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GOETHE-UNIVERSITÄT

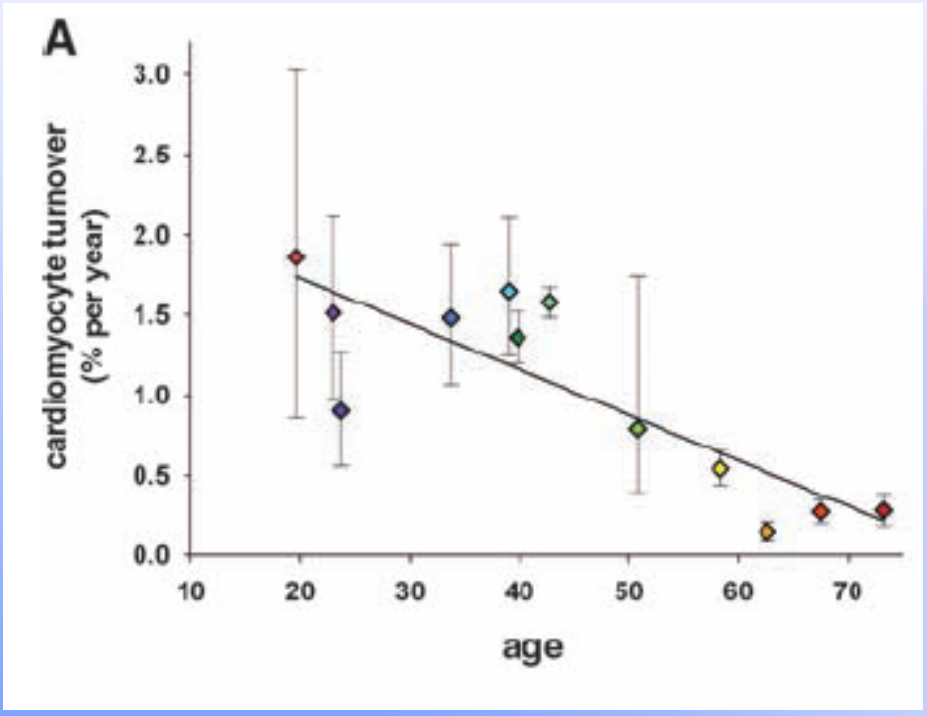
Stem cell therapy for myocardial repair

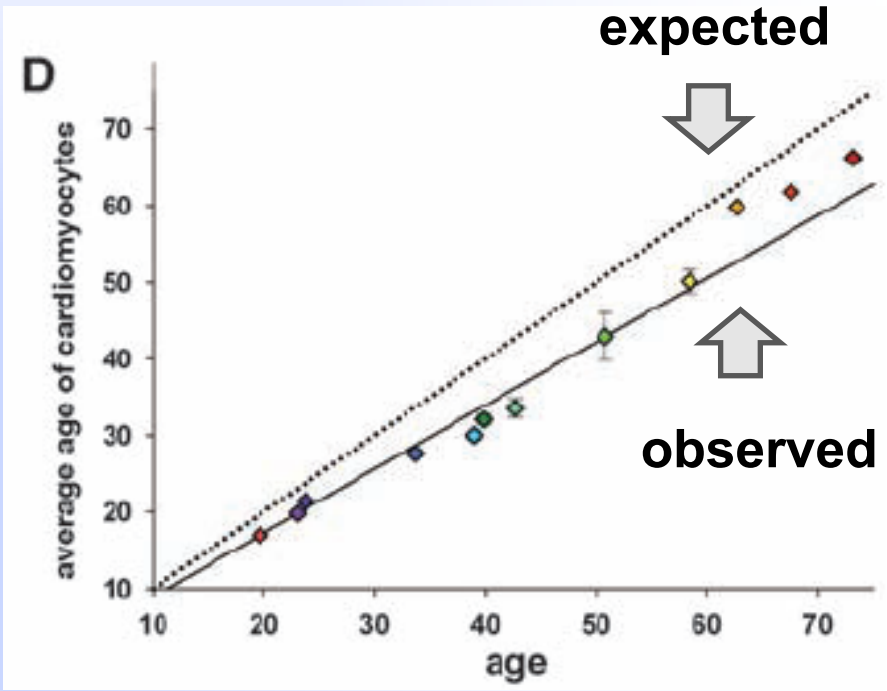
Birgit Assmus

The heart is regenerating !

Undisputable Evidence from DNA Integration of C-14

– generated during nuclear bomb testing during cold war -

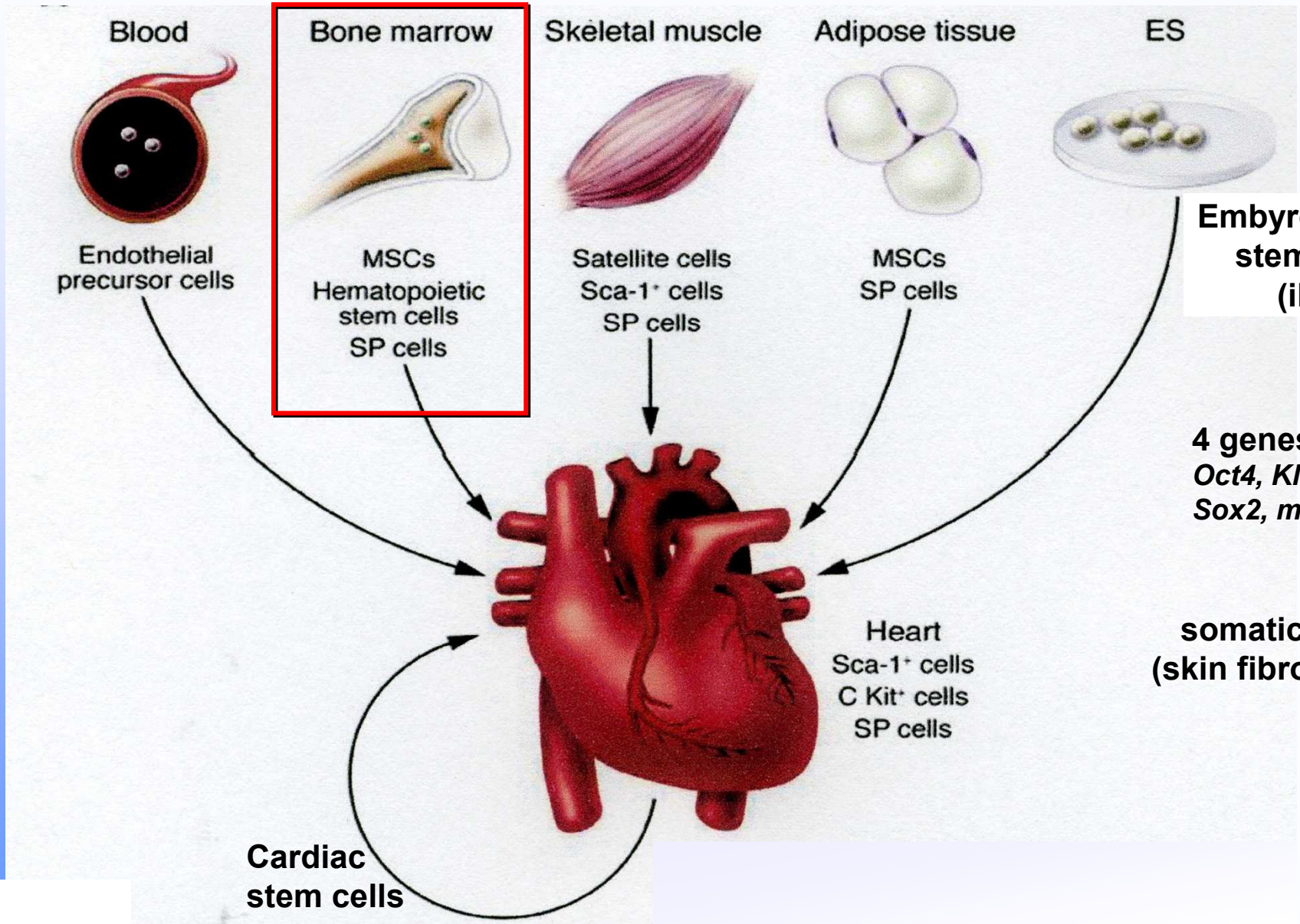




The heart muscle is younger than the body!

Bergmann O et al., Science 2009; 324:98-102

Cells for functional cardiac repair



Modified from Dimmeler et al, JCI 2005

Clinical evolution of BMC therapy for cardiovascular diseases

Phase I/II clinical trials

Phase III trials

Bone marrow-derived cells

Bone marrow mononuclear cells (BMC)

$CD133^+$

$CD34^+CXCR4^+$

$CD34^+$

Mesenchymal Stromal Cells

Cell enhancement, target region preconditioning

- Shock waves for enhancing cell engraftment
- Factors to enhance cardiac differentiation
- Repeated administration

2001/ 2002

2006

2008

2009

2013

Adipose tissue-derived cells

Cardiac stem cells

$c\text{-}kit^+$ cells

Cardiospheres

Bami

Supported by the EC under the FP7 programme

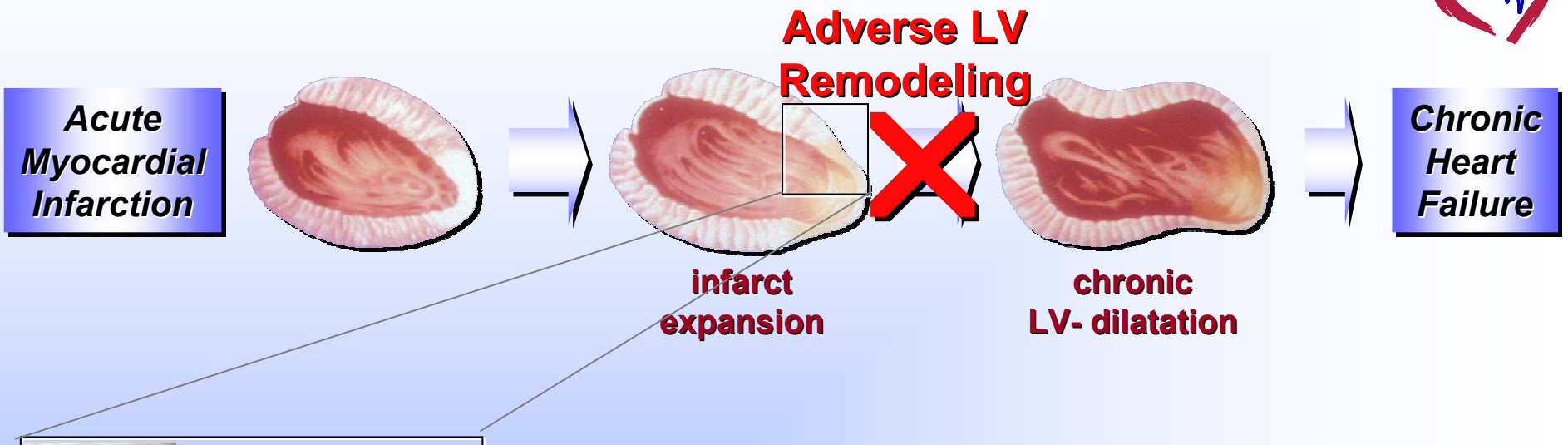
RENEWstudy

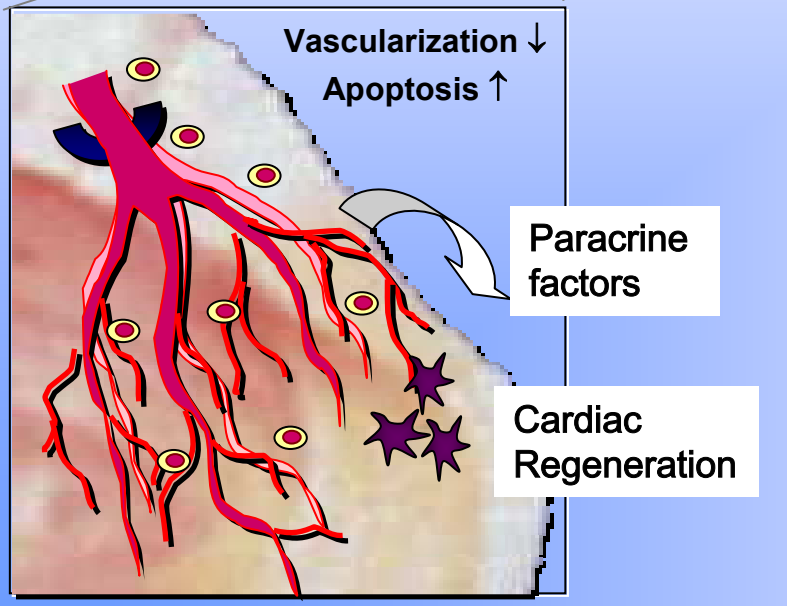
stopped end 2013

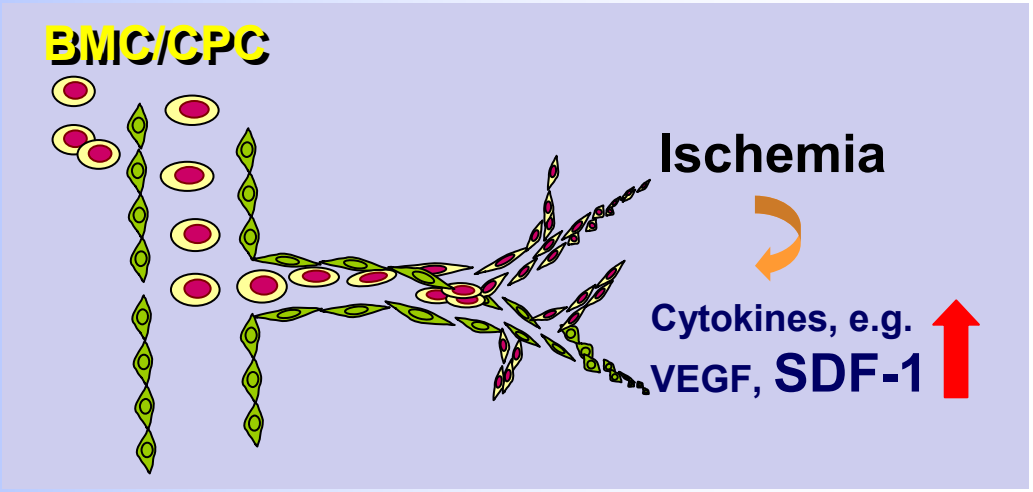
Cell therapy in cardiovascular diseases

- ⇨ *Acute Myocardial Infarction*
- ⇨ *Refractory Angina*
- ⇨ *Peripheral arterial occlusive disease*
- ⇨ *Chronic post-infarction heart failure*

