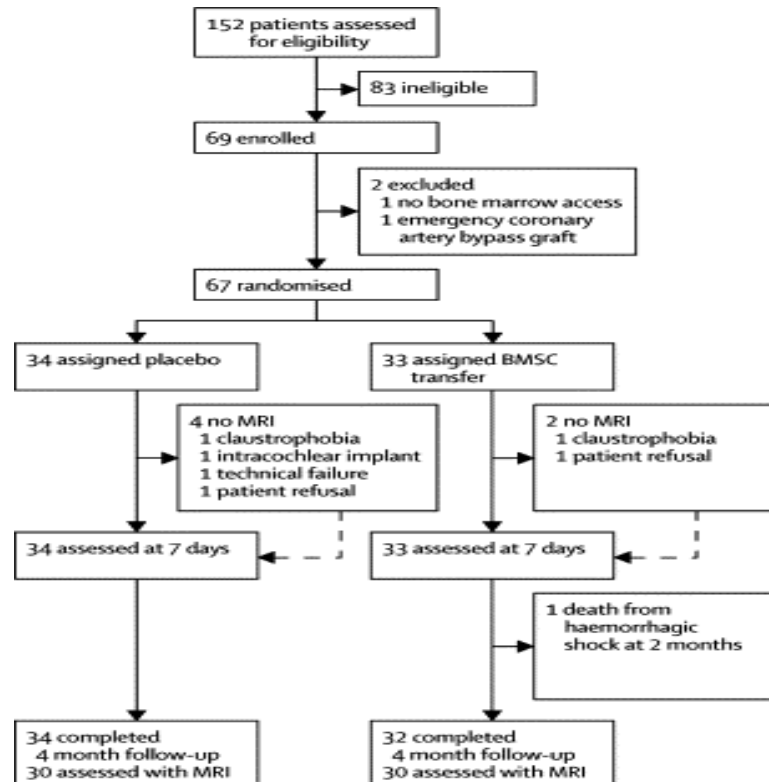
Meyer, G. P. et al. *Circulation* 2006;113:1287-1294

Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial

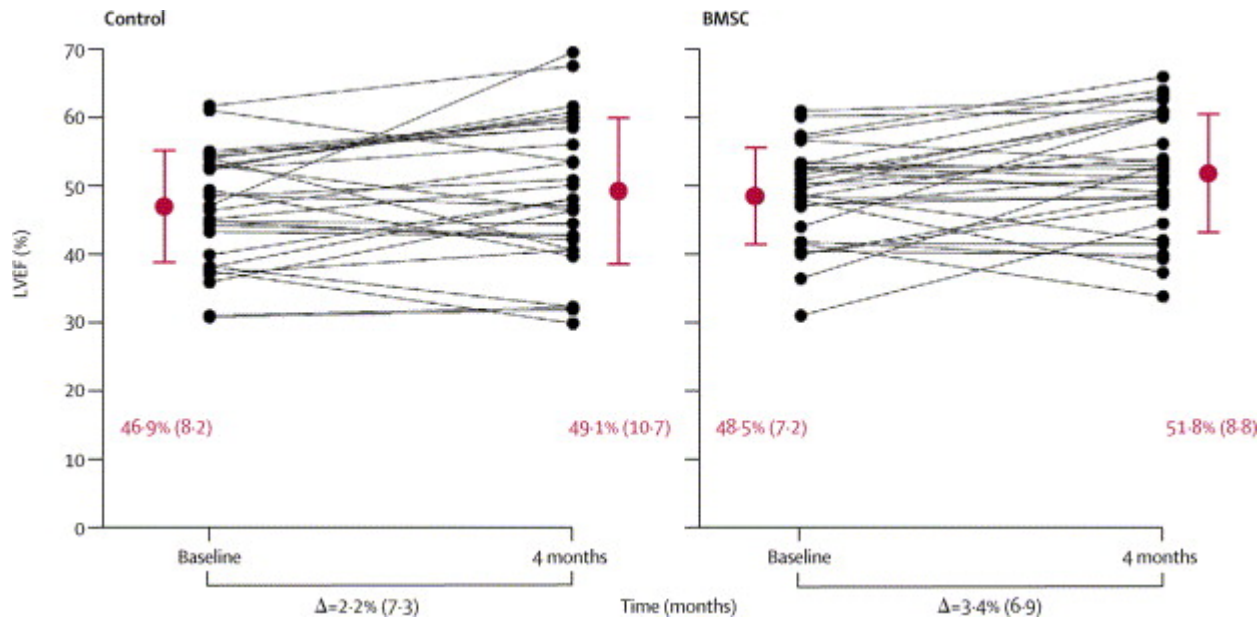


Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Janssen et al, Lancet 2006*

- Double blind PCB control.
- 34 placebo versus 33 BMSC
- Endpoint: LVEF change, infarct size, regional wall motion (MRI, PET)
- Follow up: 4 months
- Transferred cell number: 170 million mononuclear cells

