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# *Cell Therapy in STEMI: closing the clinical gap*

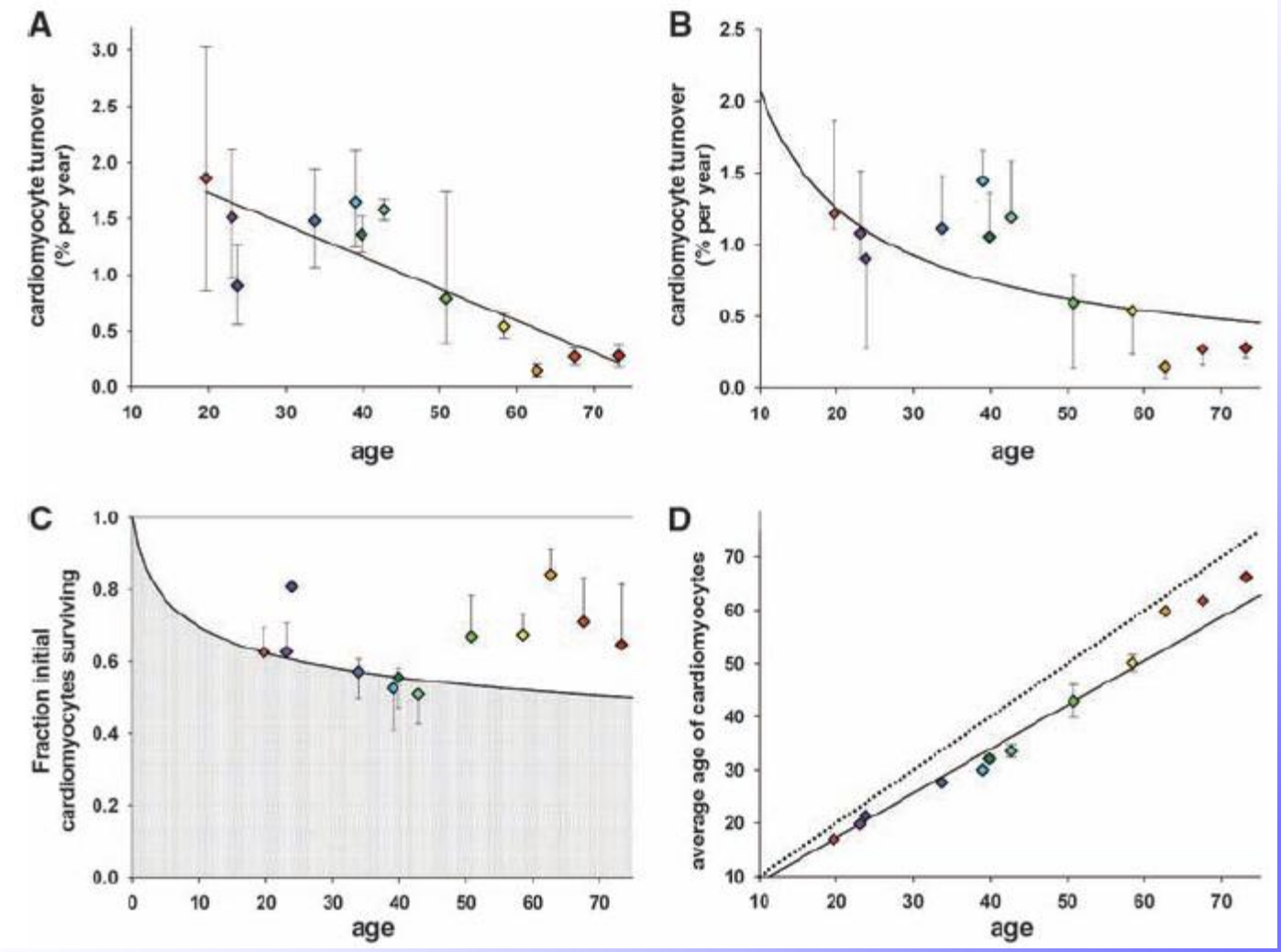
***Cardiology Update 2013, Davos, 02/2013***

***Disclosure information:*** ***t2cure (co-founder, advisor)***
***SanofiAventis (SAB)***

# The Heart is a Regenerating Organ

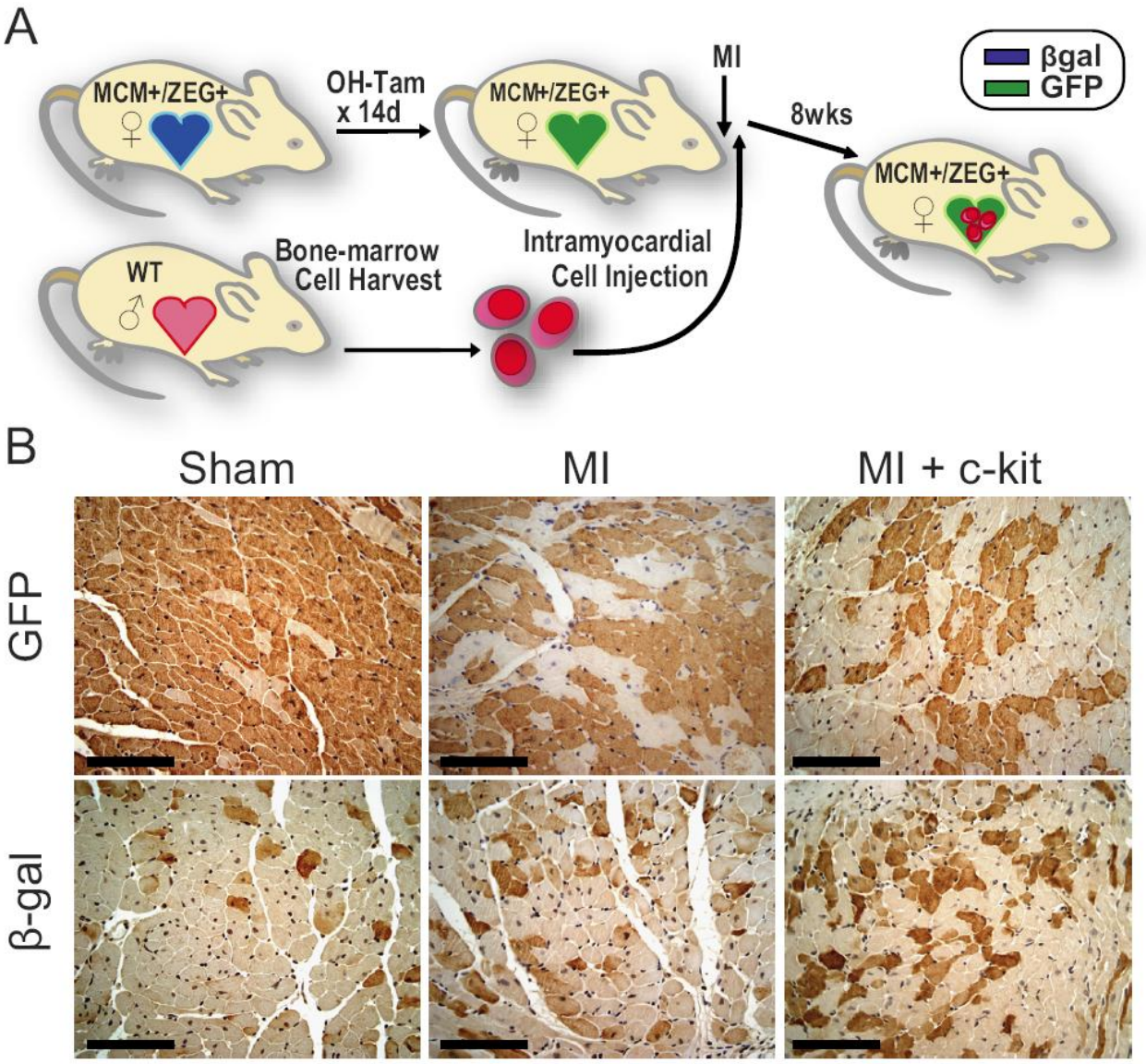
## *Undisputable Evidence from DNA Integration of C-14*