Cell Therapy in Acute Myocardial Infarction: therapeutic targets





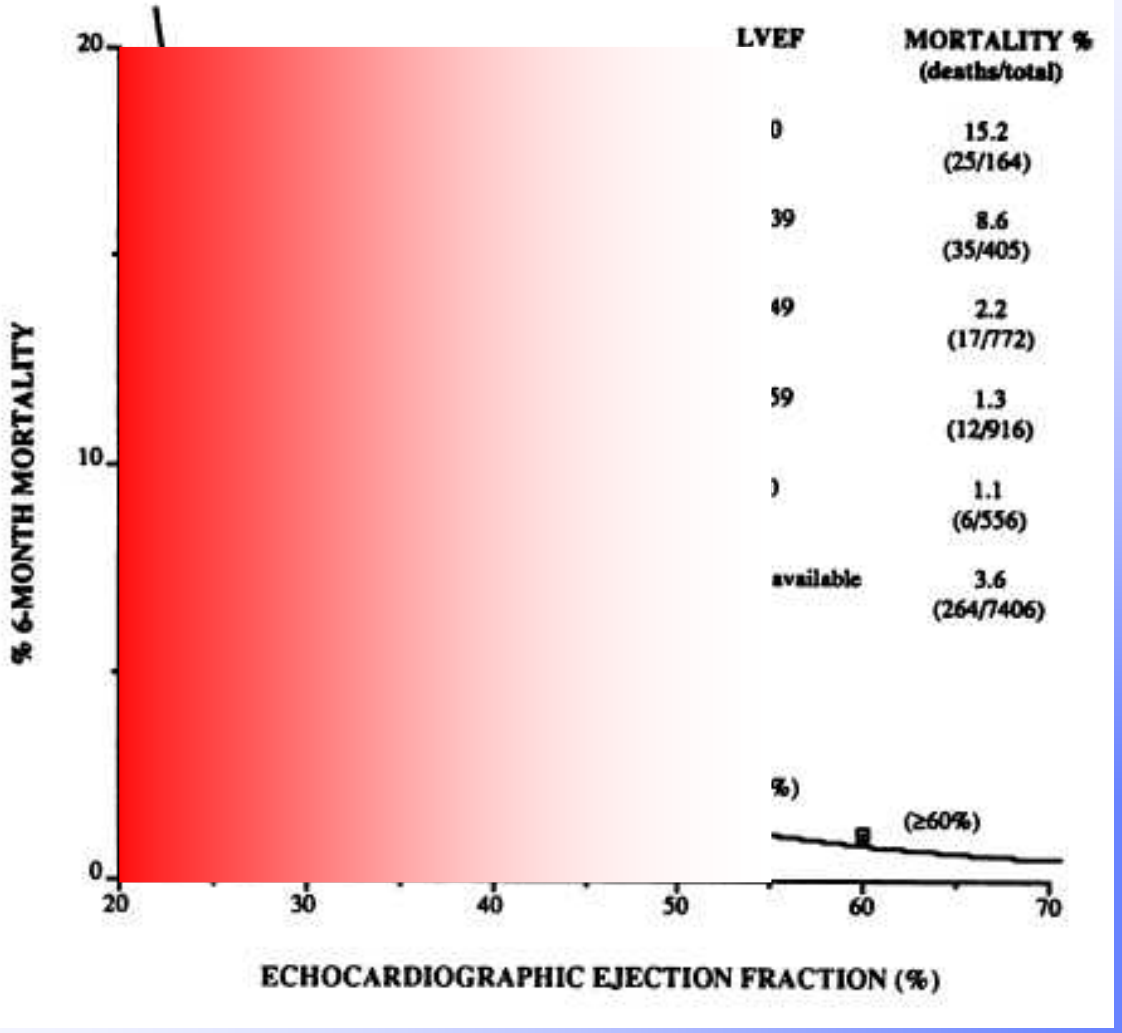


Cell Therapy for STEMI

- *The patient population at risk post-AMI*
- *Effects of cell therapy in patients at risk*
- *Derivation of the clinical benefit*

LV contractile recovery within 1 week after successful reperfusion determines clinical outcome in STEMI

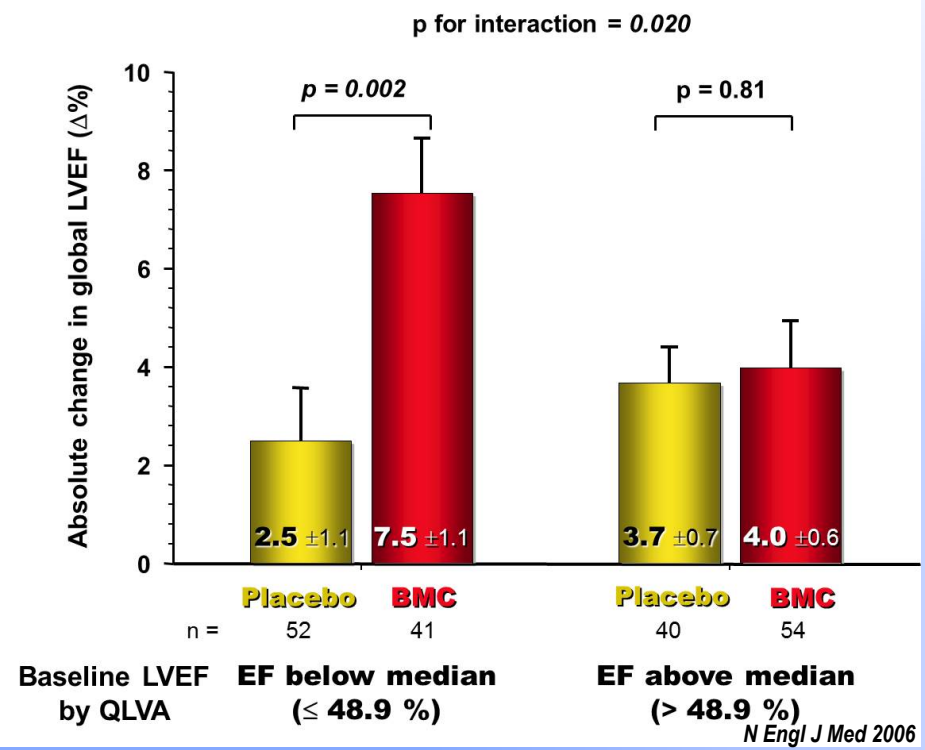
There is *no linear* correlation between mortality and ejection fraction after AMI !



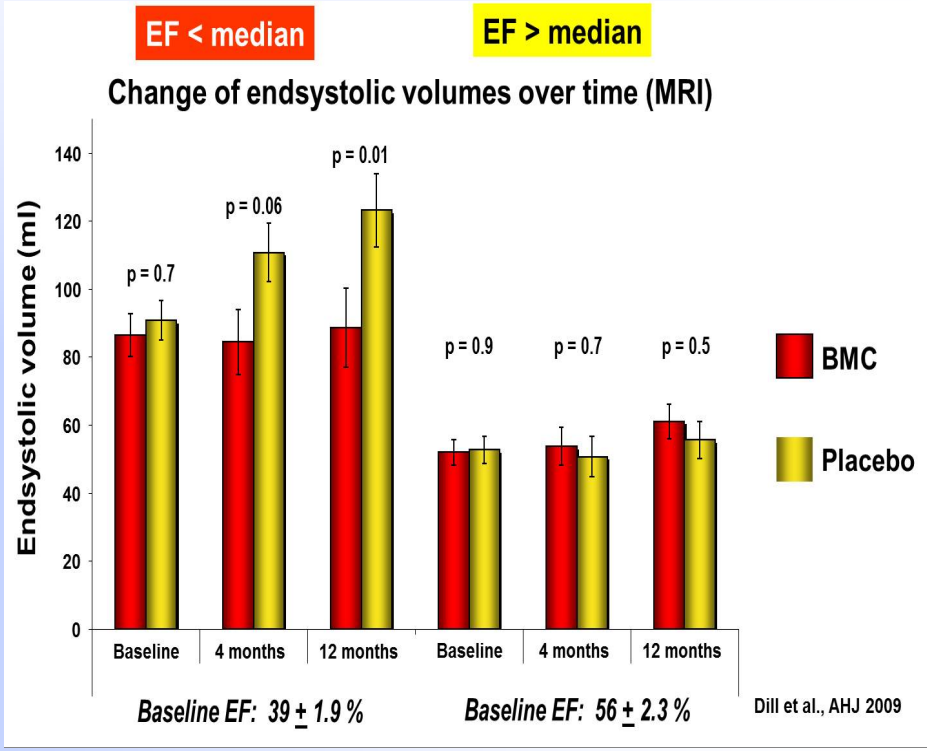
Volpi et al., Circulation 1993; 88: 416-429

Enhanced contractile recovery by BMC is confined to patients with failed initial recovery

4 months data LV angiography



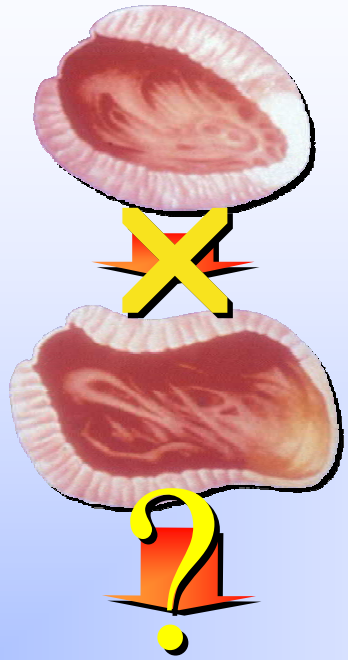
12 months data MRI



Repair-AMI: n= 204 patients; 1:1 multicentre double-blind randomized intracoronary placebo or BMC infusion 3 -7 days after successful acute reperfusion therapy

Do beneficial effects of BMC therapy on adverse remodeling translate into clinical benefit ?

acute
myocardial infarction



Left Ventricular Remodeling

- Ejection fraction ⇩
- End-systolic volume ⇧

Cardiovascular Events

- Mortality ⇧
- Ischemic events ⇧
- Rehospitalization for heart failure ⇧

Therapies preventing adverse remodelling… → *… reduce adverse cardiovascular events*

ACEI , ARB, ß-Blocker, Aldosteron-Ant., CRT

BMC therapy post-AMI

Improved clinical outcome in meta-analysis

Table 6. Clinical outcomes in BMC-treated patients compared with patients receiving standard therapy

Outcome	Peto OR	95% Confidence Interval	*P* value
All-cause mortality	0.39	0.27 to 0.55	<0.00001
Cardiac deaths	0.41	0.22 to 0.79	0.005
Recurrent MI	0.25	0.11 to 0.57	0.001
Heart failure	0.52	0.27 to 1.00	0.05
Stent thrombosis	0.34	0.12 to 0.94	0.04
In-stent restenosis	0.87	0.47 to 1.62	0.66
TVR	0.83	0.55 to 1.23	0.35
CVA	0.28	0.08 to 1.07	0.06
VT / VF	1.14	0.52 to 2.53	0.74

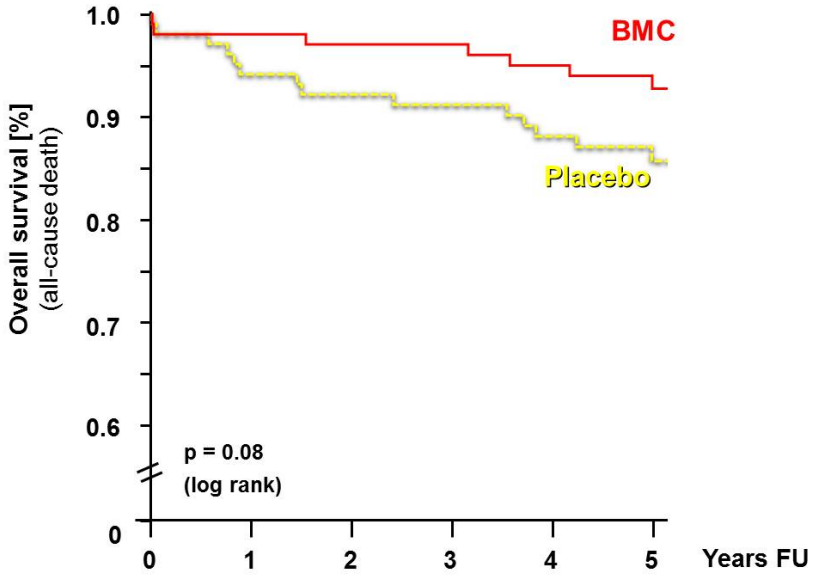
Abbreviations: BMC, bone marrow cell; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; TVR, target vessel revascularization; VF, ventricular fibrillation; VT, ventricular tachycardia.

