Application of Bone Marrow Cells for Patients with MI

- Lessons from the BOOST Program -

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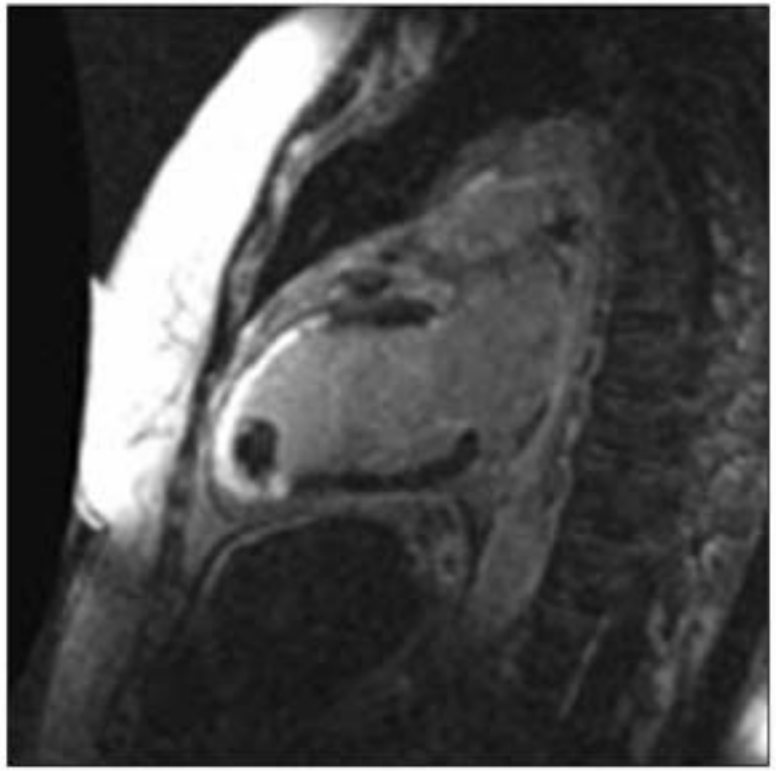
Acute Myocardial Infarction: 1970 - 2000

- Coronary Care Units
- Aspirin, Clopidogrel
- Heparin, Thrombolysis
- Gp IIb/IIIa Inhibitors
- **Acute-PCI/Stent**
- β-Blocker
- ACE-Inhibitors, AT_1-Blocker
- Statins

Large Anteroseptal MI

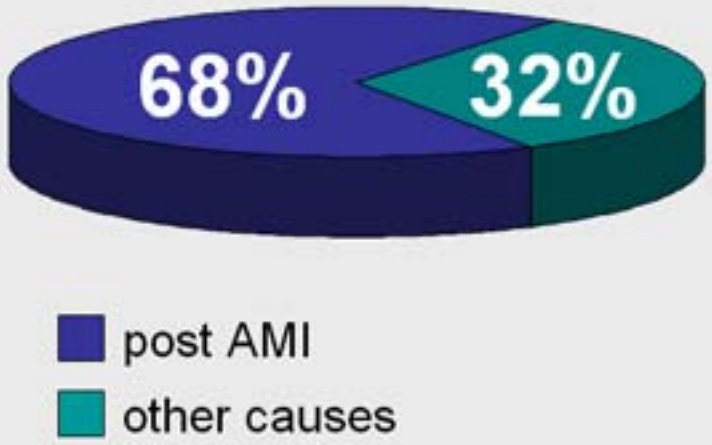
5 days after PCI with stenting and *state-of-the-art* pharmacotherapy
(just an example…)

Contrast-enhanced MRI



AMI has Become the Main Cause of Congestive Heart Failure

Causes of CHF
(20.000 patients)

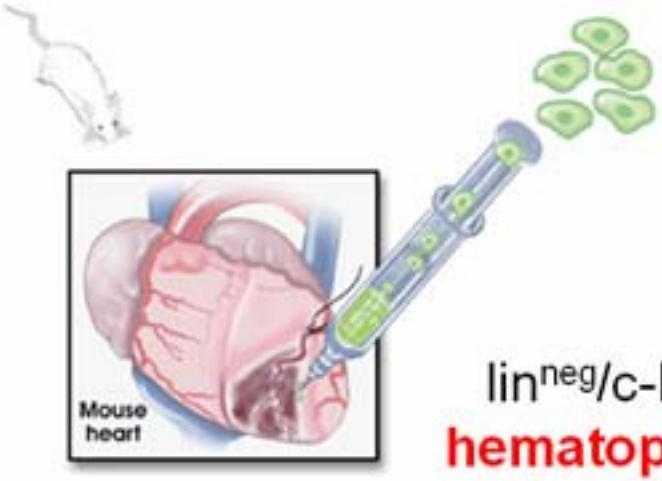


Gheorghiade & Bonow, *Circulation* (1998)

Hospital Admissions with CHF (1970 – 2000)

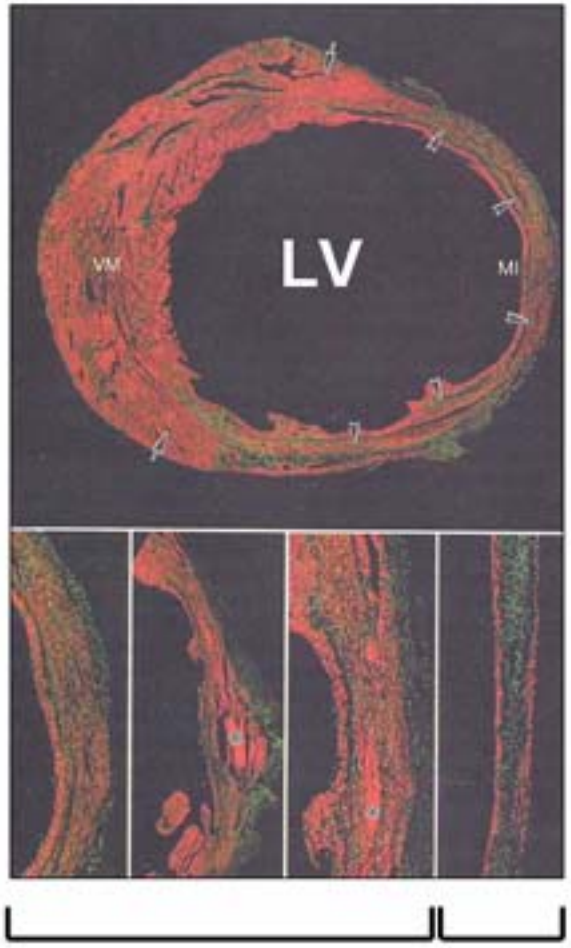
National Heart, Lung, and Blood Institute (2004)

Stem Cell Therapy to Repair the Infarcted Heart ?



$lin^{neg}/c\text{-}kit^{pos}$
hematopoietic stem cells

- Formation of viable myocardium
- Improved systolic function



Orlic et al., *Nature* (2001)

Experimental Studies of Cell Therapy post AMI

Species	Cell population	Effects
Mouse	$Lin^-/c\text{-}kit^+$ cells	**LV-function ↑**
Rat	$Ac\text{-}LDL^+$ cells	capillary density ↑ fibrosis ↓
Rat	$CD34^+$ cells	neoangiogenesis ↑ **LV-function ↑**
Rat	5AZA cells	LV perfusion ↑ **LV function ↑**
Rat	unselect. BM cells	**LV function ↑**
Pig	$CD31^+$ cells	neoangiogenesis ↑
Pig	unselect. BM cells	collaterals ↑ **LV function ↑**

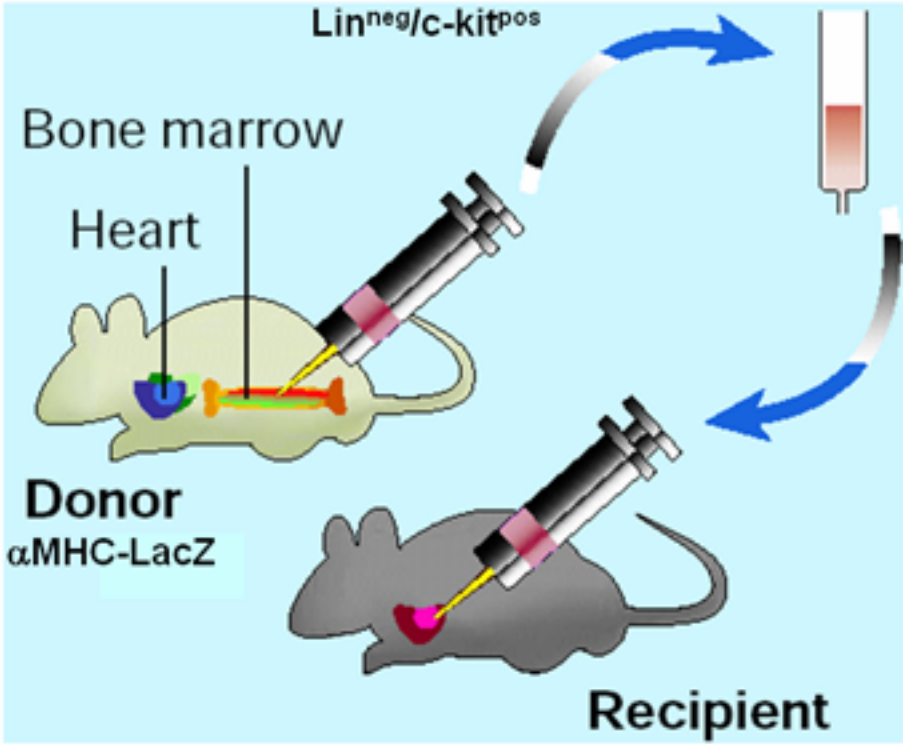
Tomita et al., *Circulation* (1999); Kobayashi et al., *J Surg Res* (2000); Orlic et al., *Nature* (2001); Fuchs et al., *JACC* (2001); Kamihata et al., *Circulation* (2001); Jackson et al., *J Clin Invest* (2001); Kocher et al., *Nat Med* (2001); Kamihata et al., *ATVB* (2002); Kawamoto et al., *Circulation* (2001, 2003)

Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts

Charles E. Murry[1], Mark H. Soonpaa[2], Hans Reinecke[1], Hidehiro Nakajima[2], Hisako O. Nakajima[2], Michael Rubart[2], Kishore B. S. Pasumarthi[2*], Jitka Ismail Virag[1], Stephen H. Bartelmez[3], Veronica Poppa[1], Gillian Bradford[2], Joshua D. Dowell[2], David A. Williams[2*] & Loren J. Field[2]

[1]*Department of Pathology, Box 357470, Room D-514 HSB, University of Washington, Seattle, Washington 98195, USA*
[2]*Wells Center for Pediatric Research, Indiana University, 1044 West Walnut Street, R4 Bldg, Room W376, Indianapolis 46202-5225, USA*
[3]*Department of Pathobiology, University of Washington, Seattle, Washington 98195, USA*

Nature (2004)



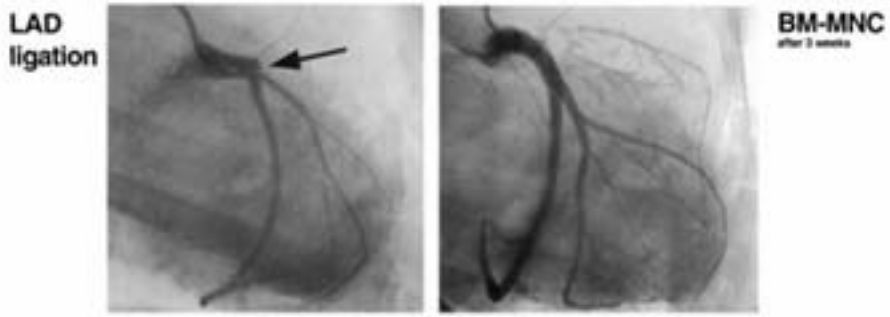
„ ...did not observe transformation of donor cells into cardiac myocytes."

„...however, cell-treated mice showed an improvement in cardiac function."

