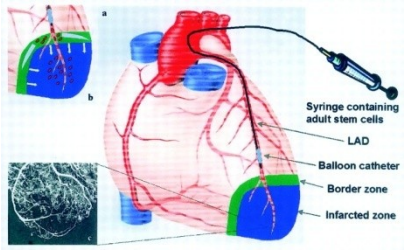
Progenitor cell therapy in acute MI



Jacob George
Tel Aviv Medical Center

The Endothelial cells as a paracrine factory

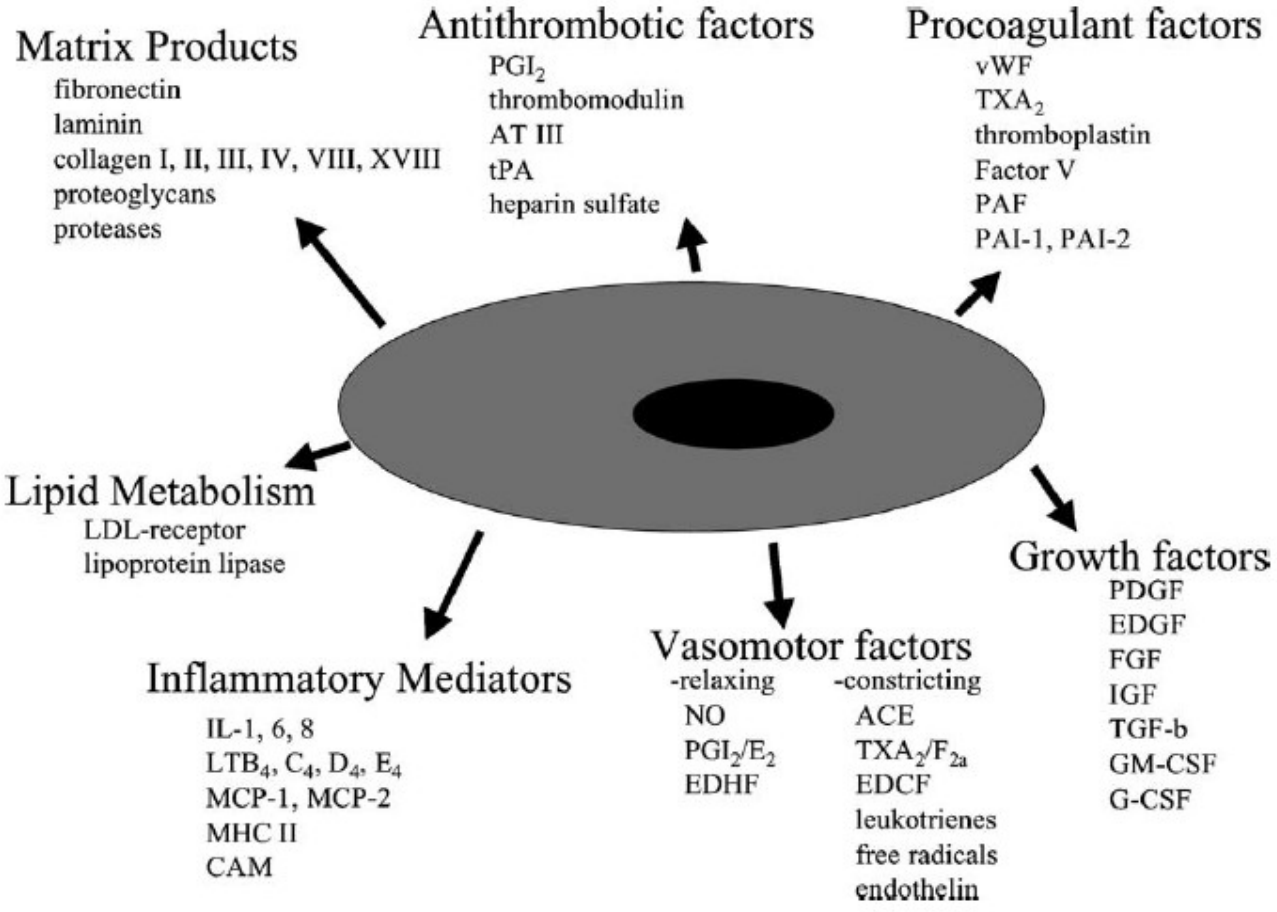
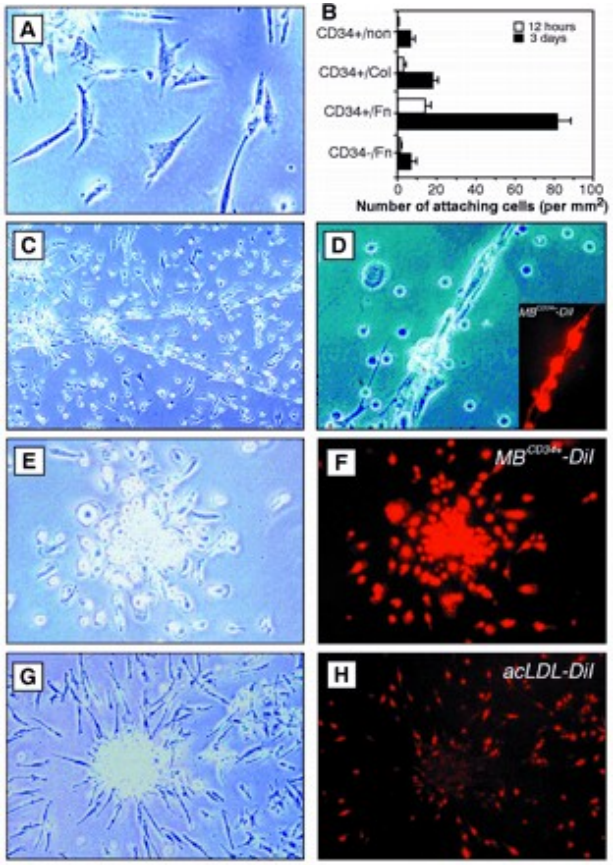


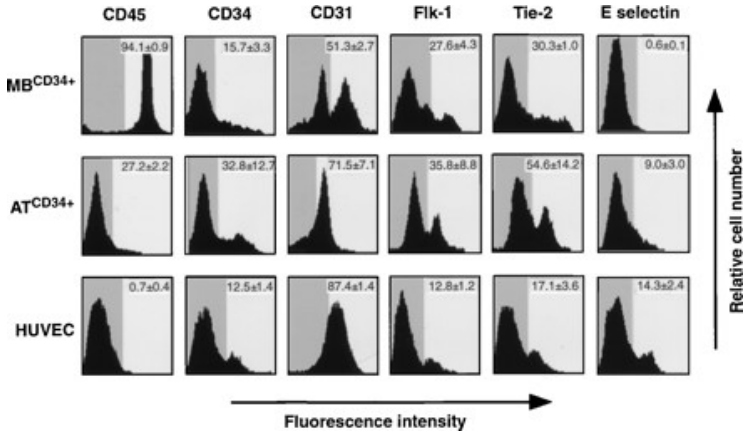
Fig. 1. Known secretory/expression products of endothelial cells relating to vessel physiology.

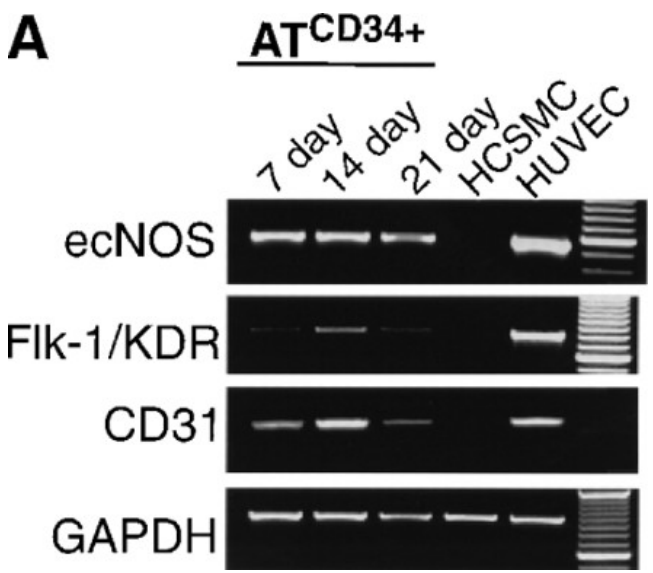
Isolation of putative progenitor endothelial cells for angiogenesis.

Asahara et al. *Science 1997*

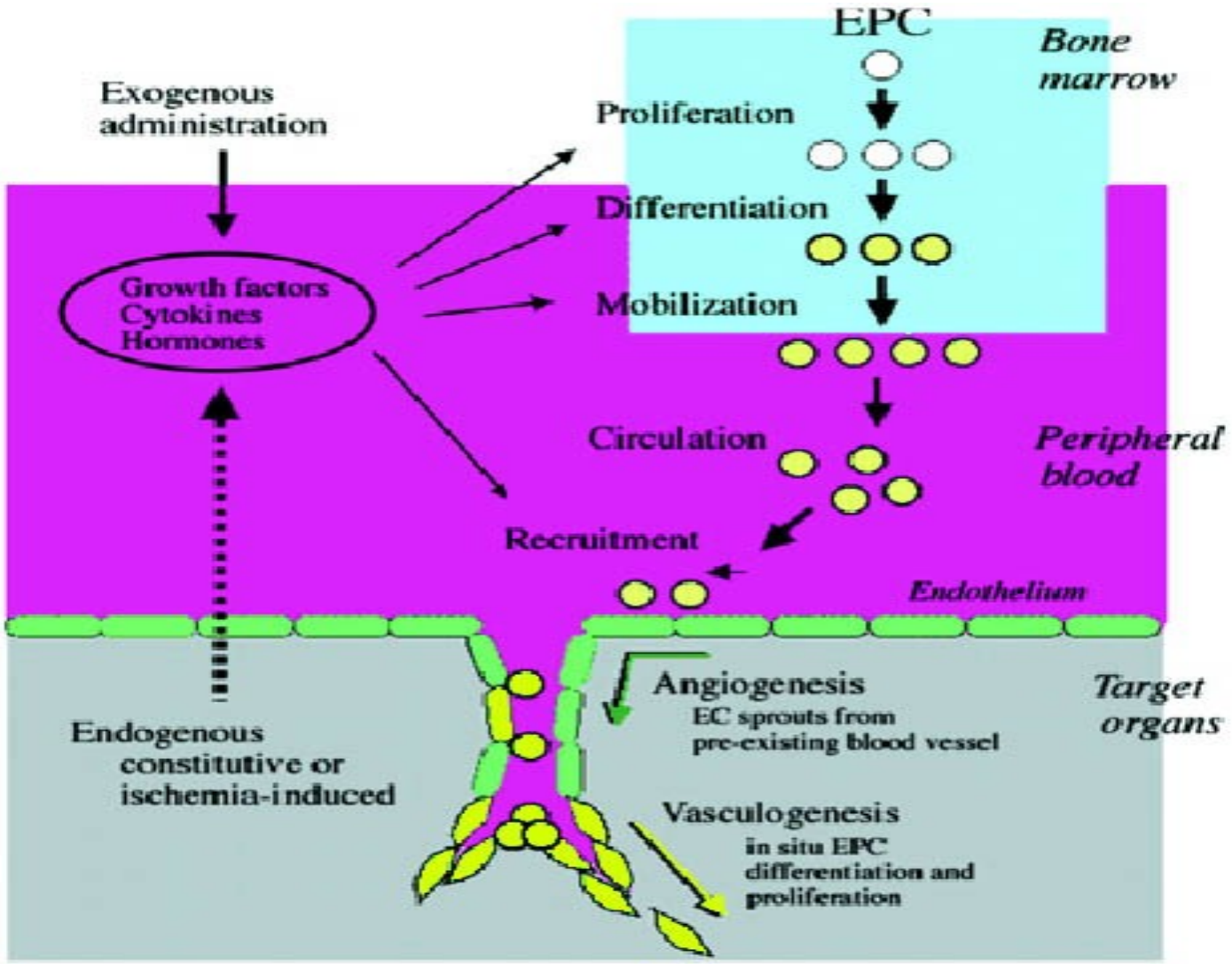


Attachment, cluster formation, and capillary network development by progenitor ECs in vitro