**– generated during nuclear bomb testing during cold war -**




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

# Activation of endogenous regeneration by bone marrow-derived cells

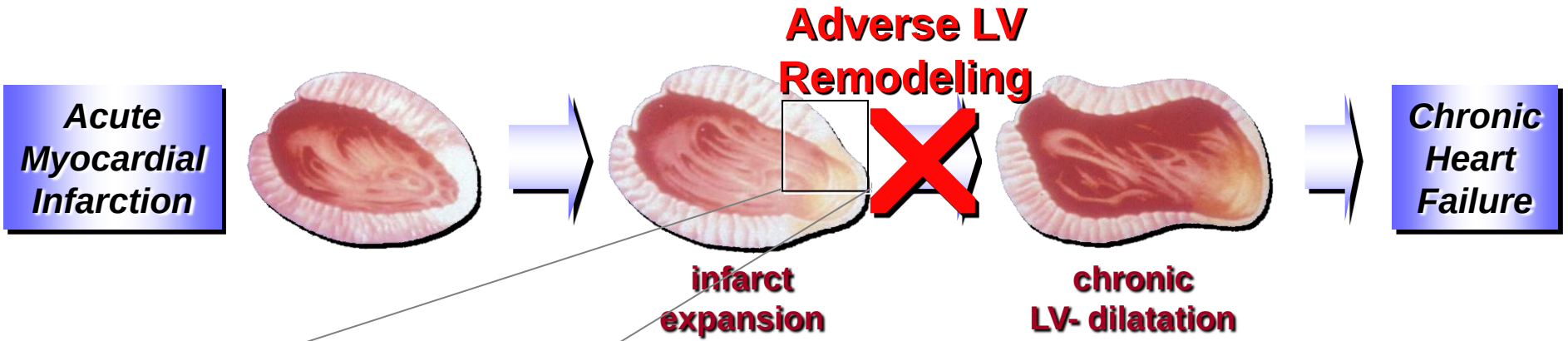


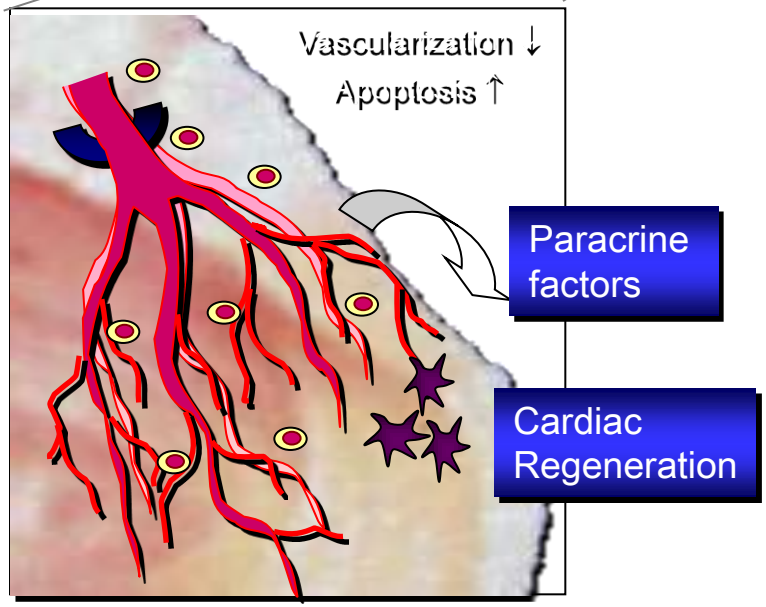

GFP+
= existing cardiomyocytes

LacZ+
= newly formed cardiomyocytes

Lofredo/Steinhauser et al, Cell Stem Cells 2011

# Cell Therapy in Acute Myocardial Infarction: therapeutic targets




**Metaanalysis of randomized and cohort studies of progenitor cell therapy in ischemic heart disease**

N = 976; overall treatment effect

+ 3.7 percentage points increase in LV-EF ( $p < 0.001$ )

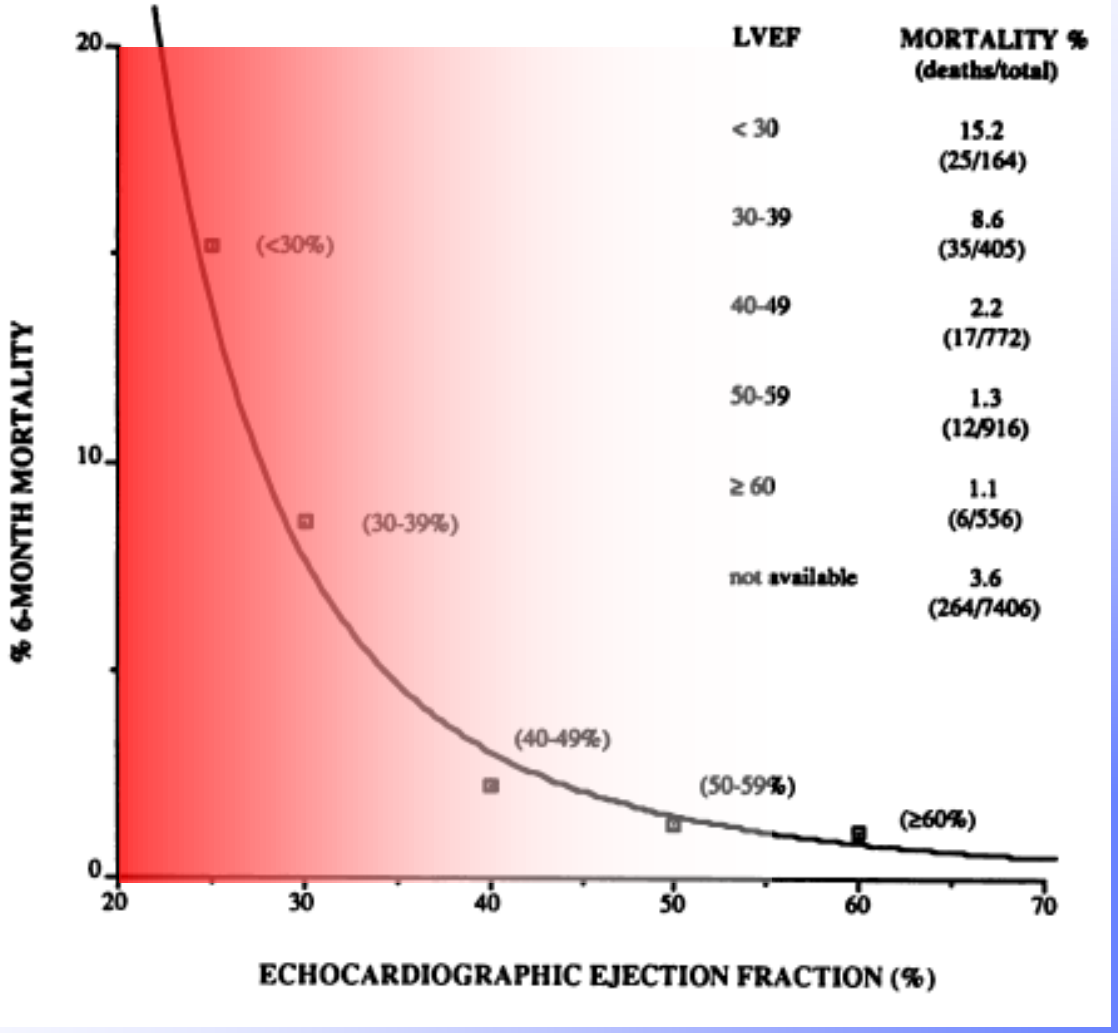
Abdel-Latif, Arch Intern Med 2007; 167:989