N = 2625 patients from 50 studies

Jeevanantham et al, Circulation, 2012

Baseline LVEF determines 5-year survival in Repair-AMI

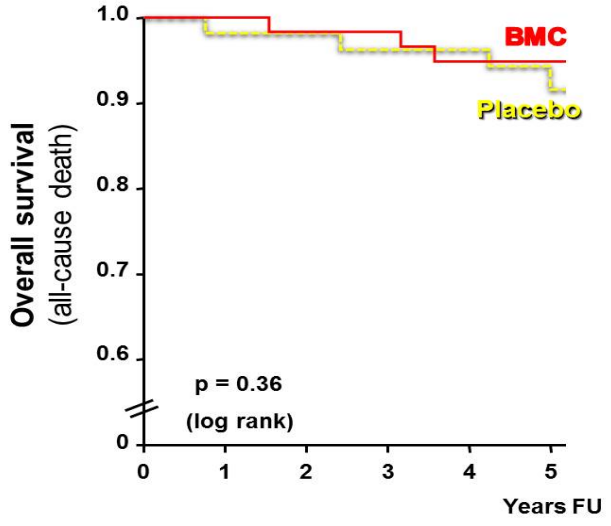
5-year survival



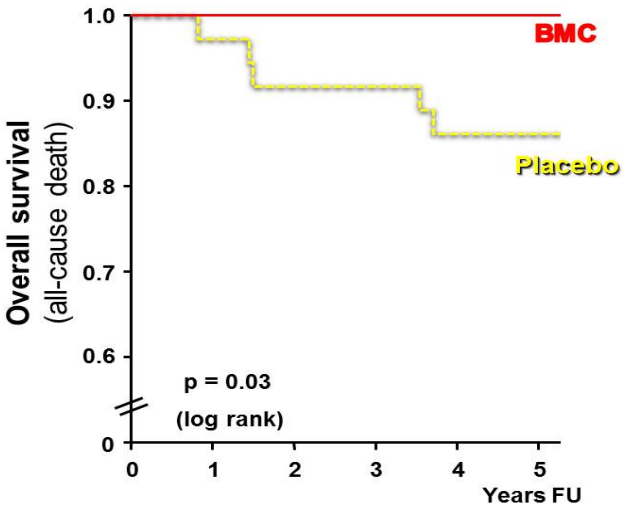
Numbers at risk						
Placebo	103	96	94	89	86	84
BMC	101	99	98	95	93	88

Assmus et al; Eur Heart J 2014

Baseline LVEF > 45%



Baseline LVEF ≤ 45%

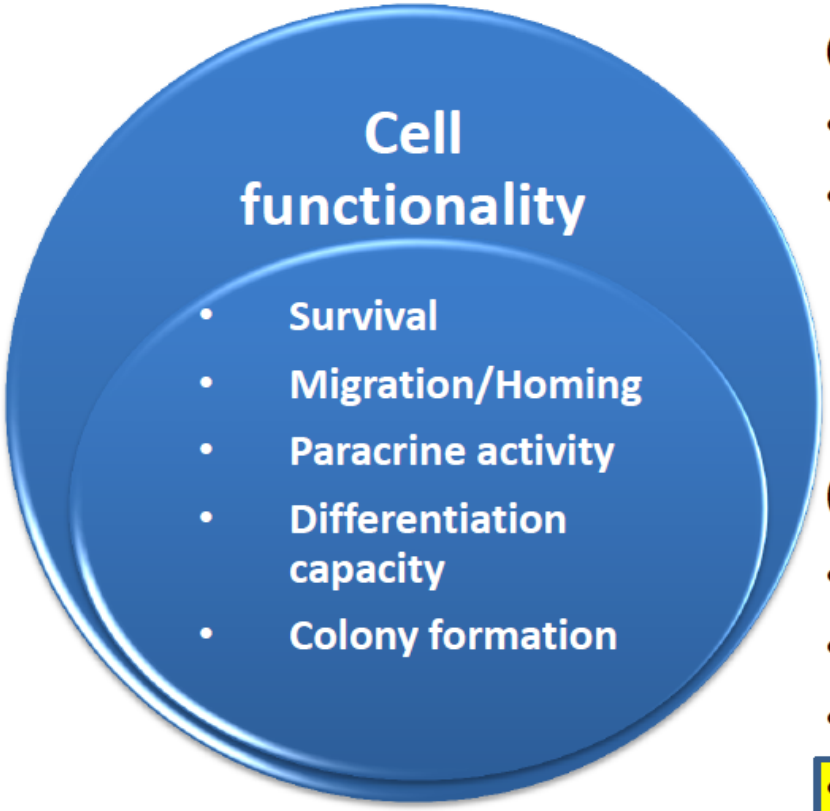


Factors influencing function of autologous BMC

Cell intrinsic factors

Patient characteristics

- Age
- Diabetes
- Heart failure
- Acute MI



Extrinsic factors

Cell preparation:

- Purity
- Contaminations (e.g. Red blood cells, granulocytes?)

Cell storage:

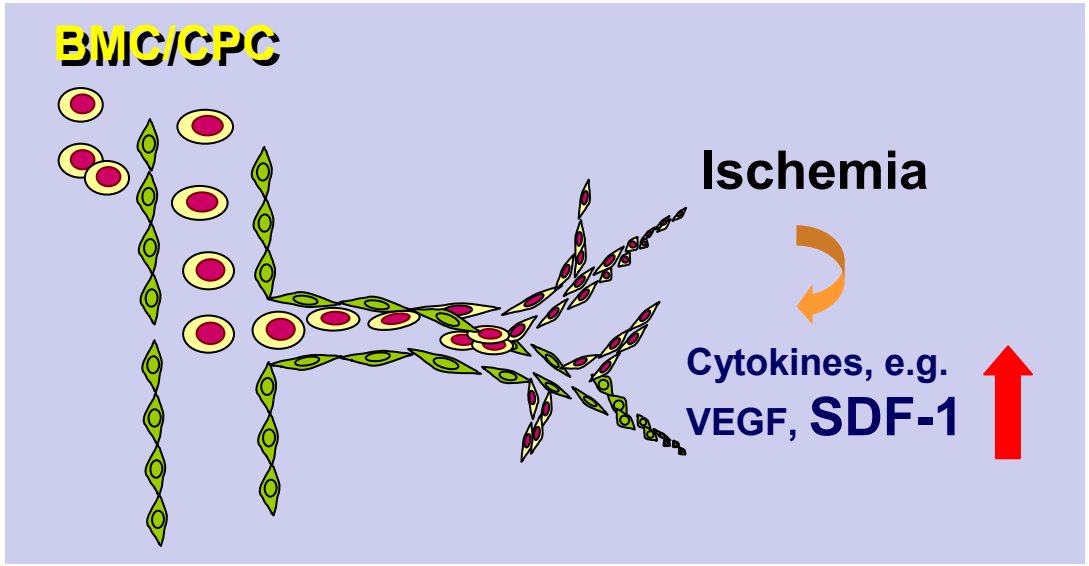
- pH (NaCl)
- Temperature
- Serum vs Plasma
- Heparin
- Nutrients/ Metabolism

Selection of clinical BMC Trials in AMI

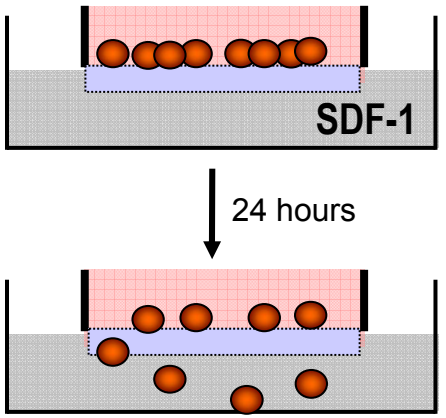
EU- Ficoll isolated BMC trials

Study	Number of pts.	Cells	Heparin in Final Cell Product	Primary Endpoint	Effects
ASTAMI	*100*	*i.c.; BM-MNC vs. standard therapy*	*5 U/ml*	*LVEF (SPECT)*	*(-) after 6 / 12 months*
BONAMI	*101*	*i.c.; BM-MNC vs. standard therapy*	*No heparin*	*Vitality (SPECT)*	*(+) vitality after 3 months* *(-) LVEF*
FINCELL	*80*	*i.c.; BM-MNC vs. medium*	*heparinized serum*	*LVEF (QLVA, echo)*	*(+) LVEF after months*
HEBE	*200*	*i.c.; BM-MNC vs. peripheral MNC vs. standard therapy*	*20 U/ml*	*reg. LV-function (MRI)*	*(-) after 4 months*
Janssens-Trial	*67*	*i.c.; BM-MNC vs. NaCl + serum*	*No heparin*	*LVEF (MRI)*	*(+) reduction infarct size* *(+) regional LV function*
Plewka et al	*60*	*i.c.; BM-MNC vs. standard therapy*	*?*	*LVEF (echo)*	*(+) LVEF after 6 months*
REGENT	*200*	*i.c.; BM-MNC vs. $CXCR4^+$ BM-MNC vs. standard therapy*	*No heparin*	*LVEF (MRI)*	*((+)) LVEF after 6 months in cell treated groups*
REPAIR-AMI	*204*	*i.c.; BM-MNC vs. medium*	*No heparin*	*LVEF (QLVA)*	*(+) LVEF after 4 months* *(+) after 12 & 24 months*

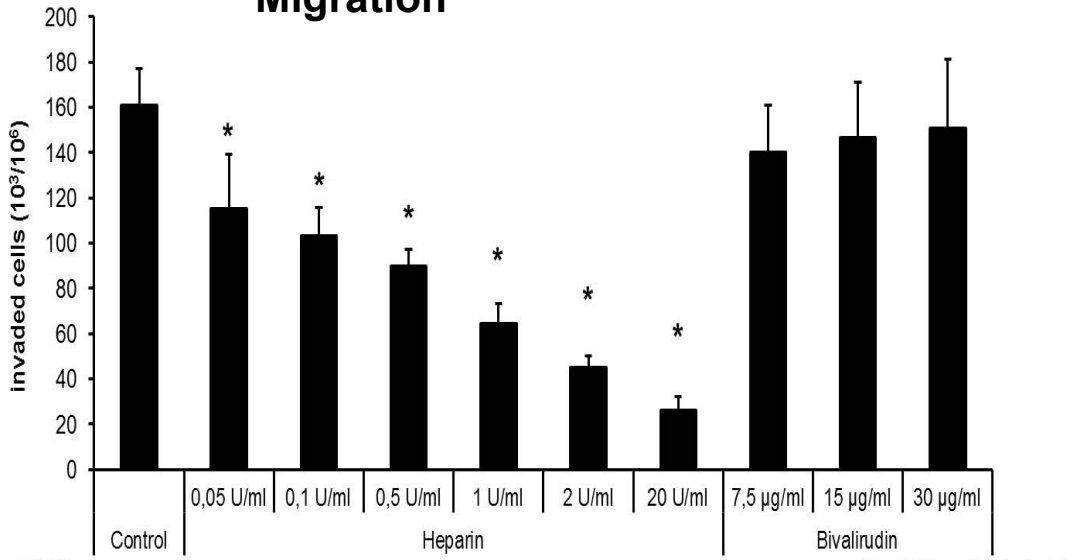
Migratory / Invasion Capacity of BMC: Effects of Heparin