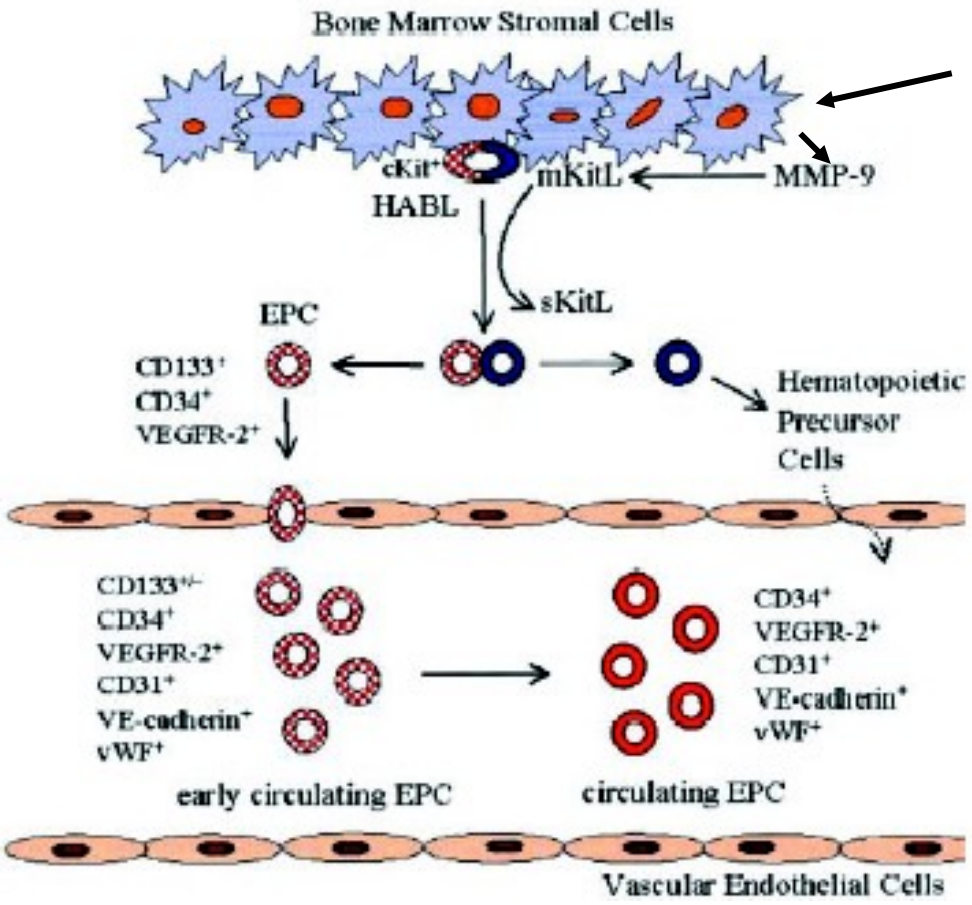


Endothelial progenitor cell hemostasis

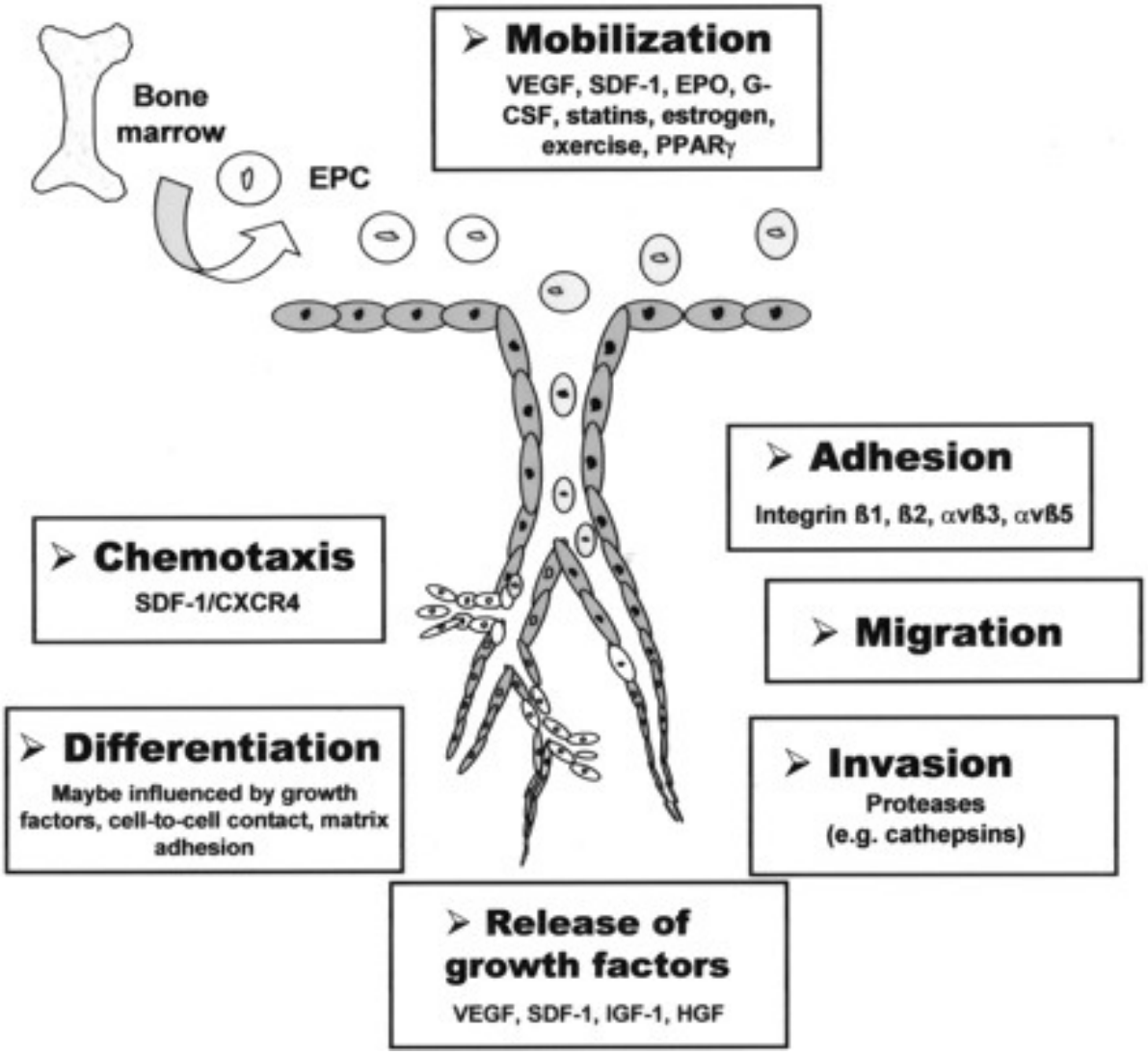


(Endothelial progenitor cells (EPC

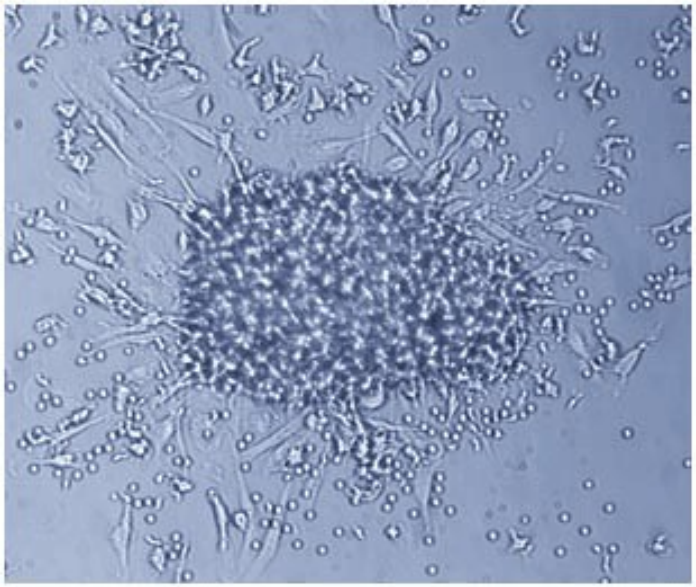
Common markers
+CD34
+Flk-1
+Sca-I
+AC133

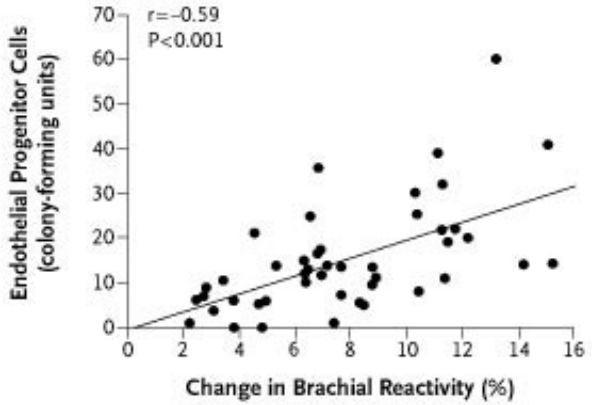


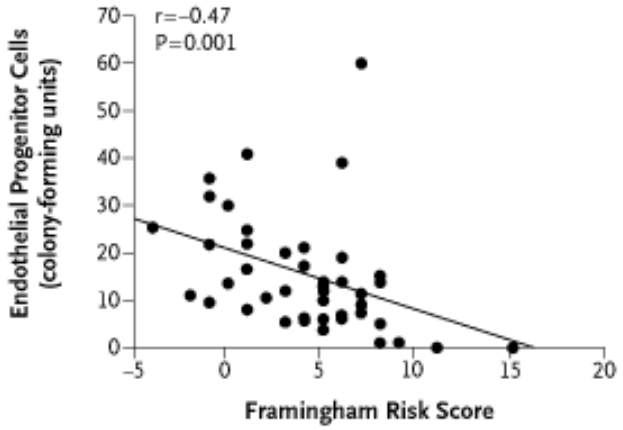
VEGF,
PIGF

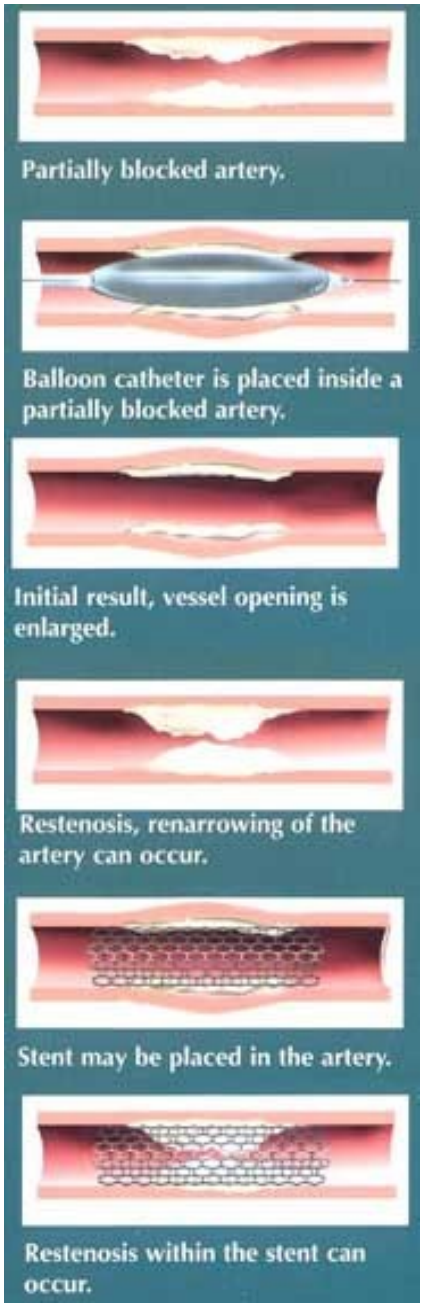

Bone marrow
EPC
➢ Mobilization
VEGF, SDF-1, EPO, G-CSF, statins, estrogen, exercise, PPARγ
➢ Adhesion
Integrin ß1, ß2, αvß3, αvß5
➢ Chemotaxis
SDF-1/CXCR4
➢ Migration
➢ Differentiation
Maybe influenced by growth factors, cell-to-cell contact, matrix adhesion
➢ Invasion
Proteases
(e.g. cathepsins)
➢ Release of growth factors
VEGF, SDF-1, IGF-1, HGF

Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *Hill et al NEJM, 2003*





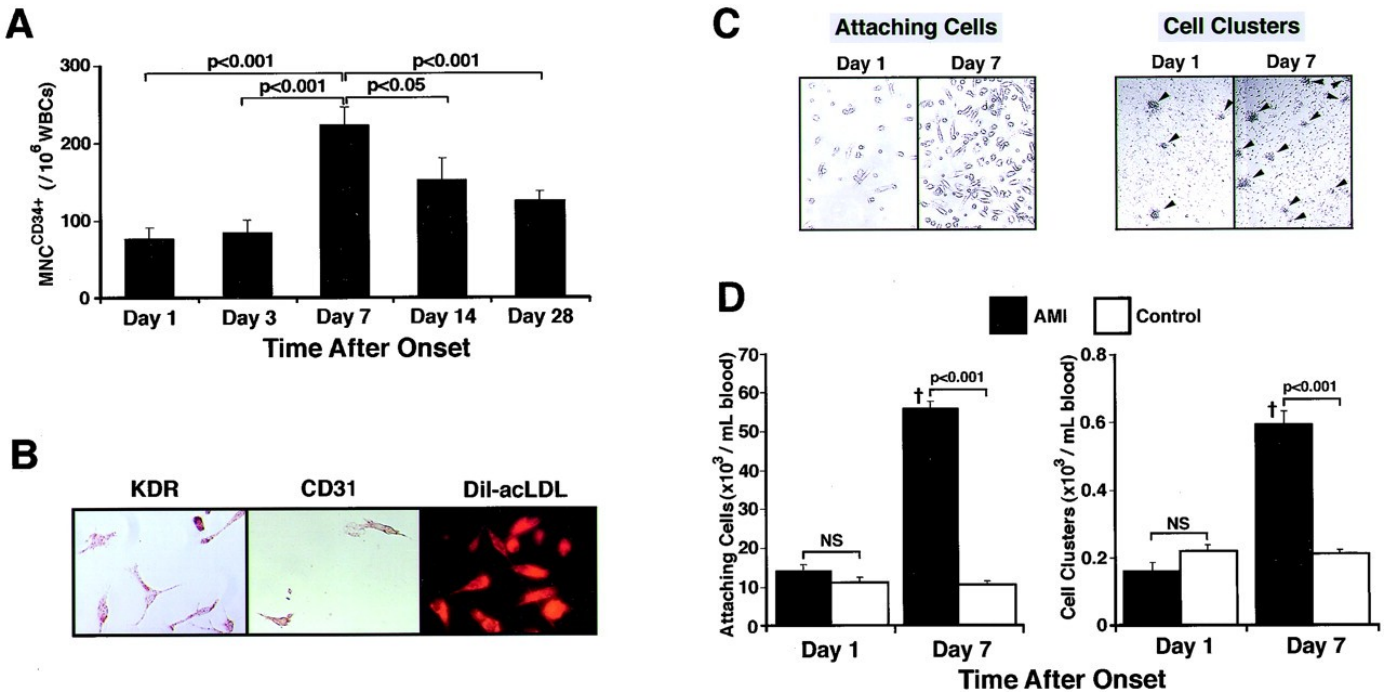




Number and adhesive properties of circulating endothelial progenitor cells in patients with in-stent restenosis. *George et al. Arterioscler Thromb Vasc Biol 2003*

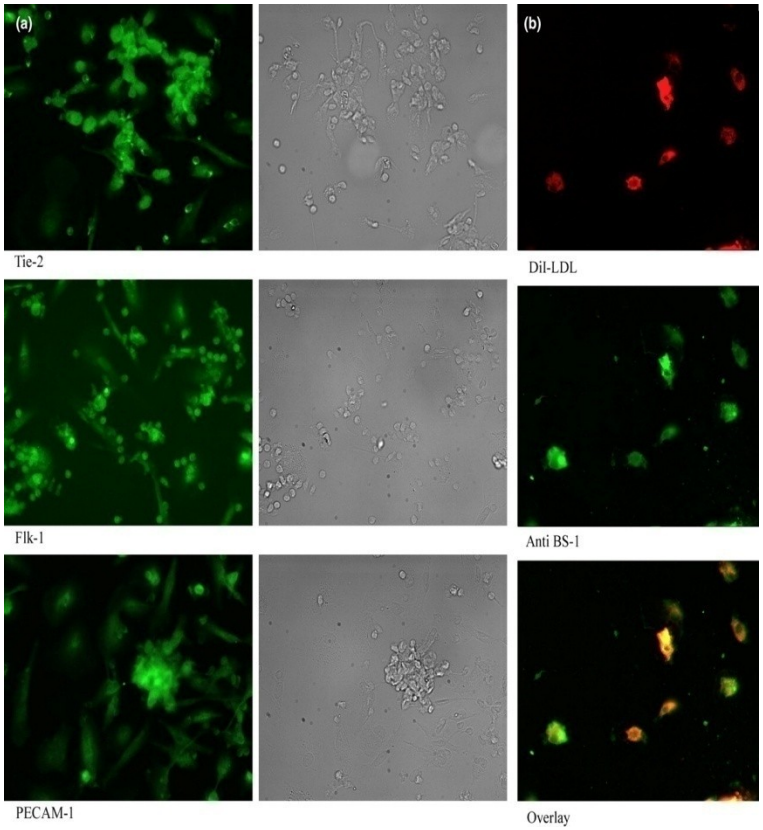
Impaired endothelialization and in stent restenosis

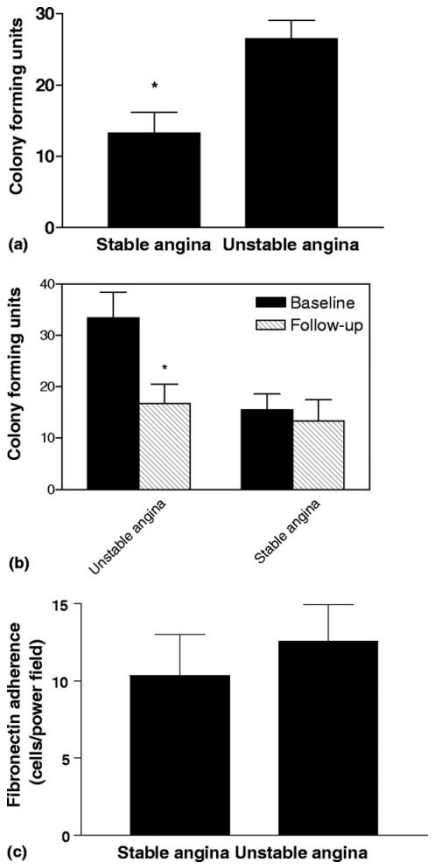
Circulating progenitors after AMI



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

Circulating endothelial progenitors in patients with ACS



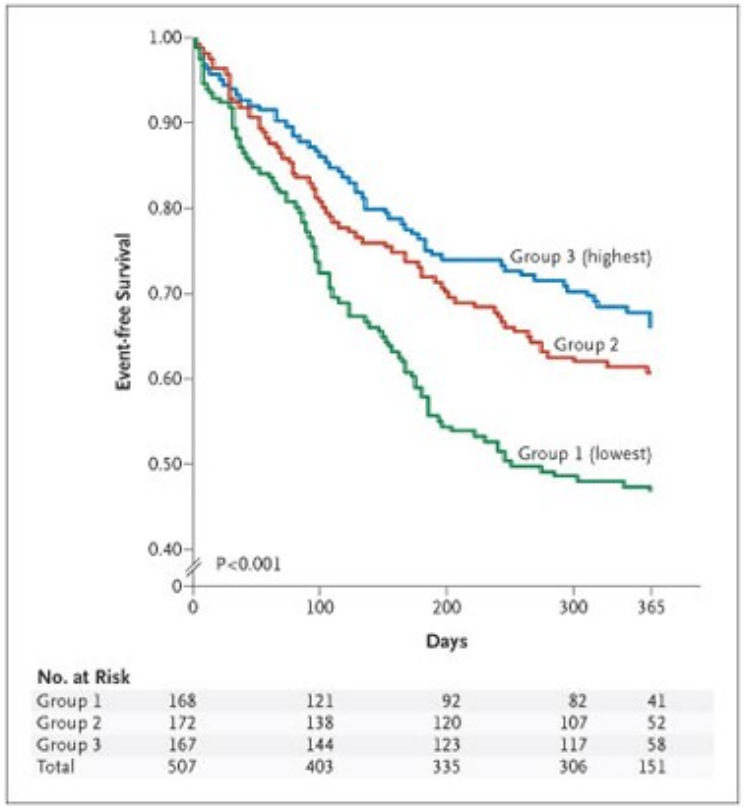


George, J. et al. Eur Heart J 2004 25:1003-1008; doi:10.1016/j.ehj.2004.03.026

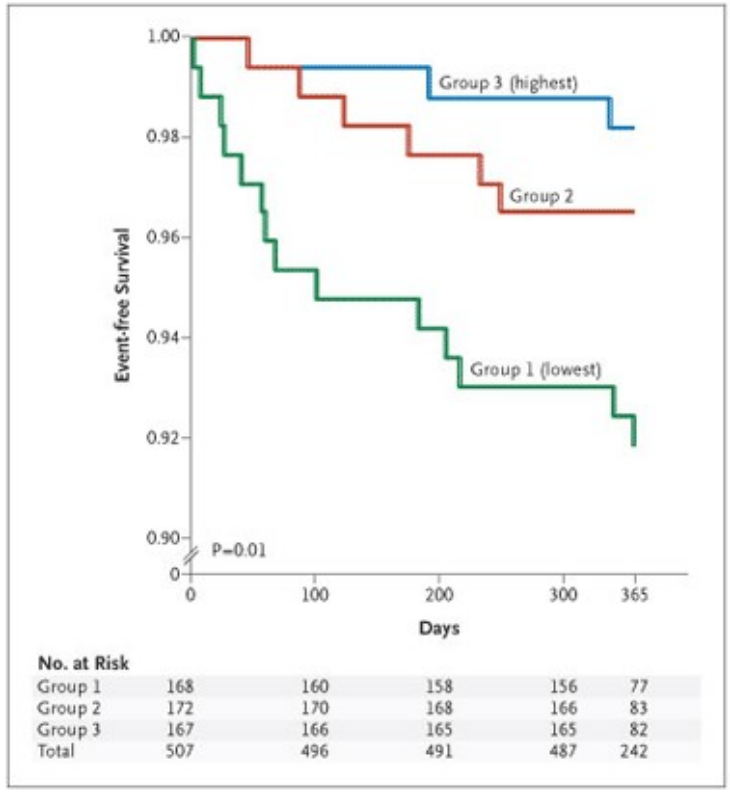
European Heart Journal

Circulating Endothelial Progenitor Cells and Cardiovascular Outcomes

(Werner et al. NEJM September, 2005



No. at Risk					
Group 1	168	121	92	82	41
Group 2	172	138	120	107	52
Group 3	167	144	123	117	58
Total	507	403	335	306	151