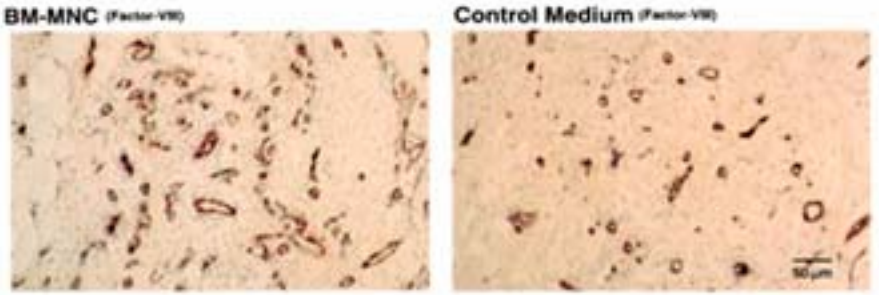
Implantation of Bone Marrow Mononuclear Cells Into Ischemic Myocardium Enhances Collateral Perfusion and Regional Function via Side Supply of Angioblasts, Angiogenic Ligands, and Cytokines

Hiroshi Kamihata, MD; Hiroaki Matsubara, MD, PhD; Takashi Nishiue, MD, PhD;
Soichiro Fujiyama, MD; Yoshiaki Tsutsumi, MD; Ryozo Ozono, MD, PhD; Hiroya Masaki, MD, PhD;
Yasukiyo Mori, MD, PhD; Osamu Iba, MD; Eriko Tateishi, MD; Atsushi Kosaki, MD, PhD;
Satoshi Shintani, MD; Toyoaki Murohara, MD, PhD;
Tsutomu Imaizumi, MD, PhD; Toshiji Iwasaka, MD, PhD

Enhanced collateral growth in the infarcted area



Enhanced capillarization



Circulation (2001)

Peripheral Blood "Endothelial Progenitor Cells" Are Derived From Monocyte/Macrophages and Secrete Angiogenic Growth Factors

Jalees Rehman, MD; Jingling Li, MS; Christie M. Orschell, PhD; Keith L. March, MD, PhD

Circulation (2003)

- VEGF
- HGF
- G-CSF

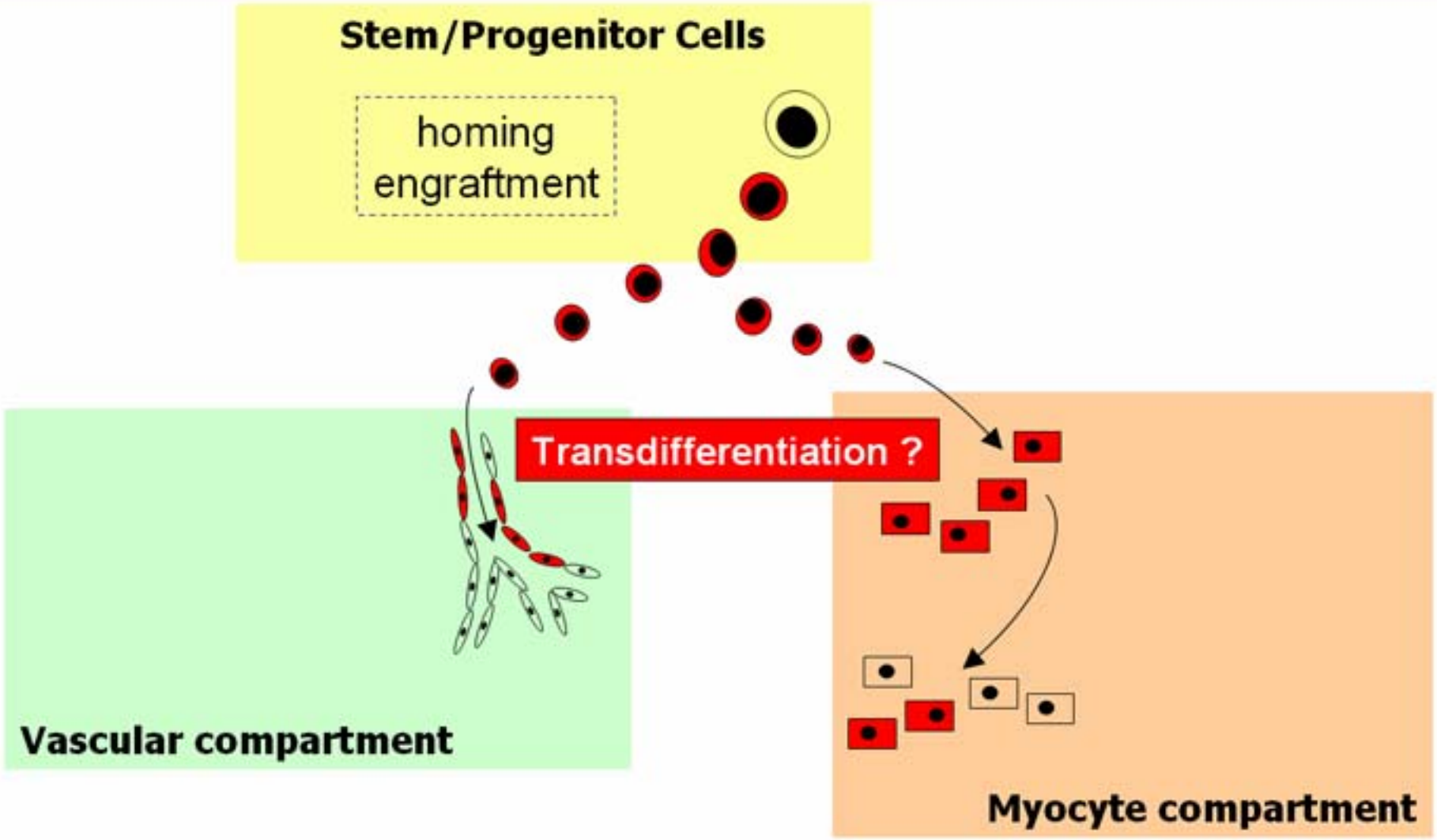
Marrow-Derived Stromal Cells Express Genes Encoding a Broad Spectrum of Arteriogenic Cytokines and Promote In Vitro and In Vivo Arteriogenesis Through Paracrine Mechanisms

T. Kinnaird, E. Stabile, M.S. Burnett, C.W. Lee, S. Barr, S. Fuchs, S.E. Epstein

Circ Res (2004)

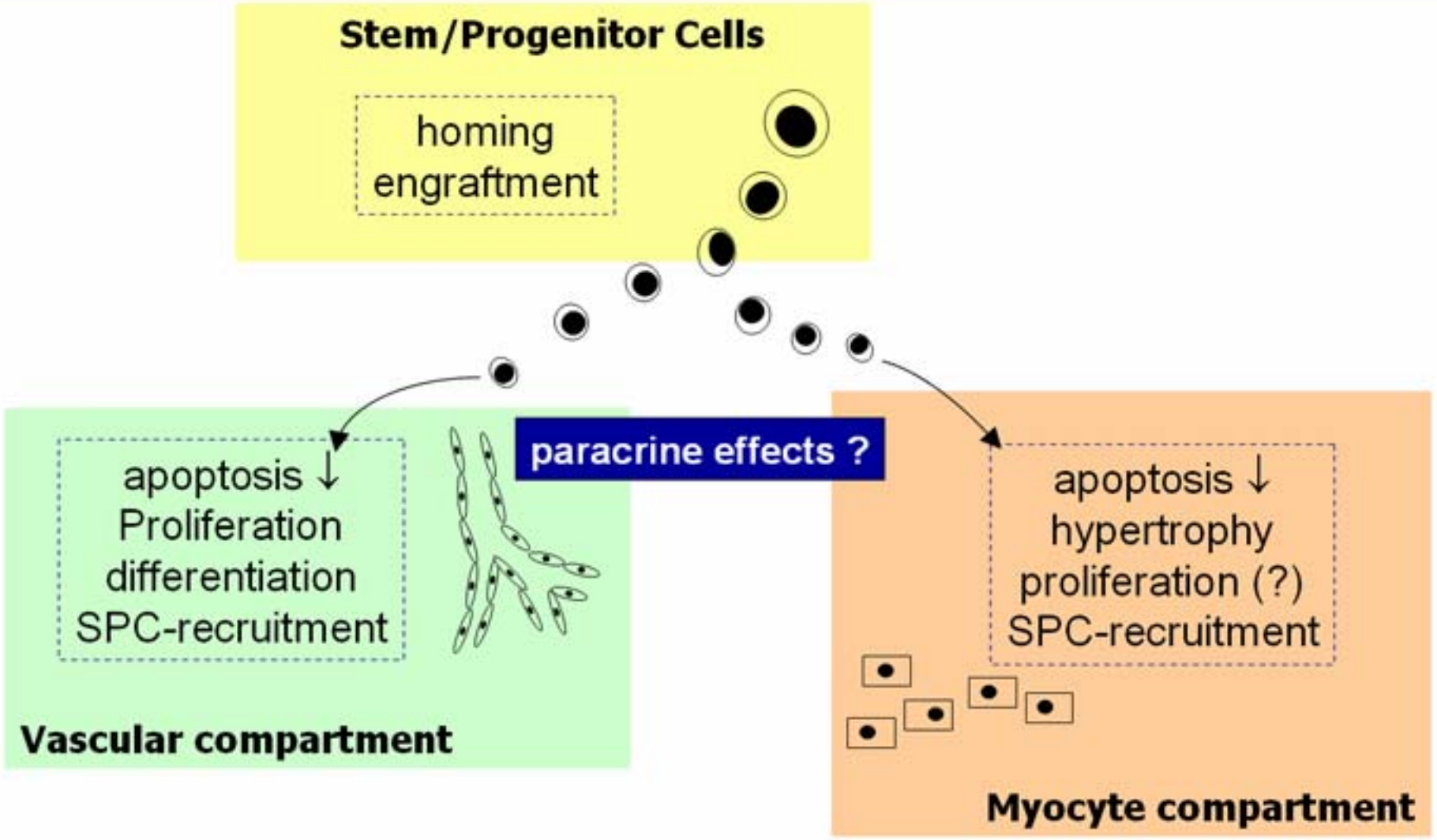
- VEGF
- HGF
- M-CSF
- FGF
- IL-6
- TNFα
- PLGF

Proposed Mechanism of Action of Cell Therapy



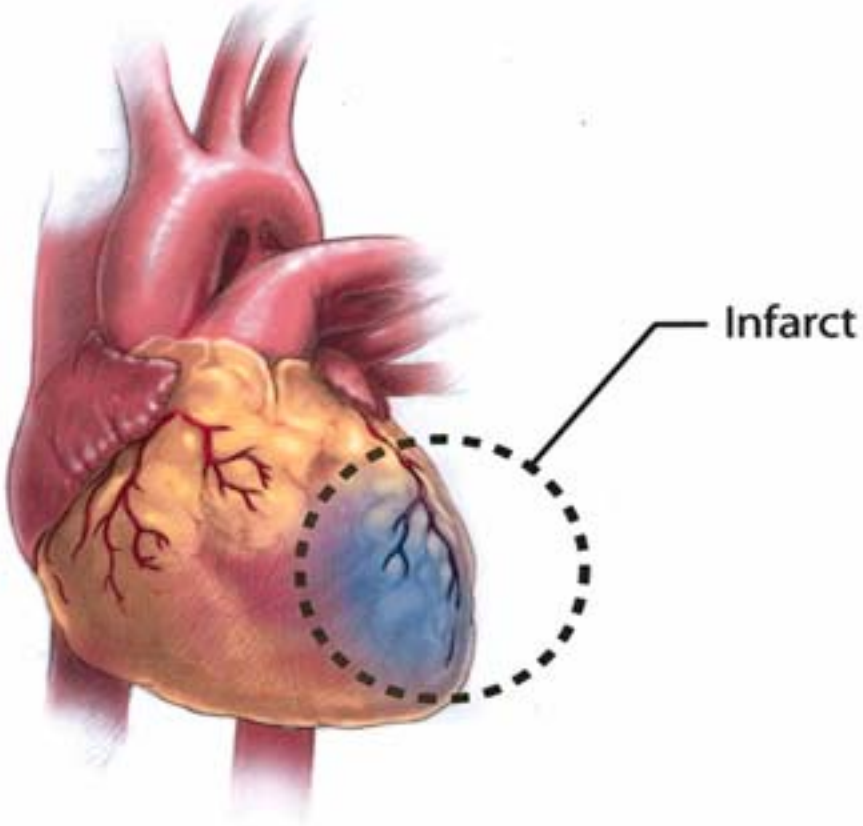
Wollert & Drexler, *Circ Res* (2005)

Proposed Mechanism of Action of Cell Therapy



Wollert & Drexler, *Circ Res* (2005)