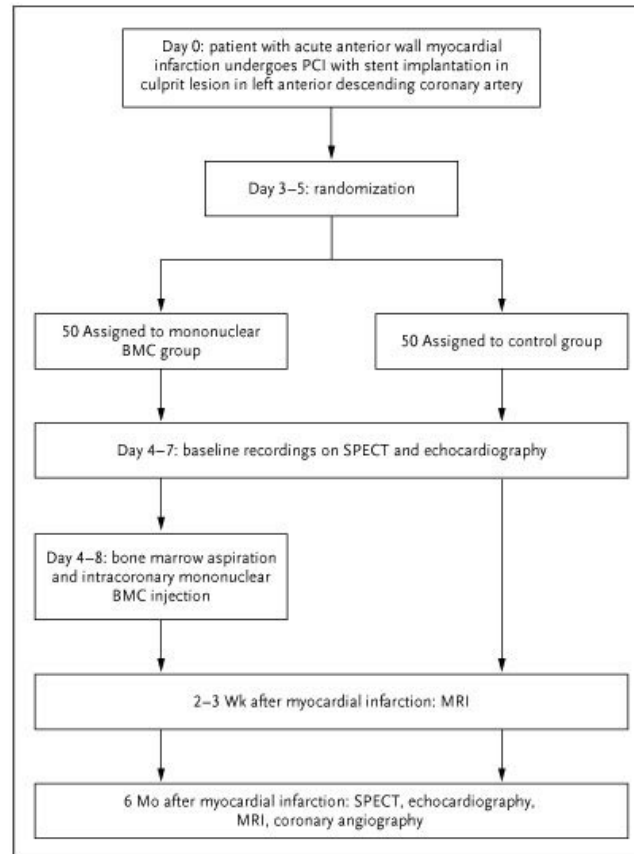


Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Janssen et al, Lancet 2006*



Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction. *Lunde, NEJM, 2006*

- Double blind Placebo control
- STEMI anterior wall
- 47 BM versus 50 placebo
- Endpoint in 6 mo: LVEF, ESV, infarct size.
- Endpoints assessed by: SPECT, MRI, Echo.
- Median time after injection: 6 days
- Median number of transferred cells: 100 millions



Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction. *Lunde, NEJM, 2006*

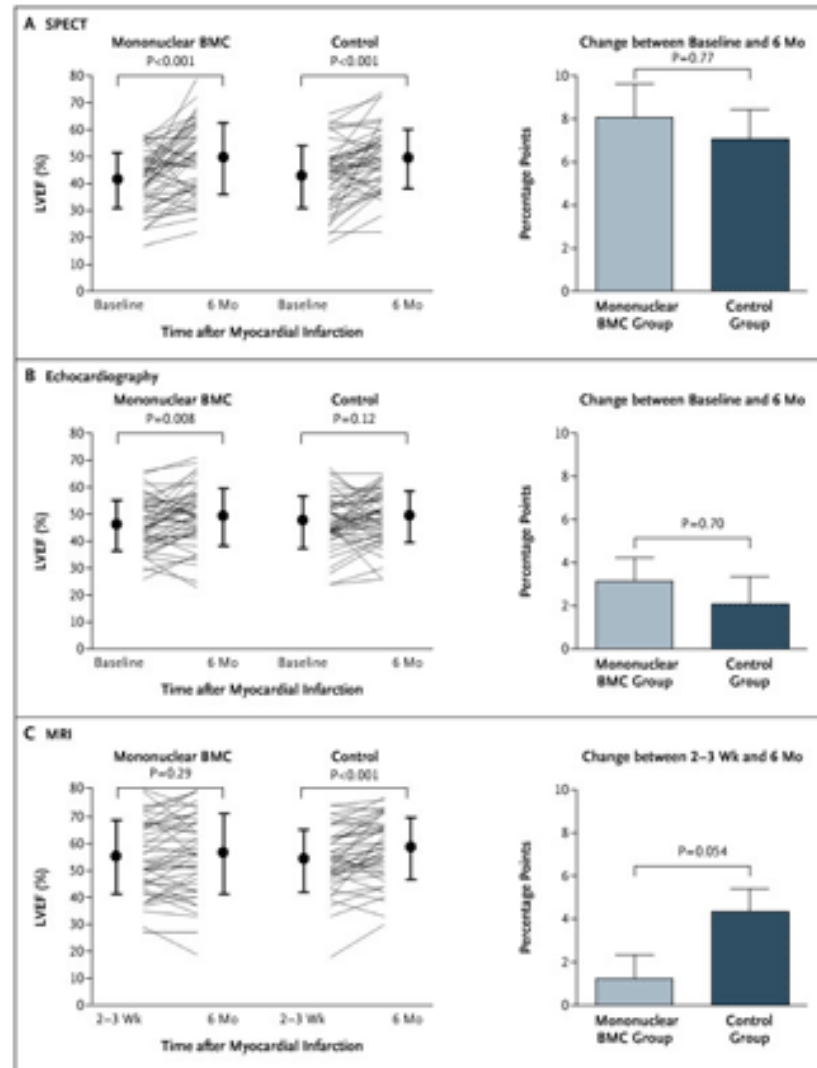
Table 2. LVEF, End-Diastolic Volume, and Infarct Size on SPECT and Echocardiography at Baseline and 6 Months after Myocardial Infarction.*