in-vitro migration assay



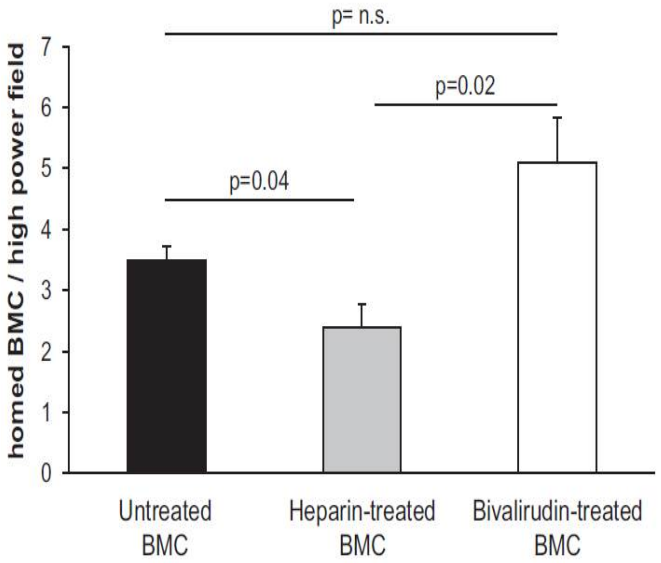
Migration



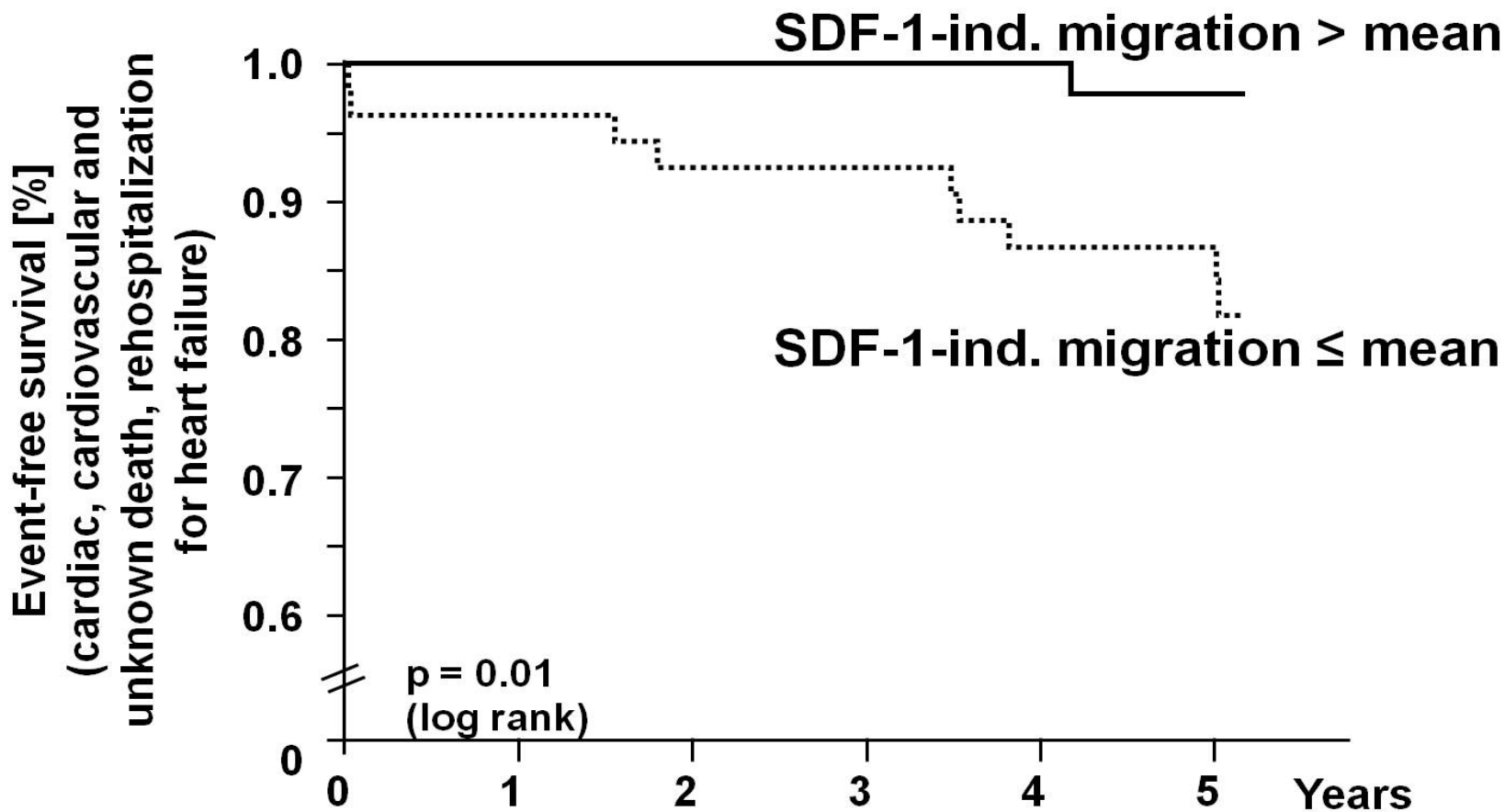
* p≤0.05 vs Control; n≥3

Circ Res 2012

Homing of BMC in ear wound model



Functional capacity of the applied BMC predicts clinical outcome at 5 years



Numbers at risk						
Migration ≤ 170	53	51	49	48	45	44
Migration > 170	48	48	48	46	45	42

Eur Heart J 2014

Supported by the EC under the FP7 programme

BAMI Clinical Trial Design

(ESC Cell Therapy Trial Consortium)

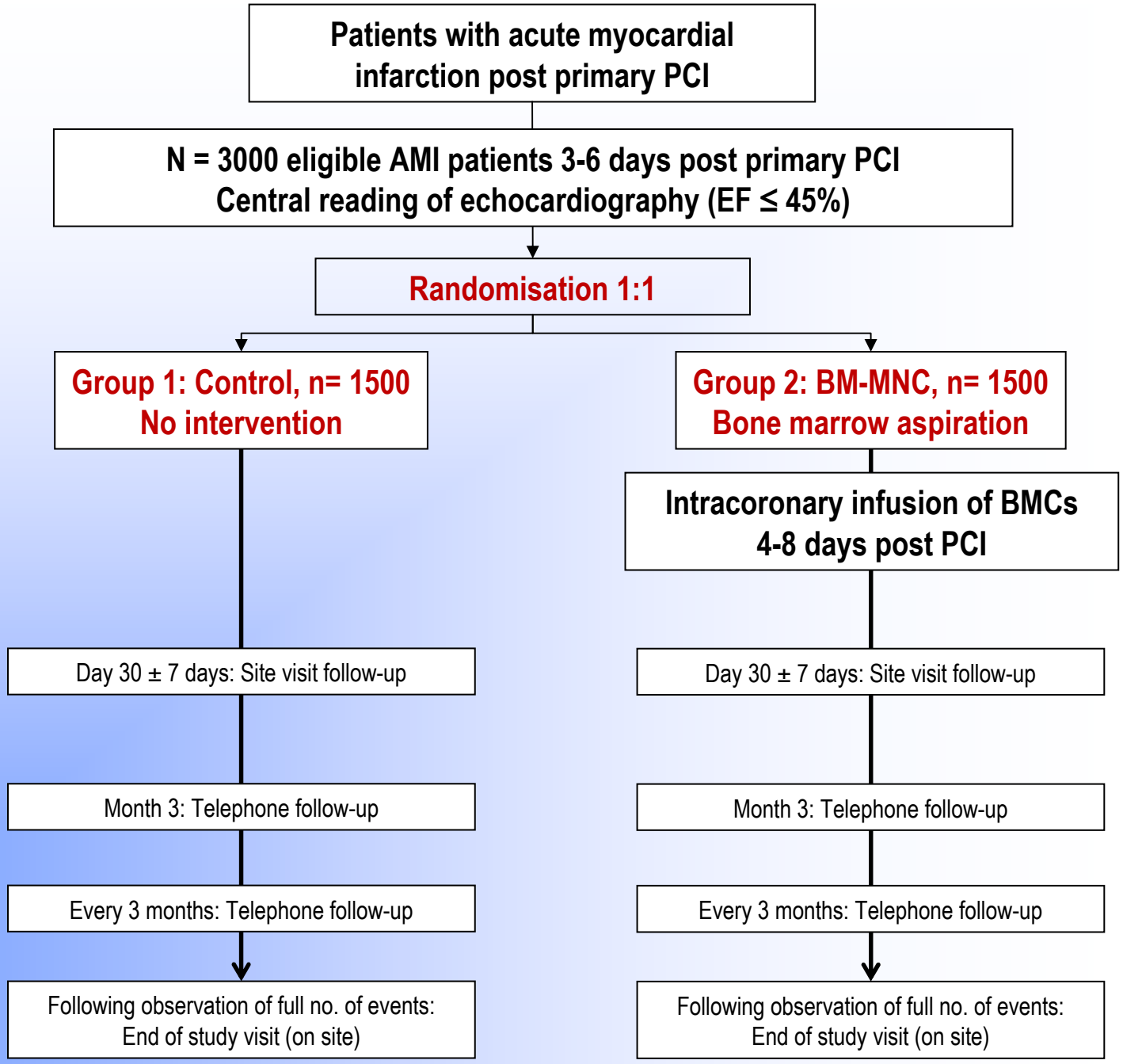
‚The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells on all-cause mortality in STEMI‘

- *1:1 randomized, controlled, no placebo group*
- *intracoronary BMC administration vs. standard care*
- *approx. 3000 patients, event-driven trial design*
- ***primary endpoint: all-cause mortality***
- *Inclusion criterion: LVEF < 45% 3-6 days after successful reperfusion by quantitative echo core lab analysis*
- *Aim: to reduce 2-year mortality by 25%*
- *anticipated mortality in control group: 11.5% at 2 years*
- *11 participating European countries*
- *6 core cell processing facilities across Europe*
- *first patient in: Q3 / 2013*

Bami

Supported by the EC under the FP7 programme

Study flowchart



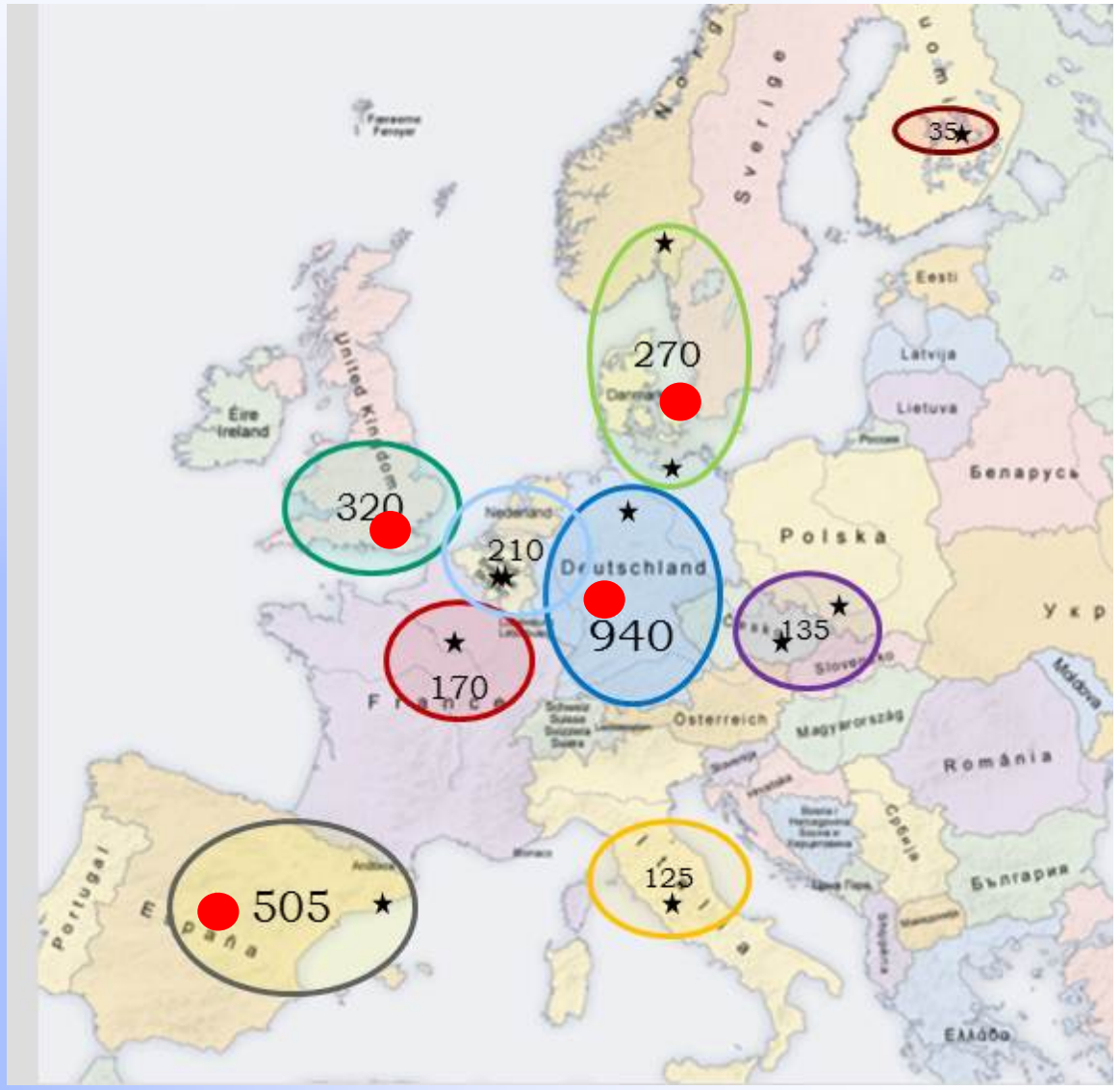
Cell processing centers and patient distribution

Supported by the EC under the FP7 programme

- The Royal London Hospital, London, UK
- **Hospital Gregorio Maranon, Madrid, Spain**
- **Rigshospitalet University Hospital, Copenhagen, Denmark**
- Universitaire Ziekenhuizen, Leuven, Belgium
- **BSD, Institute for Transfusion Medicine, Frankfurt, Germany**

potentially eligible patients @ day 4-5 post AMI (EF≤45)

Start Sept 2013,
8 Sept 2014: n = 51 patients

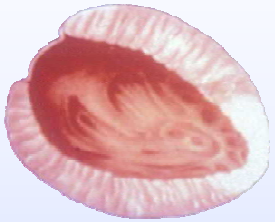


Cell therapy in cardiovascular diseases

- Acute Myocardial Infarction
- Refractory Angina
- Peripheral arterial occlusive disease
- Chronic post-infarction heart failure

Challenges in Cell Therapy of Chronic Heart Failure

Acute Infarction

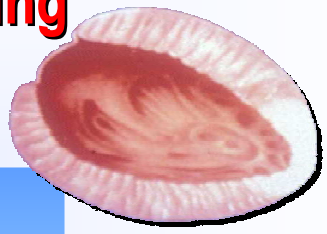


LV- Dilatation

Chronic Heart Failure

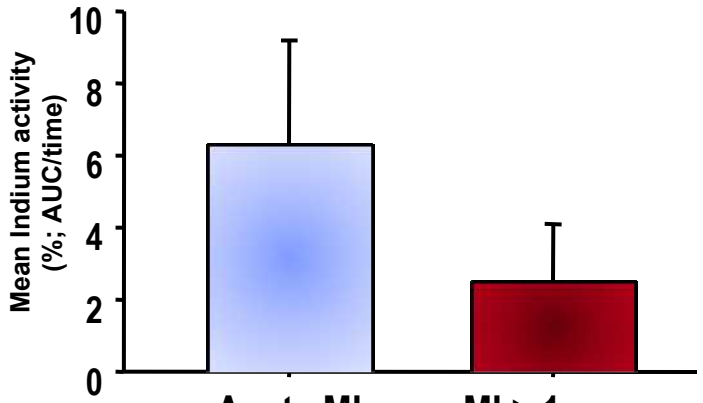
Reverse LV Remodeling

?