Randomized Clinical Trials of BMC Therapy post AMI



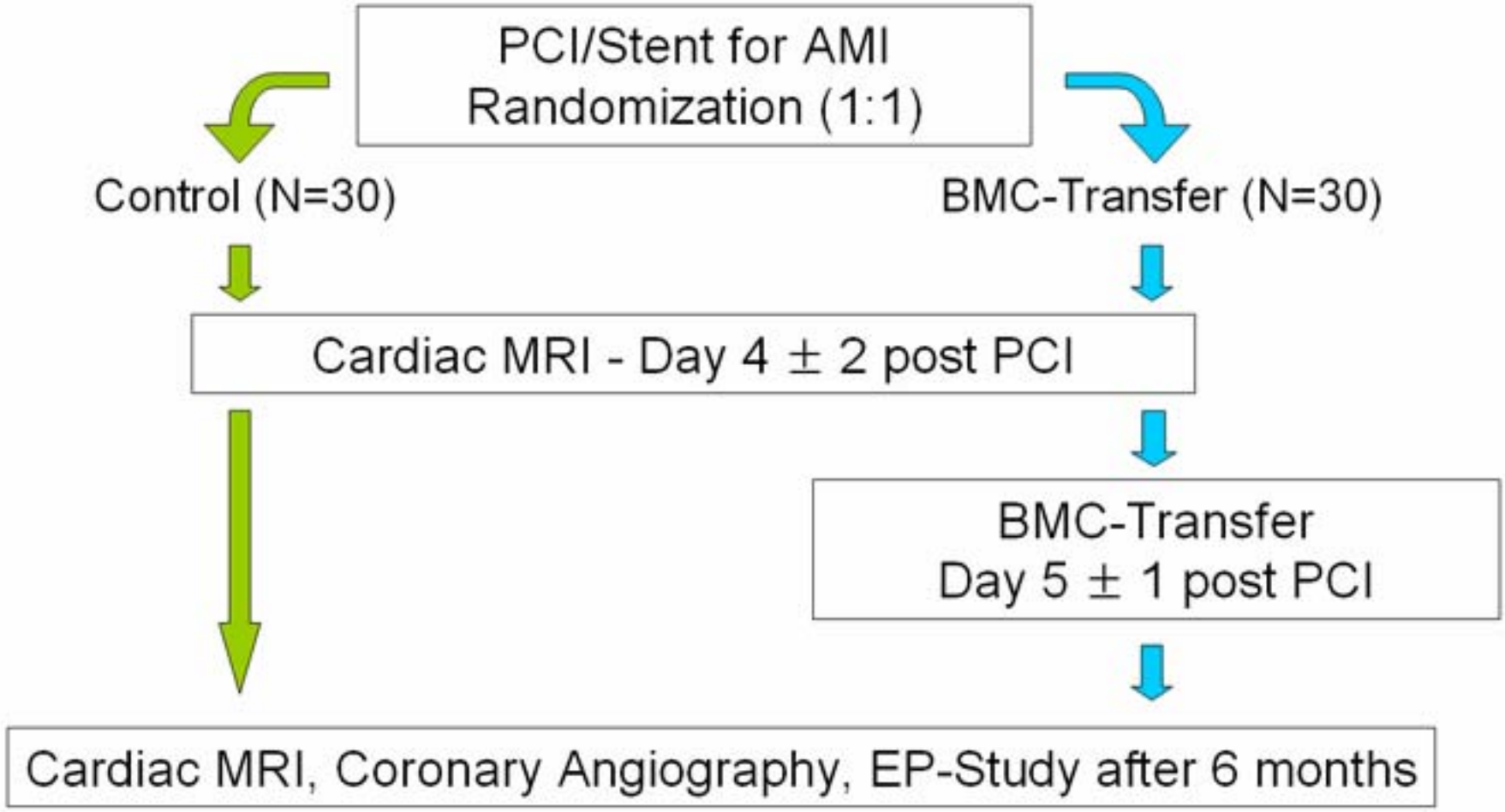
BOOST
(Wollert et al., *Lancet* 2004)

REPAIR-AMI
(Schächinger et al., *AHA* 2005)

Janssens et al.
(Janssens et al., *Lancet* 2006)

ASTAMI
(Lunde et al., *AHA* 2005)

Flow Chart of the BOOST Trial



Change in LV ejection fraction (MRI) after 6 months = primary endpoint

Bone marrow aspirate
128 ± 33 mL

Gelatin-polysuccinate density gradient-sedimentation

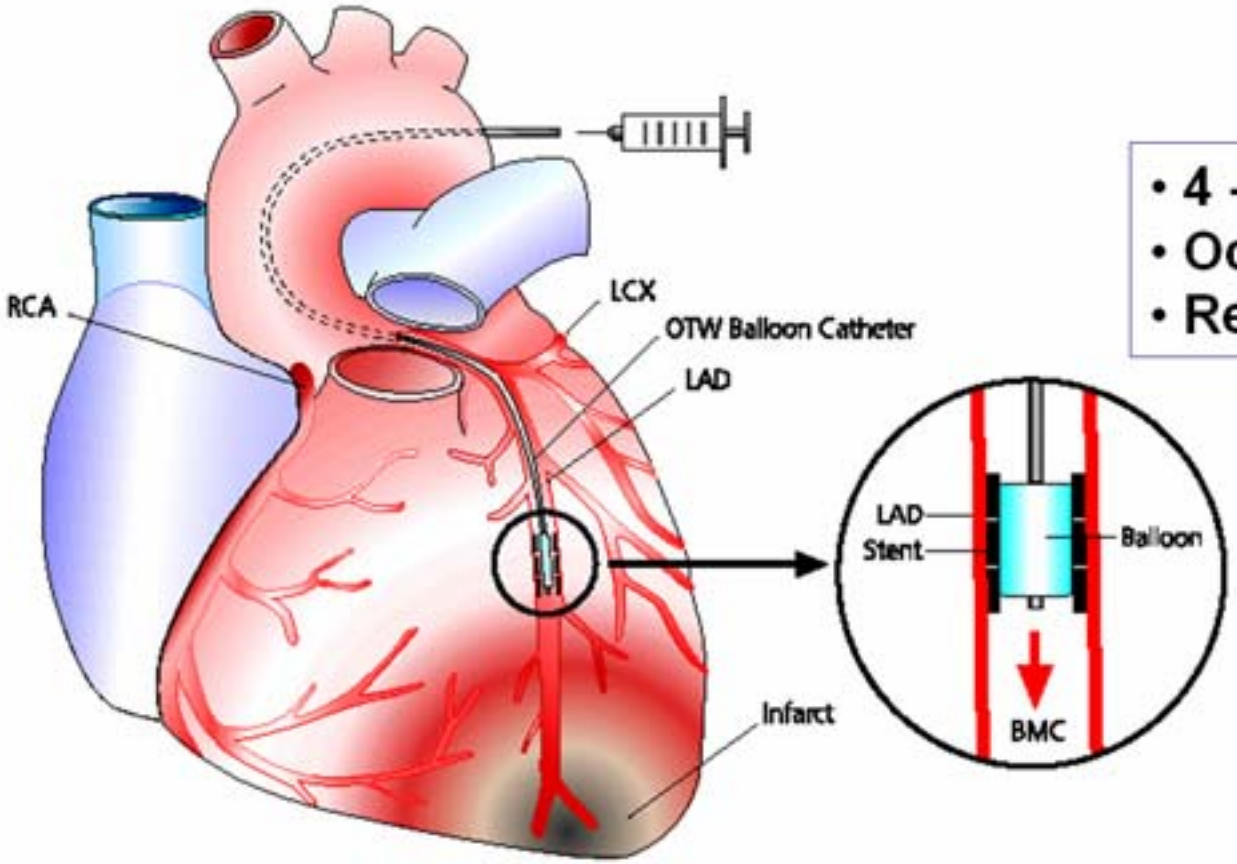
75 ± 12 % of all nucleated cells

Final product

volume:	26 ± 4 mL
nucleated cells:	25 ± 9 x 10^8
cell viability:	99 ± 2 %
$CD34^{pos}$ cells:	9 ± 6 x 10^6
colony-forming cells:	4 ± 3 x 10^6
hematocrit:	31 ± 11 %
thrombocytes:	182 ± 93 x 10^6 / mL

Intracoronary Cell Transfer

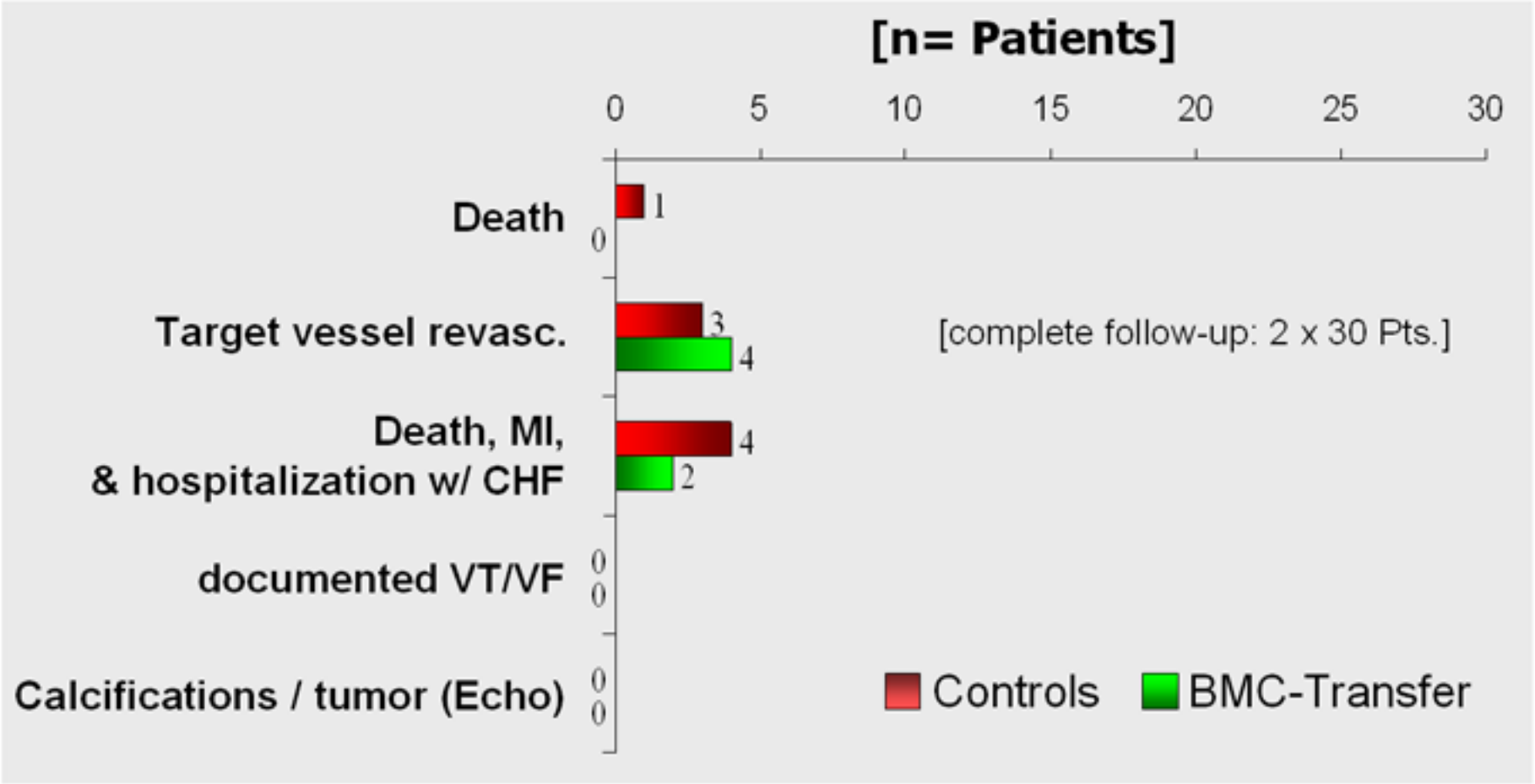
BM-Cells were infused via the central lumen of an OTW-balloon catheter into the infarct artery
(6 ± 1 days after symptom onset; 5 ± 1 days after primary PCI



- **4 - 5 Infusions**
- **Occlusion: 2.5 - 4 min**
- **Reperfusion: 3 min**

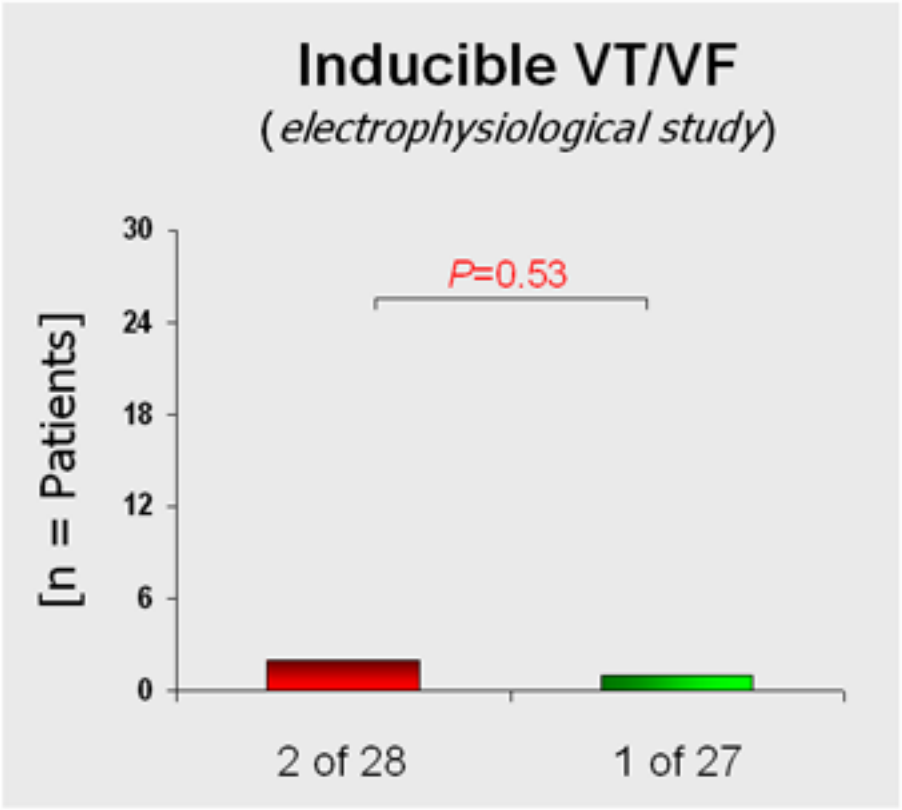
Safety of Cell Therapy ?