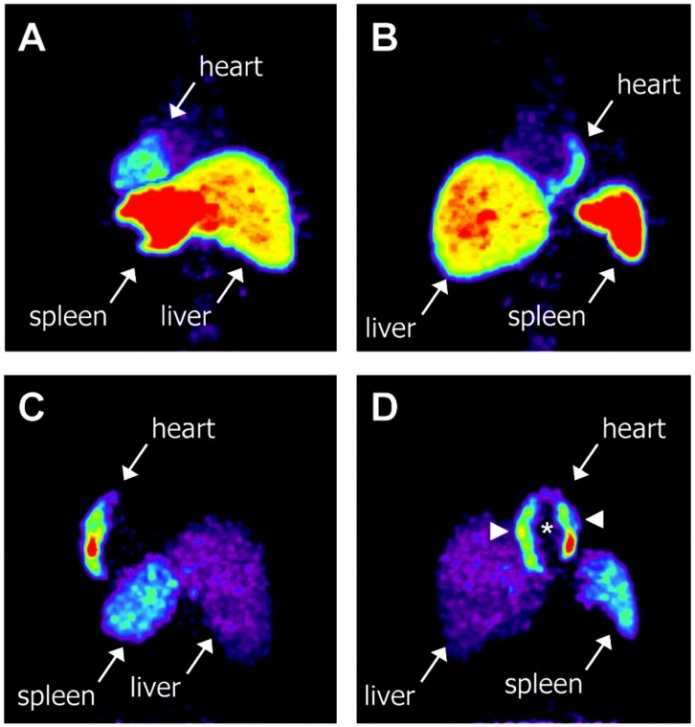


No. at Risk					
Group 1	168	160	158	156	77
Group 2	172	170	168	166	83
Group 3	167	166	165	165	82
Total	507	496	491	487	242

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 18F-FDG-labeled BMCs



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

Circulation

Which cell to be used for myocardial therapy

- Bone Marrow derived MSC
- EPC (PB BM)
- Cardiomyocyte
- De differentiated EPC ($CD133+$, $KDR+$)

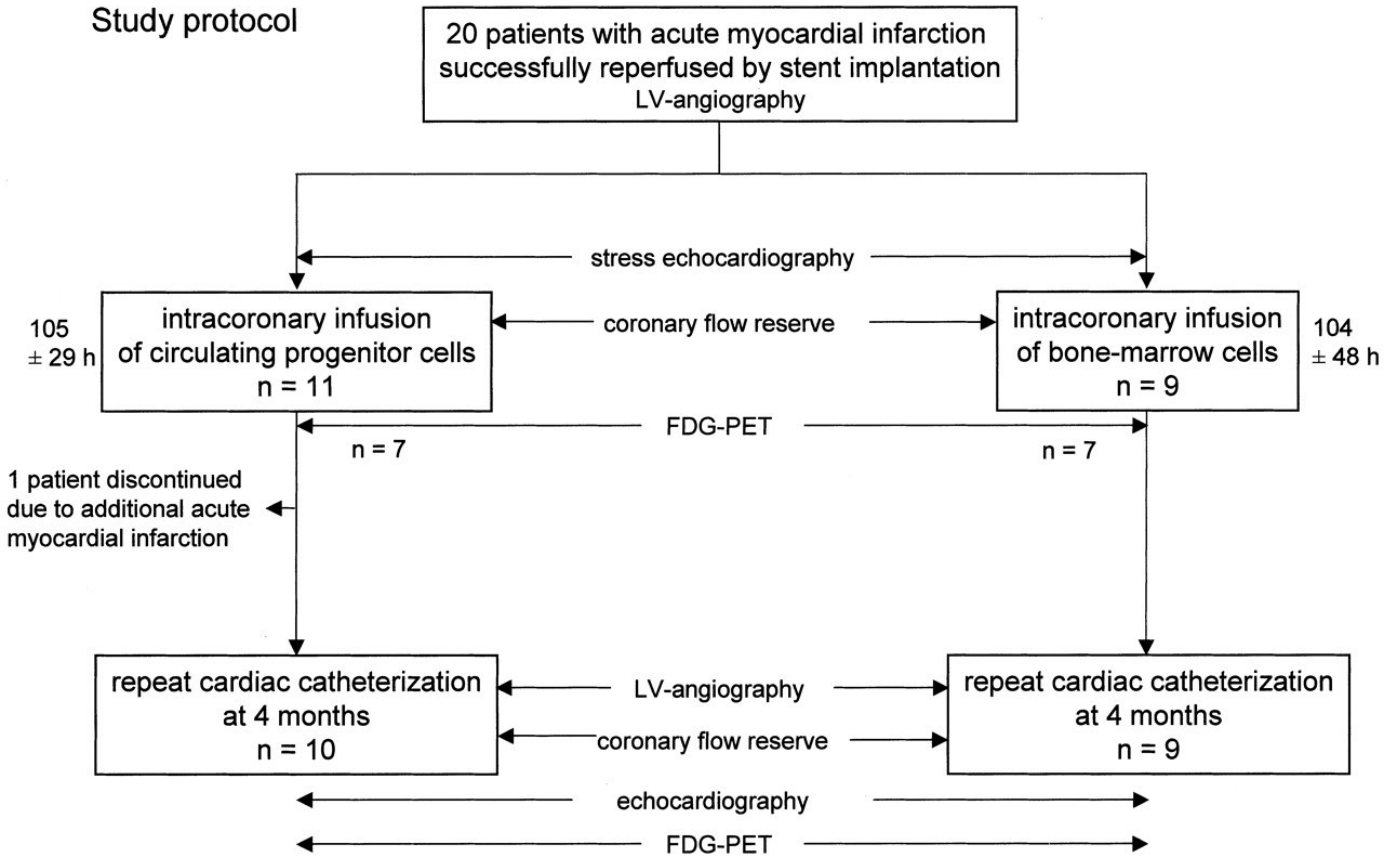
Delivery modes of cells

Intravenous

Intracoronary

Intramyocardial

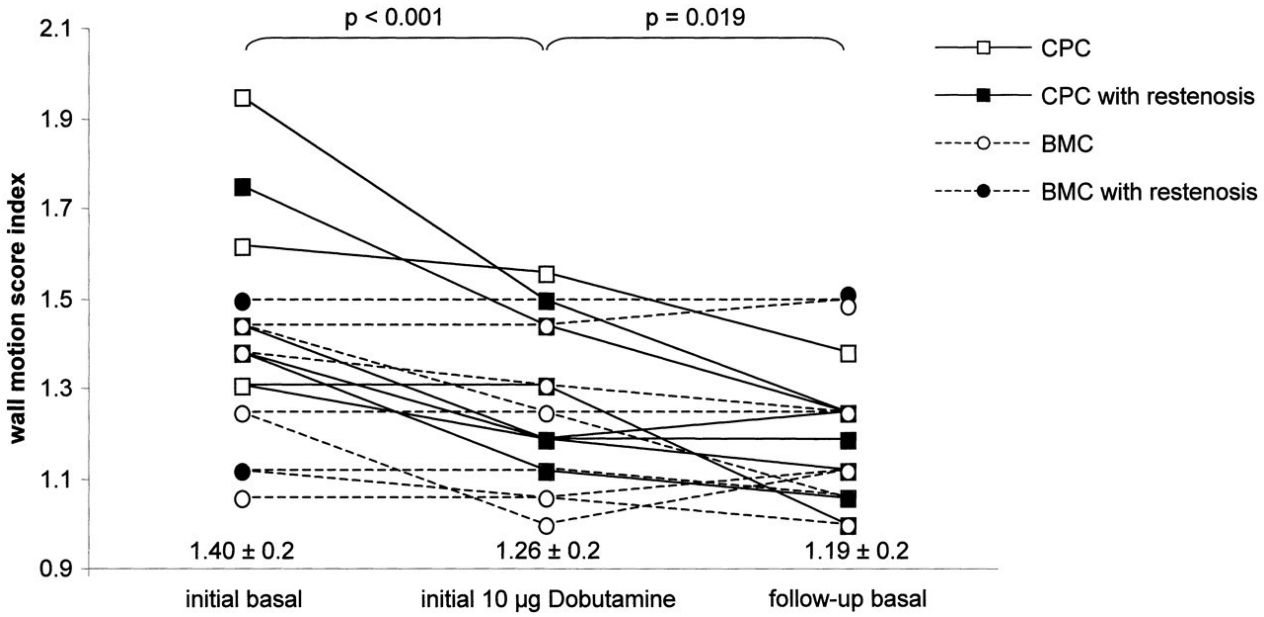
TOPCARE-AMI *Assmus, et al, Circ 2002*



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

Circulation

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

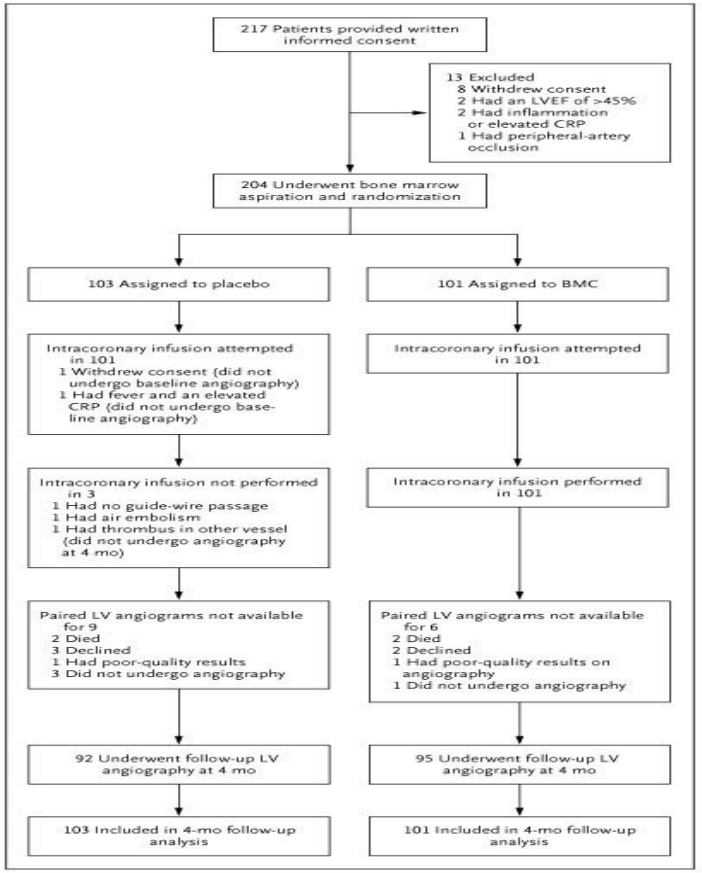


Assmus, B. et al. Circulation 2002;106:3009-3017

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

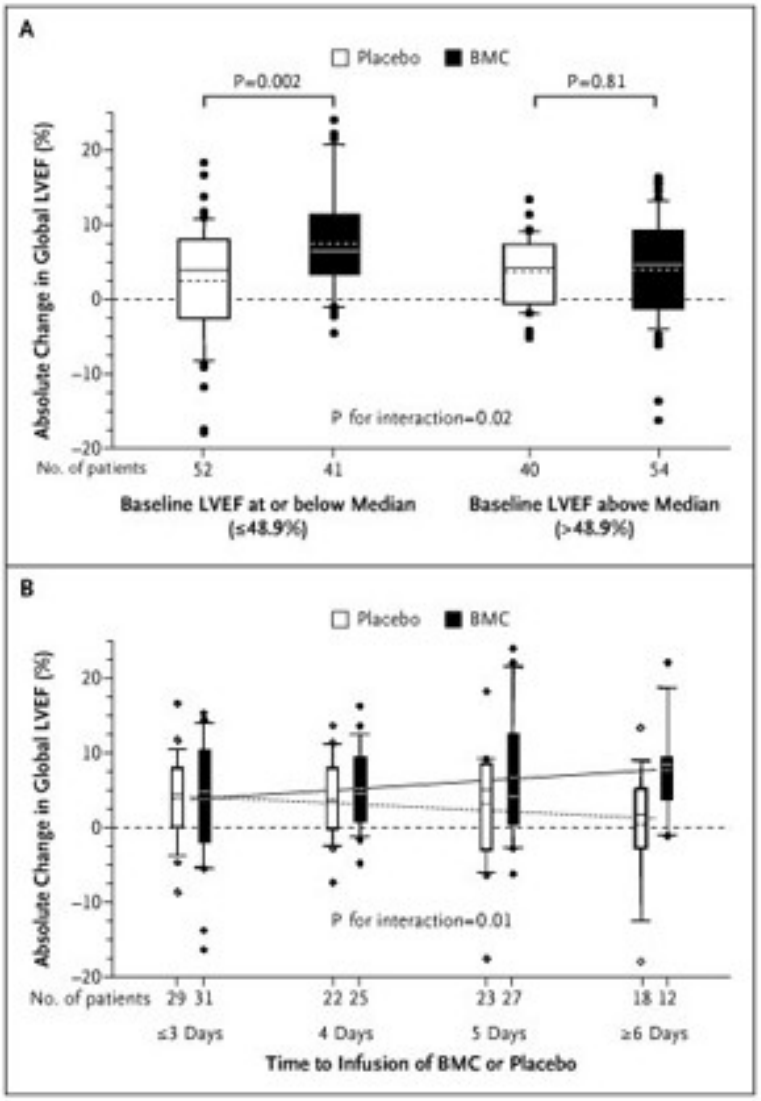
Table 2. Quantitative Measures of Left Ventricular Function.*