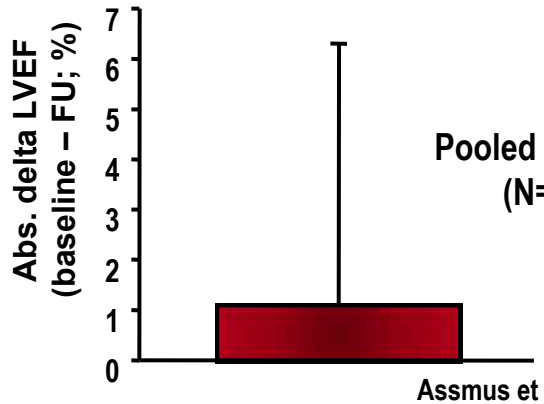
- ‘healed‘ infarction
- established scar
- lack of inflammation
- remodeled LV
- chronically ill patient

Impaired homing of progenitor cells in chronic heart failure



Schächinger et al, Circ 2008

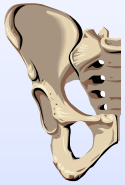
Effects of i.c. administration of progenitor cells in CHF

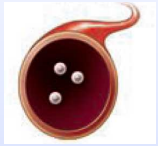


Assmus et al, NEJM 2006
Kang et al, Circ 2006

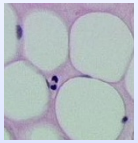
Need for novel cell sources or enhancement strategies for cell therapy in chronic heart failure

Pretreatment of progenitor cells

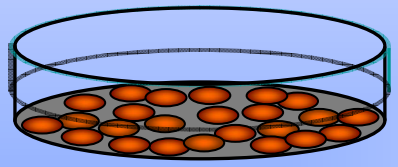

Bone marrow


Blood


Skeletal muscle

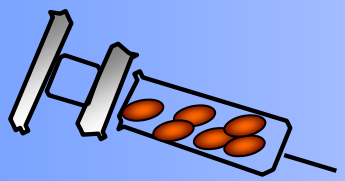

Adipose tissue

Cardiac stem cells



genes

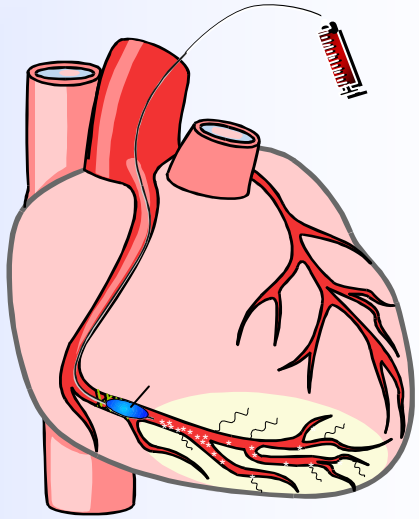
small molecules



Repetitive applications

Recruitment in target tissue

Cell therapy



Pretreatment of the target region

shock wave pretreatment

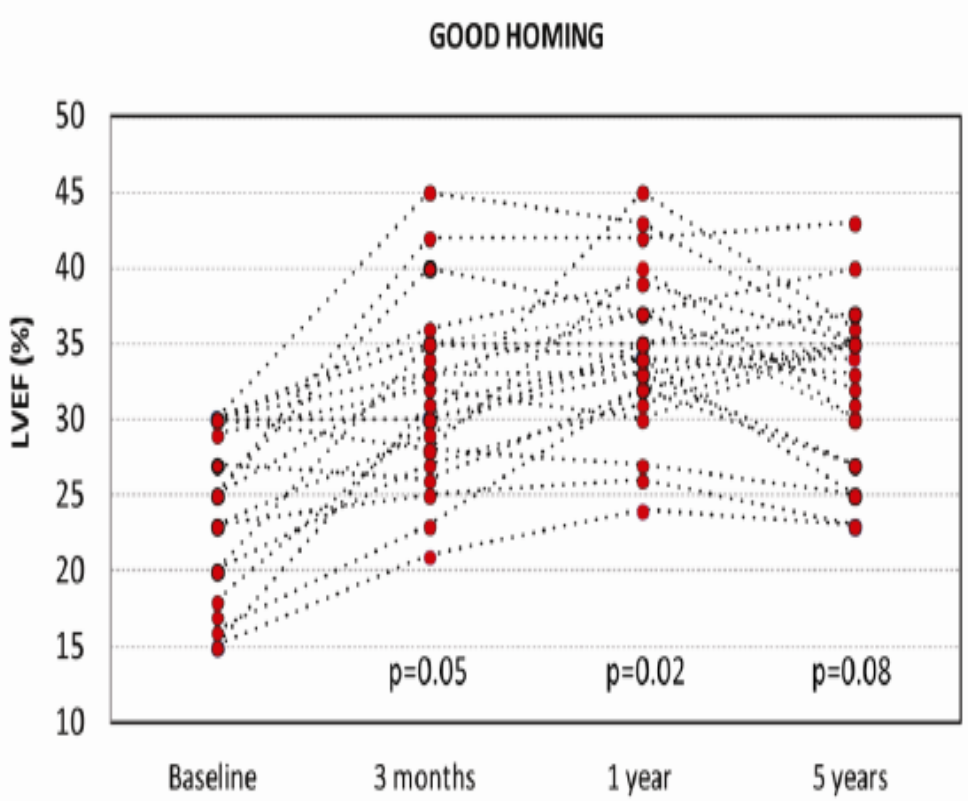
nanofiber-based delivery

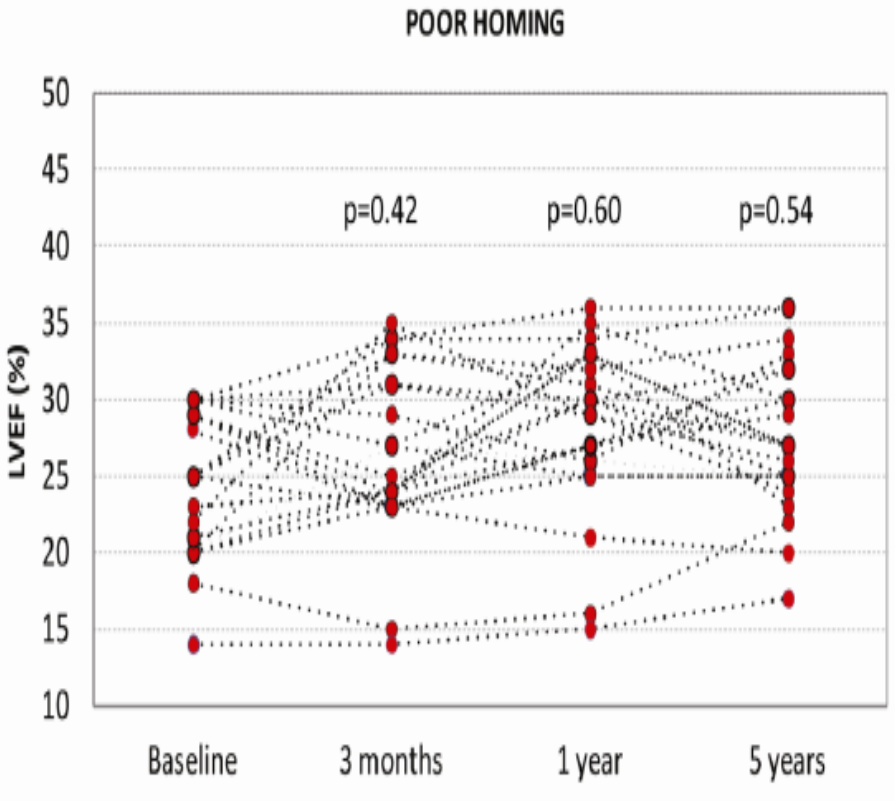
Seeger et al, Nat Clin Pract Cardiovasc Med, 2007

Circulation Research January 4, 2013 **Editorial**

Early Cardiac Retention of Administered Stem Cells Determines Clinical Efficacy of Cell Therapy in Patients With Dilated Cardiomyopathy

Birgit Assmus, Andreas M. Zeiher



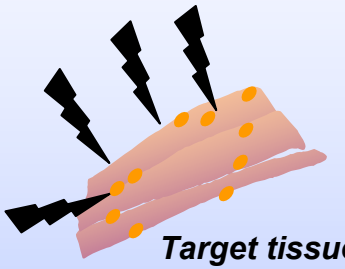


Vrtovec B,…,Wu JC; Circ Res 2013

Shock Wave Application may Improve Cell Homing to Target Area

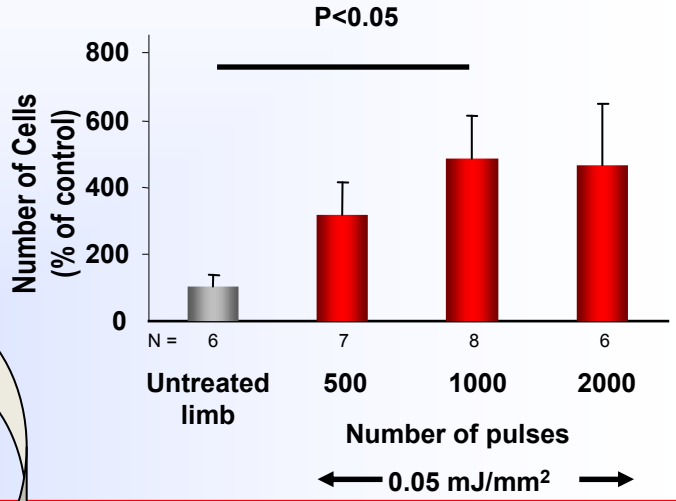
Shock Wave Pretreatment

1.



3. Injection of cells

Homing



2. Release of chemoattractant factors in target tissue after 24 h

VEGF & SDF-1
(attraction & retention of BMC)

(Aicher et al, Circulation 2006)

2-D-Echo-guided cardiac shockwave application

- Coil High Voltage pulse
- Membrane (Magnetic field)
- Rapid membrane movement
- Shock wave produced in water bellow
- Shockwave focused by acoustic lens