Analysis	Baseline		6 Mo		Change between Baseline and 6 Mo		Treatment Effect Change (95% CI)	P Value
	Mononuclear BMC Group (N=50)	Control Group (N=50)†	Mononuclear BMC Group (N=50)	Control Group (N=50)	Mononuclear BMC Group (N=50)	Control Group (N=50)		
SPECT								
LVEF (%)	41.3±10.4	42.6±11.7	49.3±13.2	49.3±11.0	8.1±11.2	7.0±9.6	0.6 (-3.4 to 4.6)	0.77
End-diastolic volume (ml)	162.3±59.1	148.0±46.3	151.1±52.9	146.0±50.0	-11.2±36.0	-1.8±17.6	-7.0 (-18.0 to 4.0)	0.21
Infarct size (%)	43.8±17.4	38.3±21.1	32.8±20.4	30.5±20.9	-11.0±12.7	-7.8±8.7	-2.8 (-7.1 to 1.6)	0.21
Echocardiography								
LVEF (%)	45.7±9.4	46.9±9.6	48.8±10.7	49.0±9.5	3.1±7.9	2.1±9.2	0.6 (-2.6 to 3.8)	0.70
End-diastolic volume (ml)	136.1±30.5	132.0±34.6	145.0±42.0	142.7±45.2	8.9±28.5	10.8±29.1	-1.9 (-13.4 to 9.6)	0.74

* Plus-minus values are means ±SD. The change between baseline and 6 months, as well as the treatment effect, was calculated for patients for whom data from both time points were available. Treatment-effect data and P values were obtained from analysis of covariance.

† SPECT readings for LVEF and end-diastolic volume could not be obtained for two patients in the control group at baseline owing to irregular heart rhythm.

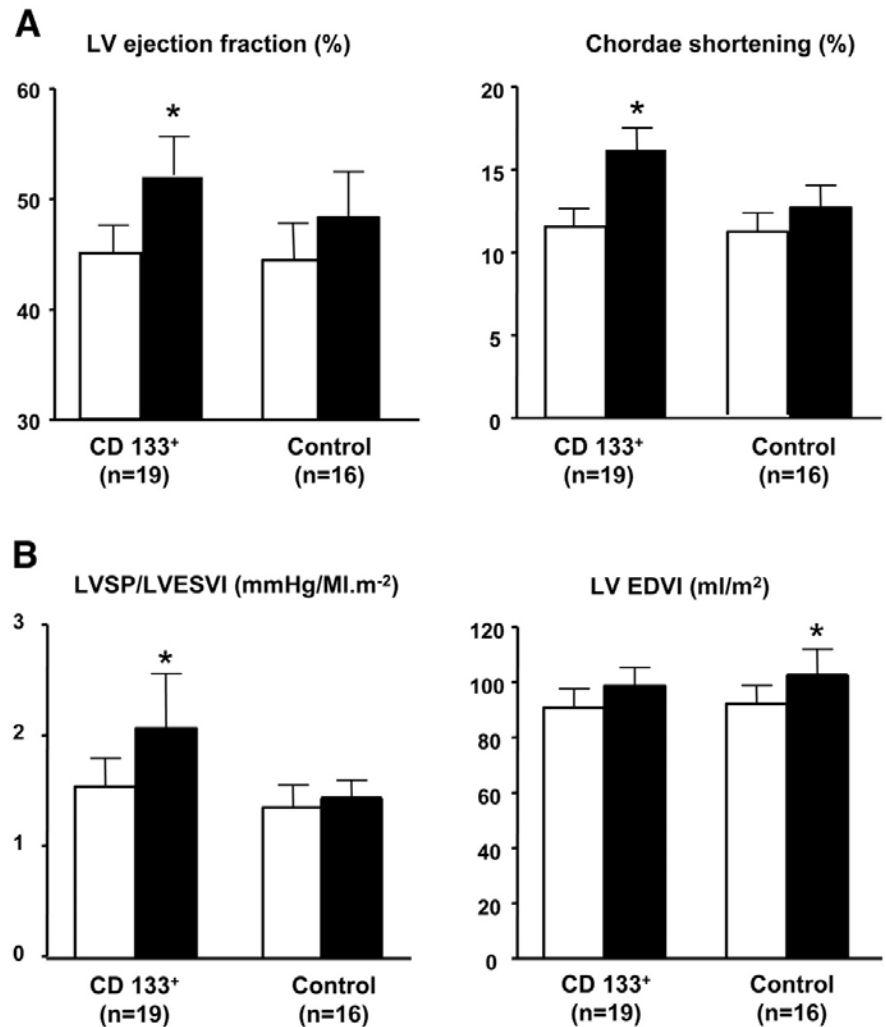
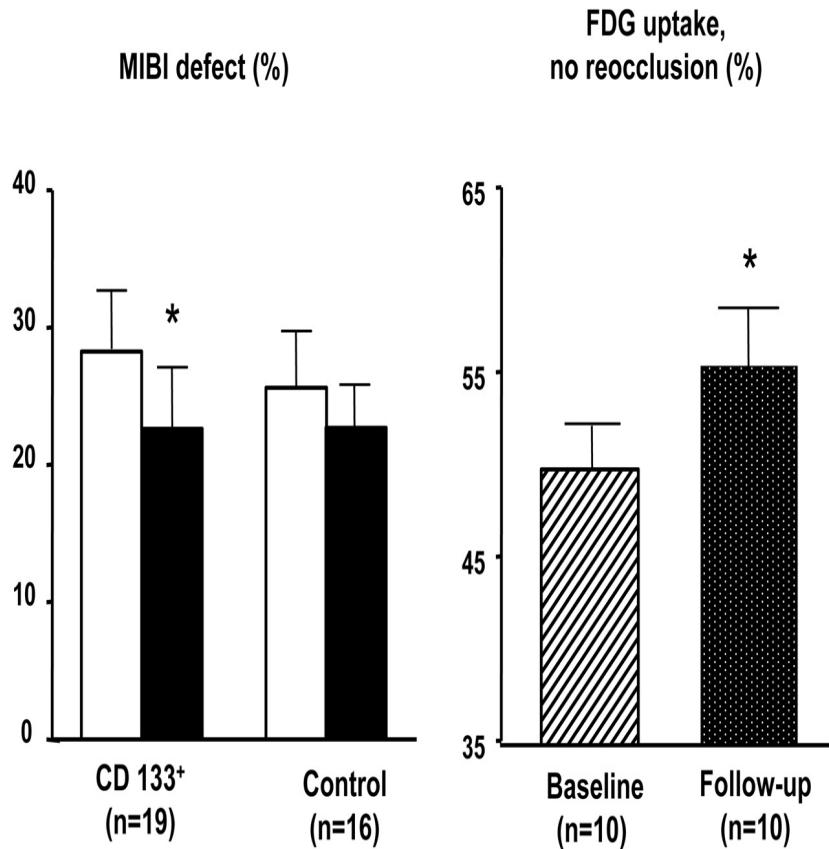
Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction. *Lunde, NEJM, 2006*