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	

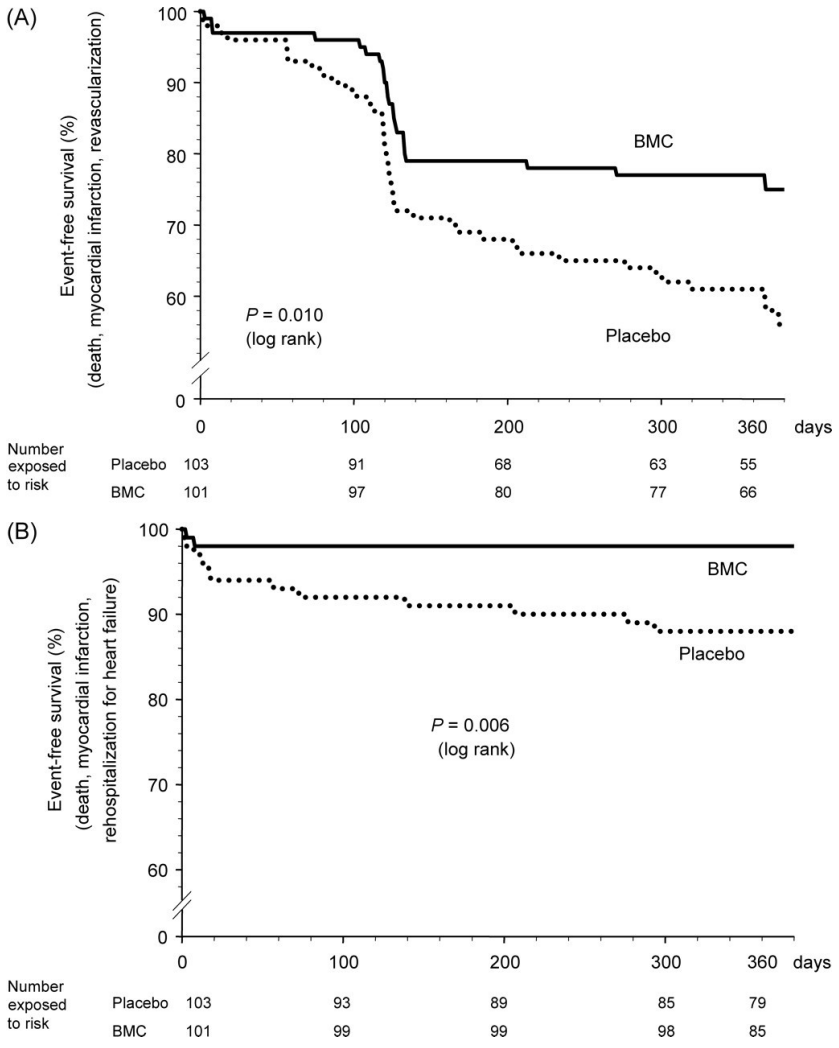
* Plus–minus values are means ±SD. P values were determined by analysis of variance.
† P=0.05 by nonparametric testing.
‡ P=0.04 by nonparametric testing.
§ P=0.07 by nonparametric testing.
¶ P=0.06 by nonparametric testing.
‖ P=0.09 by nonparametric testing.
** Values represent the cumulative analysis 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



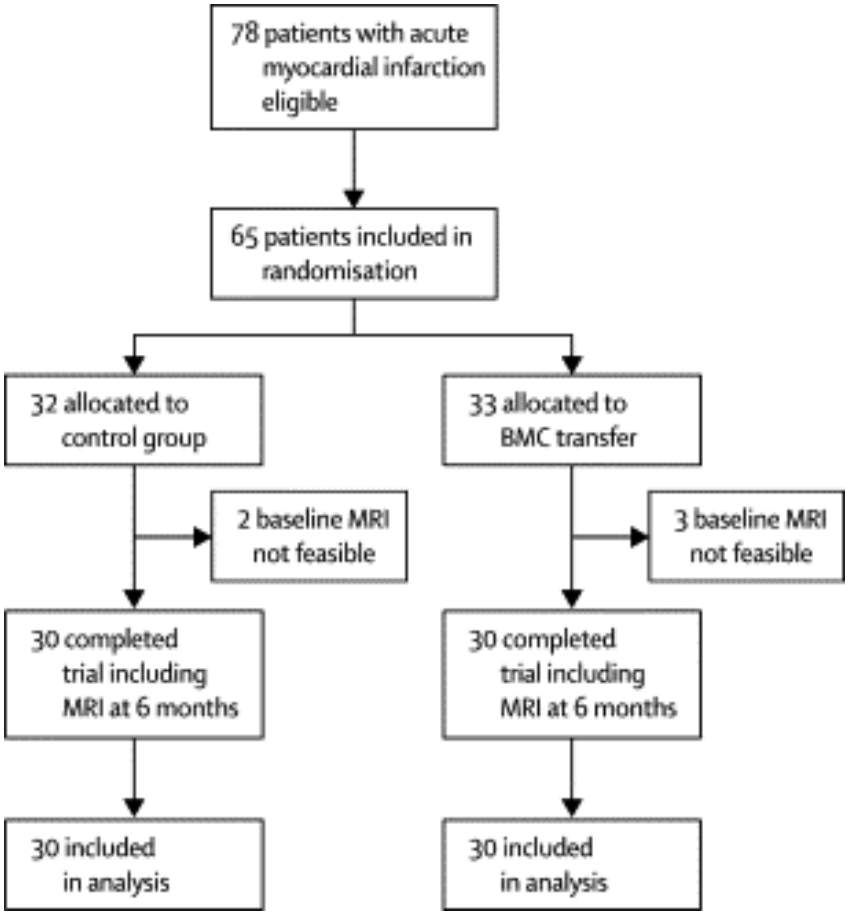
Kaplan-Meier event-free survival analysis



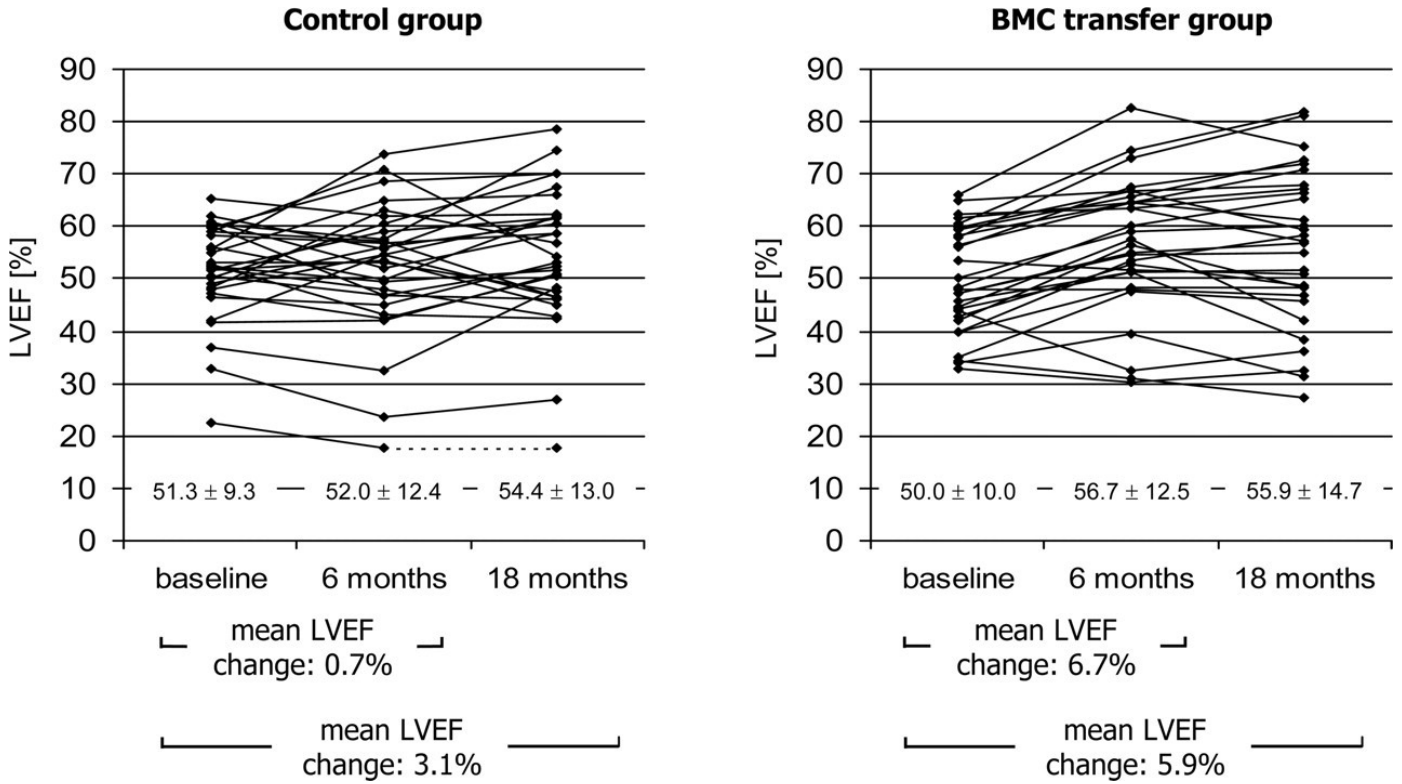
Schachinger, V. et al. Eur Heart J 2006 27:2775-2783; doi:10.1093/eurheartj/ehl38