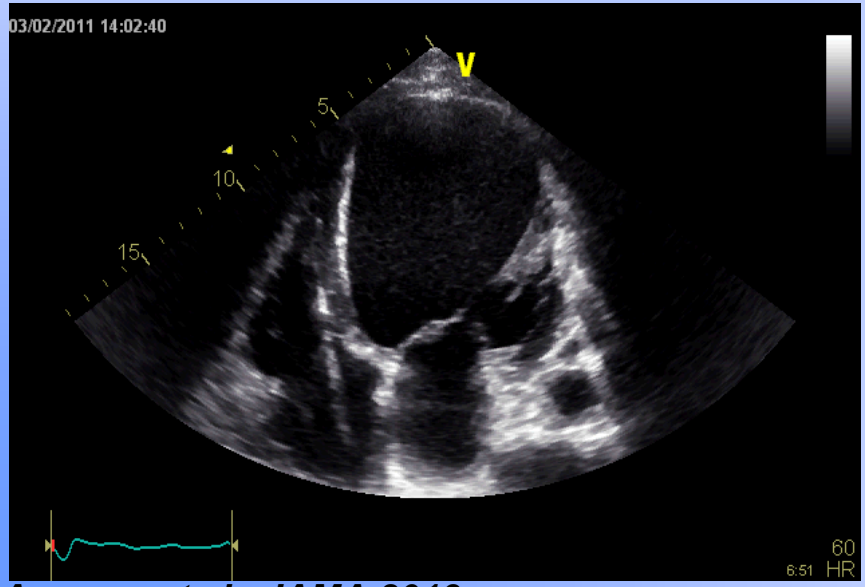
Shockwave generator

Power generator with Energy level control unit and ECG synchronization

ECG Trigger

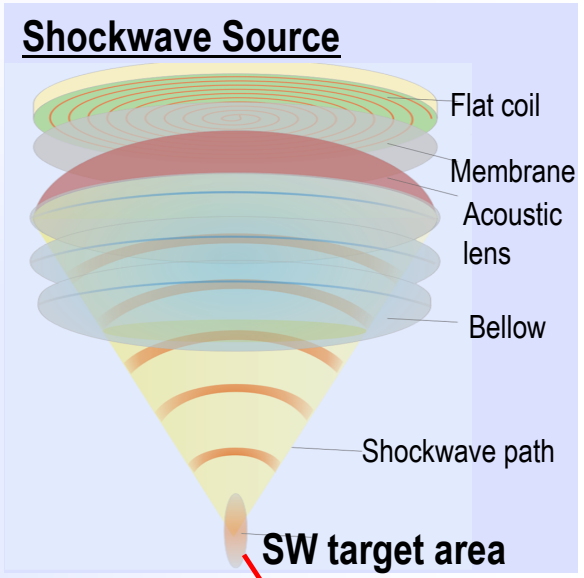
Patient

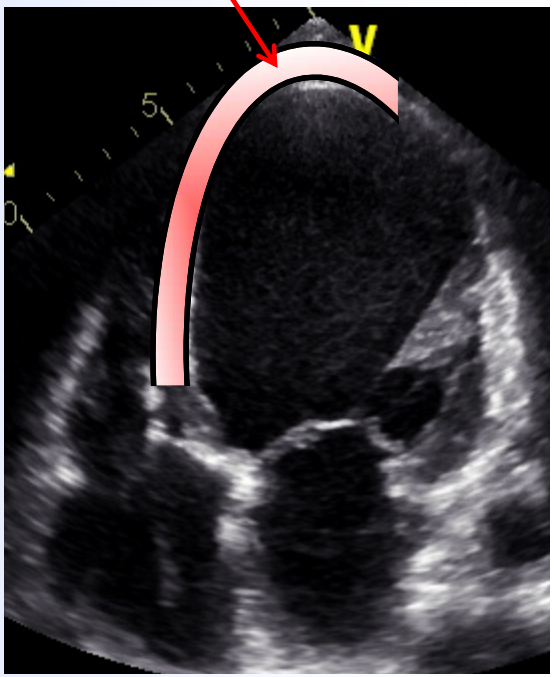
Live 2D integrated Ultrasound Imaging



Assmus et al., JAMA 2013

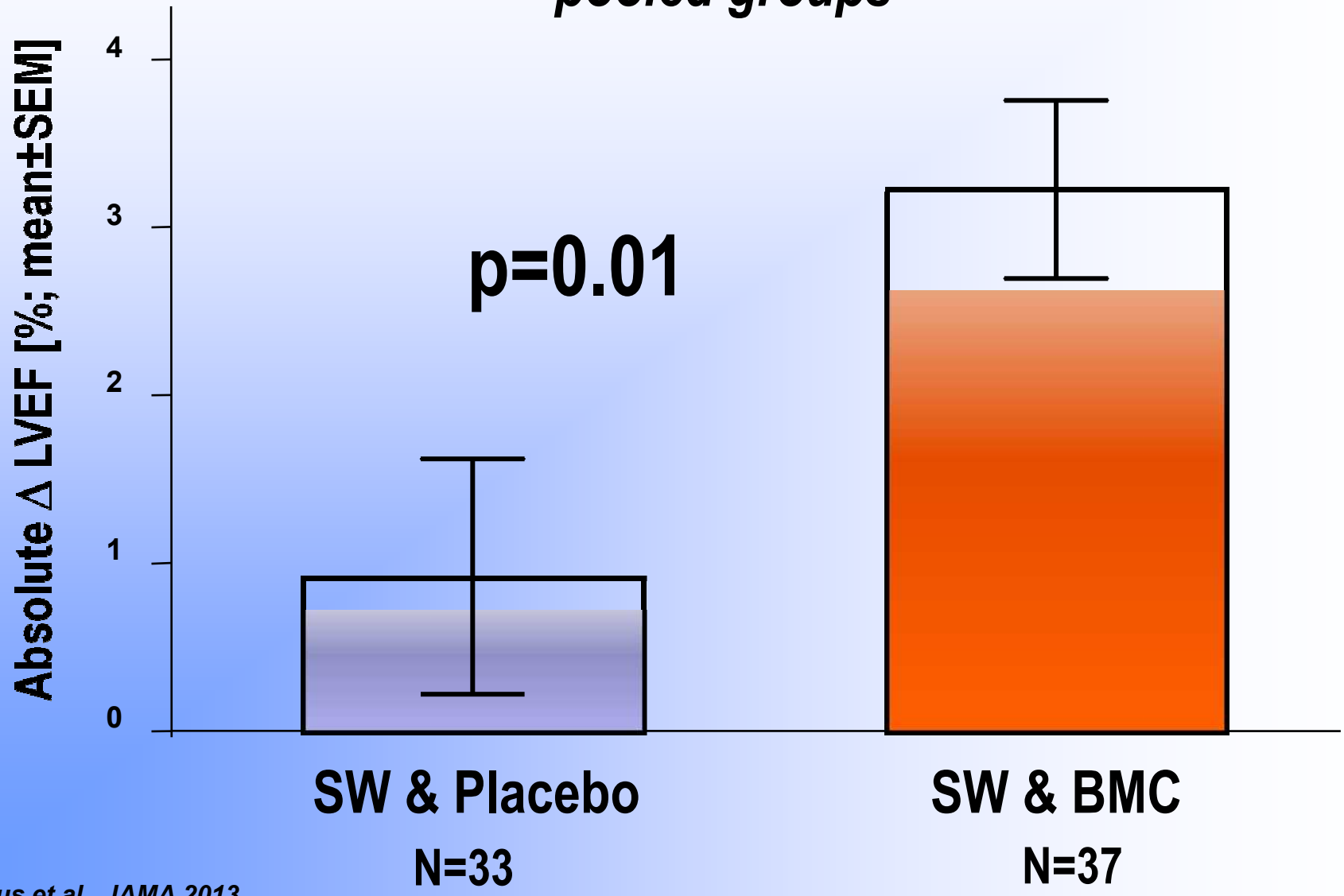
Custom build by
Dornier Med Tech Systems
Wessling, Germany





Primary endpoint: absolute change in LVEF at 4 months

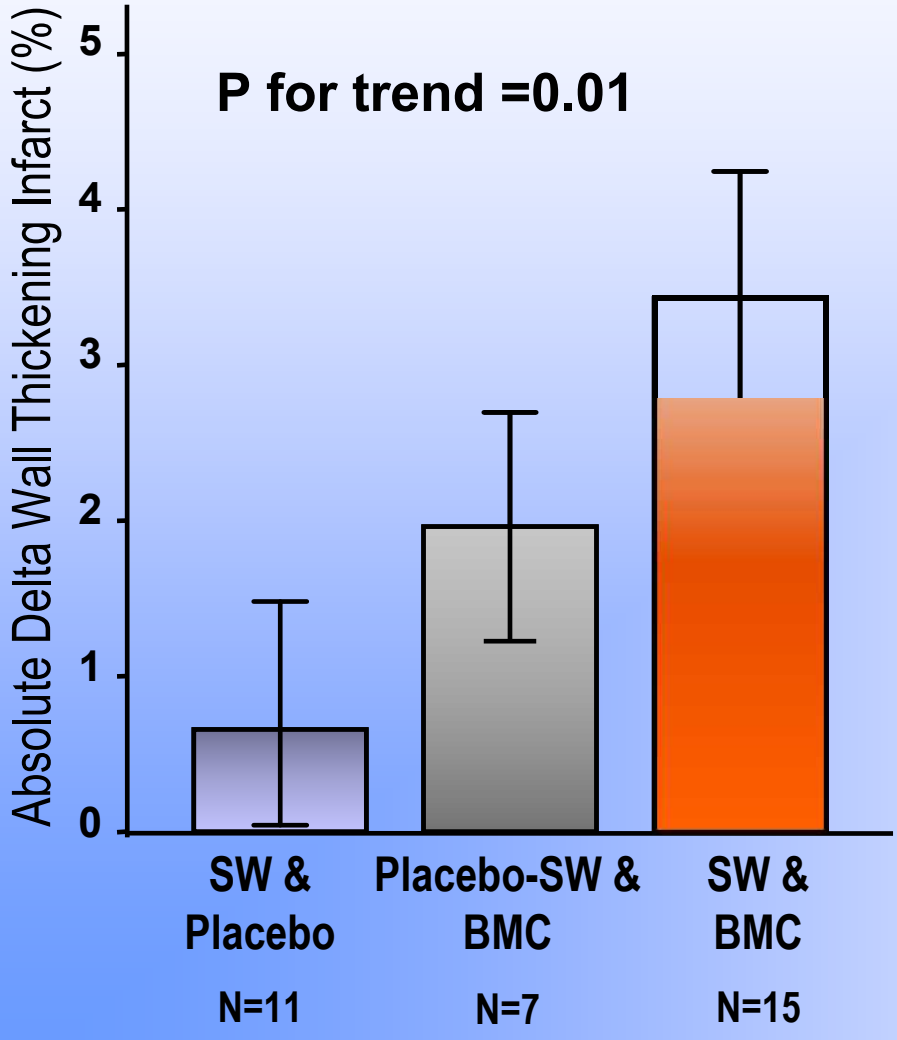
- pooled groups -



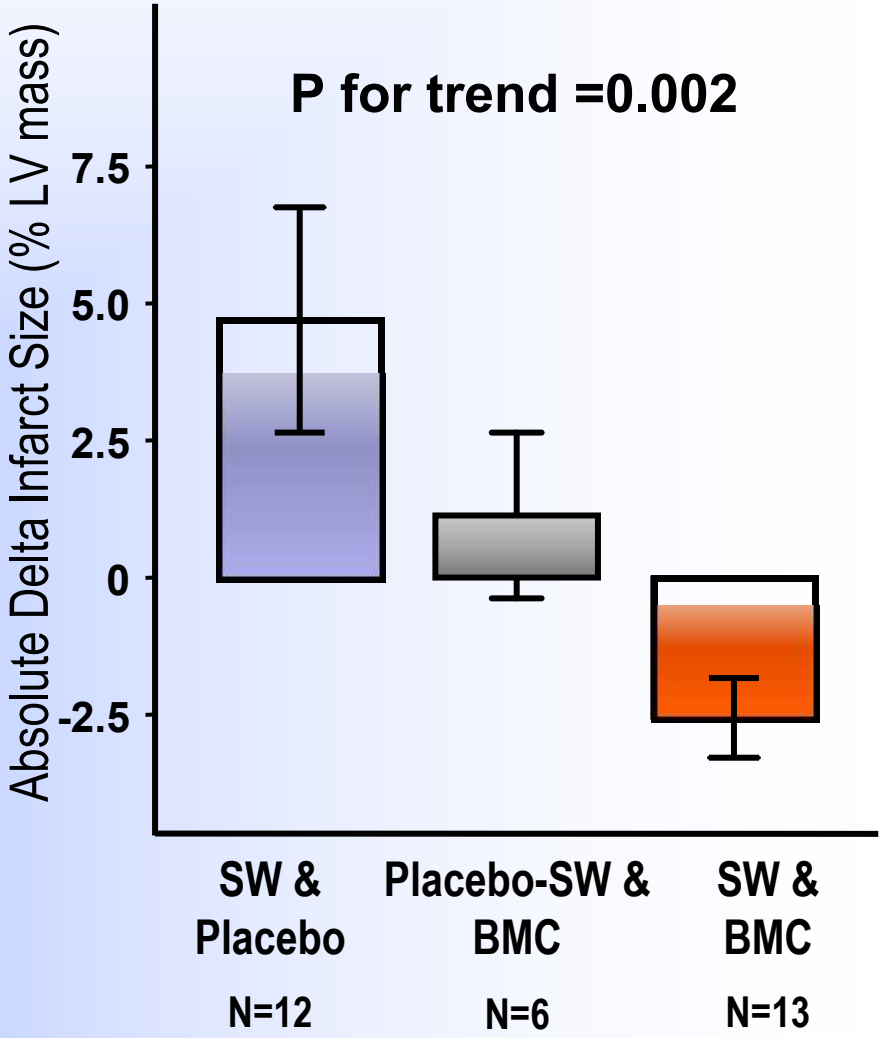
Assmus et al., JAMA 2013

Mechanistic Insights by MRI substudy

Increased infarct wall thickening



Decreased infarct size



Assmus et al., JAMA 2013

Hazard ratios for MACE at 3-year follow-up

All-cause death

Cardiac Death

Re-MI

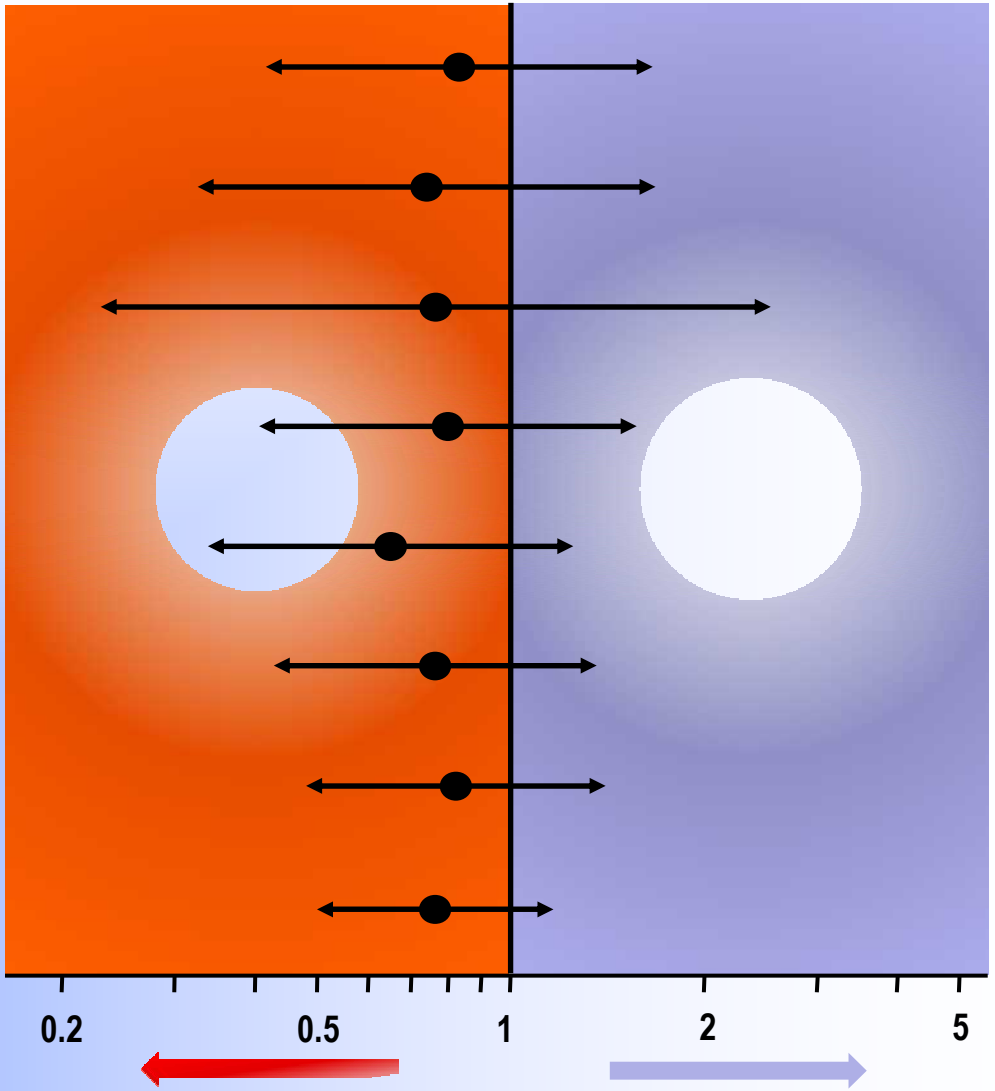
Rehospitalization for CHF

Ventricular Tachycardia

Cardiac death and rehospitalisation for heart failure

Cardiac death, rehospitalisation for heart failure, and re-AMI

Cardiac death, rehospitalisation for heart failure, re-AMI and VT



Assmus et al., JAMA 2013

Conclusions

Cell therapy with autologous BMC is a realistic option in patients with large acute myocardial infarction ☺ ☺