# 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 !**

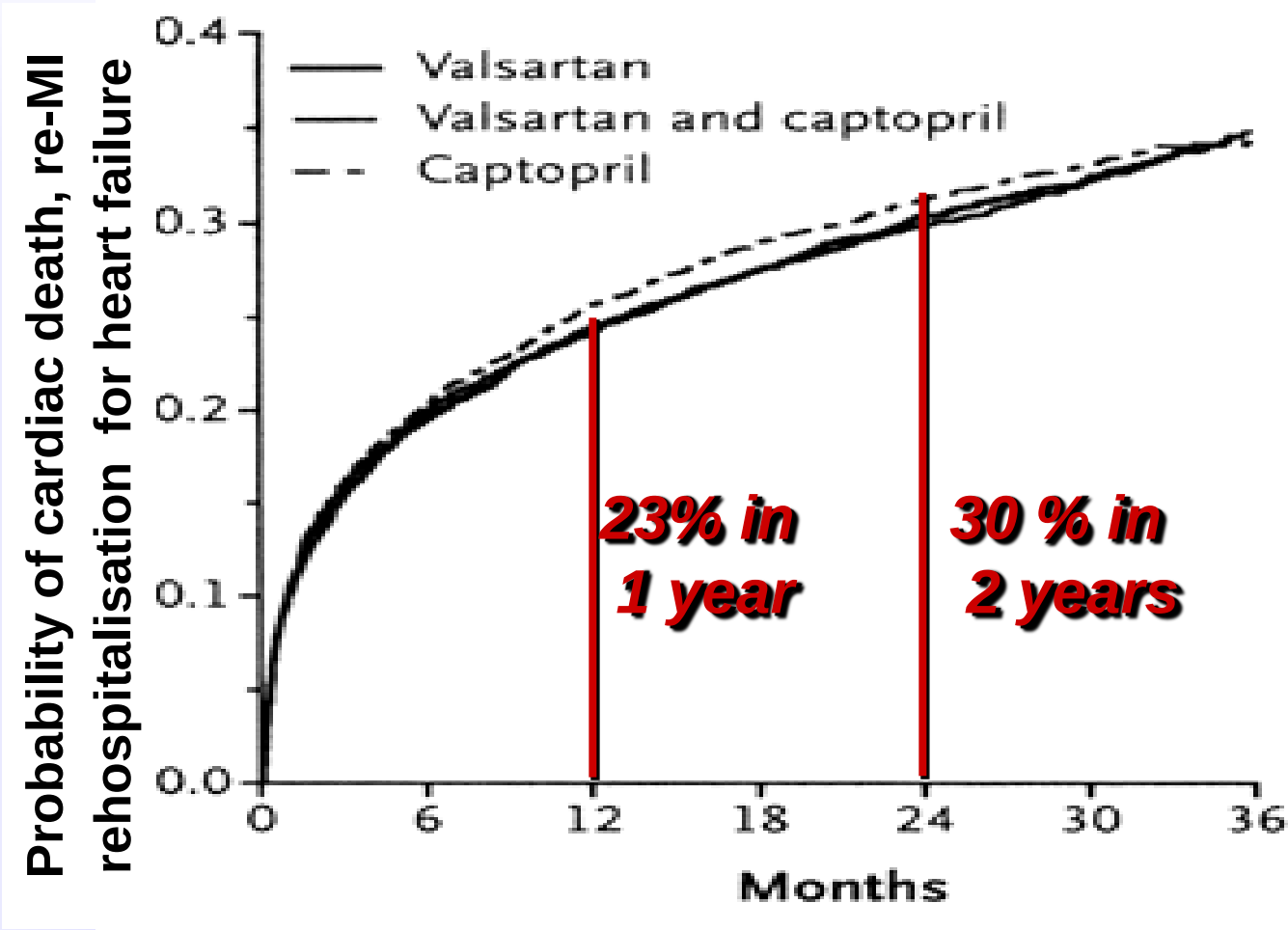



*Volpi et al., Circulation 1993; 88: 416-429*

# VALIANT

## Valsartan in Acute Myocardial Infarction Trial

- 14703 patients
- STEMI
- 0.5 - 10 days
- **EF < 40%**
- Killlip I-III
- Diuretics 60%,
- Beta-Blocker 71%

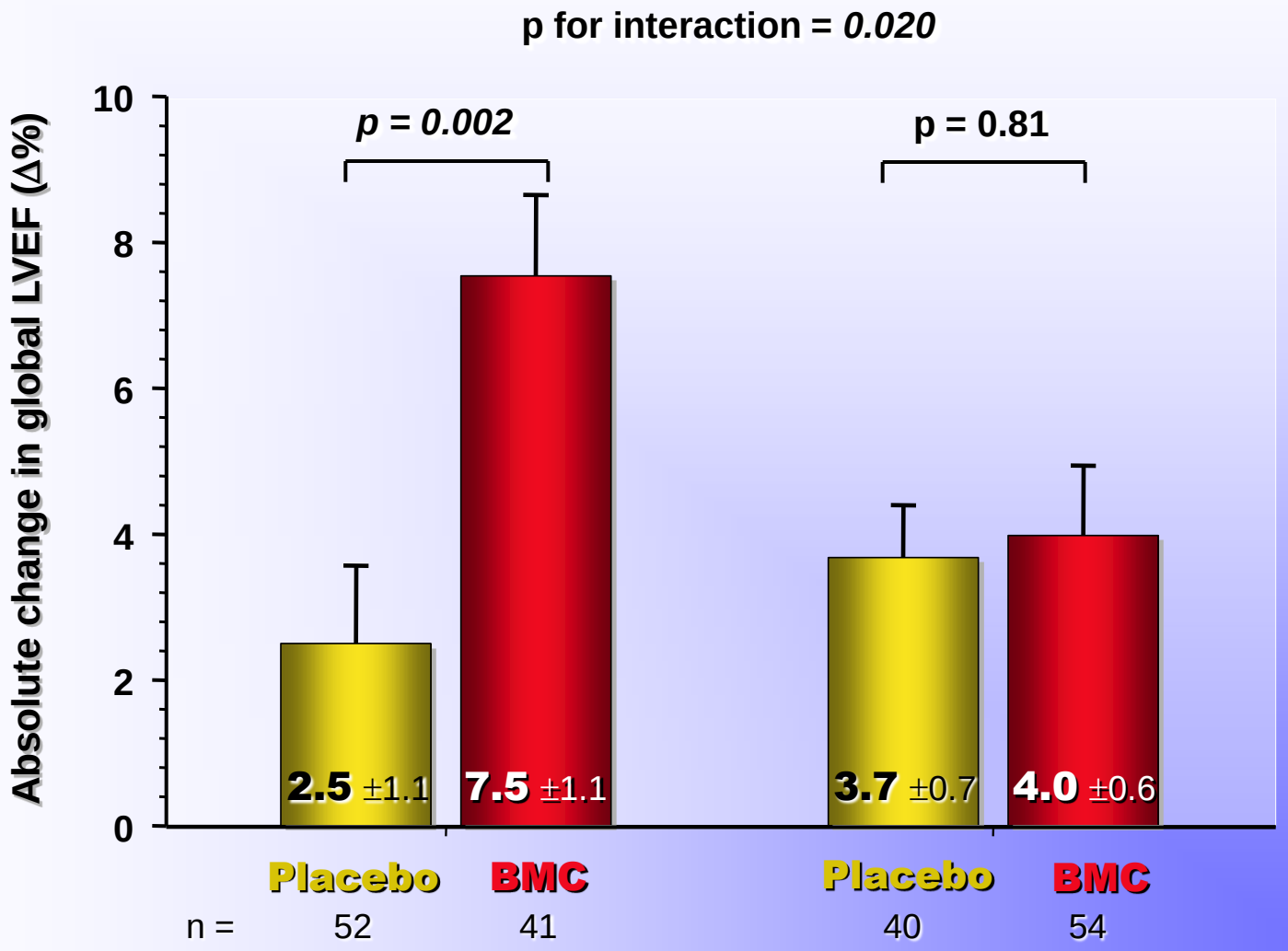



NEJM 2003, 349: 1893-1906

# Cell Therapy for Ischemic Heart Failure

- ⇨ *The patient population at risk post-AMI*
- ⇨ *Effects of cell therapy in patients at risk*

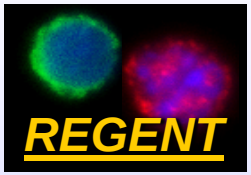
# Enhanced contractile recovery by BMC is confined to patients with failed initial recovery