Intracoronary Injection of CD133-Positive Enriched Bone Marrow Progenitor Cells Promotes Cardiac Recovery After Recent Myocardial Infarction . *Bartunek et al. Circ. 2005*

- 19 CD133+ BMC versus 16 controls
- MIBI SPECT, LV angiogram, PET
- 4 Month follow up with repeat imaging.
- Median time after PCI – 11.6 days.

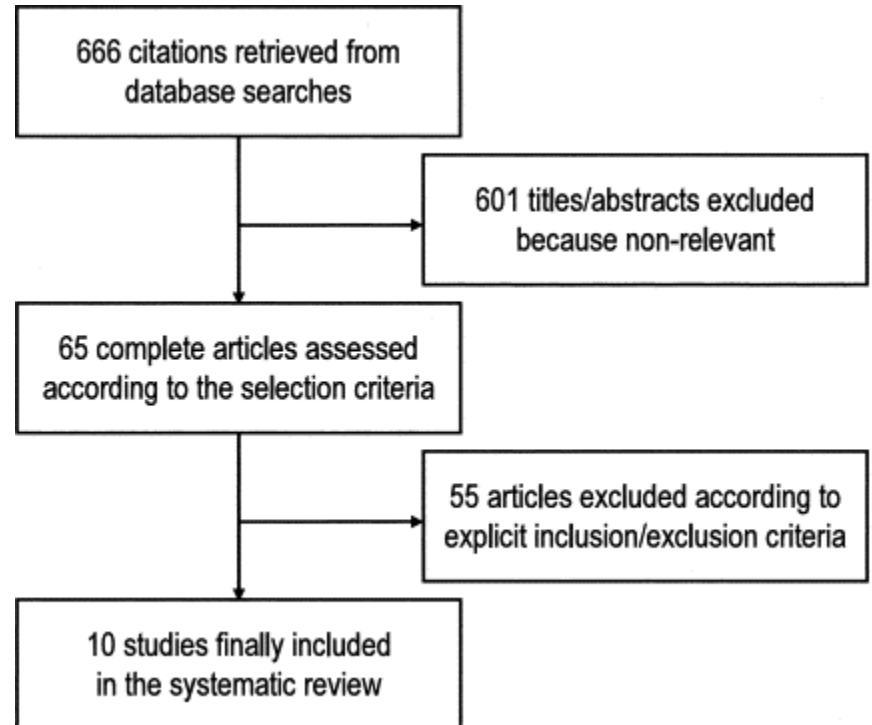
LV function and perfusion in treated patients and controls



Bartunek, J. et al. *Circulation* 2005;112:I-178-I-183

Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of AMI: Meta-Analysis of Controlled Clinical Trials

- A 3% improvement in LVEF
($p < 0.0001$)
- A 7.5 ml reduction in LV ESV
($p < 0.002$)
- LVEDV not statistically changed
- No significant effect on MACE
- A significant reduction in reinfarction