➡ **EU-sponsored mortality trial**

Bami

Supported by the EC under the FP7 programme

Cell therapy with autologous BMC in patients with chronic post-infarction heart failure: application and single therapy are safe, but have minor efficacy ;

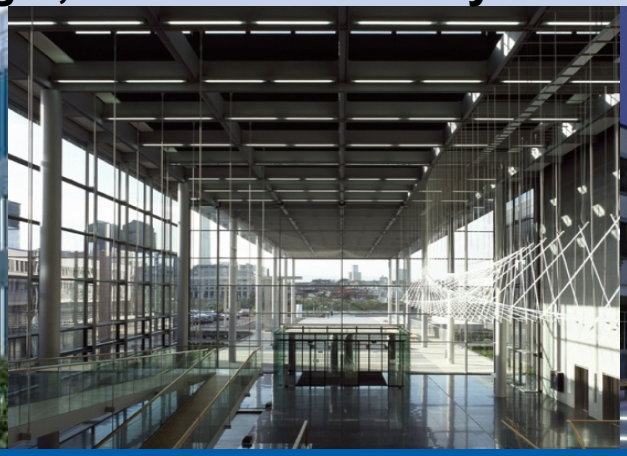
Enhancement stragies are under way

- different cell types (cardiomyocyte progenitor cells)

- pretreatment of target tissue (shockwave)

- repeated applications (Repeat trial)

Med. Klinik III, Kardiologie, Goethe University


Andreas Zeiher & Stefanie Dimmeler

Florian Seeger, Stephan Fichtlscherer, Jörg Honold, Brigitte Luu

Former contributers:

Volker Schächinger, Salvatore de Rosa, David Leistner, Ulrich Fischer-Rasokat Ralf Lehmann

Institute of Cardiovascular Regeneration
Centre for molecular medicine

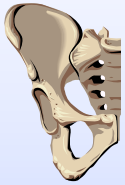
Cardiology Studies Coordinating Centre (CSCC):
Stephanie Estel, Daniela Höhl, Carmelo Smorta, Anne Krämer, Marga Müller-Ardogan

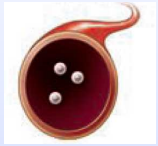
Support:

DFG (SFB 834, TR-SFB23)
Excellence Cluster ECCPS
LOEWE
Leducq Foundation: Transatlantik Network of Excellence
European Union: ERC Advanced Grant, Endostem

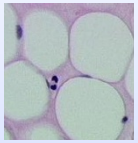
Need for novel cell sources or enhancement strategies for cell therapy in chronic heart failure

Pretreatment of progenitor cells

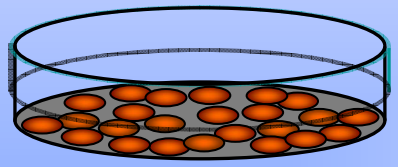

Bone marrow


Blood


Skeletal muscle

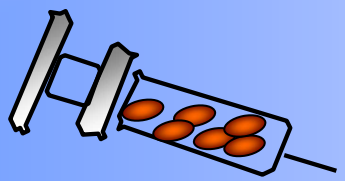

Adipose tissue

Other sources



genes

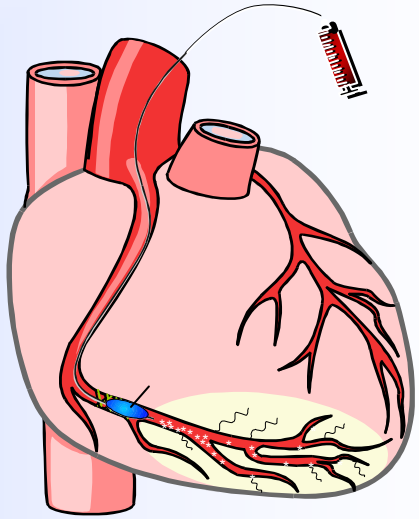
small molecules



Repetitive applications

Recruitment in target tissue

Cell therapy



Pretreatment of the target region

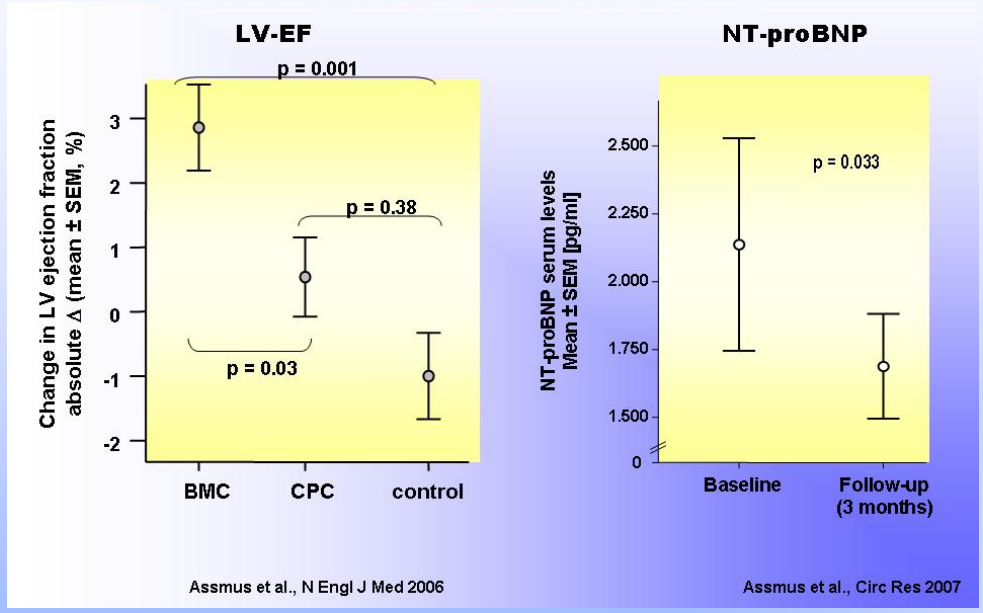
shock wave pretreatment

nanofiber-based delivery

Seeger et al, Nat Clin Pract Cardiovasc Med, 2007

BMC therapy in CHF – effects on mortality?

Small but significant effects on LV function



- initiation of an ongoing registry in 2005
- open to all patients presenting with CHF at our centre
- patients were offered repeated treatment at 4 months at time of first treatment (not to long-distance travellers)

Comparison of observed and model-predicted * mortality in 297 consecutive patients treated with intracoronary BMC infusion.

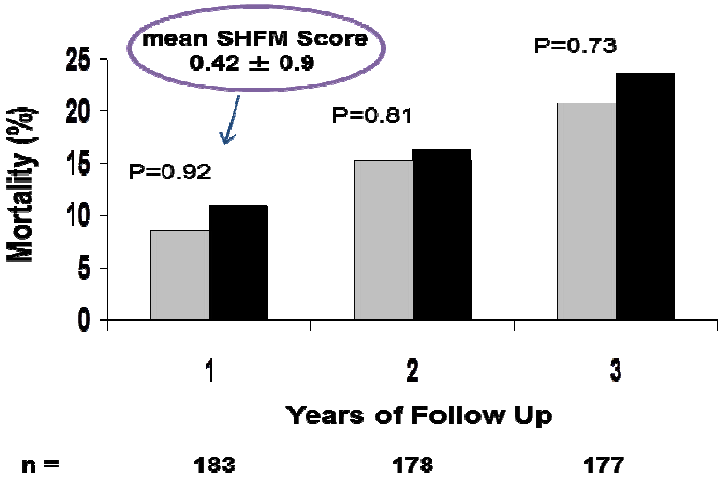
Seattle Heart Failure Model (SHFM):

- multivariable risk model that predicts all-cause and cause-specific mortality in CHF
- age, gender, etiology of cardiomyopathy, hemodynamics, LVEF, treatment incl. devices, lab values
- validated in 9942 patients from large clinical trials: ELITE2, Val-HeFT, UW, RENAISSANCE, IN-CHF)

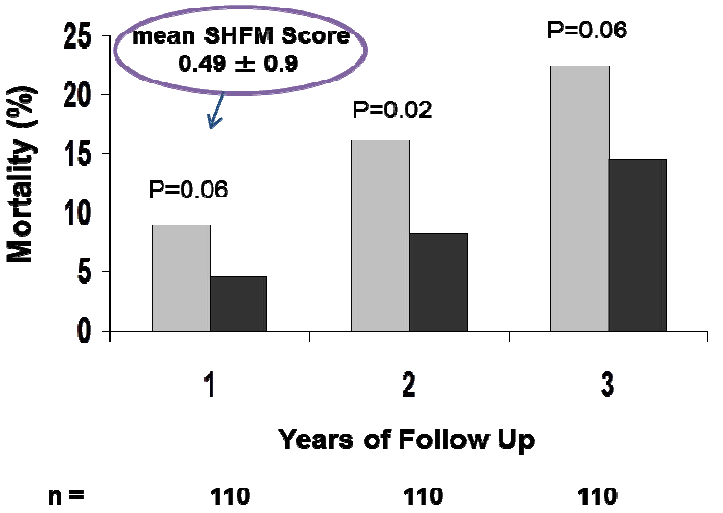
Only repeated intracoronary BMC treatment is associated with lower mortality than SHFM-model predicted mortality

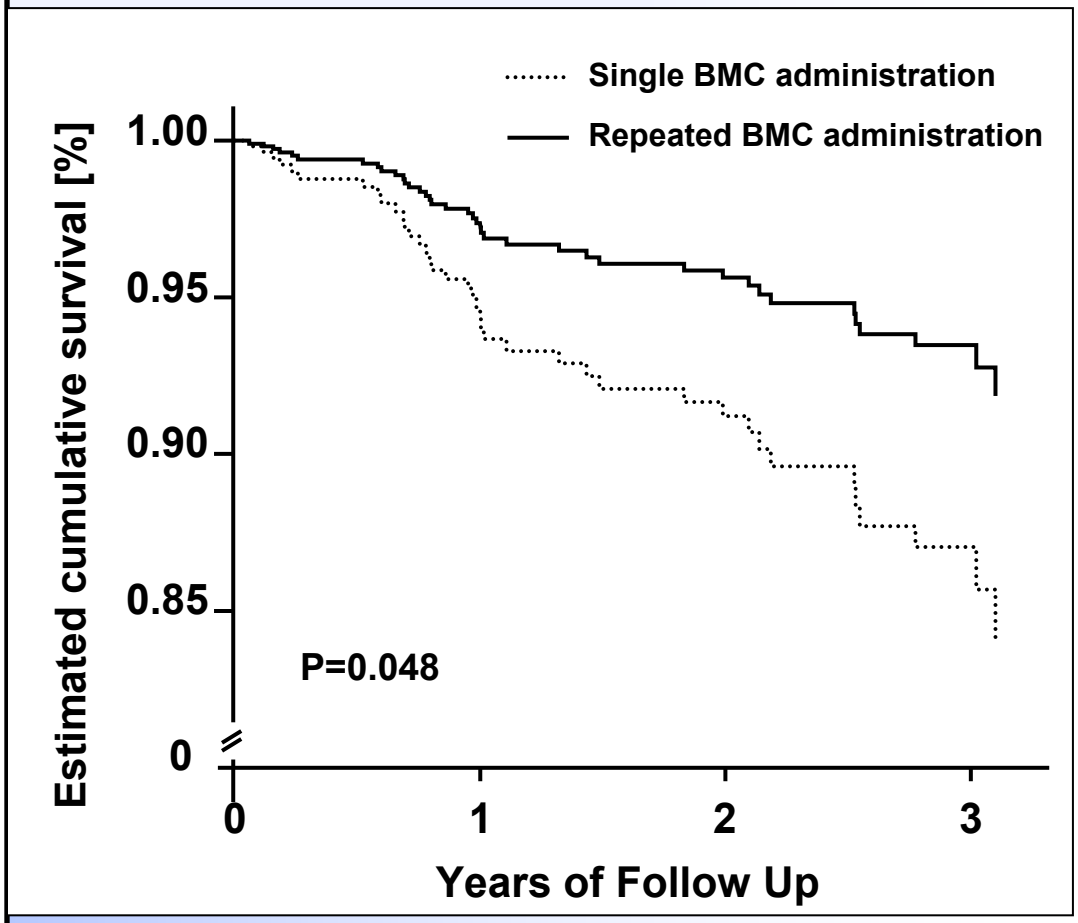
N = 297 patients; repeated treatment offered at 4 months FU

Single BMC Administration (n=186)