European Heart Journal

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



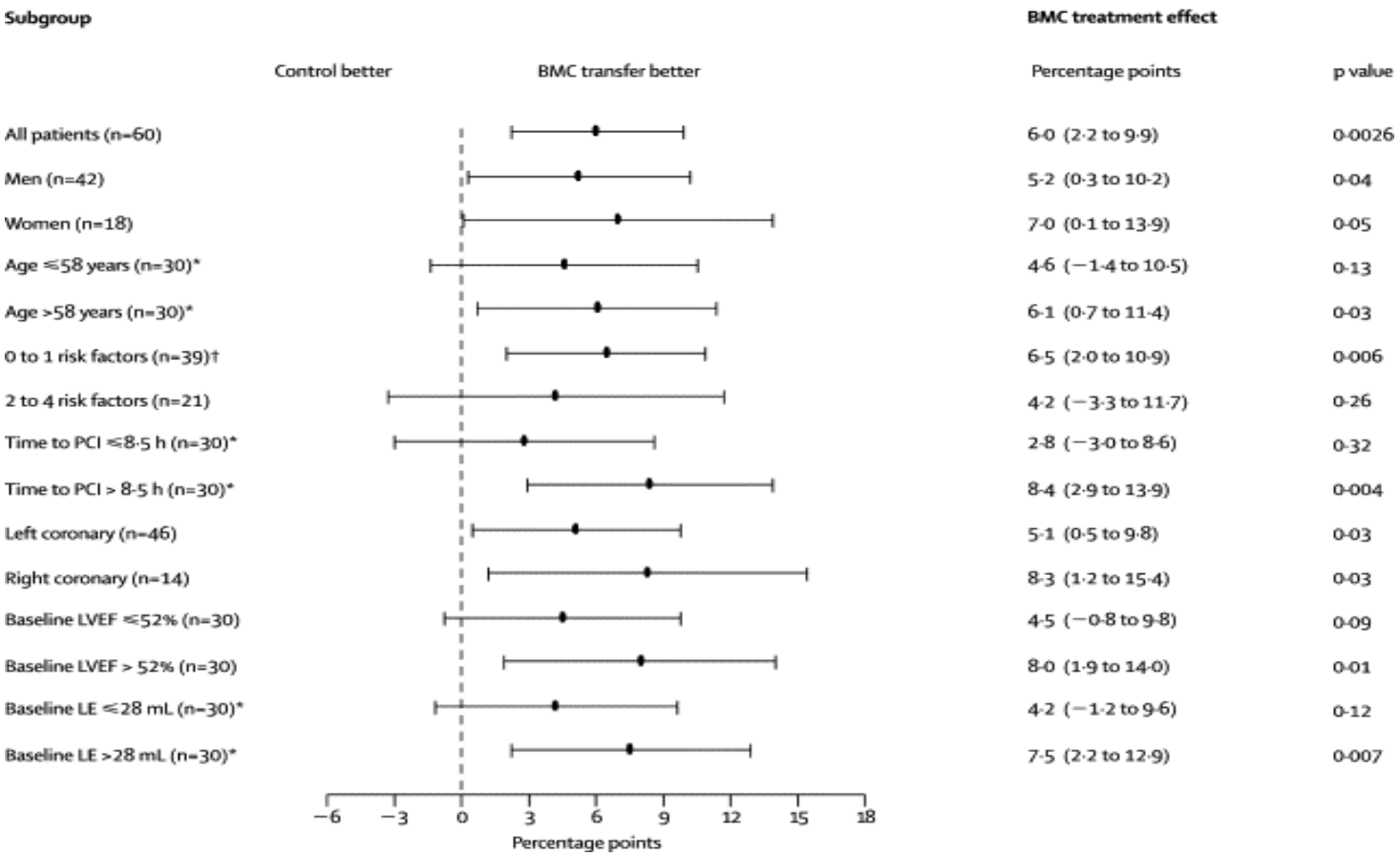
Global LVEF at baseline and at 6- and 18-month follow-up BOOST trial



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

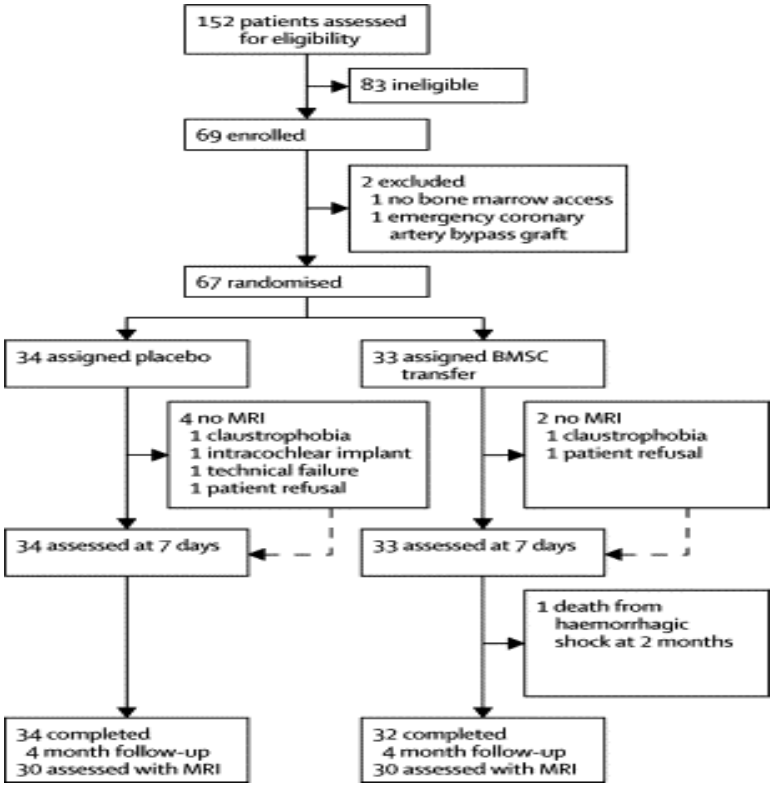
Circulation

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

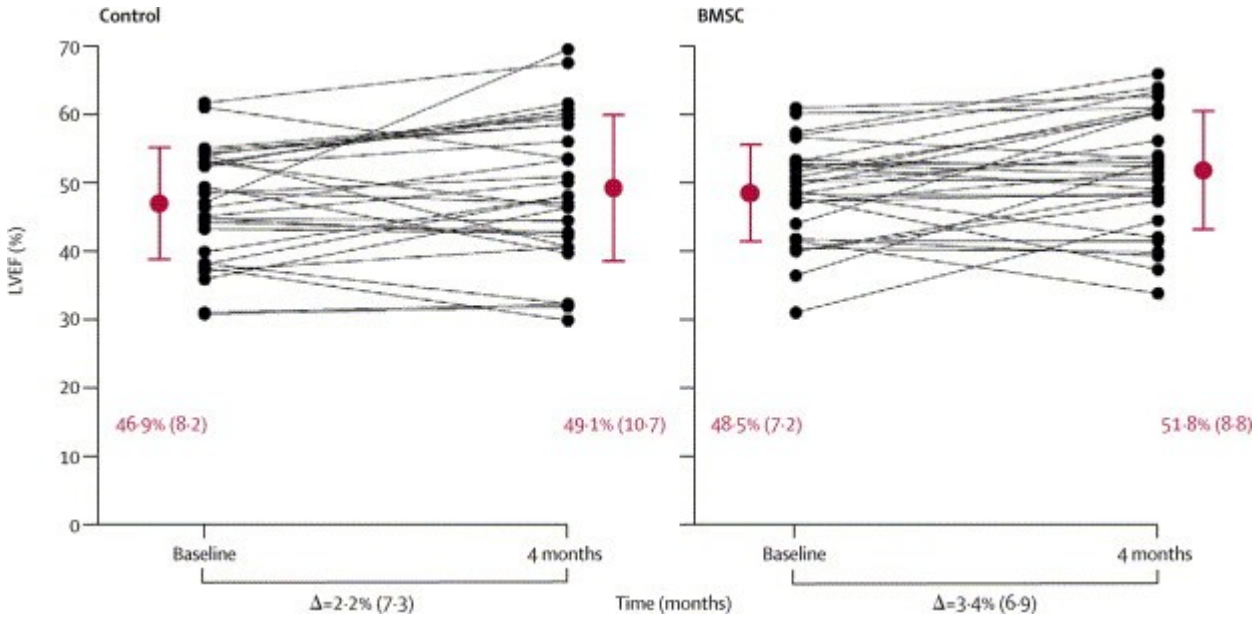


Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Janssen et al, Lancet 2006*

- 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

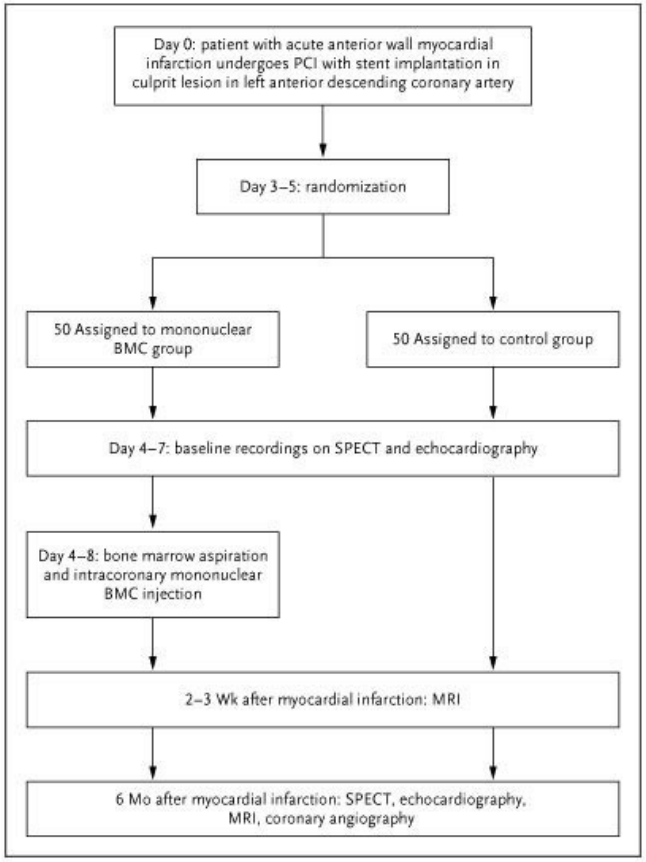


Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Janssen et al, Lancet 2006*



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*

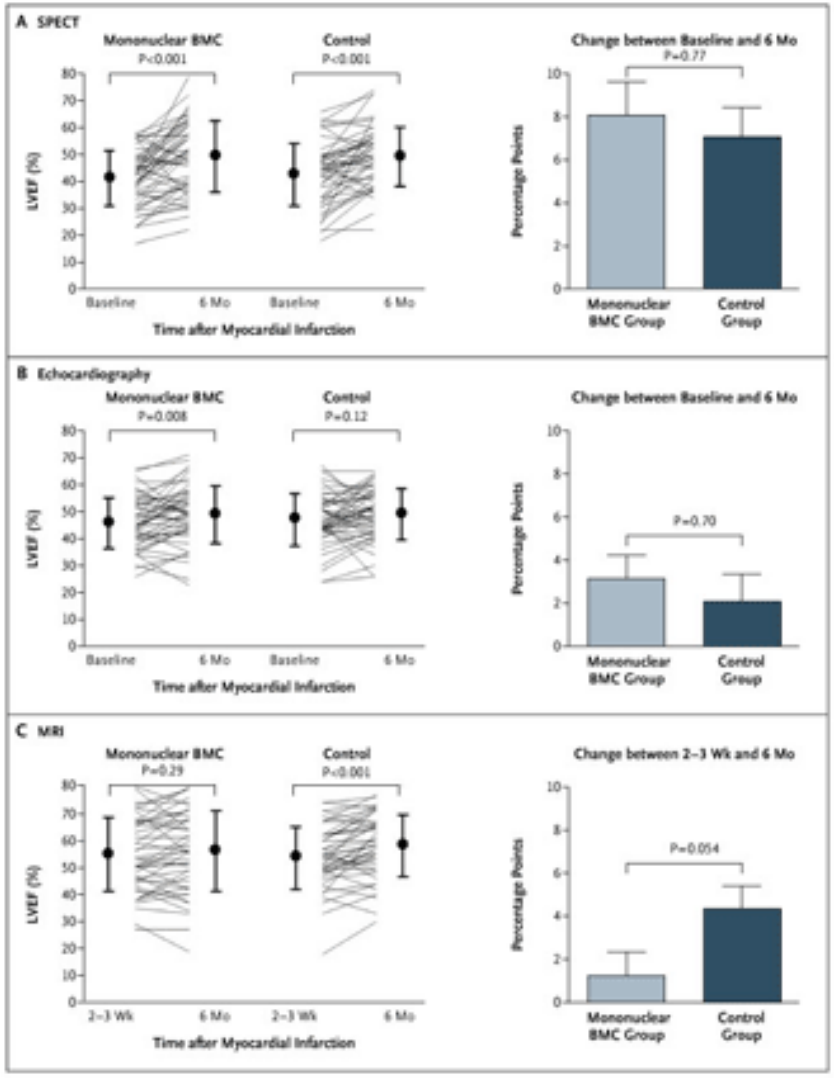
Table 2. LVEF, End-Diastolic Volume, and Infarct Size on SPECT and Echocardiography at Baseline and 6 Months after Myocardial Infarction.*

Analysis	Baseline		6 Mo		Change between Baseline and 6 Mo		Treatment Effect	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)	Change (95% CI)	
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.