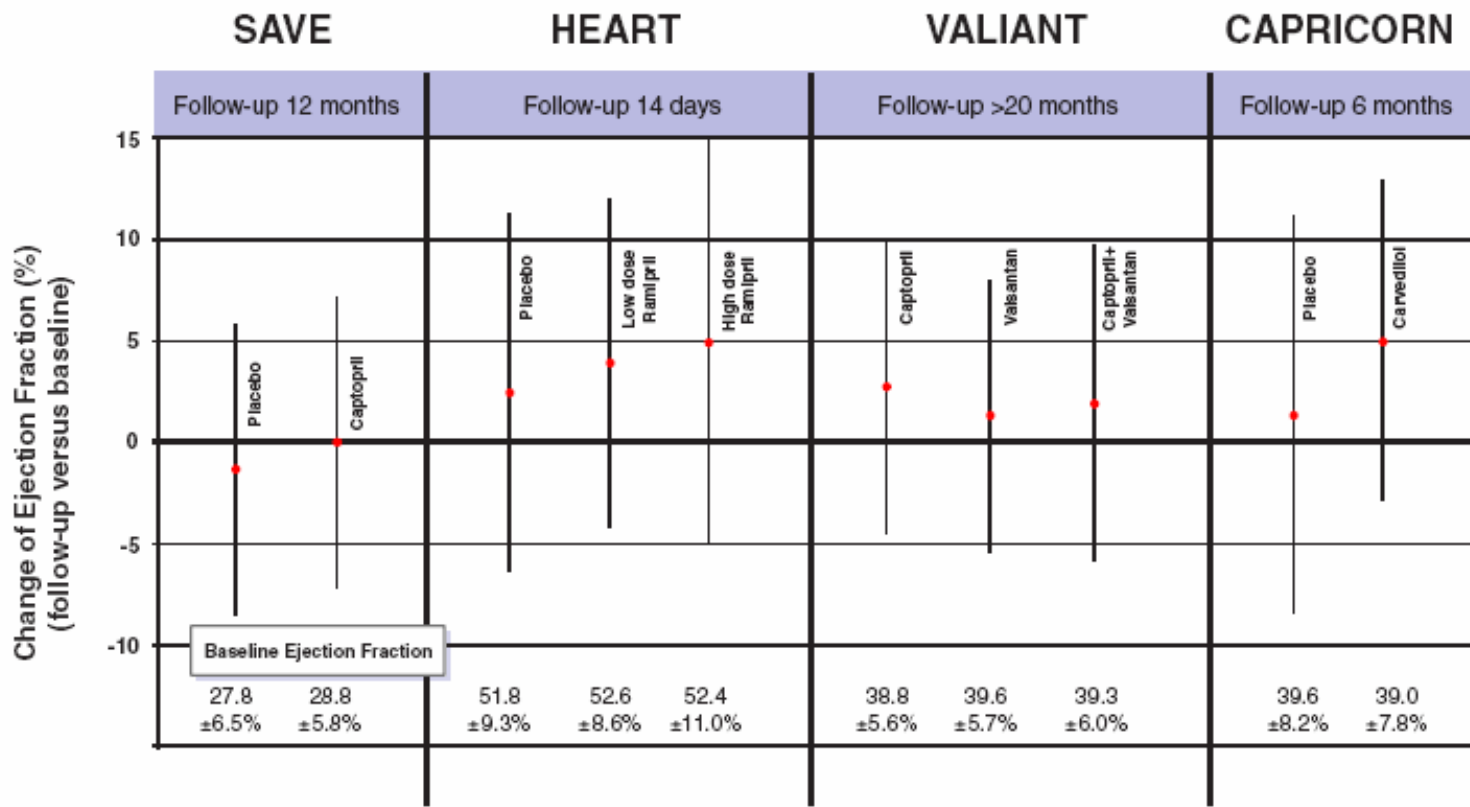


Figure 1 Changes in Left Ventricular Echocardiographic Ejection Fraction From Baseline to Follow-Up

Conclusions

- Marginal effect on global LVEF.
- Fair Safety profile
- Feasible.
- Can not discriminate pts most likely to benefit due to small numbers.

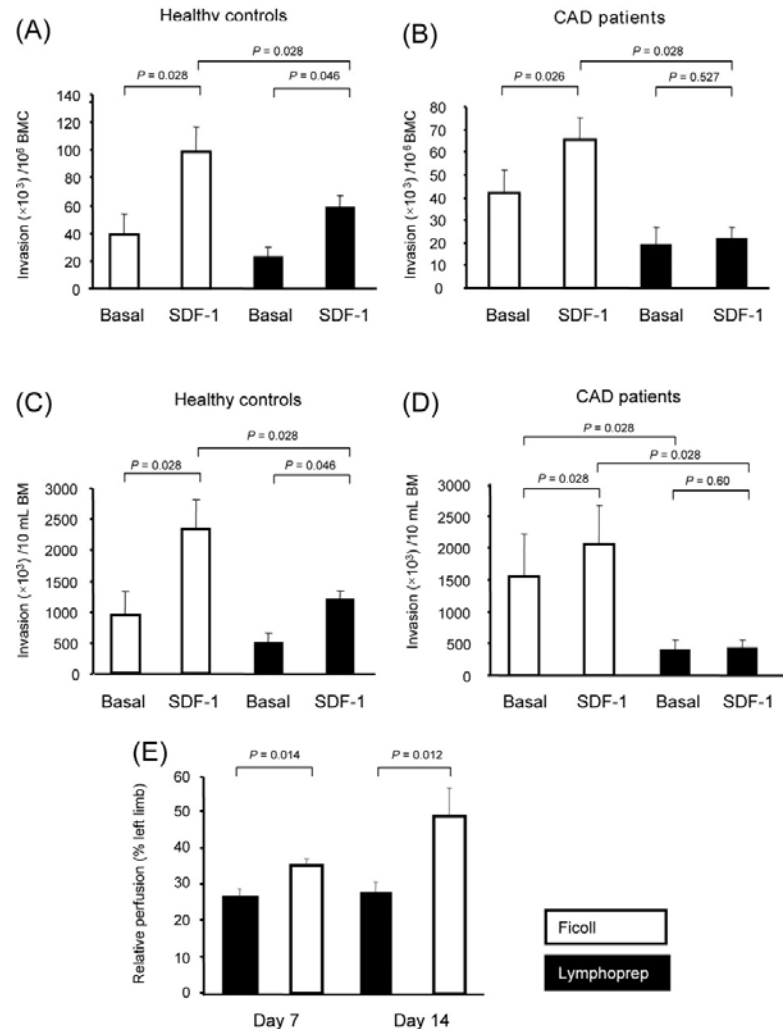
Potential explanation for the conflicting results

- Timing of Cell transfer with relation to PCI (REPAIR AMI).
- The nature of injected cells (total BM versus CD133).
- Use of imaging to quantify endpoints (LVEF).
- Severity of LV compromise.
- Different numbers of cells.
- Different preparations of cells.