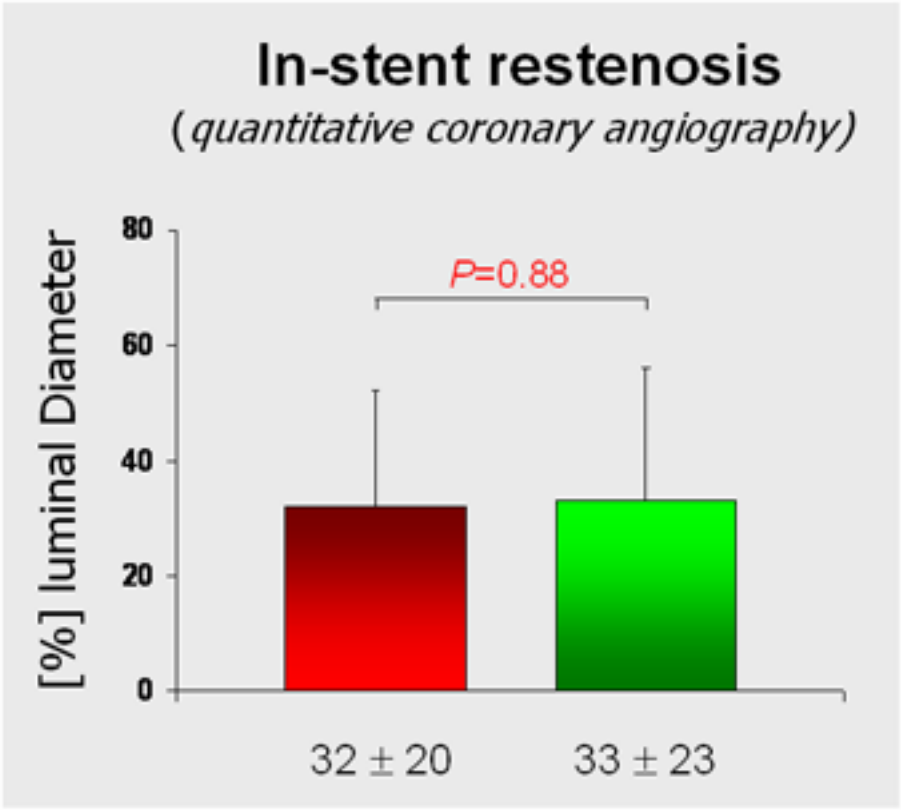
- 18 Months' Follow-up from the BOOST-Study -



Safety of Cell Therapy ?

- Data from the BOOST-Study -

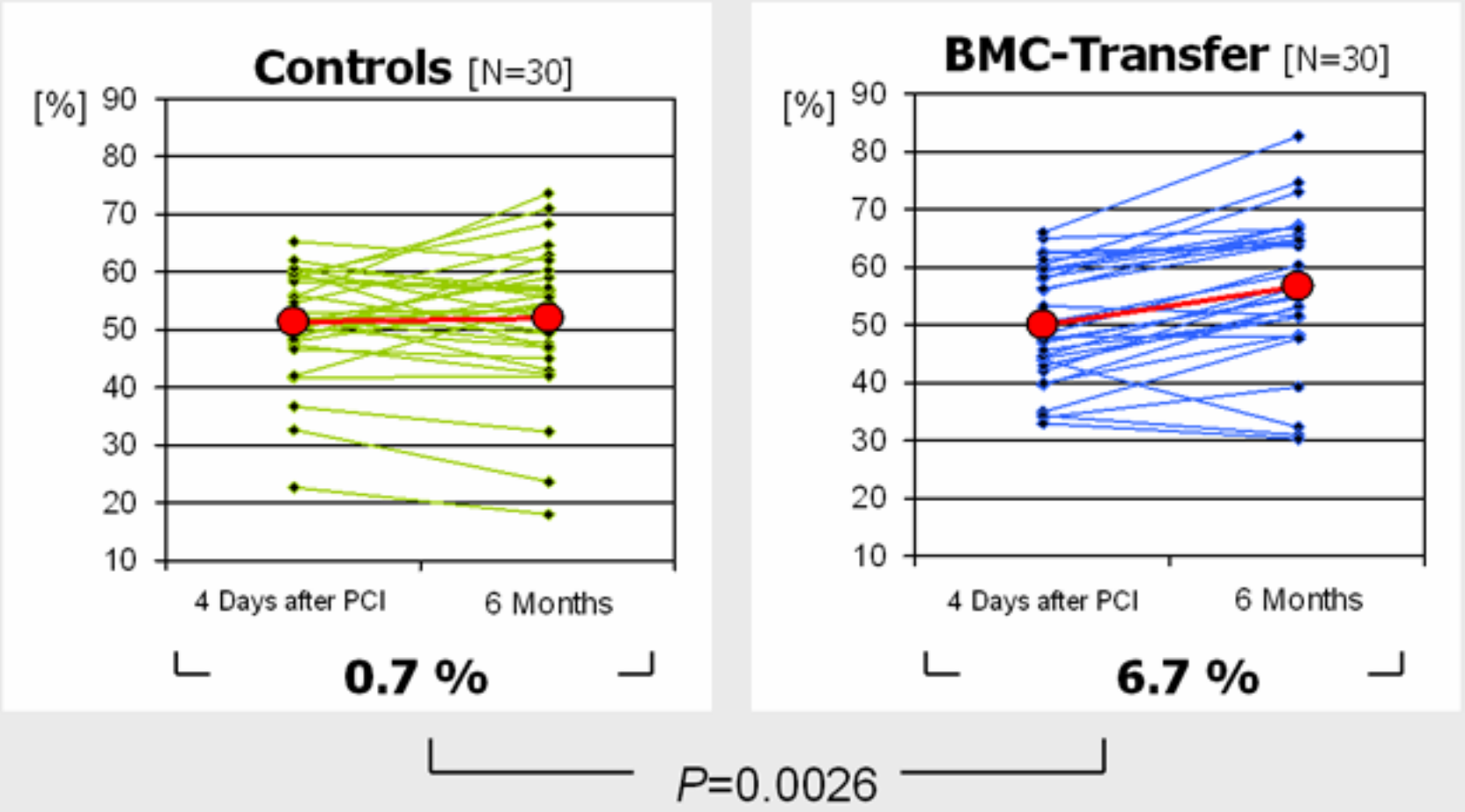




Controls BMC-Transfer

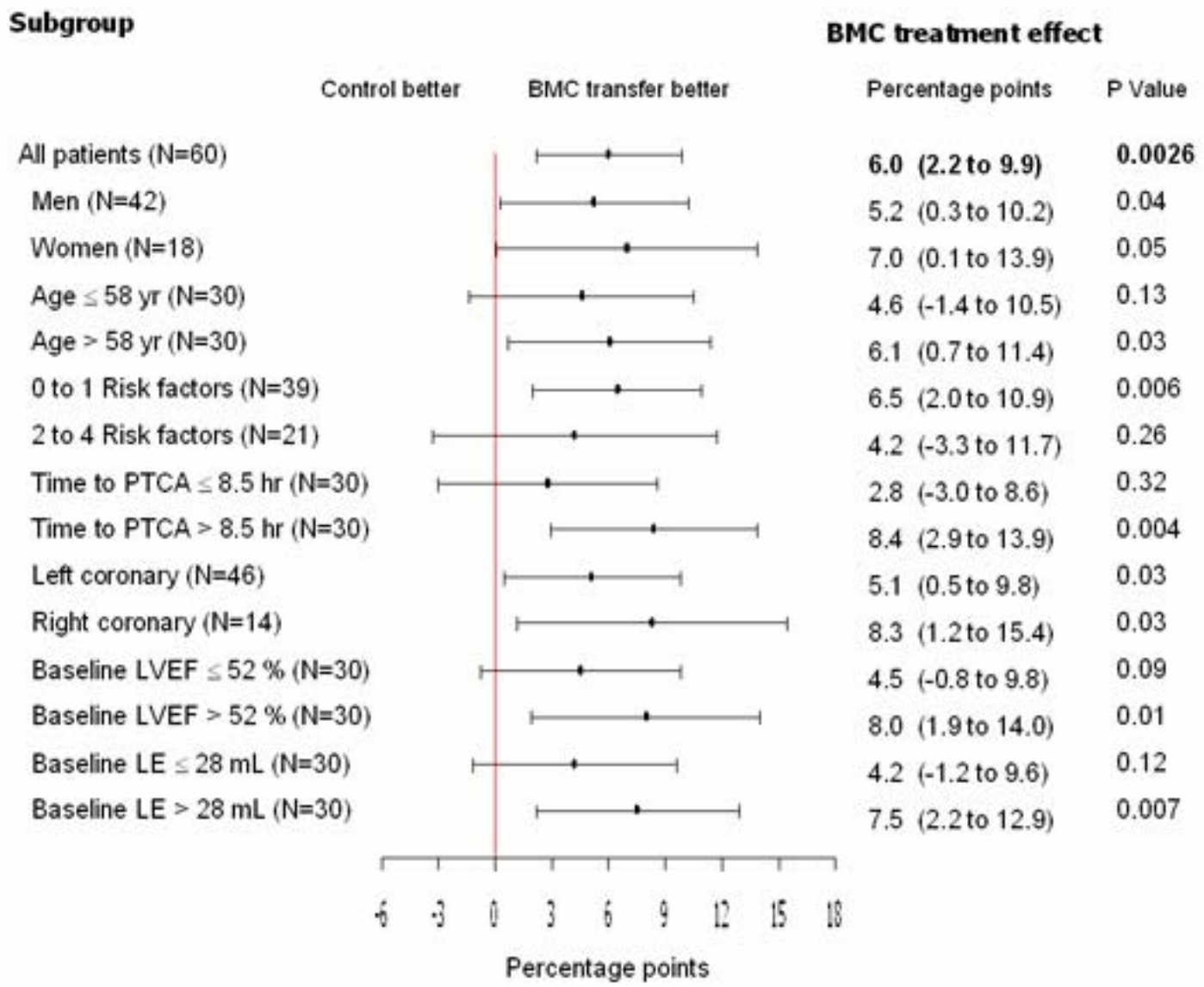
LV-Ejection Fraction after 6 Months

(MRI evaluated by 2 blinded observers)

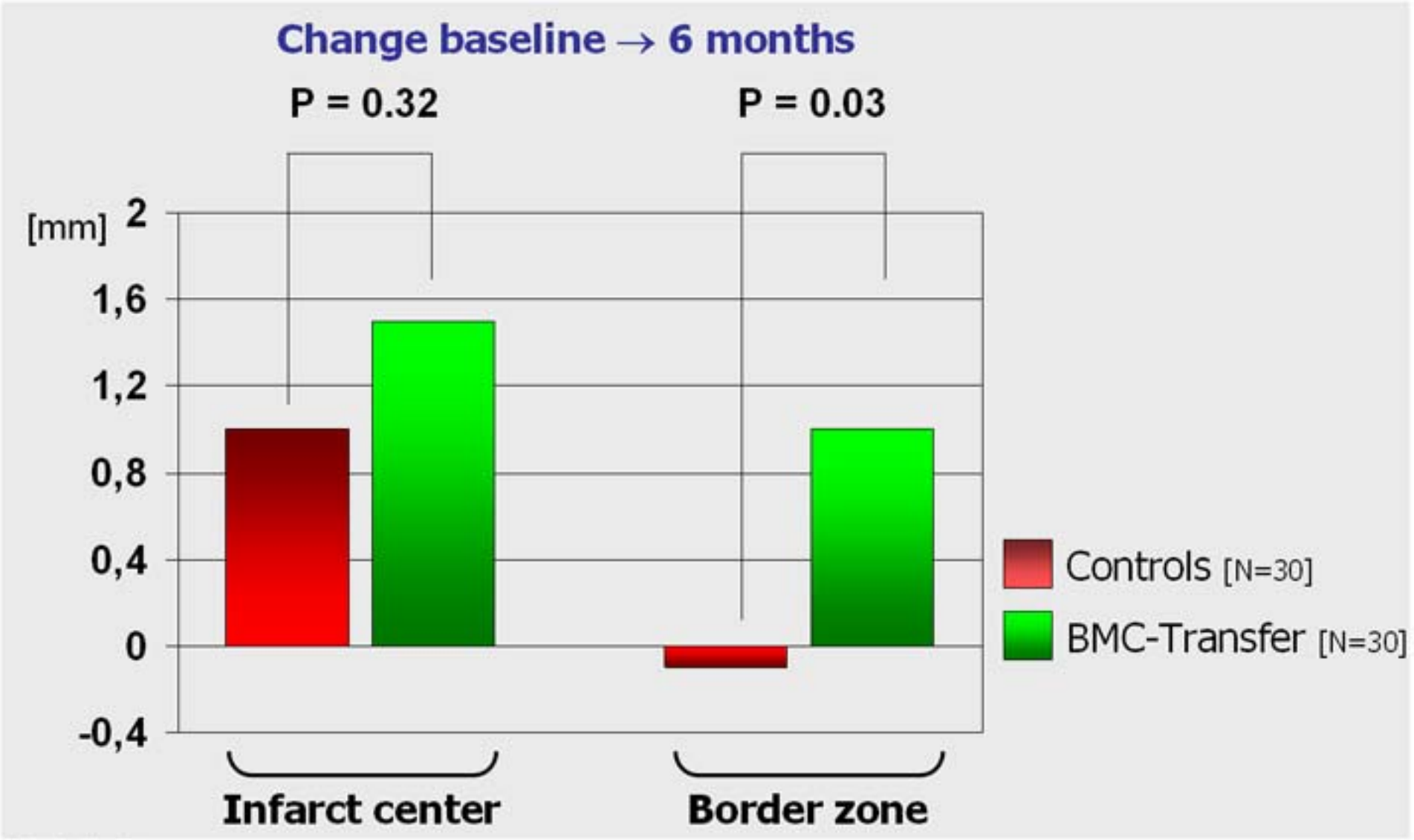


Wollert et al. *Lancet* (2004)