Repeated BMC Administration (n=111)





observed

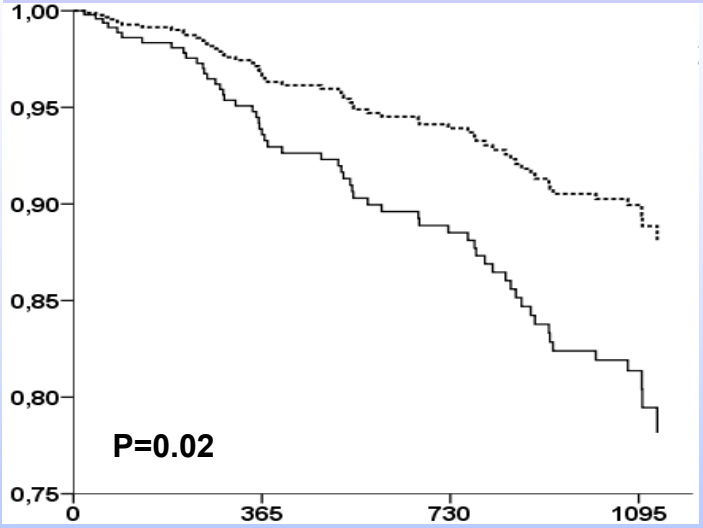
Model-predicted

De Rosa, … Zeiher, Assmus
under revision

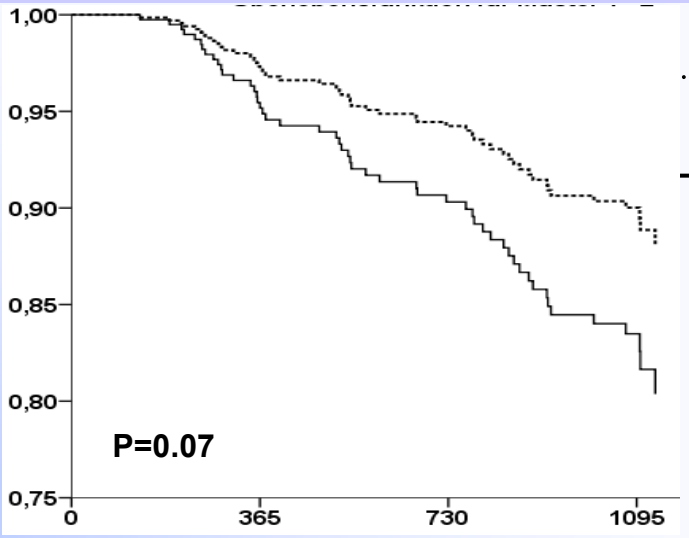
Only repeated intracoronary BMC treatment is associated with lower mortality than SHFM-model predicted mortality

Mortality

Total cohort analysis



Landmark analysis



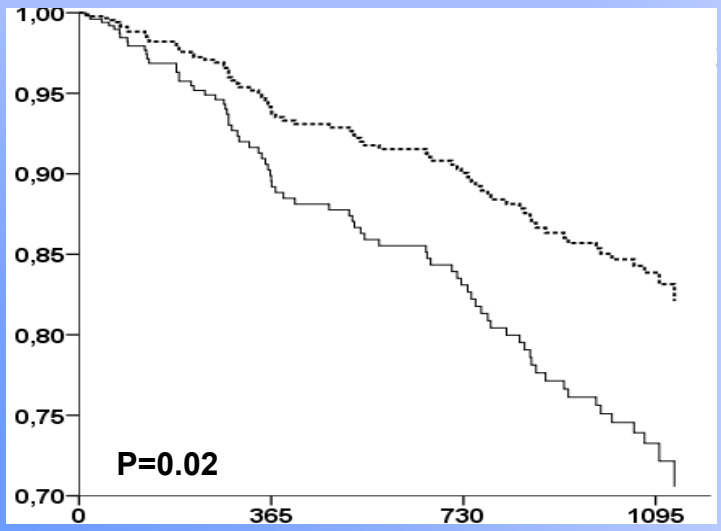
Estimated cumulative survival

repeated BMC administration

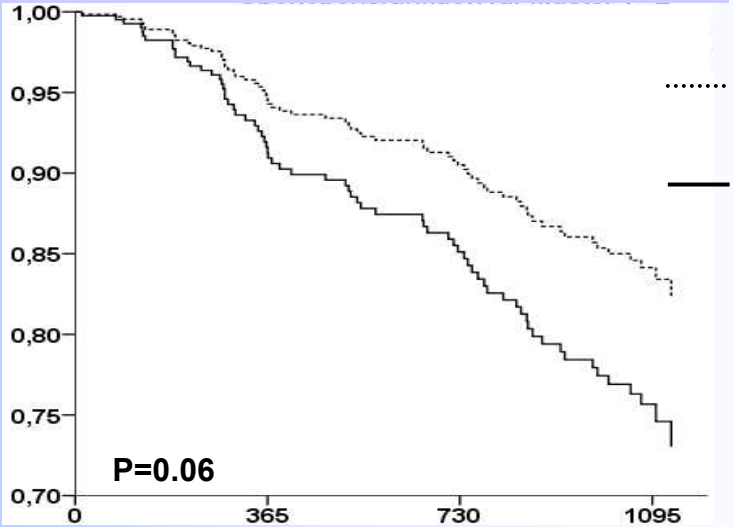
single BMC administration

Death and rehospitalization

Total cohort analysis



Landmark analysis



Estimated event-free survival

repeated BMC administration

single BMC administration

Trial Flowchart

Started Dec. 2013

N = 668 patients with post-infarction heart failure
Open infarct vessel / bypass

Randomisation 1:1

Group 1

1. intracoronary infusion of BMC
N=334

Visit

Visit

Visit

Visit

Group 2

1. intracoronary infusion of BMC
N=334

2. intracoronary infusion of BMC

Visit

Visit

Visit

4 months

8 months

24 months; primary endpoint

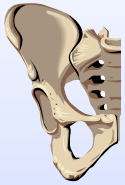
60 months; end of study

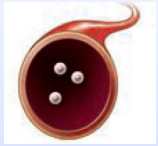
Primary endpoint: Mortality at 2 years

Secondary endpoint: Rehospitalization for CHF, cardiac death, HTX/LVAD

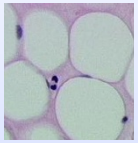
Need for novel cell sources or enhancement strategies for cell therapy in chronic heart failure

Pretreatment of progenitor cells

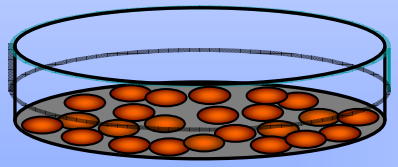

Bone marrow


Blood


Skeletal muscle

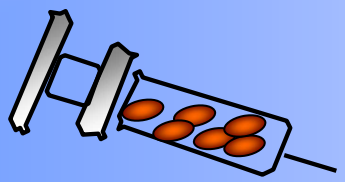

Adipose tissue

Other sources



genes

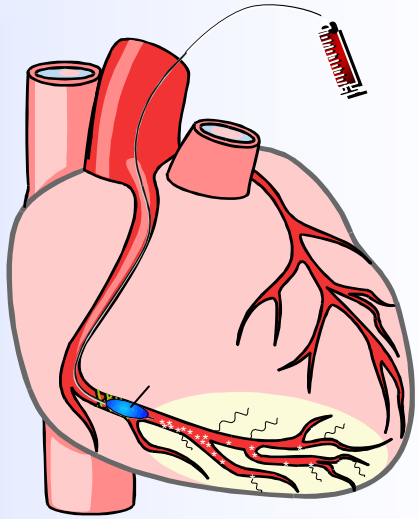
small molecules



Repetitive applications

Cell therapy

Recruitment in target tissue

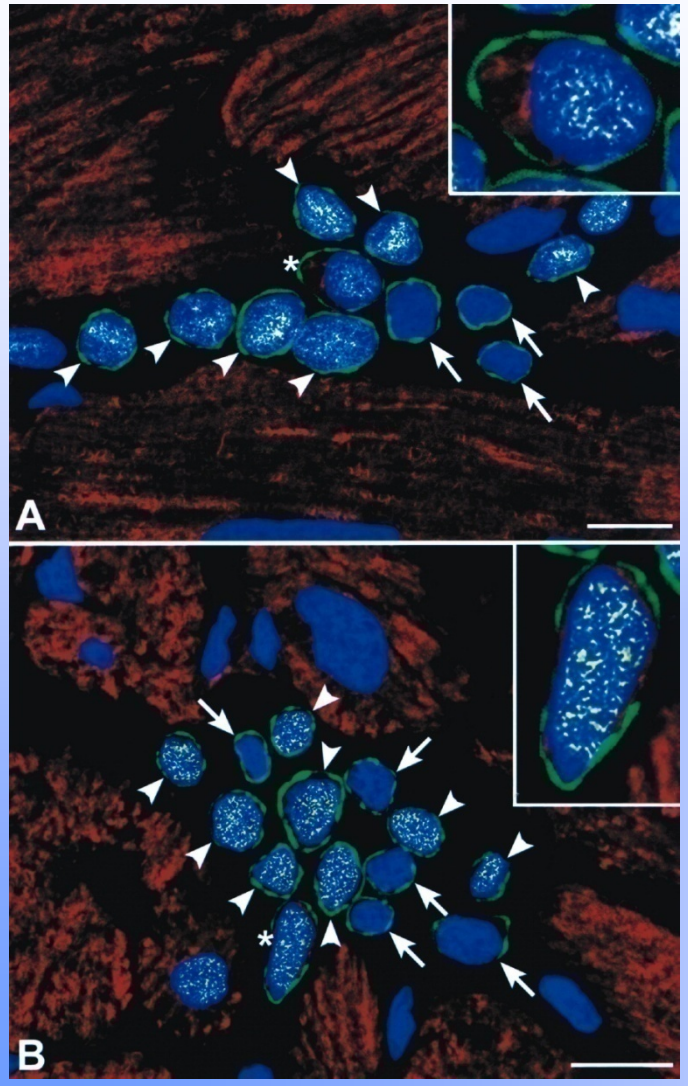


Pretreatment of the target region

- *shock wave pretreatment*
- *nanofiber-based delivery*

Seeger et al, Nat Clin Pract Cardiovasc Med, 2007

Cardiac stem cells: the heart´s little helper



Beltrami et al, Cell 114(6):763-76, 2003

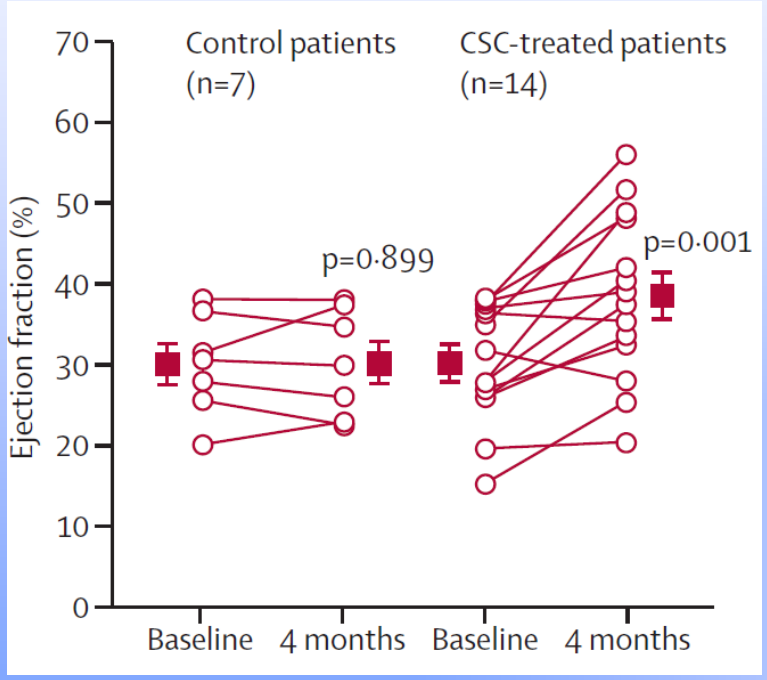
- **c-kit (mouse, dog, human)**
  (Beltrami, Cell 2003)
- **Sca-1 (mouse)**
  Sca-1-like (dog, human)
  (Oh et al, PNAS 2003)
- **Cardiospheres (murine, human)**
  (Messina et al, Circ Res 2004)
- **Islet (postnatal mouse, human)**
  (Laugwitz et al, Nature 2005)

Cell therapy with cardiac stem cells

c-kit+ CSC (Scipio trial)

(Bolli et al Lancet 2011)

Ejection Fraction at 4 Months After CSCs

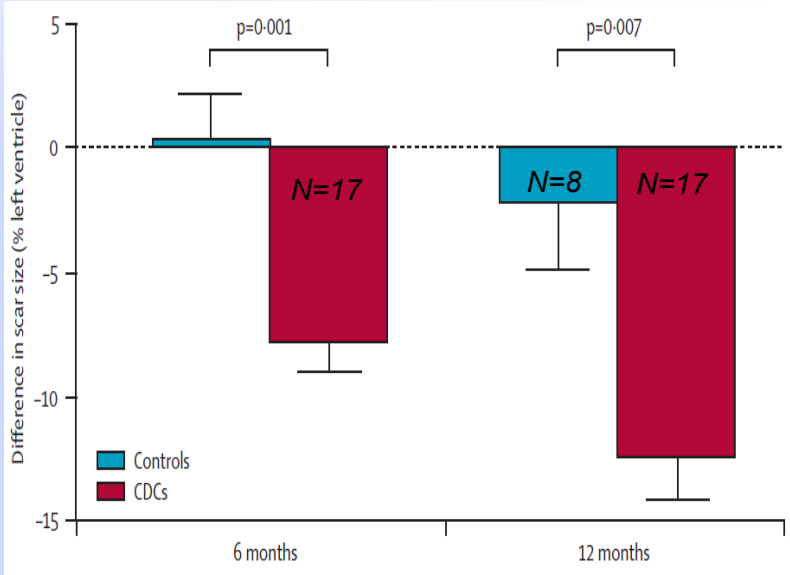


Cells expanded from atrial samples obtained during CABG

Cardiospheres (Caduceus trial)

(Makkar et al Lancet 2012)

Infarct size reduction at 6 and 12 months after Cardiospheres



- ***No difference in EF or volumes***

Cells expanded from endomyocardial biopsies

2009

First patient treated

2011

Phase I data: presented AHA 2011