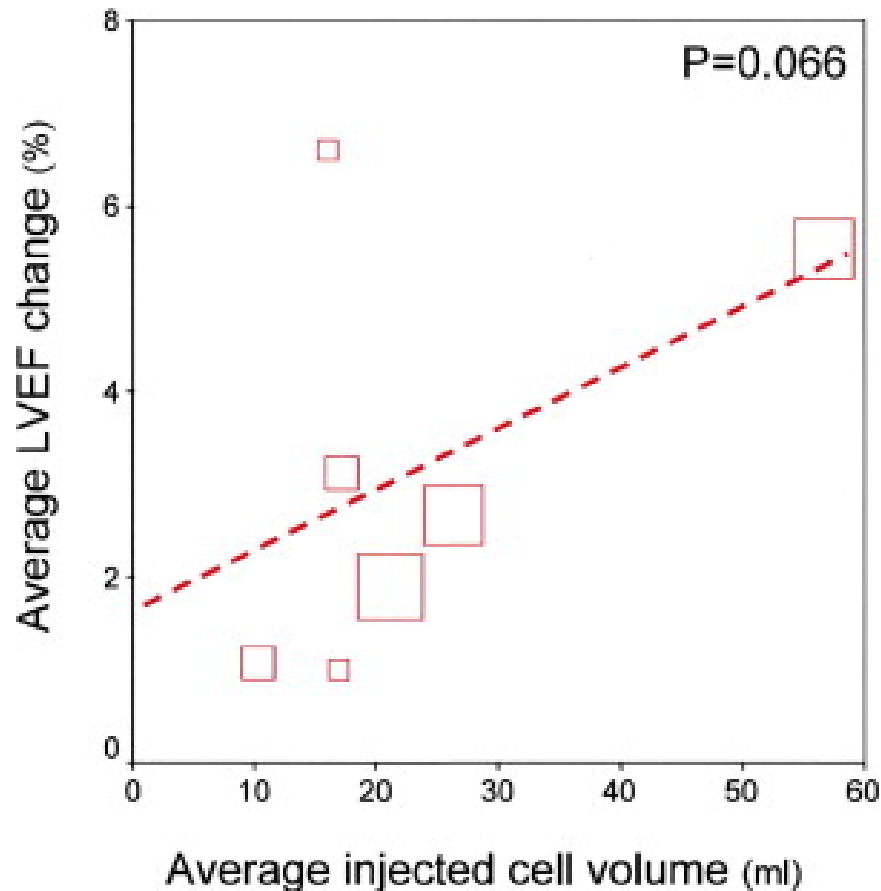


Cell isolation procedures matter: a comparison of different isolation protocols of bone marrow mononuclear cells used for cell therapy in patients with acute myocardial infarction. *Seeger et al, EHJ. 2007*

	Ficoll protocol	Lymphoprep protocol	P-value
Recovery of BMC (10^6)	13 ± 25.5	7.6 ± 19.1	0.027
Viability (%)	0 ± 99	0 ± 99	1.0
CD45 ⁺ /CD34 ⁺ BMC (10^5)	4.8 ± 6.8	3.6 ± 4.4	0.043
CFU	3919 ± 5270	2425 ± 3891	0.023
MSC	123 ± 230	160 ± 161	0.015
CXCR4 ⁺ BMC	851 ± 1357	292 ± 447	0.02
Basal invasion ($\times 10^3$)	1307 ± 1244	384 ± 448	0.04
SDF-1 invasion ($\times 10^3$)	1287 ± 2195	501 ± 822	0.02
Perfusion in hindlimb ischaemia (%)	23 ± 48	7.5 ± 26	0.012



Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of Acute Myocardial Infarction A Collaborative Systematic Review and Meta-Analysis of Controlled Clinical Trials. *Lipinsky et al. JACC, 2007*



L'Abbé plot shows the overall trend toward a statistically significant association between average volume injected in the culprit coronary artery and average change in left ventricular ejection fraction (LVEF) across included studies (**squares**), with the size of each square proportional to sample size. This trend supports the presence of a dose-response relationship.

Unsolved Questions

1) How to define an endothelial progenitor cells?

- Origin of endothelial progenitor cells?
- Definition of subpopulation with different functional capacities ?

2) Signals for EPC homing and differentiation in vivo

- Optimization of ex vivo culture conditions to enhance the benefit of cell therapy?
- Influence of the severity of vascular damage on the contribution of EPCs to regeneration?

3) Mechanisms of action

- Transdifferentiation capacity of different progenitor cells
- Importance of paracrine effects

**CARDIOSphere-Derived autologous Stem Cells to Reverse
ventricular dysfunction (CADUCEUS)**
This study is currently recruiting participants.