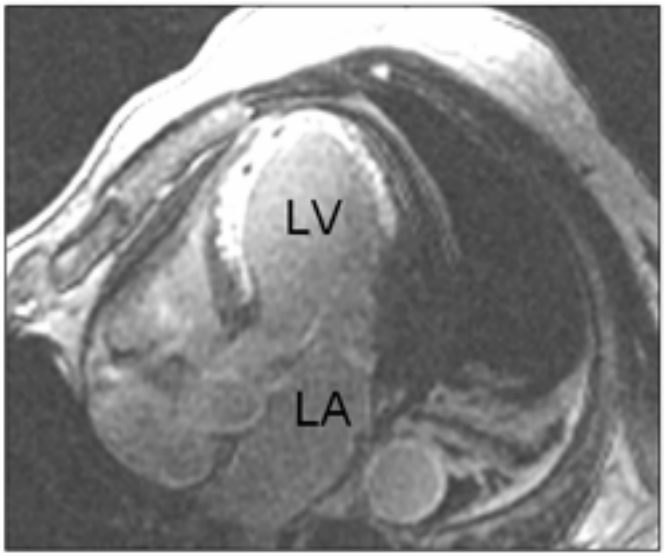
Subgroup Analyses



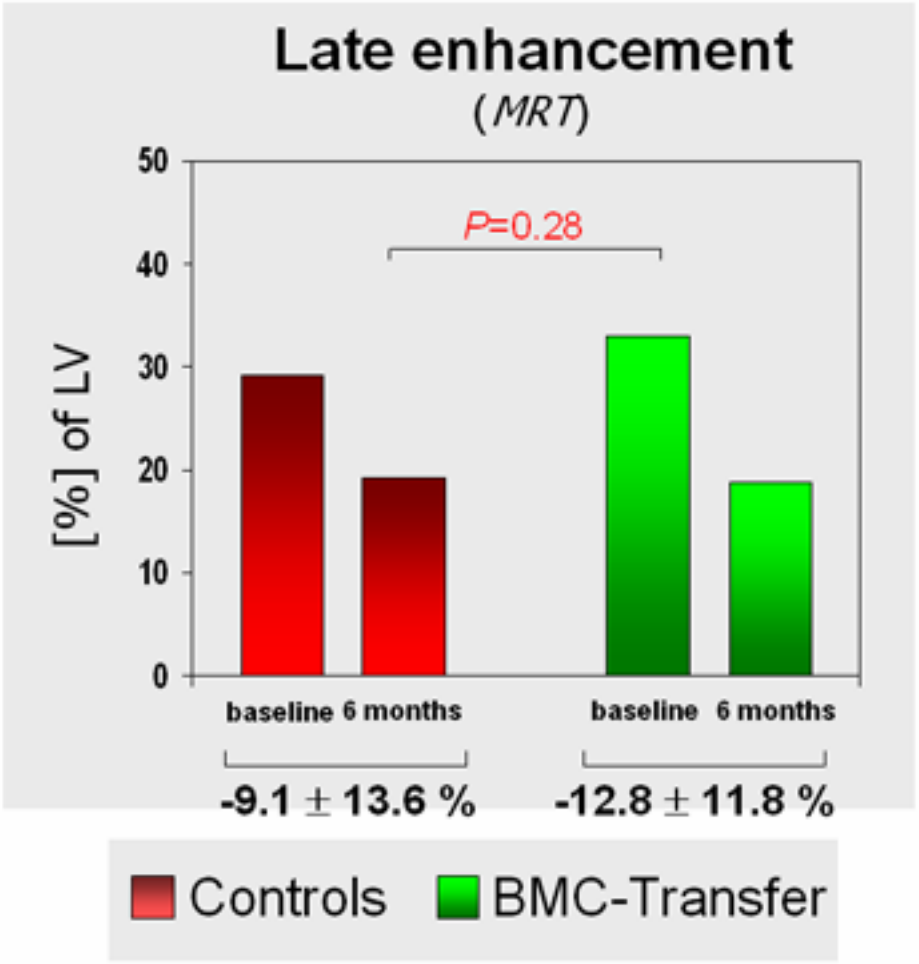
Effects of BMC Therapy on Regional LV Function



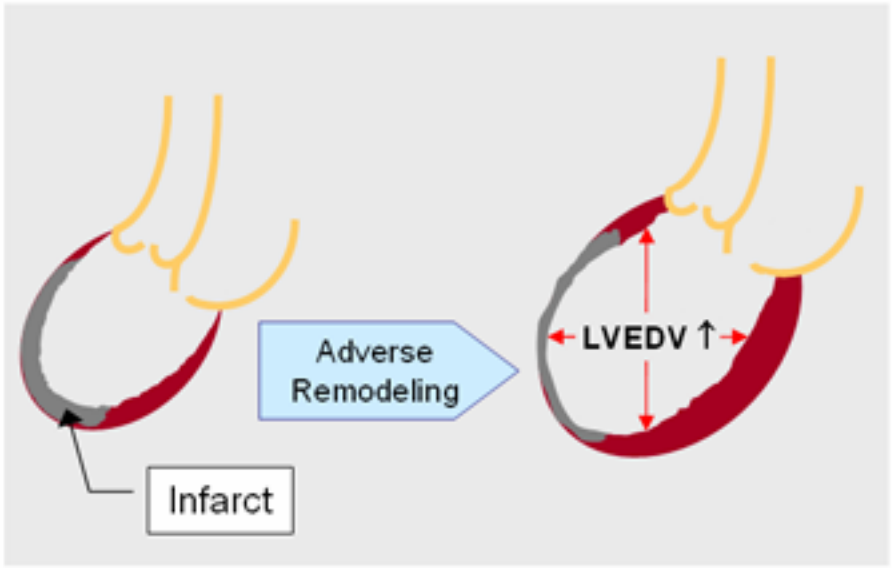
Effect of BMC-Transfer on Infarct Size
- Late enhancement -

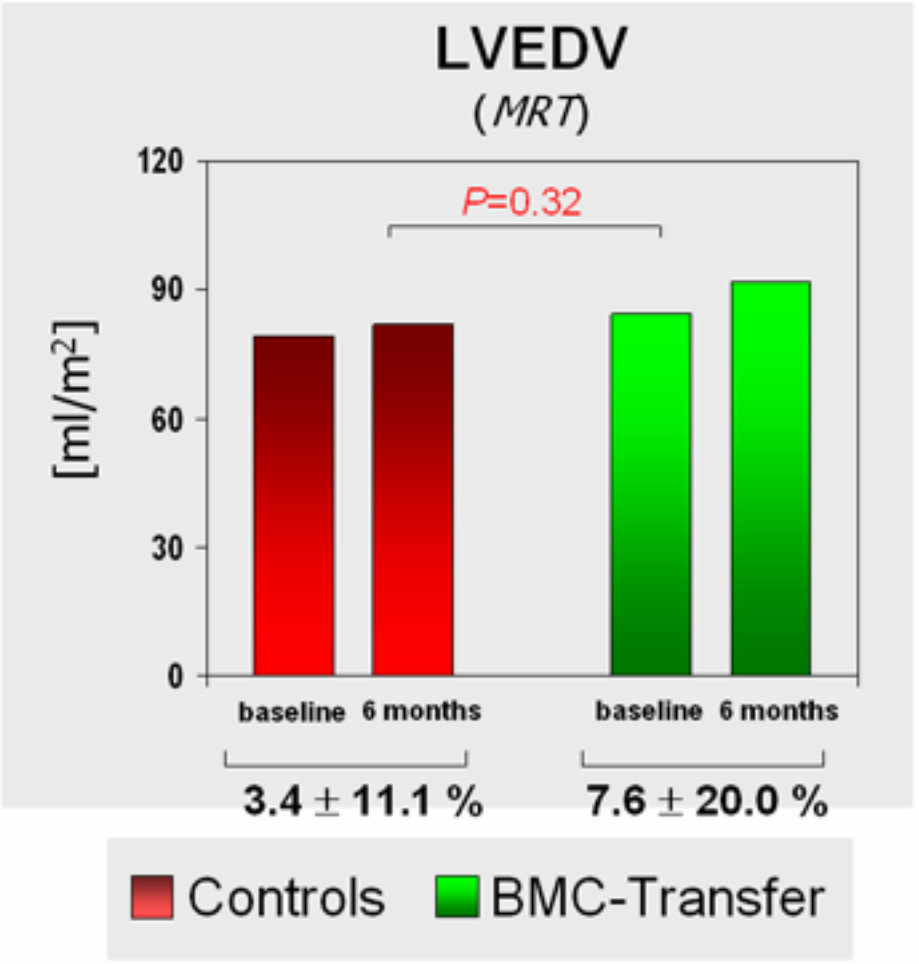


late enhancement:
Measure of infarct size
(and tissue edema)

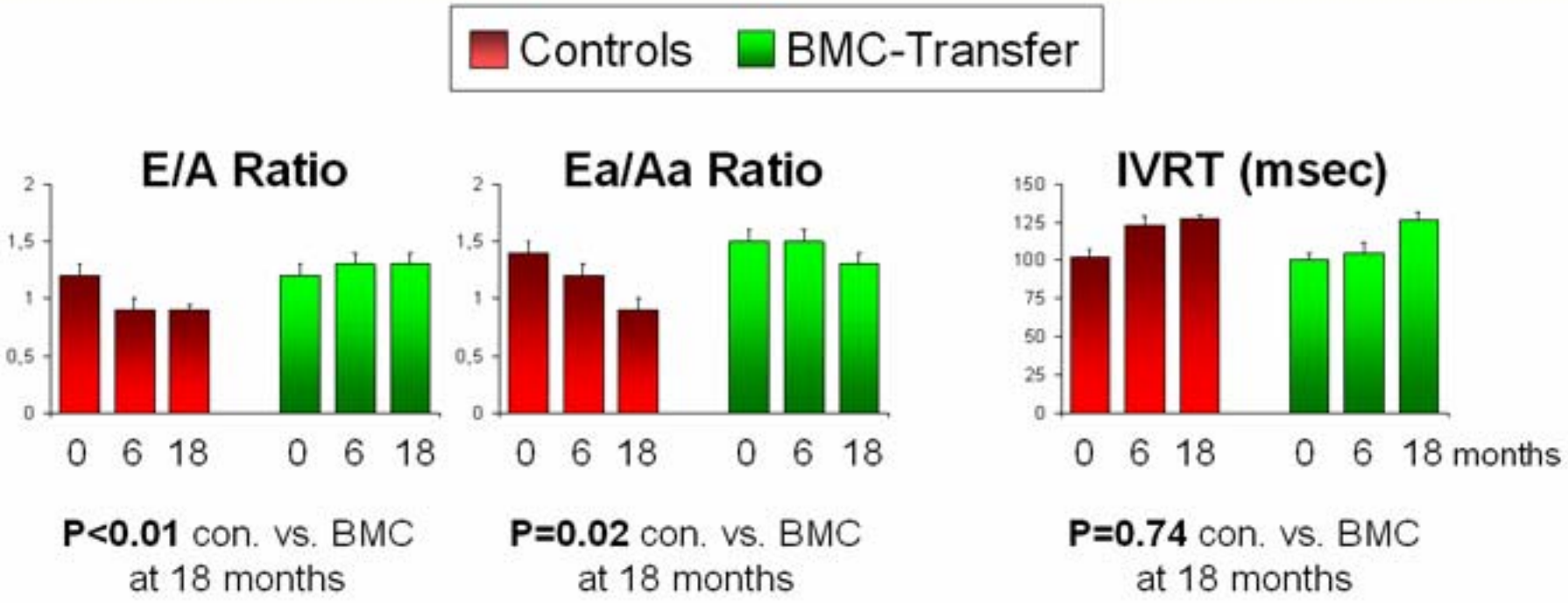


Effect of BMC-Transfer on LV Remodeling
- LV end-diastolic volumes -





Impact on Diastolic Function (BOOST)