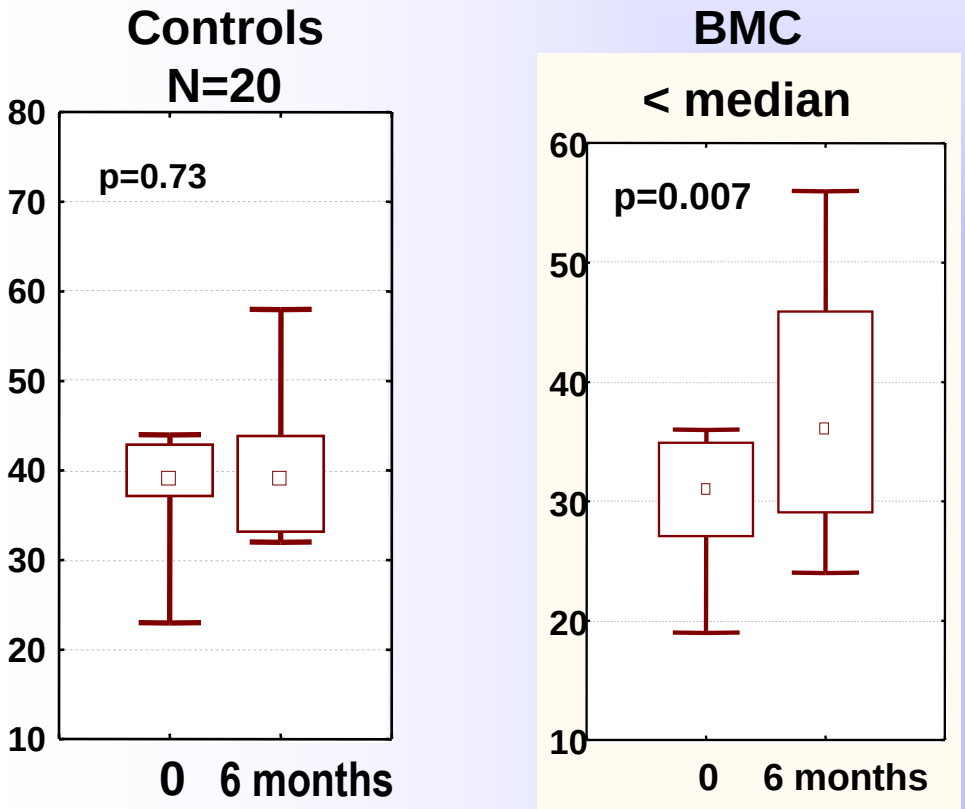



*Schächinger et al., N Engl J Med 2006*

# Enhanced contractile recovery by BMC in patients with failed initial recovery – results of recent controlled trials

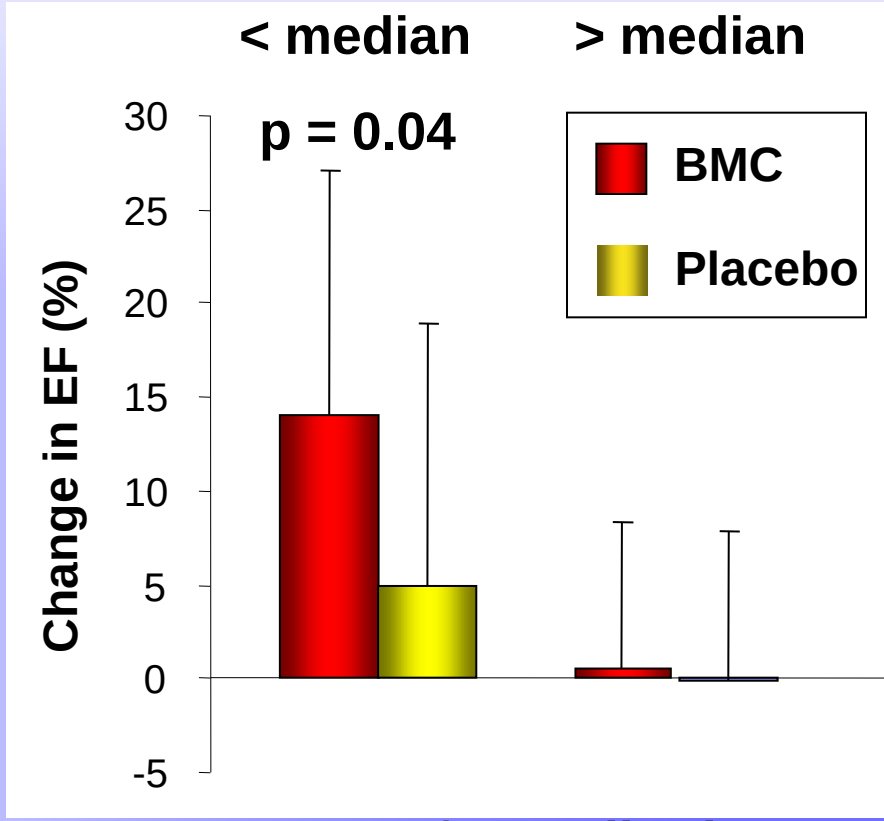
## REGENT trial




Courtesy of M Tendera, European Heart Journal, 2009

## FINNCELL trial



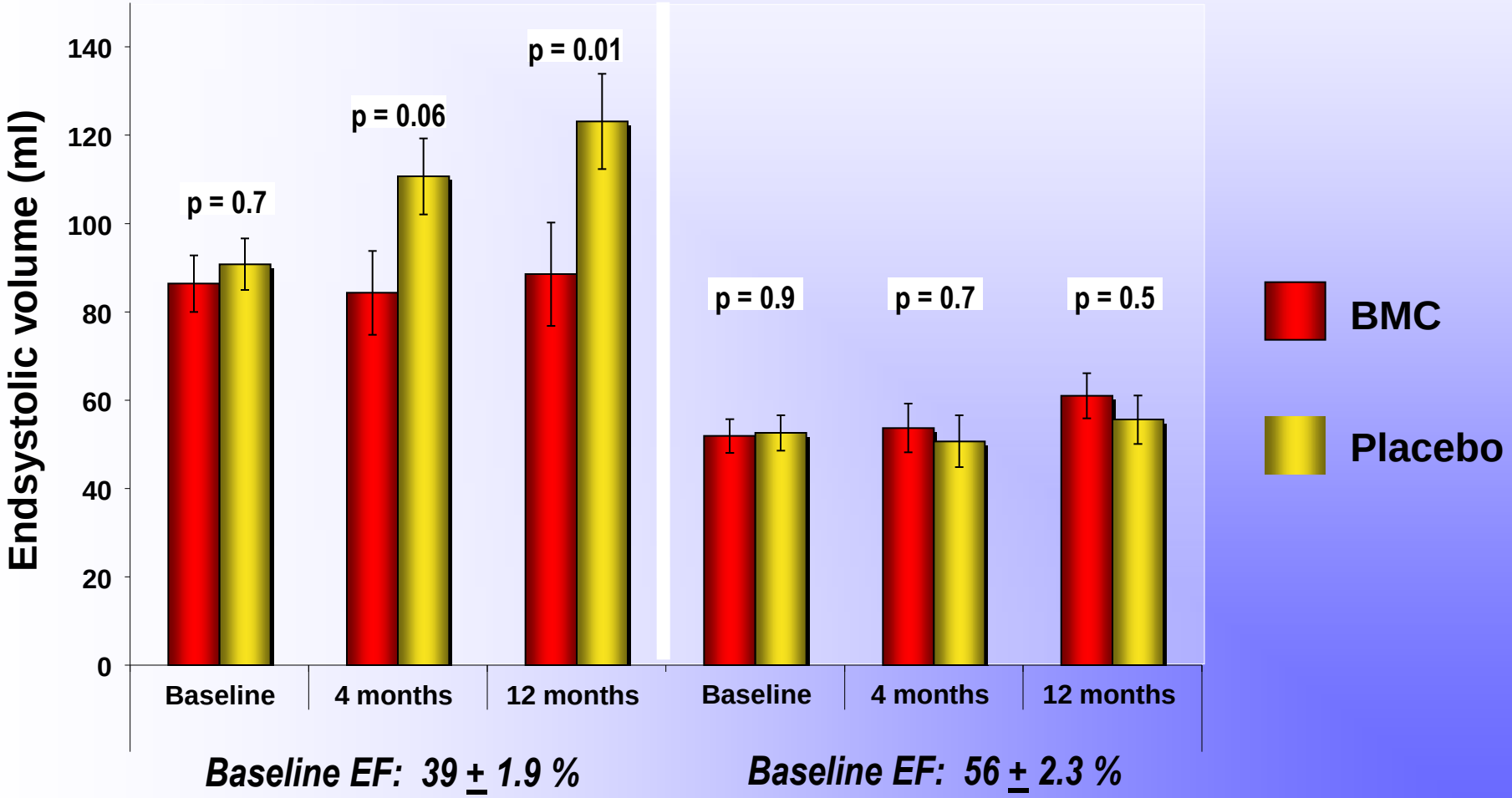

Courtesy of H. Huikuri, European Heart Journal, 2008

# Adverse remodeling is confined to patients with failed initial recovery of EF and abrogated by BMC therapy

**EF < median**

**EF > median**

## Change of endsystolic volumes over time (MRI)

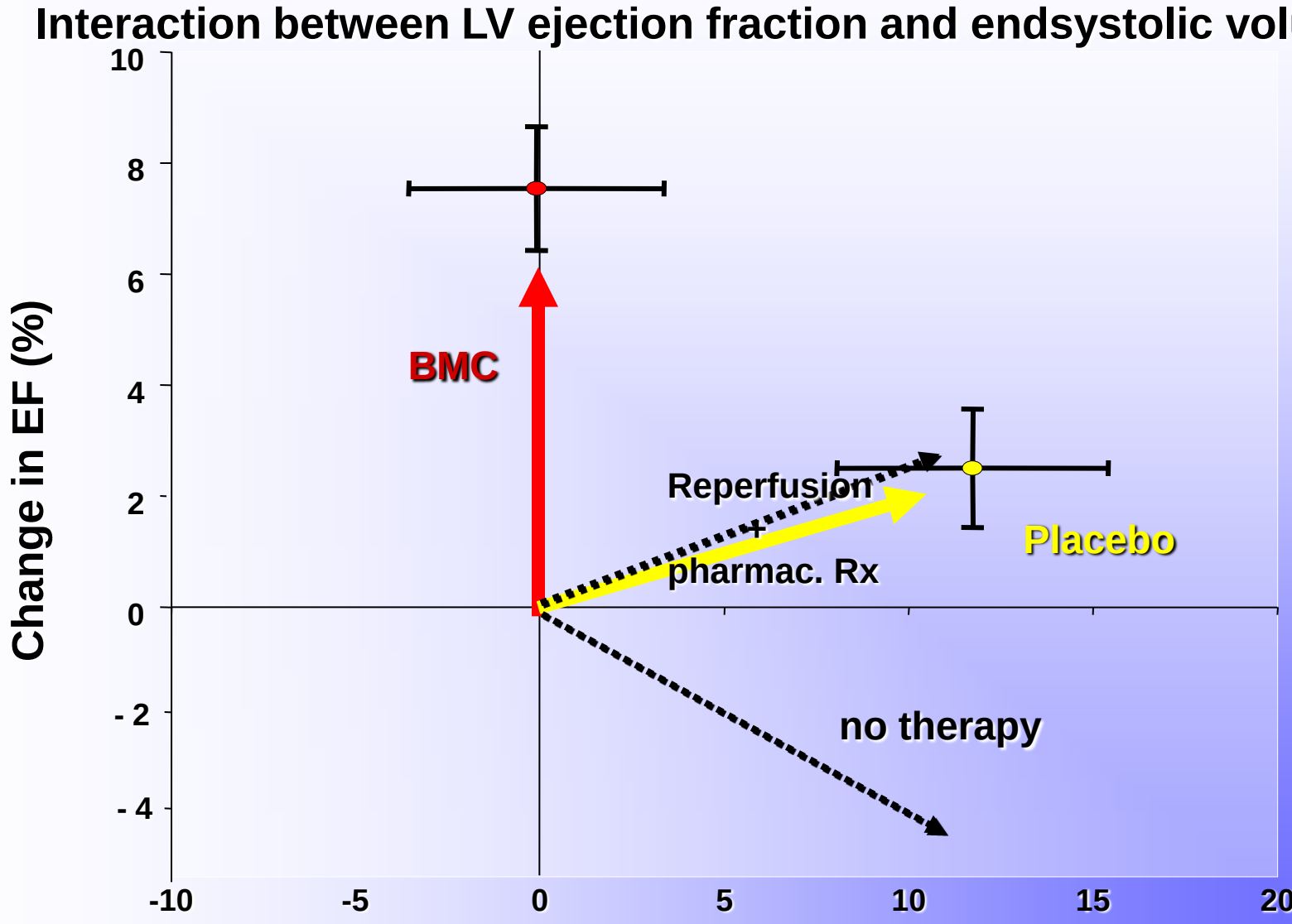



***Baseline EF: 39 ± 1.9 %***

***Baseline EF: 56 ± 2.3 %***

Dill et al., AHJ 2009

# Intracoronary BMC Administration Profoundly Modifies LV Remodeling

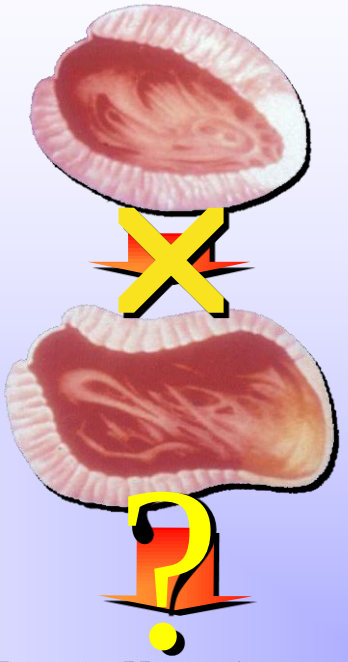



**EF ≤ 48.9%**
**p = 0.007**

EJHF 2009

# 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.*

# BMC therapy post-AMI
## Improved clinical outcome in meta-analysis

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

**Adult Bone Marrow Cell Therapy Improves Survival and Induces Long-Term Improvement in Cardiac Parameters: A Systematic Review and Meta-Analysis**

Vinodh Jeevanantham, Matthew Butler, Andre Saad, Ahmed Abdel-Latif, Ewa K. Zuba-Surma and Buddhadeb Dawn