Sponsors and
Collaborators: **Cedars-Sinai Medical Center**
[National Institutes of Health \(NIH\)](#)
[National Heart, Lung, and Blood Institute \(NHLBI\)](#)
Johns Hopkins University
The EMMES Corporation

Information provided by: Cedars-Sinai Medical Center

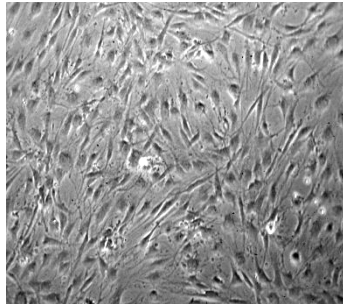
ClinicalTrials.gov Identifier: NCT00893360

Study Type: **Interventional**
Study Design: **Treatment, Randomized, Open Label, Dose Comparison, Parallel
Assignment, Safety Study**
Official Title: **A Phase I Randomized, Dose Escalation Study of the Safety and Efficacy
of Intracoronary Delivery of Cardiosphere-Derived Stem Cells in
Patients With Ischemic Left Ventricular Dysfunction and a Recent
Myocardial Infarction**

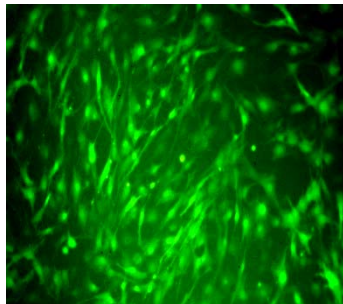
CELL THERAPY STUDIES- A GLIMPSE INTO THE FUTURE

HIF-1/2 α overexpression in endothelial progenitor cells

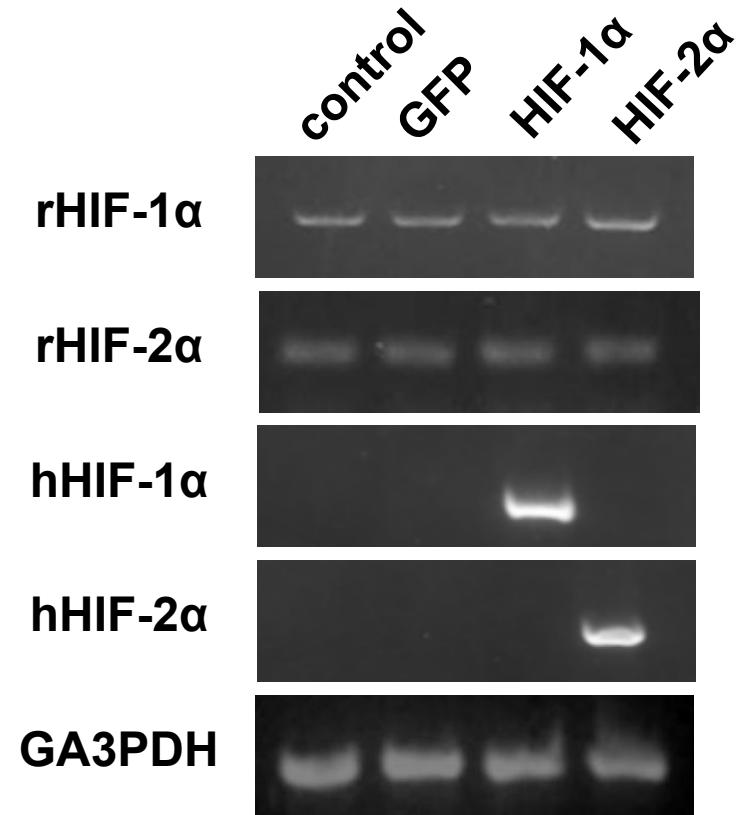
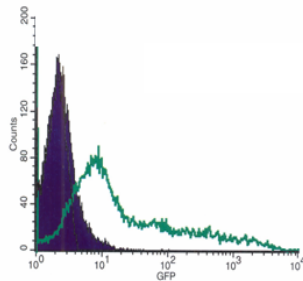
phase contrast



retroviral transduction



GFP analysis



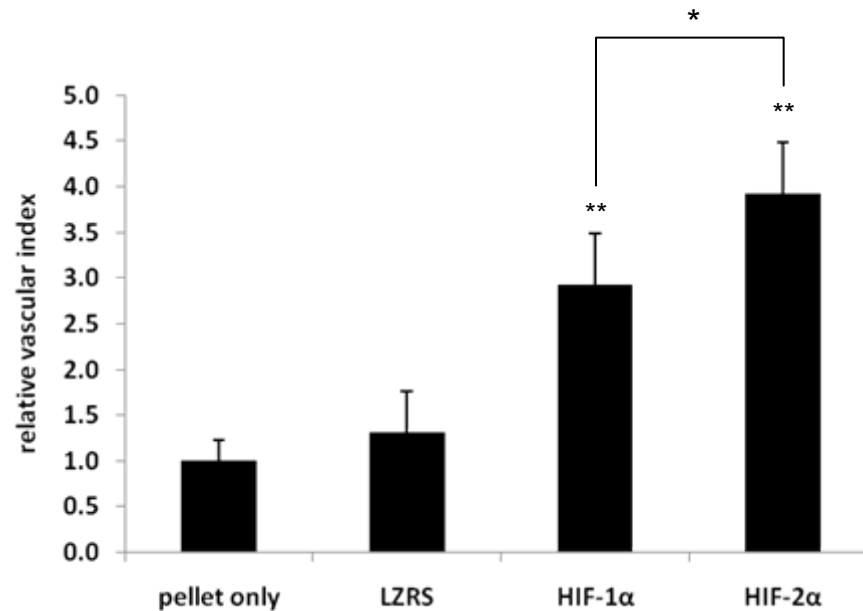
CELL THERAPY STUDIES- A GLIMPSE INTO THE FUTURE