P<0.01 con. vs. BMC at 18 months

P=0.02 con. vs. BMC at 18 months

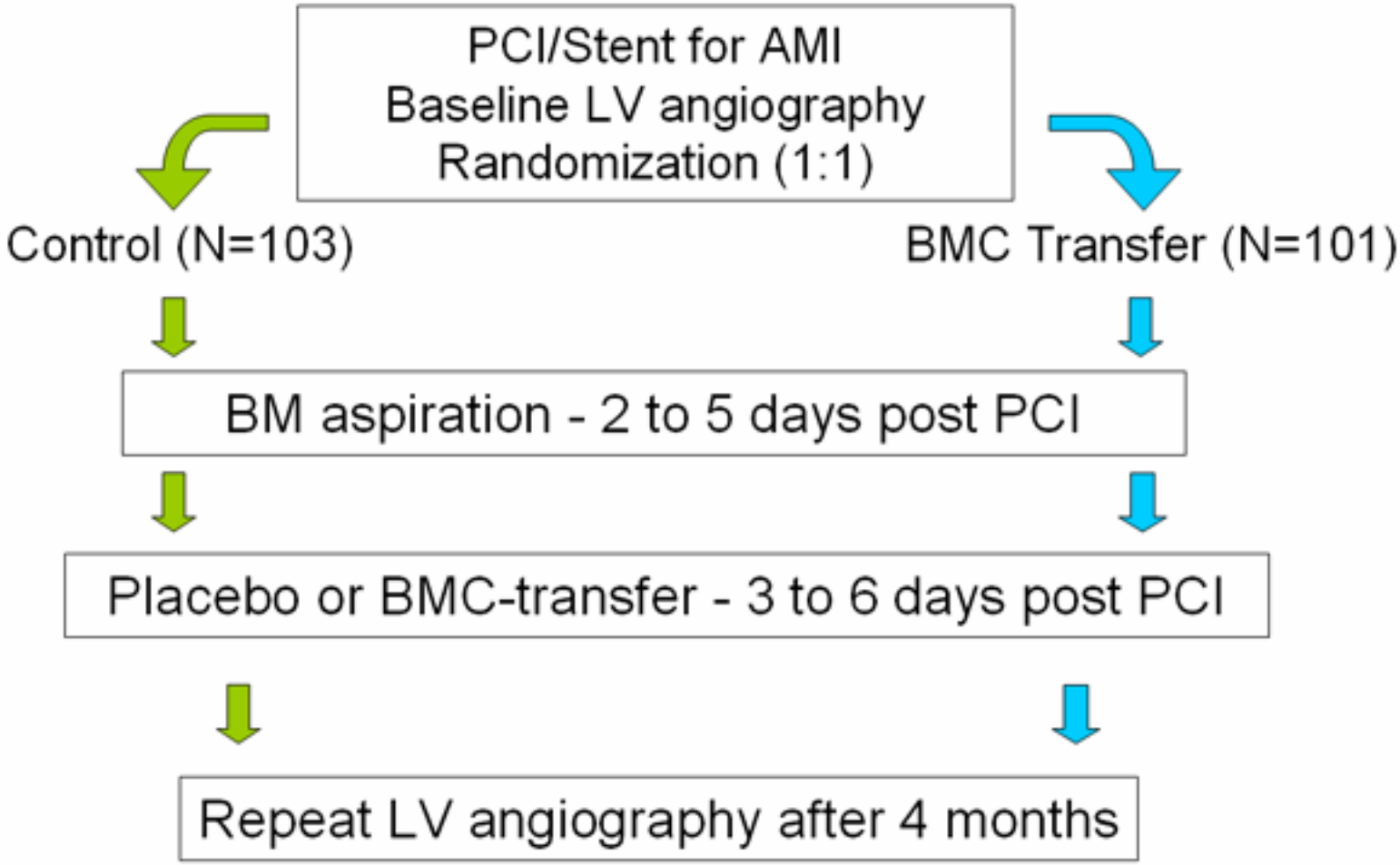
P=0.74 con. vs. BMC at 18 months

Significant effects on E/A ratio and Ea/Aa ratio but not on IVRT suggest that cell therapy may positively affect ventricular stiffness but not active relaxation

Schaefer et al., *Eur Heart J* (2006)

Flow Chart of the REPAIR-AMI Trial

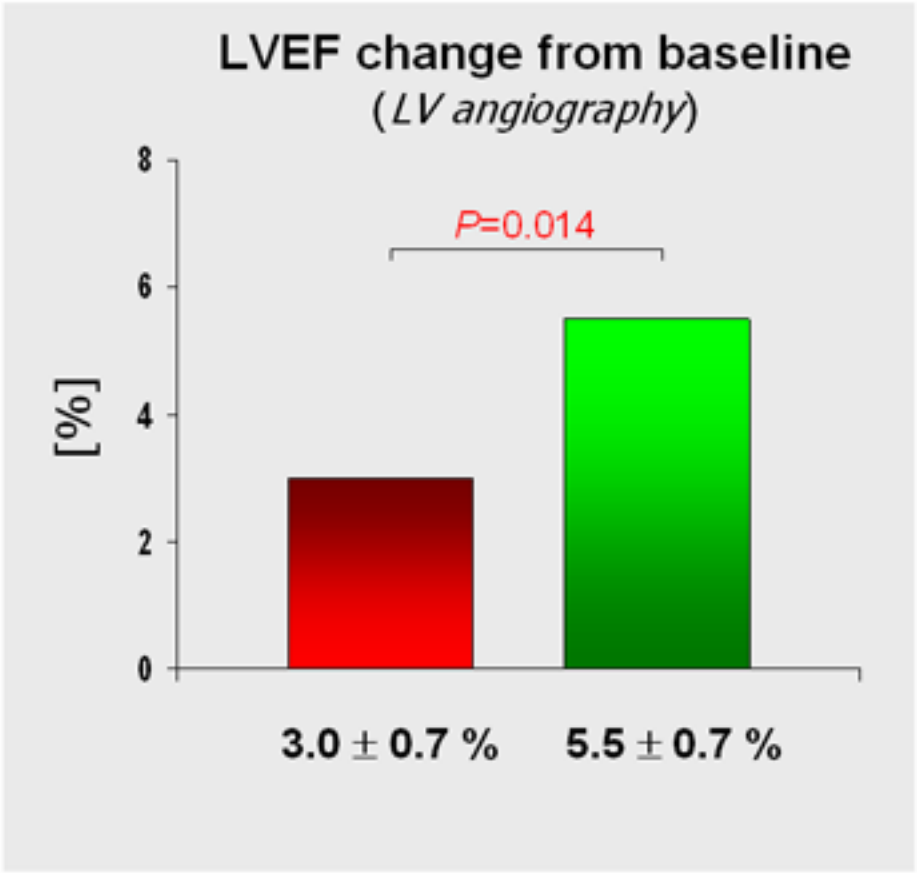
(Schächinger et al., AHA 2005)

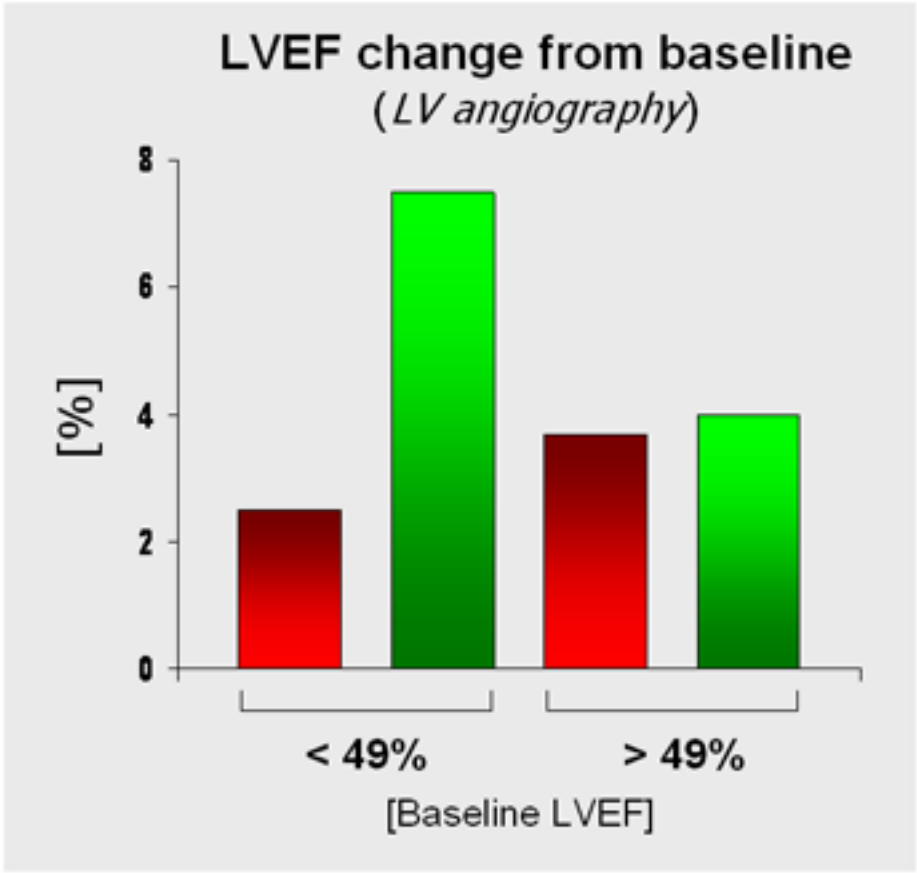


Change in LV ejection fraction after 4 months (LV angio) = primary endpoint

REPAIR-AMI

(Schächinger et al., AHA 2005)





Controls BMC-Transfer

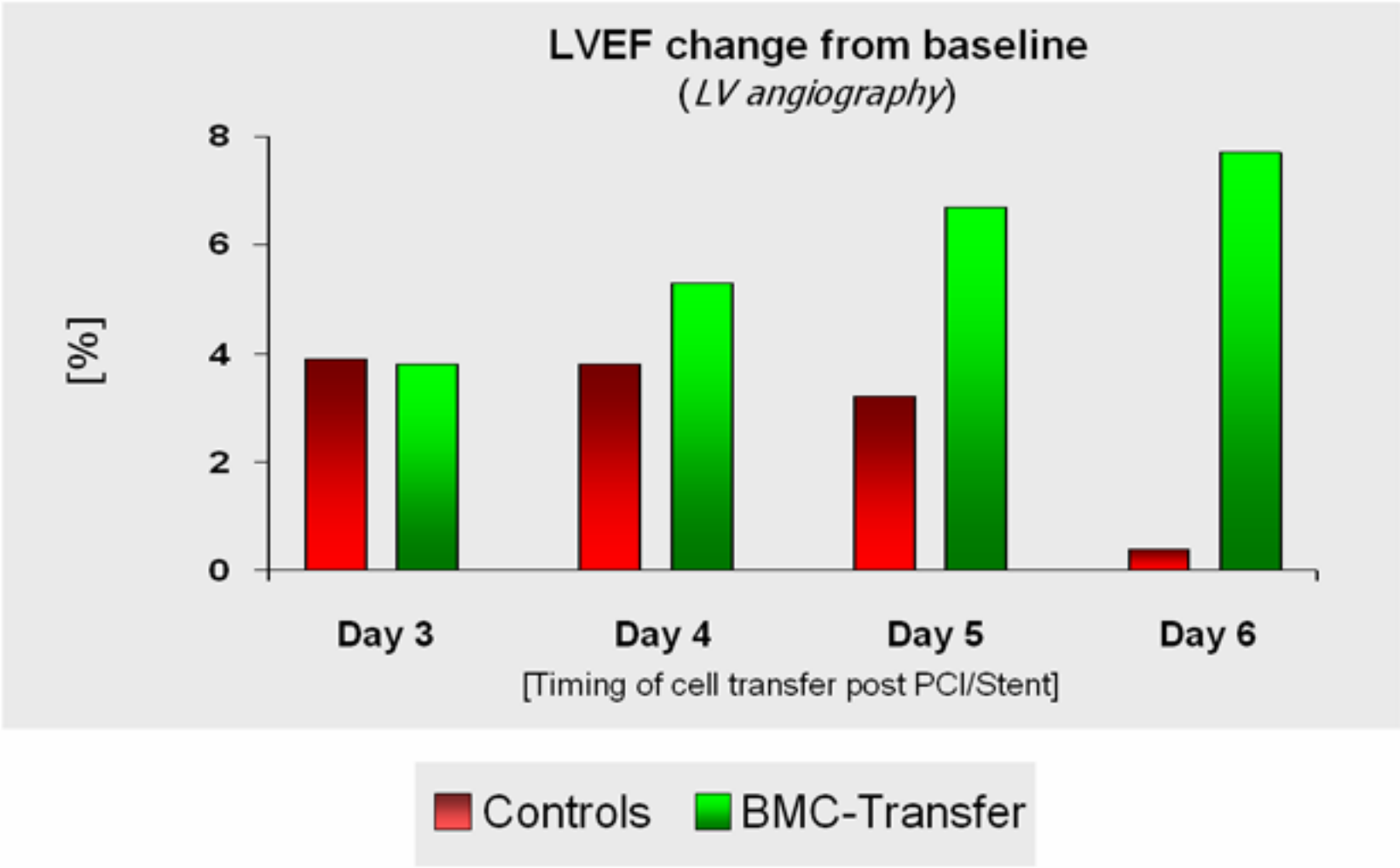
Two Trials have been Negative: Why ?