***Background*** - Despite rapid clinical translation and widespread enthusiasm, the therapeutic benefits of adult bone marrow cell (BMC) transplantation in patients with ischemic heart disease (IHD) continue to remain controversial. A synthesis of the available data is critical to appreciate and underscore the true impact of this promising approach.

***Methods and Results*** - A total of 50 studies (enrolling 2,625 patients) identified by database searches through January 2012 were included. Weighted Mean Differences for changes in left ventricular (LV) ejection fraction (LVEF), infarct size, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) were estimated using random effects meta-analysis.

# BMC therapy post-AMI
## Improved clinical outcome in meta-analysis

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

***N = 2625***

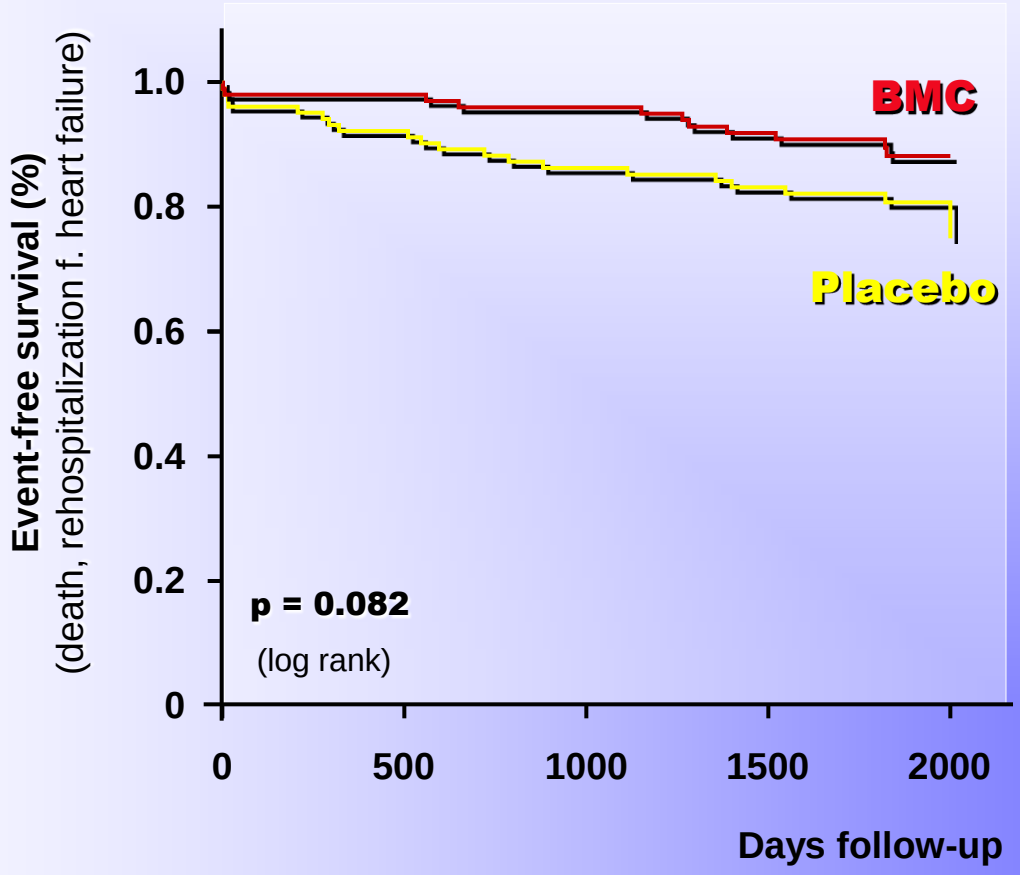
| Outcome | Peto OR | 95% Confidence Interval | *P* value |
|---|---|---|---|
| All-cause mortality | 0.39 | 0.27 to 0.55 | <0.00001 |
| Cardiac deaths | 0.41 | 0.22 to 0.79 | 0.005 |
| Recurrent MI | 0.25 | 0.11 to 0.57 | 0.001 |
| Heart failure | 0.52 | 0.27 to 1.00 | 0.05 |
| Stent thrombosis | 0.34 | 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.

Circulation , published online June 22, 2012

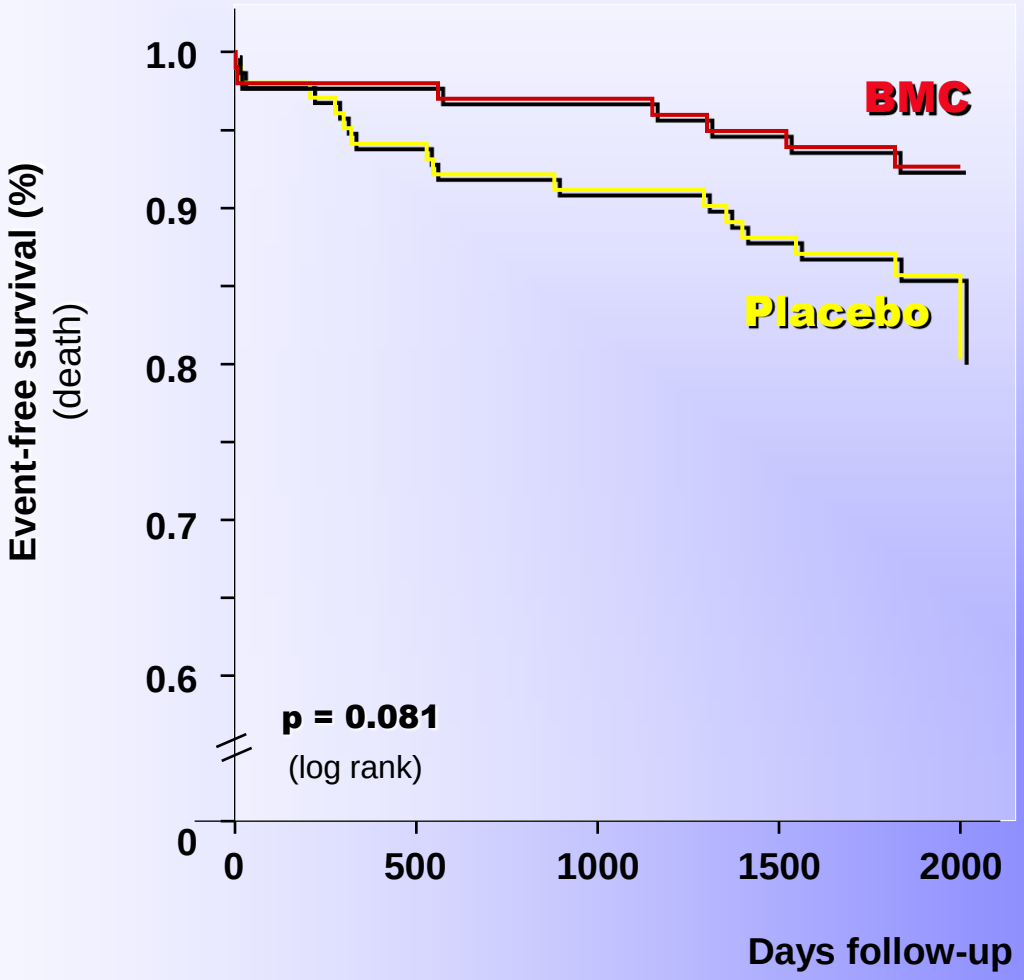
# 5 years clinical follow up
## - Kaplan Meier Analysis -