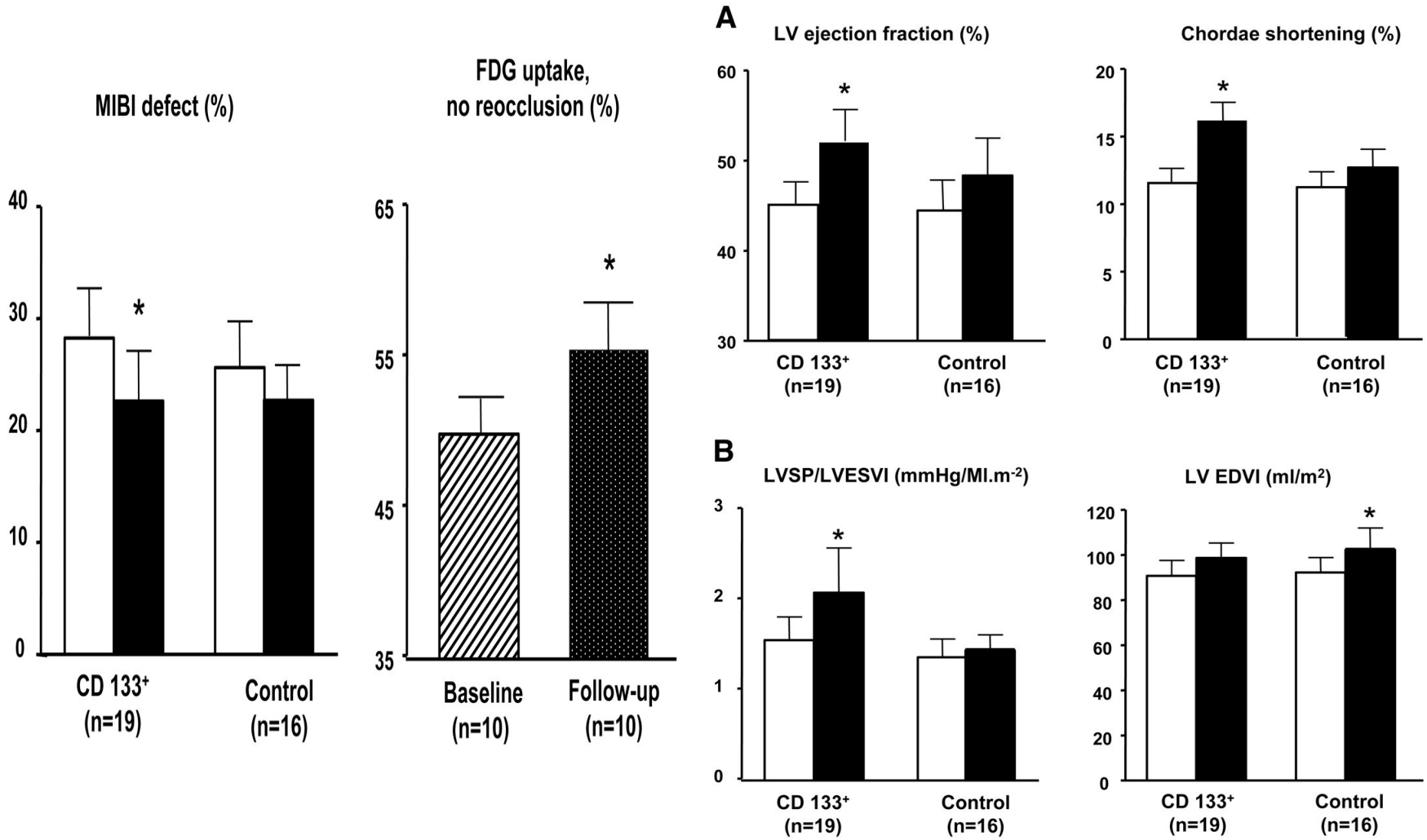
Intracoronary Injection of Mononuclear Bone Marrow Cells in Acute Myocardial Infarction. *Lunde, NEJM, 2006*



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

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

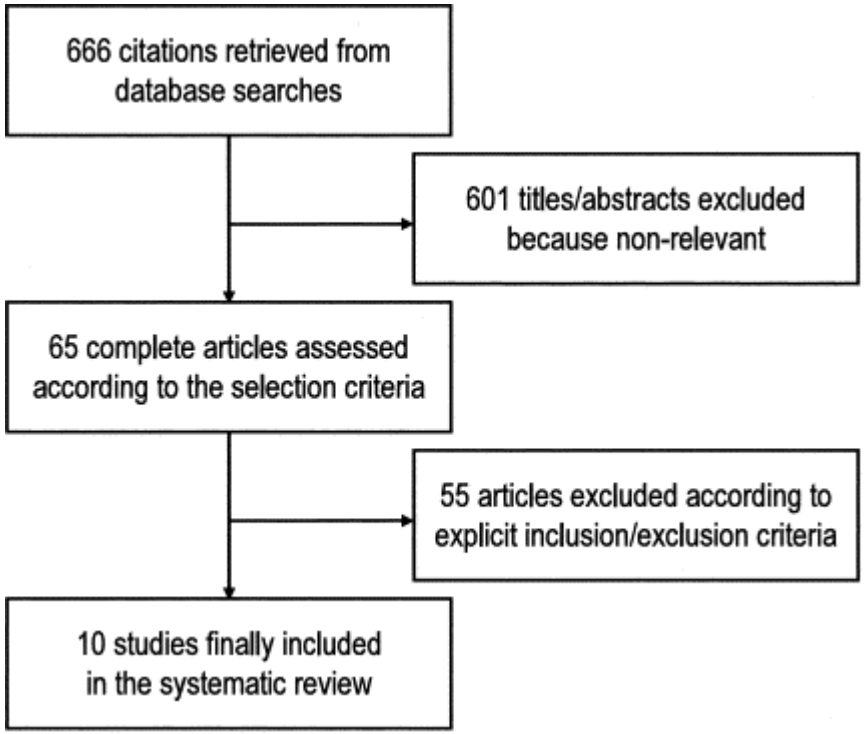
LV function and perfusion in treated patients and controls



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

Circulation

Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of AMI: Meta-Analysis of Controlled Clinical Trials. Lipinsky et al. JACC, 2007

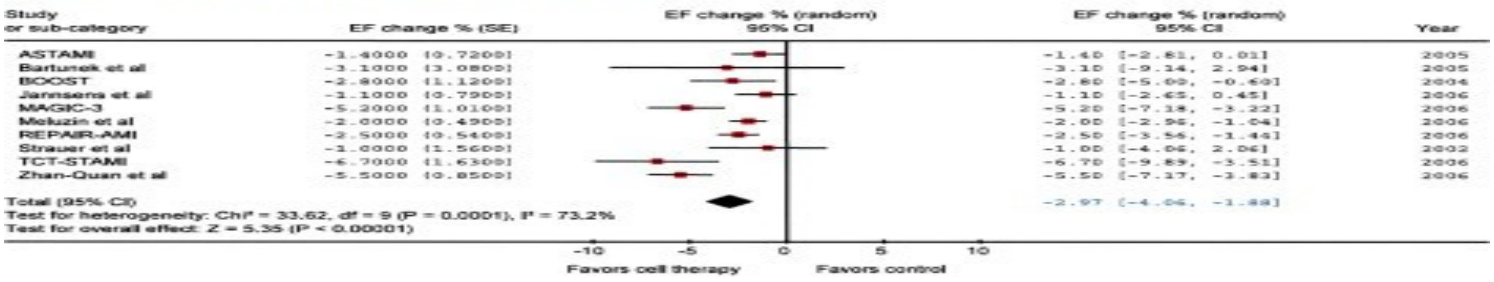


Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of Acute Myocardial Infarction A Collaborative Systematic Review and Meta-Analysis of Controlled Clinical Trials. Lipinsky et al. JACC, 2007

Study	Year	Design	Patients Enrolled (Patients at Follow-Up)	Cell Type	Follow-Up (Months)	Primary End Point	Imaging Modality for LVEF Assessment
Strauer et al. (10)	2002	Non-RCT	20 (20)	BMC	3	LVEF	LV angiography
Bartunek et al. (11)	2005	Non-RCT	35 (35)	BMC	4	Safety, LVEF	LV angiography, SPECT
Jannsens et al. (8)	2006	RCT	67 (66)	BMC	4	LVEF	Cardiac MRI
BOOST (7)	2006	RCT	60 (60)	BMC	18	LVEF, safety	Cardiac MRI
Zhan-Quan et al. (12)	2006	Non-RCT	70 (58)	PMC	6	LVEF, LV volumes, WMSI	Echocardiography
MAGIC CELL-3-DES (13)	2006	RCT	56 (50)	PMC	6	LVEF	Cardiac MRI
TCT-STAMI (14)	2006	RCT	20 (20)	BMC	6	LVEF	Echocardiography, SPECT
ASTAMI (12) and [ ]	2006	RCT	100 (97)	BMC	6	LVEF, EDV, infarct size	SPECT, MRI echo
REPAIR-AMI ( )	2006	RCT	204 (187)	BMC	12	LVEF	LV angiography
Meluzin et al. (16)	2006	RCT	66 (66)	BMC	3	Infarct zone systolic function	SPECT

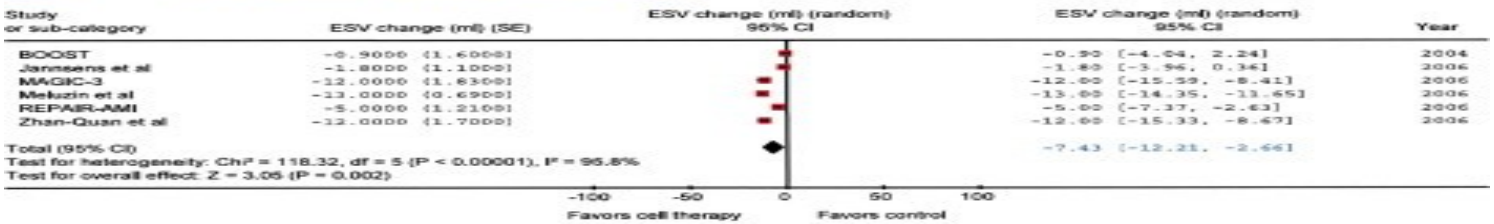
A

Comparison: Cell therapy vs control in acute myocardial infarction
Outcome: Change in ejection fraction from baseline to follow-up



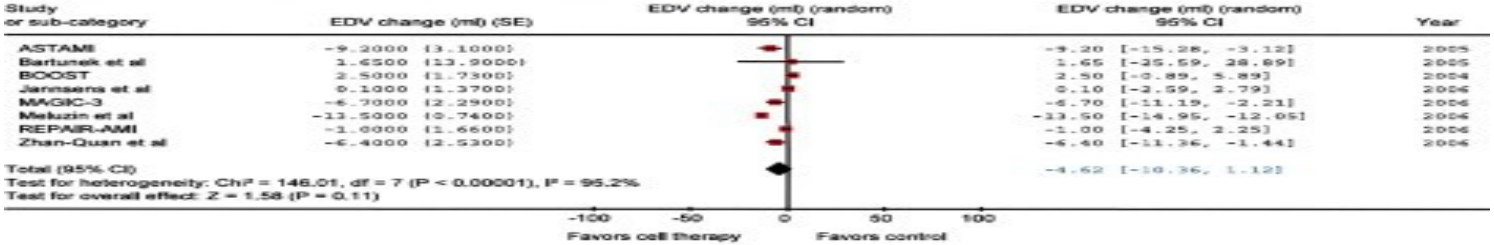
B

Comparison: Cell therapy vs control in acute myocardial infarction
Outcome: Change in end-systolic volume from baseline to follow-up