Study	Effects	Design	Timing of Cell Tx
BOOST	LVEF ↑	randomized-controlled	4-8 days post PCI
REPAIR-AMI	LVEF ↑	placebo-controlled	3-6 days post PCI
Janssens	LVEF ~	placebo-controlled	24 hours post PCI
ASTAMI	LVEF ~	randomized-controlled	4-6 days post PCI

Wollert et al., *Lancet* (2004); Schächinger et al., *AHA* (2005); Janssens et al., *Lancet* (2005); Lunde et al., *AHA* (2005)

REPAIR-AMI

(Schächinger et al., AHA 2005)



Two Trials have been Negative: Why ?

Study	Effects	Design	Timing of Cell Tx	Cell Type
BOOST	LVEF ↑	randomized-controlled	4-8 days post PCI	**all nucleated BMCs** (gelatine sedimentation)
REPAIR-AMI	LVEF ↑	placebo-controlled	3-6 days post PCI	**MN-BMCs only** (Ficoll)
Janssens	LVEF ~	placebo-controlled	24 hours post PCI	**MN-BMCs only** (Ficoll)
ASTAMI	LVEF ~	randomized-controlled	4-6 days post PCI	**lymphocytic BMCs** (Lymphoprep™)

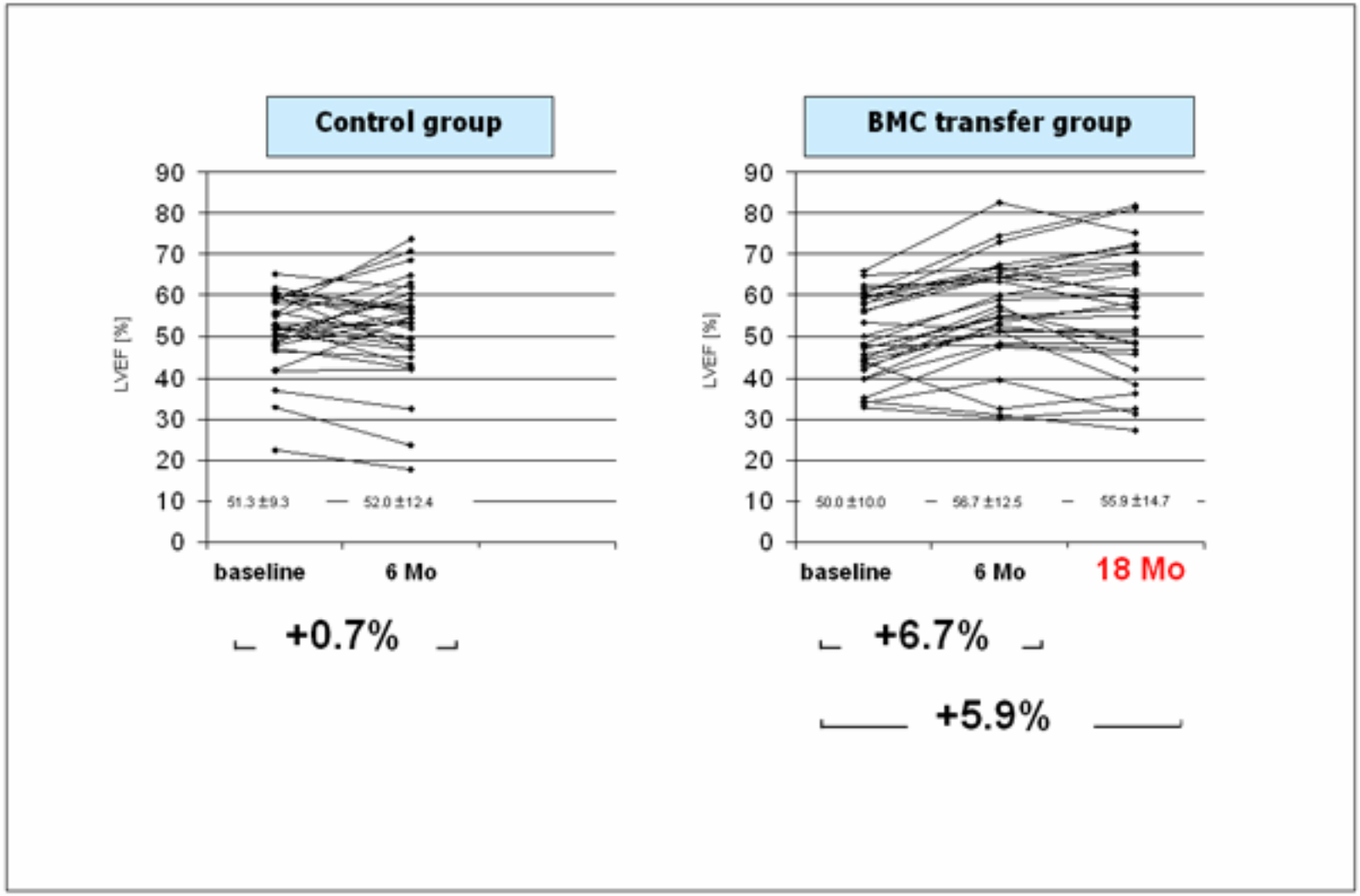
Procedural issues such as timing of cell transfer and cell type may be critical and need to be further refined

Wollert et al., *Lancet* (2004); Schächinger et al., *AHA* (2005); Janssens et al., *Lancet* (2005); Lunde et al., *AHA* (2005)

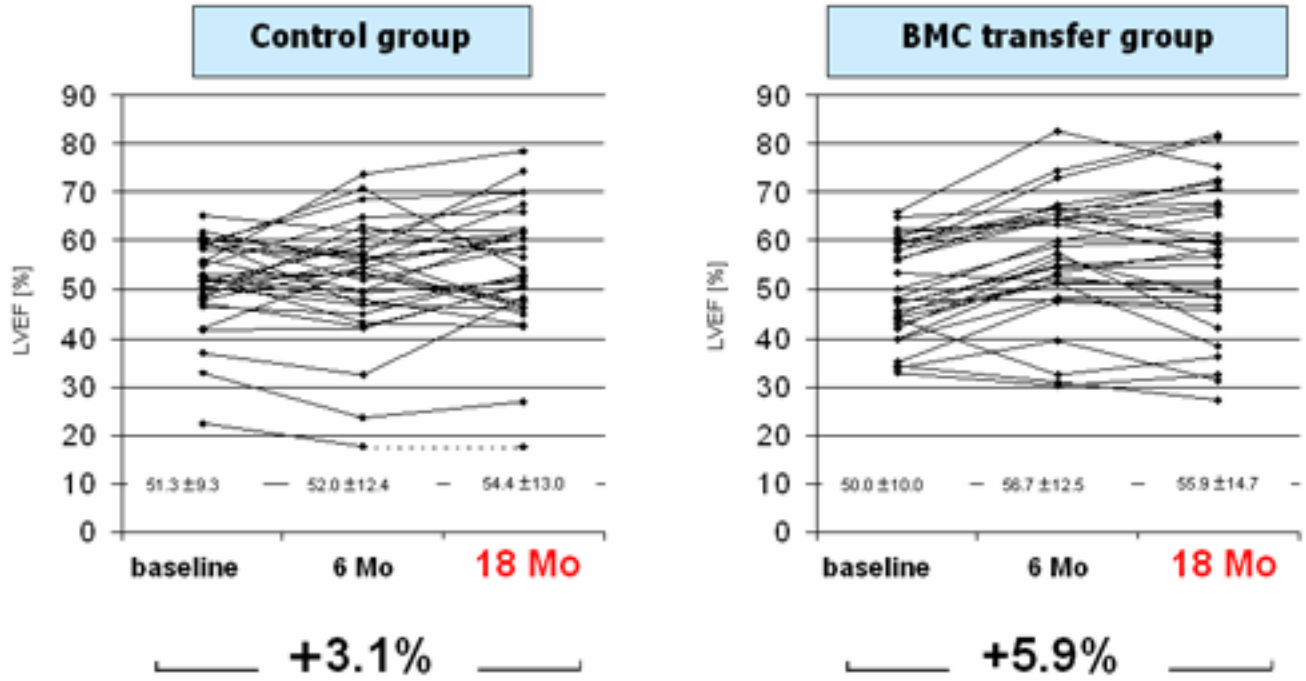
What about the long-term effects of nucleated BMC transfer on LVEF ?

→ 18 months' follow-up data from the BOOST trial

Therapy Effect is Maintained after 18 Months



...but the Control Group Catches up

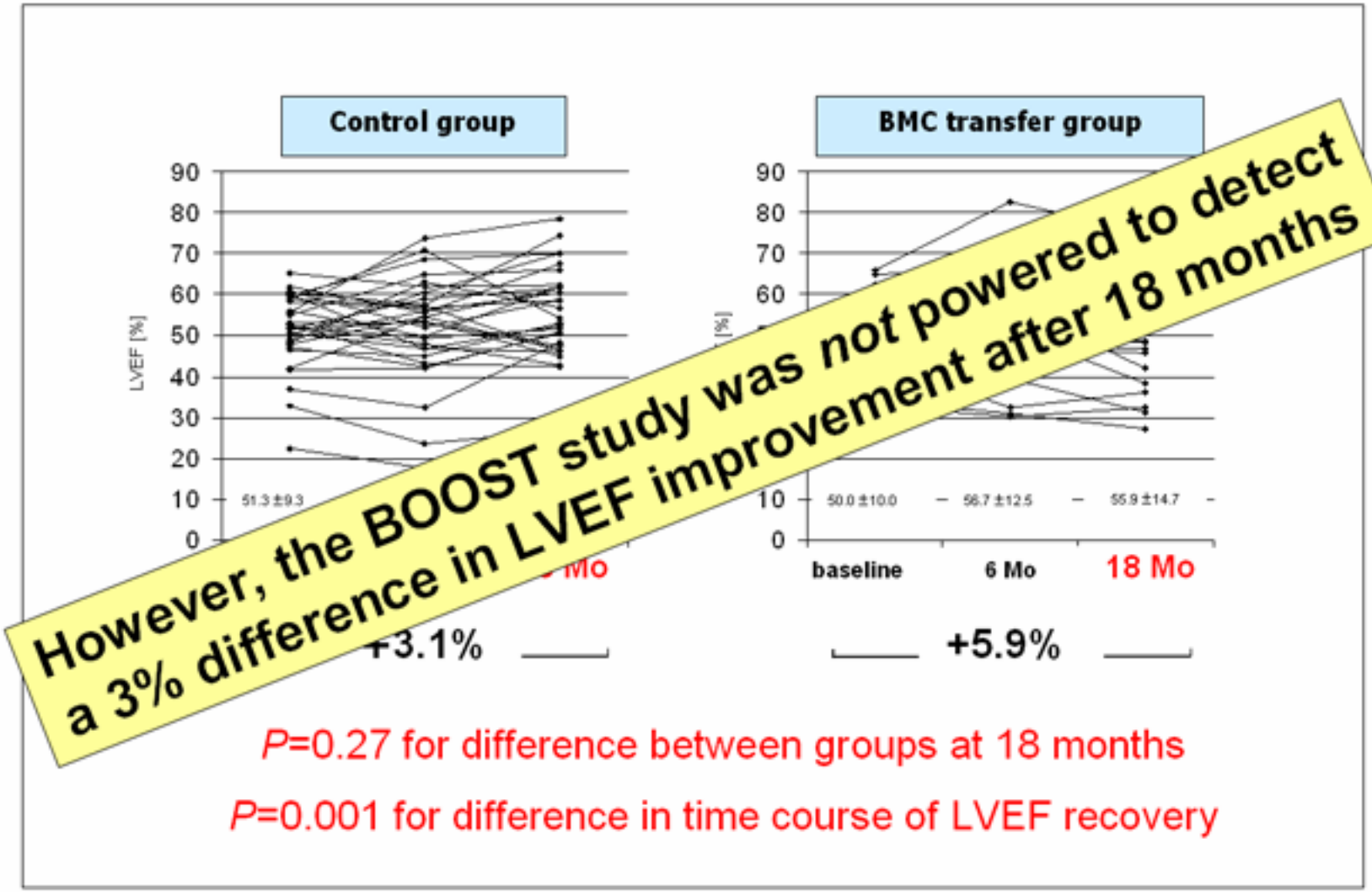


P=0.27 for difference between groups at 18 months

P=0.001 for difference in time course of LVEF recovery

Meyer, Wollert et al., *Circulation* (2006)

...but the Control Group Catches up



Meyer, Wollert et al., *Circulation* (2006)

Can We Use MRI at Baseline to Predict Benefit at 18 Months ?