### Death & rehospitalization for heart failure

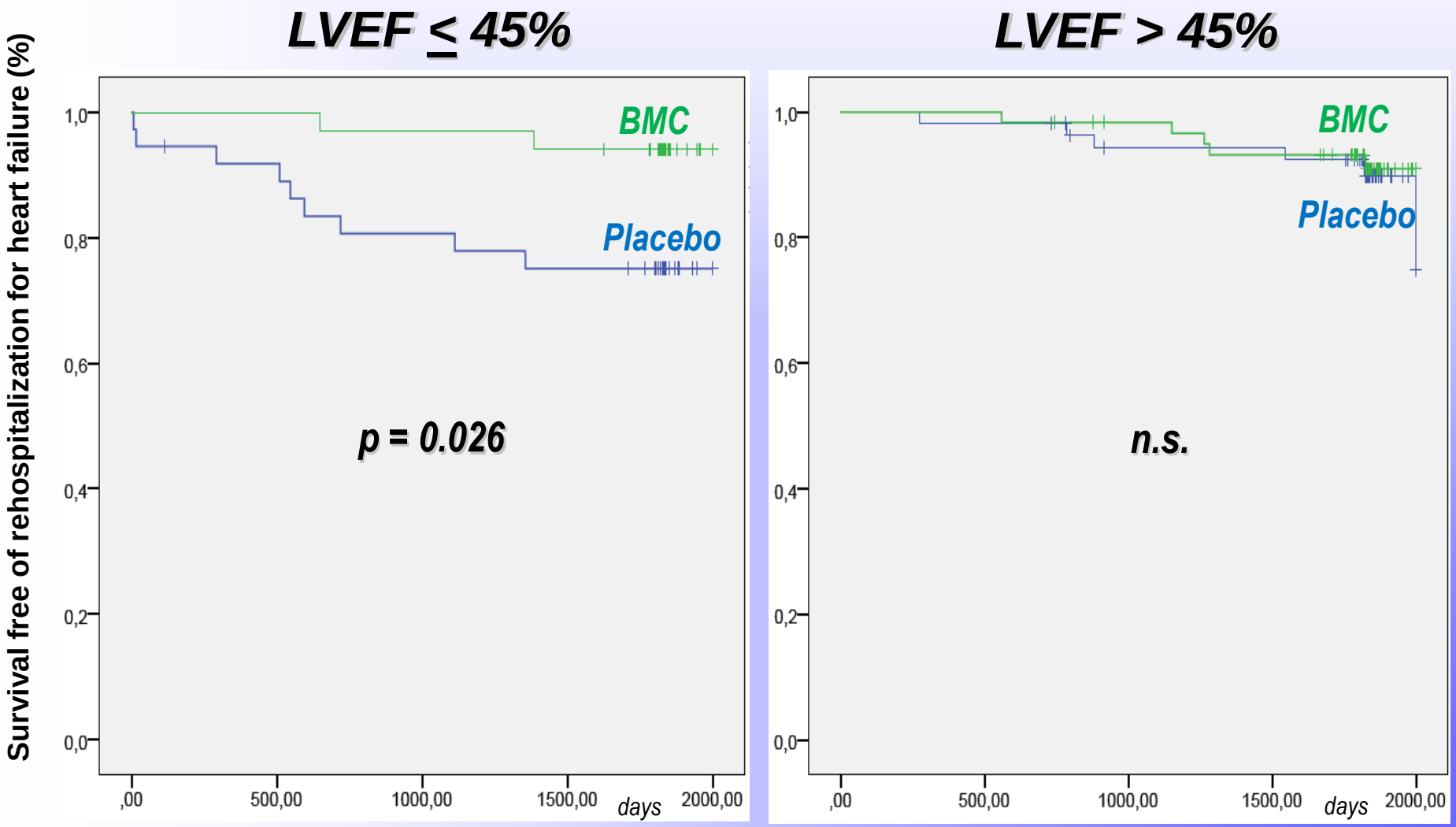


# 5 years clinical follow up
## - Kaplan Meier Analysis -

### Death



# Baseline LVEF determines long-term effects of BMC therapy in STEMI



# *Closing the gap in cell therapy of STEMI*

**In patients with acute post-infarction heart failure despite successful reperfusion therapy**

⇨ ***a large-scale clinical endpoint trial is warranted to document the effects on mortality and morbidity***

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: Q4 / 2012

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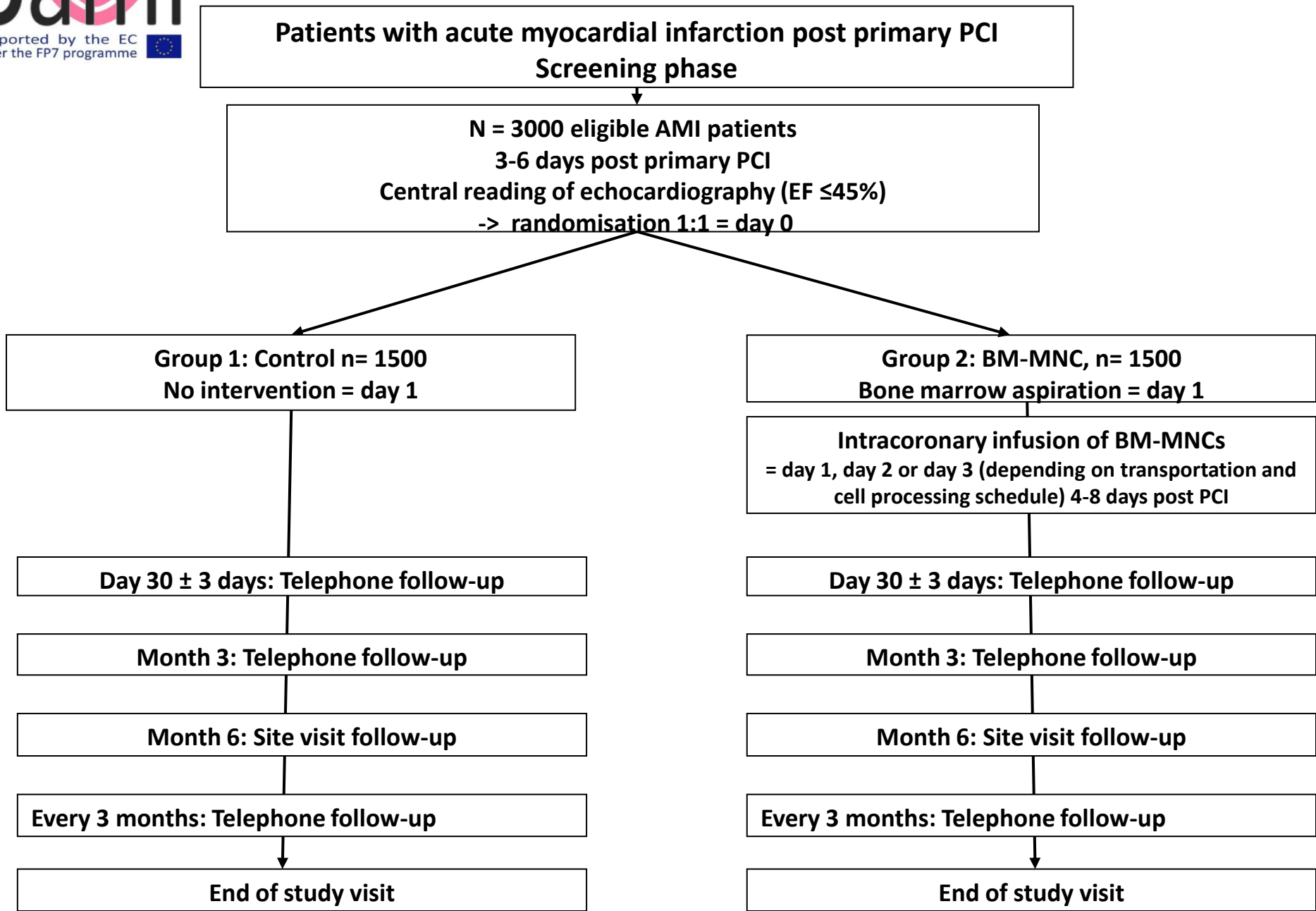
# Clinical Trial Design