Day 0

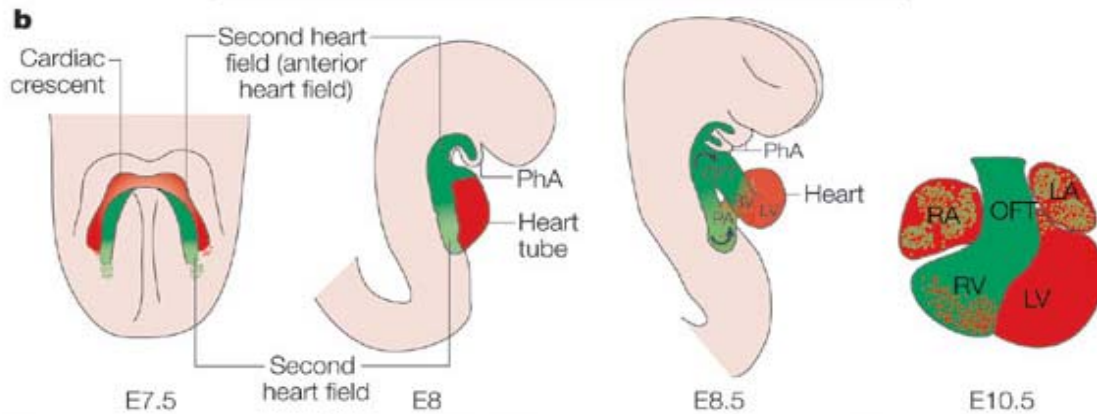
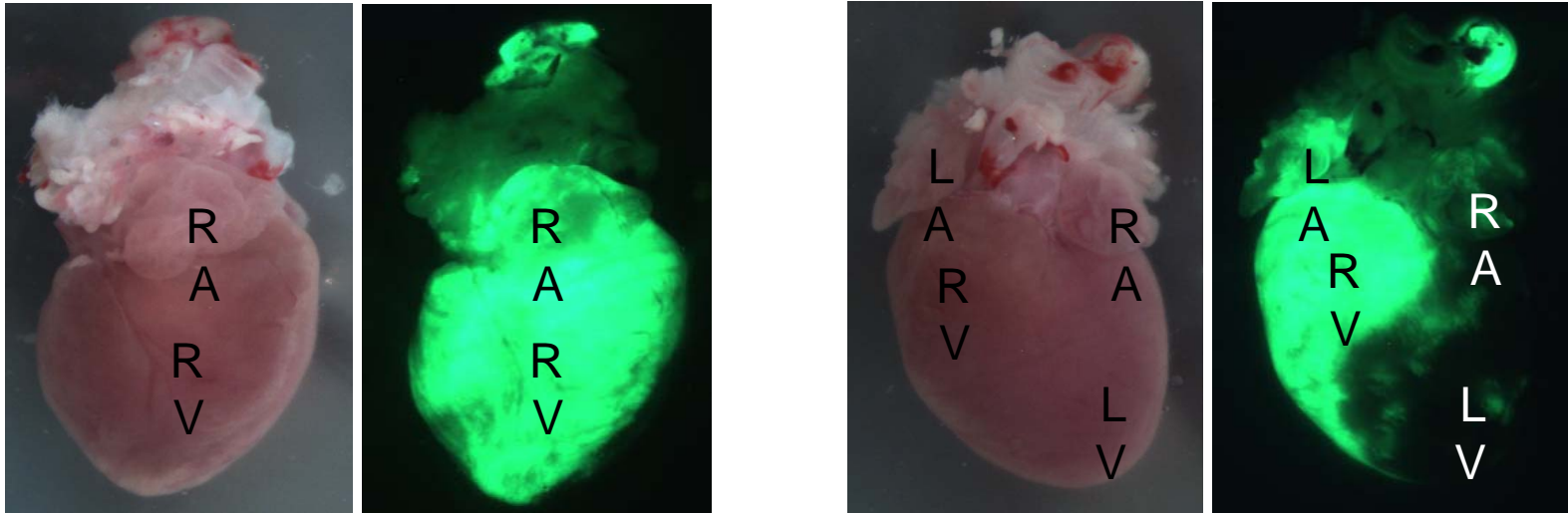
Day 8

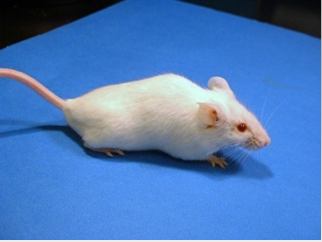
**bFGF pellet
implantation
+
Injection of
HIF- α transduced
cells**



***Isl1/cre/Z/EG* mouse's heart - *Isl1* progeny is marked with eGFP**

***Isl1*-IRES-Cre/R26R x *Z/EG* double reporter mice :**





Isl1 gene transfer to the peri infarct mouse's heart