Baseline

...Ejection Fraction

...LVEDV

...Late Enhancement

...Microvascular Obstruction

...Infarct Transmurality

Do not predict which patients still benefit after 18 months

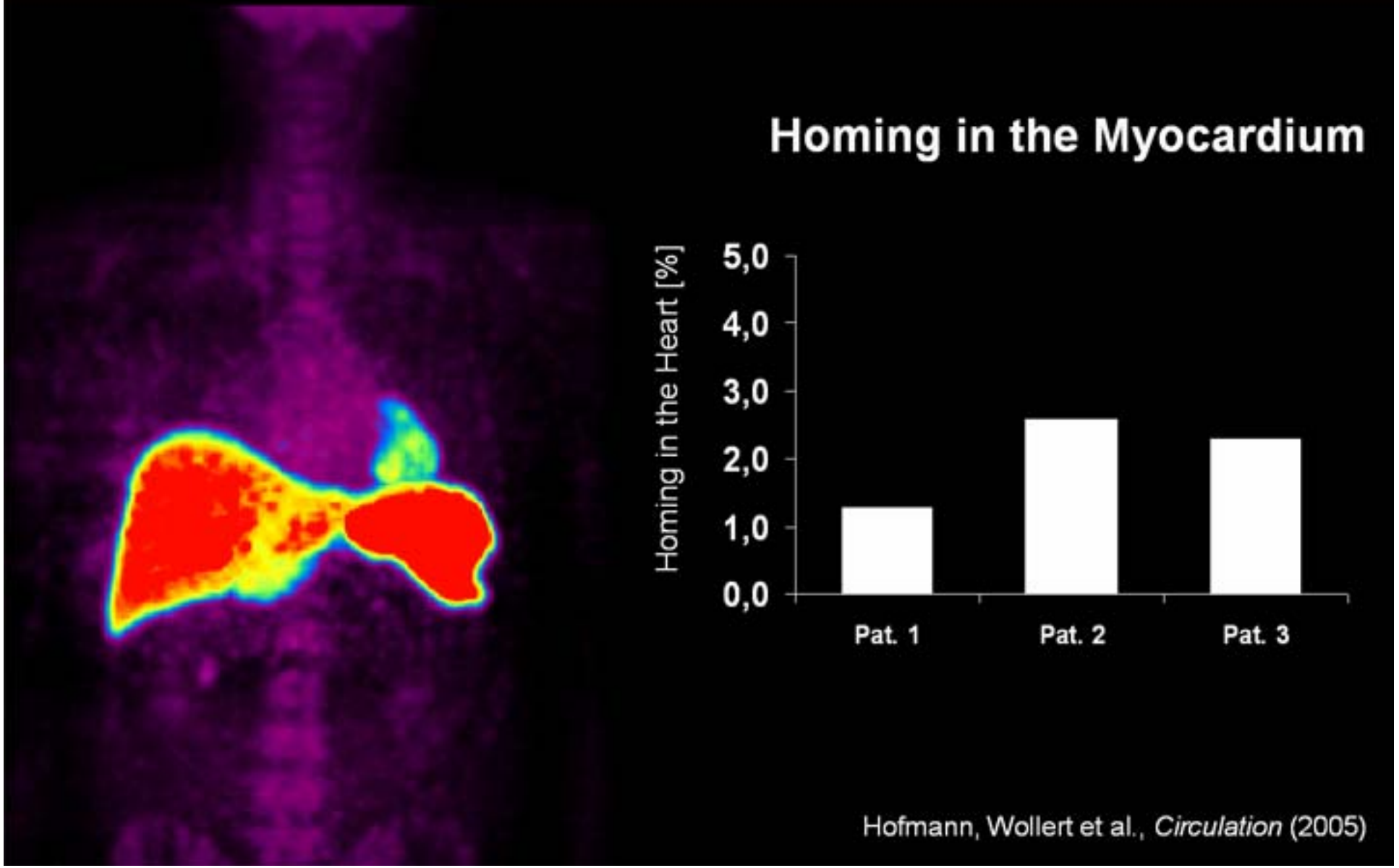
Meyer, Wollert et al., *Circulation* (2006)

Are bone marrow cells merely speeding up the recovery of LV function that can be achieved also with prolonged ACE-inhibition and β-blockade ?

And if so, do the patients benefit from such accelerated LVEF recovery ?

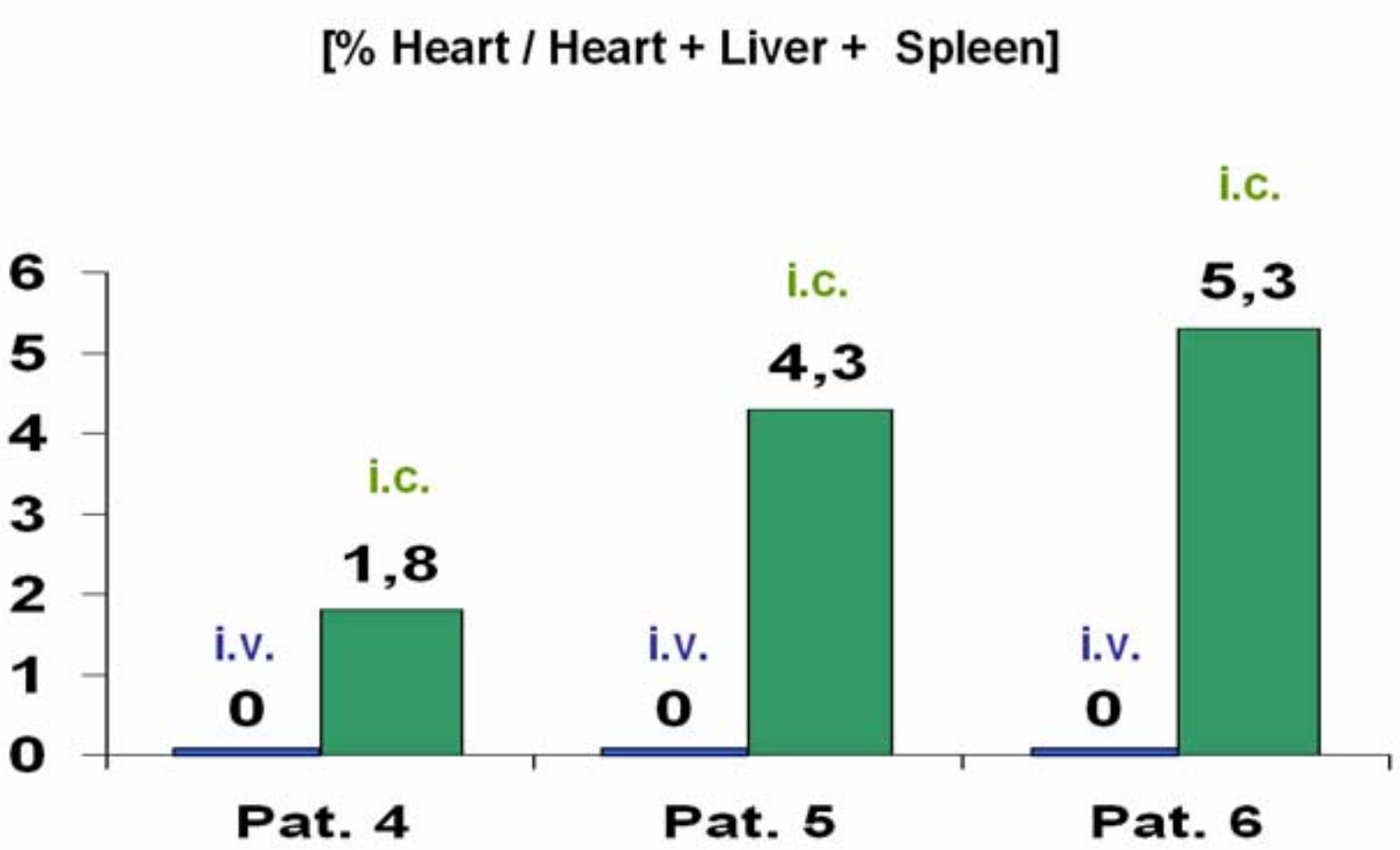
Are we effectively delivering the cells by intracoronary transfer ?

Homing of ^{18}F-FDG labeled unselected BMCs after i.c. Transfer

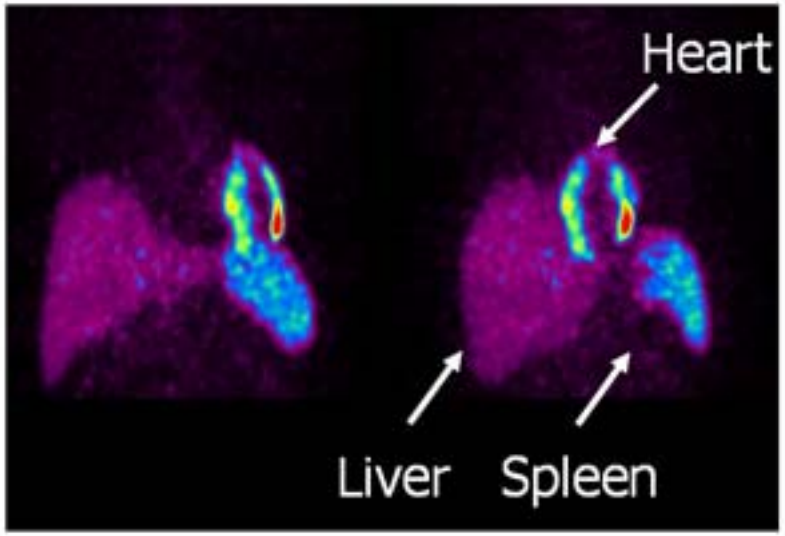


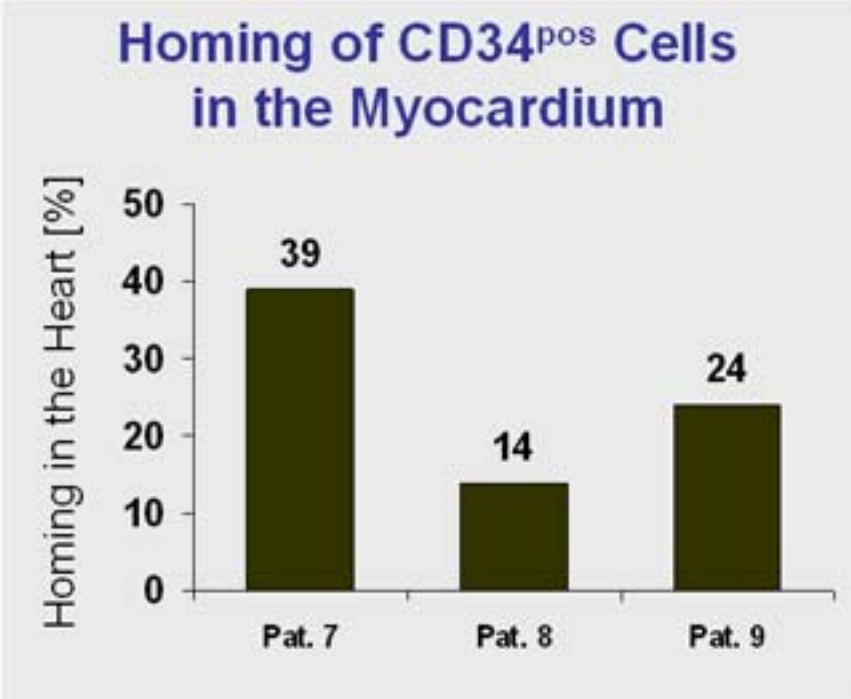
Hofmann, Wollert et al., *Circulation* (2005)

Homing of ^{18}F-FDG labeled unselected BMCs after i.v. Transfer



Homing of ^{18}F-FDG labeled CD34^{pos} BMCs after i.c. Transfer





Summary and Conclusions

Cell therapy post AMI might work !

Intracoronary BMC transfer has the potential to enhance the recovery of LV systolic function after AMI
(with the right cell preparation method, and right timing of cell transfer)

Intracoronary BMC transfer appears to promote lasting benefits on LV diastolic function

Considering that less than 5% of BMCs are detectable in the infarcted area after cell transfer, methods to increase the homing capacity of the cells should be explored to enhance the therapeutic potential of BMCs

Outcome trials are needed to determine if patients benefit clinically from bone marrow cell transfer after AMI (mobidity and mortality)

Considering that BMCs appear to have no impact on infarct size and LV remodeling, they probably do not make new myocardium. The potential of cells with true transdifferentiation capacity
(ES-cells, resident cardiac stem cells, or multipotent bone marrow-derived stem cells, spermatogonial stem cells) **needs to explored to fully realize the promise of myocardial regeneration**

?