# Cell processing centers and patient distribution

Bami

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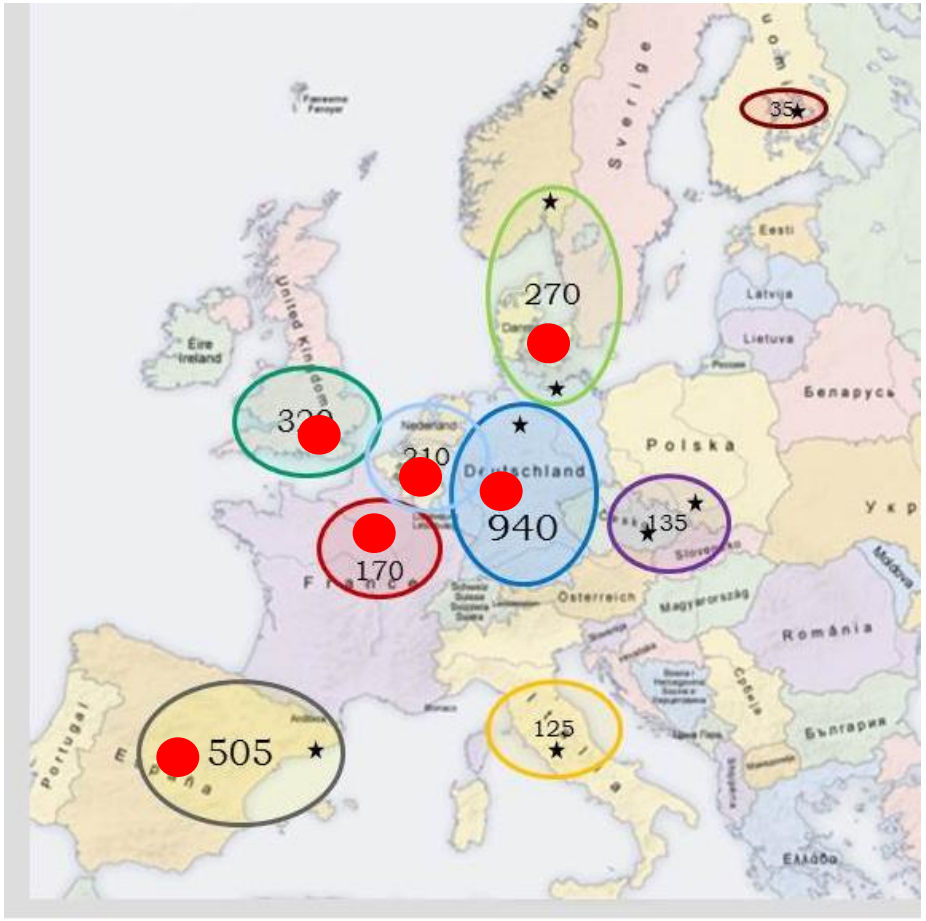
## Cell Processing Centers

- The Royal London Hospital, London, UK
- Hopitaux de Paris, Hopital Saint Louis, Paris, France
- Hospital Gregorio Maranon, Madrid, Spain
- Rigshospitalet University Hospital, Copenhagen, Denmark
- Universitaire Ziekenhuizen, Leuven, Belgium
- BSD, Institute for Transfusion Medicine Frankfurt, Germany

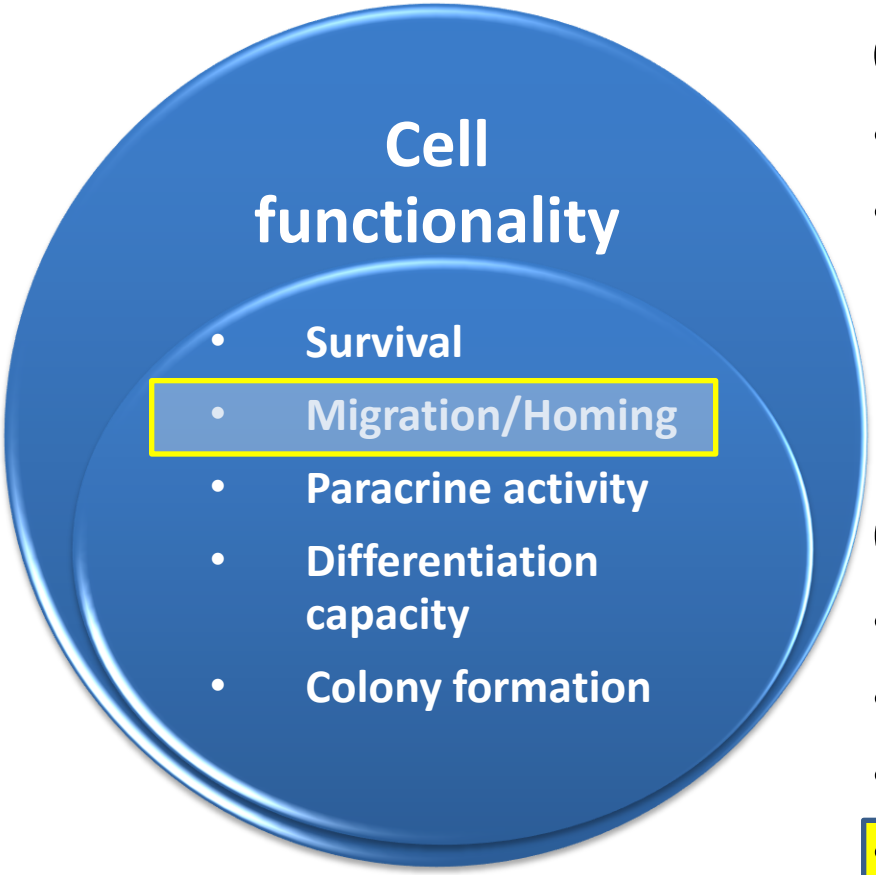


# Factors influencing function of autologous BMC

## Cell intrinsic factors

**Patient characteristics**

- Age
- Diabetes
- Heart failure
- Acute MI




## Extrinsic factors

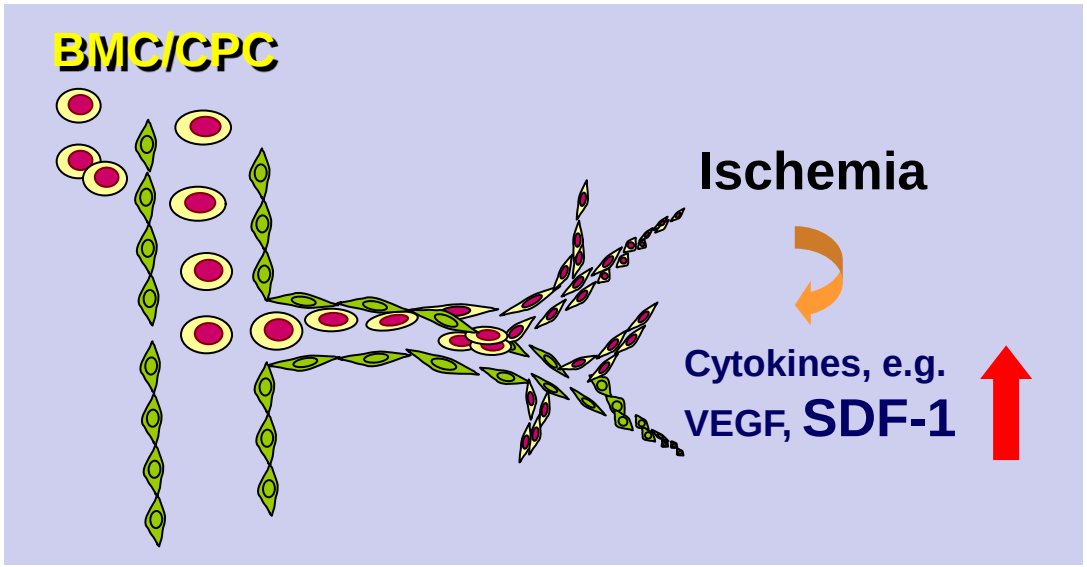
**Cell preparation:**

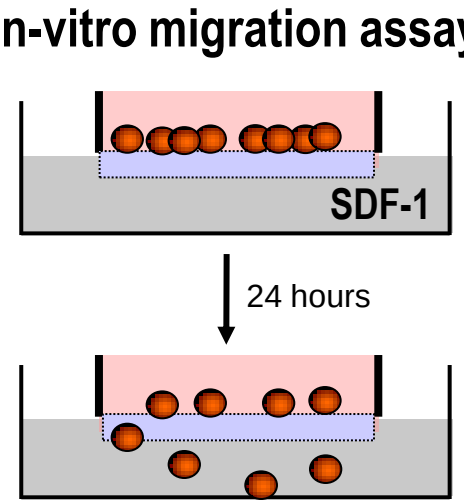
- Purity
- Contaminations (e.g. Red blood cells, granulocytes?)