C

Comparison: Cell therapy vs control in acute myocardial infarction
Outcome: Change in end-diastolic volume from baseline to follow-up



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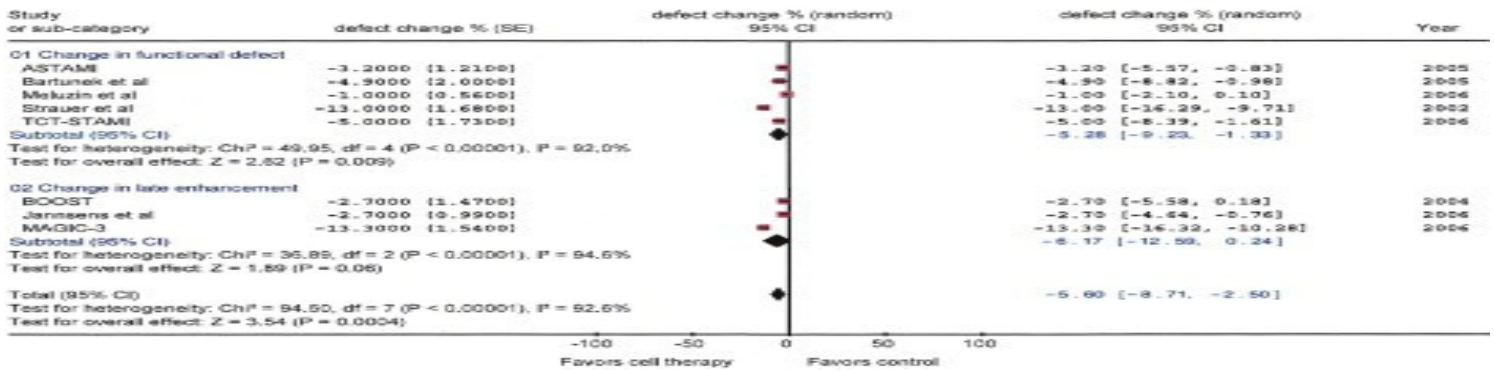
Comparison: Cell therapy vs control in acute myocardial infarction
Outcome: Change in functional defect or late enhancement from baseline to follow-up



Conclusions

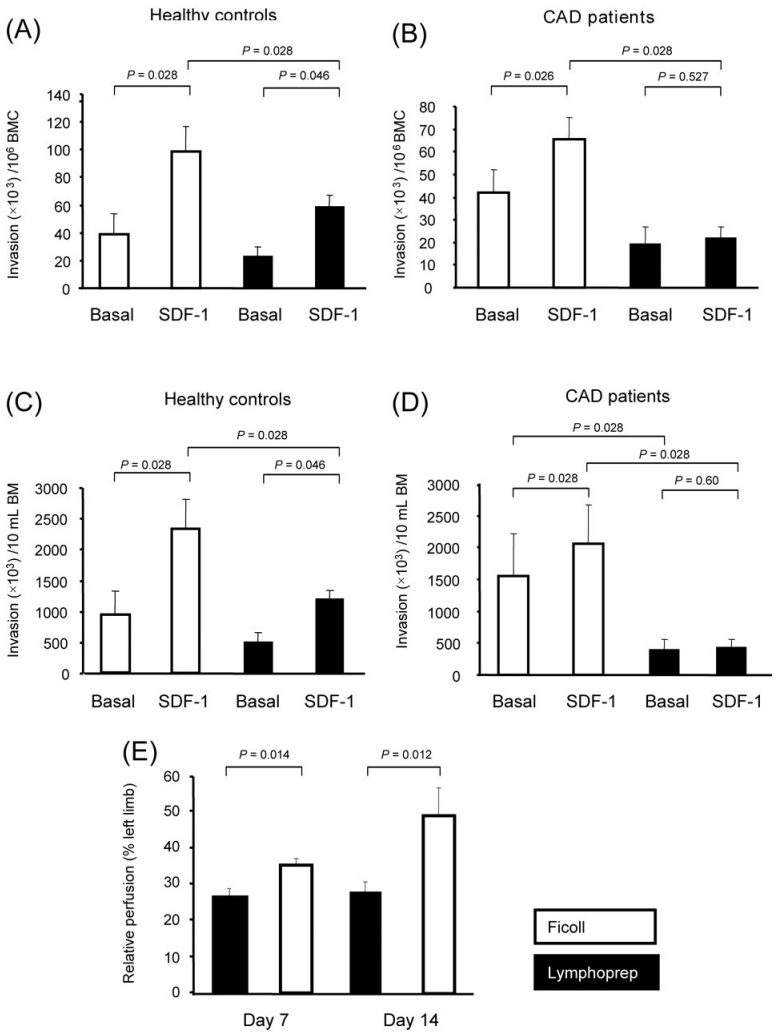
- Marginal effect on global LVEF.
- Fair Safety profile
- Feasible.
- Cannot discriminate pts most likely to benefit due to small numbers.

Potential explanation for the conflicting results

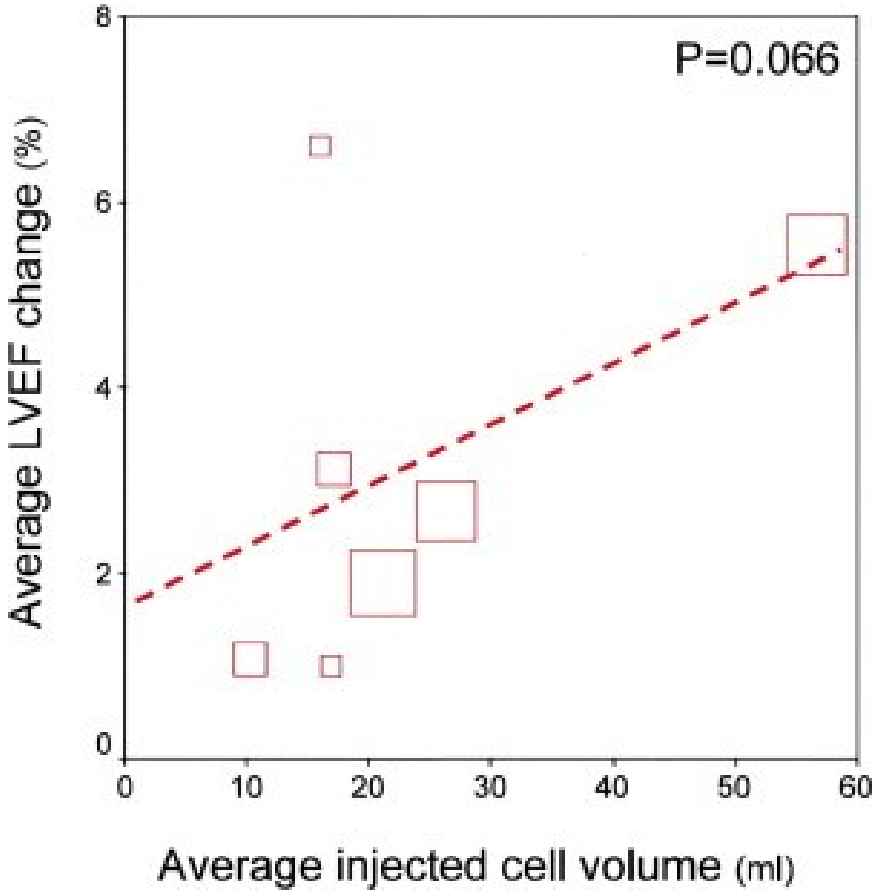
- Timing of Cell transfer with relation to PCI (REPAIR AM).
- The nature of injected cells (total BM versus CD133+).
- Use of imaging to quantify endpoints (LVEF).
- Severity of LV compromise.
- Different numbers of cells.
- Different preparations of cells.

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
CD_{45}^+/CD_{34}^+	4.8 ± 6.8	3.6 ± 4.4	0.043
(+ BMC (10^5			
CFU	3919 ± 5270	2425 ± 3891	0.023
MST	123 ± 230	160 ± 161	0.015
$CXCR_4^+$	851 ± 1357	292 ± 447	0.02
Basal invasion	1307 ± 1244	384 ± 448	0.04
SDF-1 (200 ng) invasion	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'Abé 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

?How to define an endothelial progenitor cells (1

?Origin of endothelial progenitor cells-

Definition of subpopulation with different-

? functional capacities

Signals for EPC homing and differentiation in vivo (2

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

Mechanisms of action (3

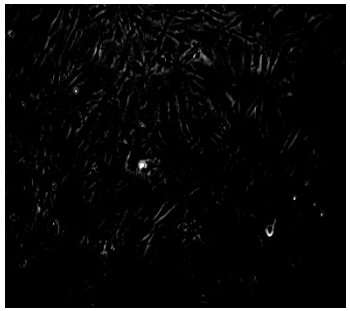
Transdifferentiation capacity of different progenitor cells-

Importance of paracrine effects-

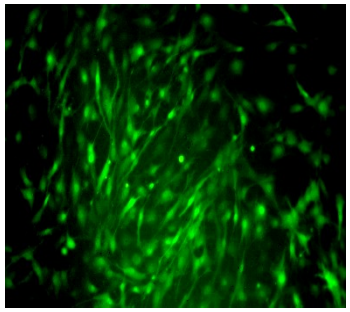
CELL THERAPY STUDIES- A GLIMPSE INTO THE FUTURE

HIF-1/2α overexpression in endothelial progenitor cells

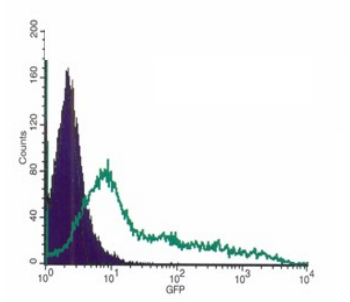
phase contrast

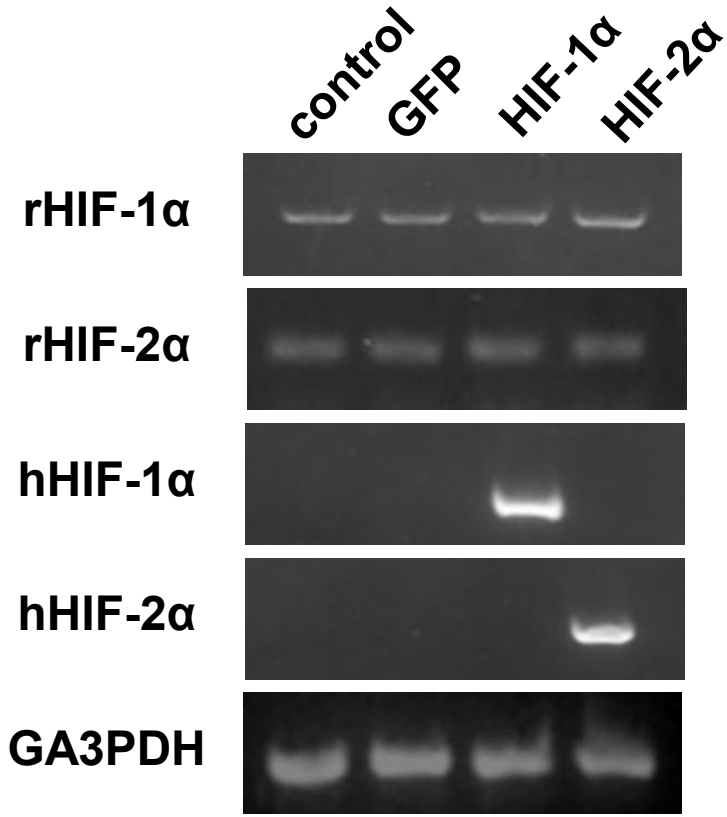


retroviral transduction



GFP analysis





CELL THERAPY STUDIES - A GLIMPSE INTO THE FUTURE

Day 0

Day 8

bFGF pellet implantation + Injection of HIF-α transduced cells