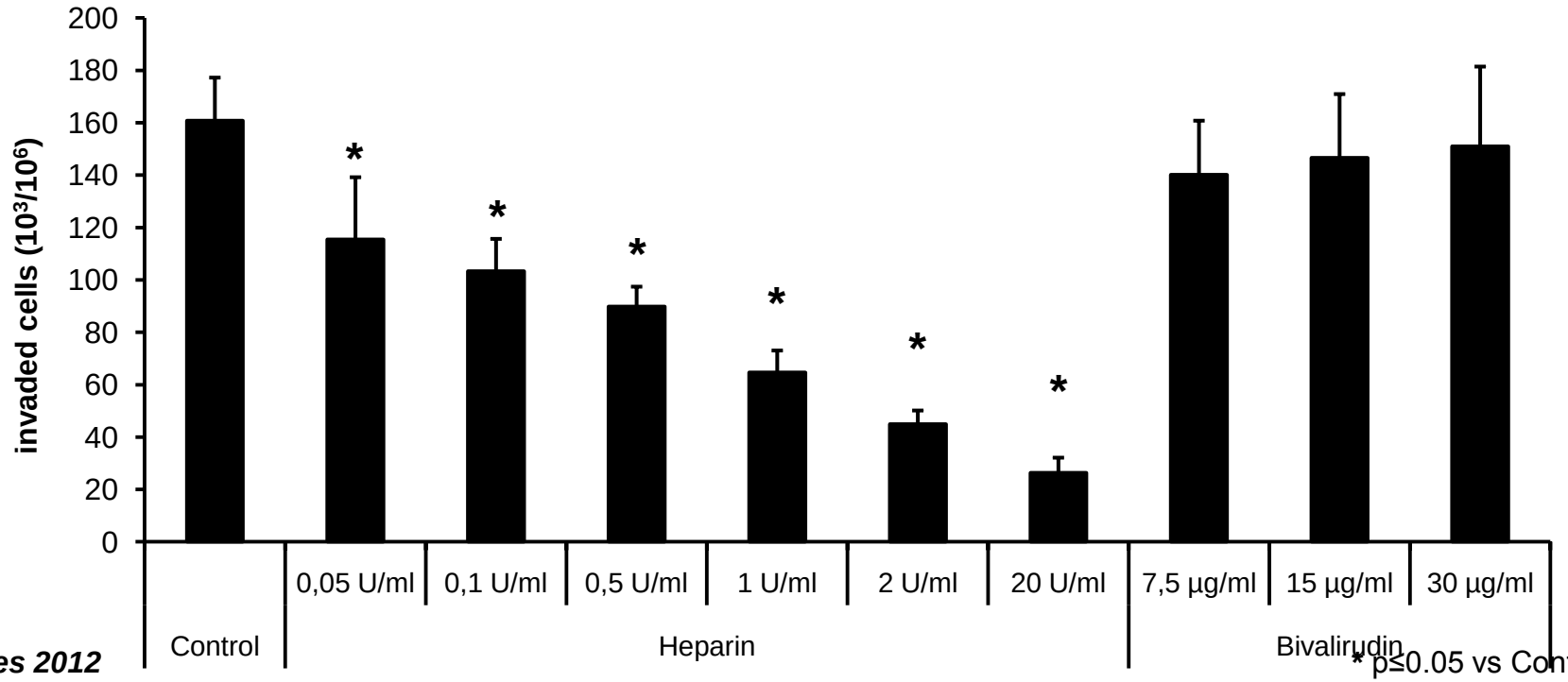
**Cell storage:**

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

# Migratory / Invasion Capacity of BMC: Effects of Heparin




*Circ Res 2012*

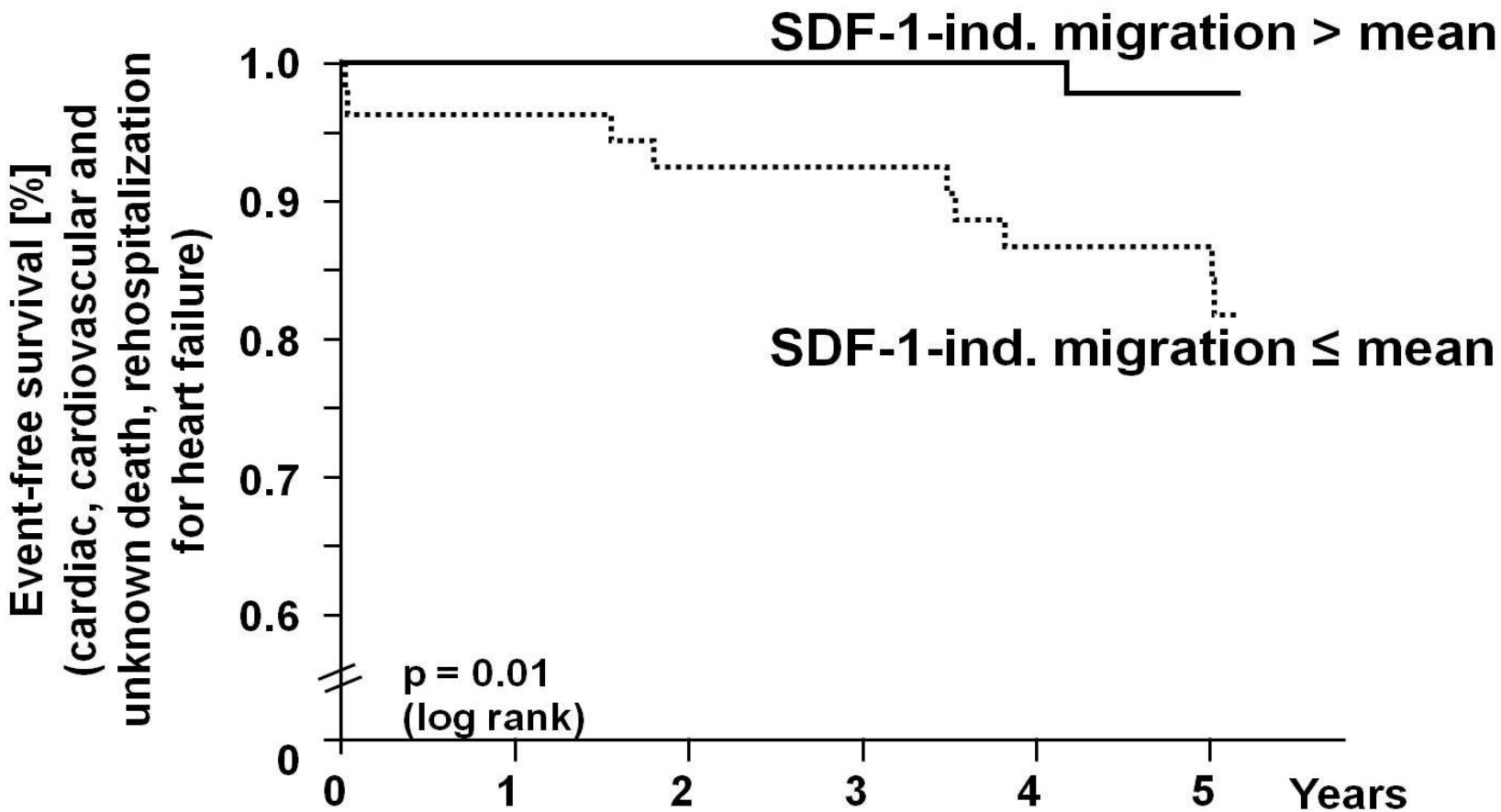
* p≤0.05 vs Control; n≥3

# Heparin Use in Clinical BMC Trials in AMI

## 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*<br>*(-) 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*<br>*(+) 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*<br>*(+) after 12 & 24 months* |

# 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 |

*Assmus et al.,AHA 2012*

Bami

Supported by the EC under the FP7 programme

# Clinical Trial Design

## *Premedication prior to BM-MNC application*

- ASS and Clopidogrel / Prasugrel / Ticagrelor should be loaded prior to coronary angiography according to standard guidelines.
- Bivalirudin should be given prior to the cell administration procedure. Heparin including low molecular weight heparin is not allowed during cell administration. Syringes and catheters may not be flushed with heparin containing solutions.


REPAIR-AMI

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