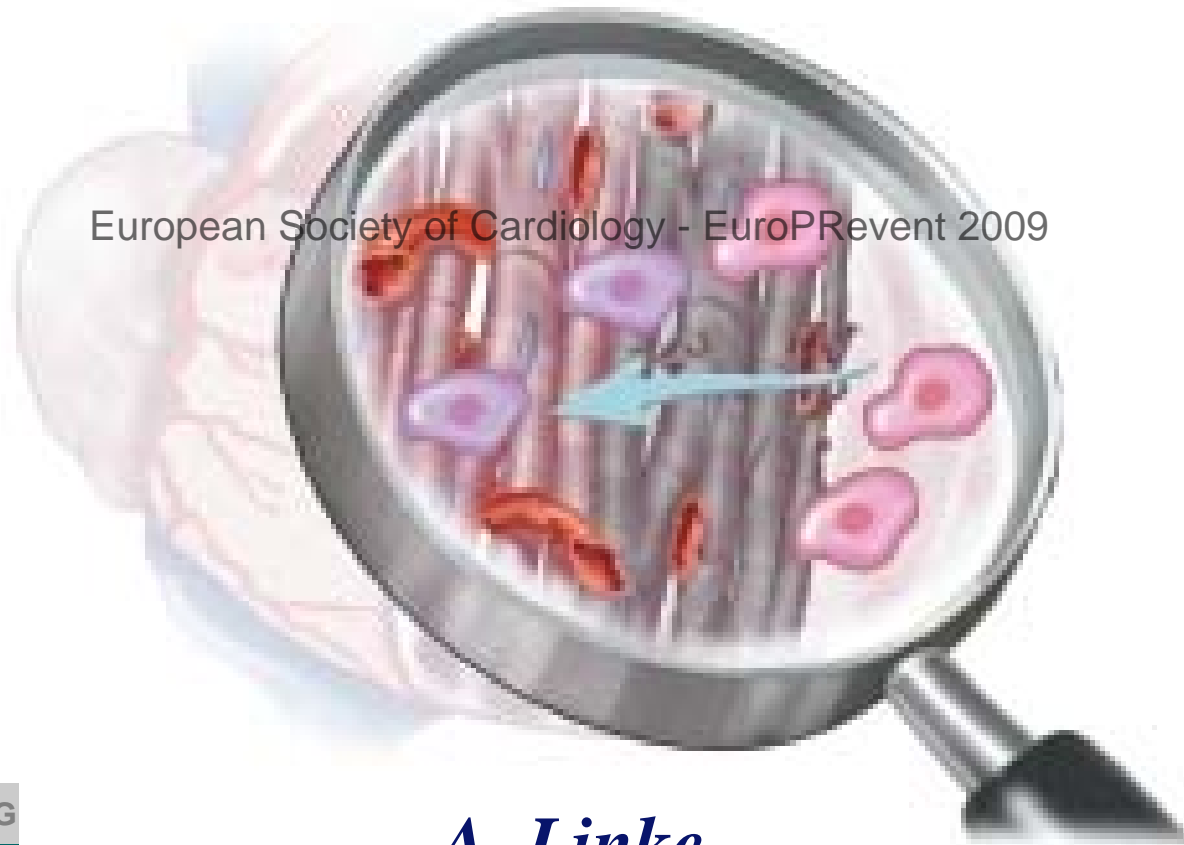




# New challenges and future aspects in cardiovascular medicine:

## Stem Cells



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# Pharmacotherapy in CHF: What are the guidelines ?

**Post-MI  
LV Dysfunktion**

**NYHA  
I**

**NYHA  
II-III**

**NYHA  
IV**



AIRE / SAVE / TRACE  
(Ramipril/Captopril/  
Trandolapril)

SOLVD Prevent / Treat  
(Enalapril)

CONSENSUS  
(Enalapril)

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VALIANT  
(Valsartan)

CHARM Added  
(Candesartan)

ValHeft  
(Valsartan)



CAPRICORN  
(Carvedilol)

US Carvedilol / MERIT HF/ CIBIS II  
(Carvedilol / Metoprolol / Bisoprolol)

COPERNICUS  
(Carvedilol)



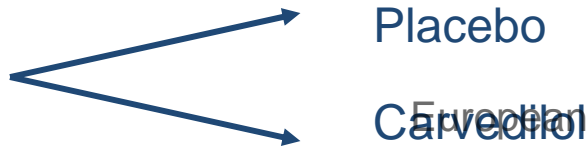
EPHESUS  
(Eplerenone)

RALES  
(Spironolactone)

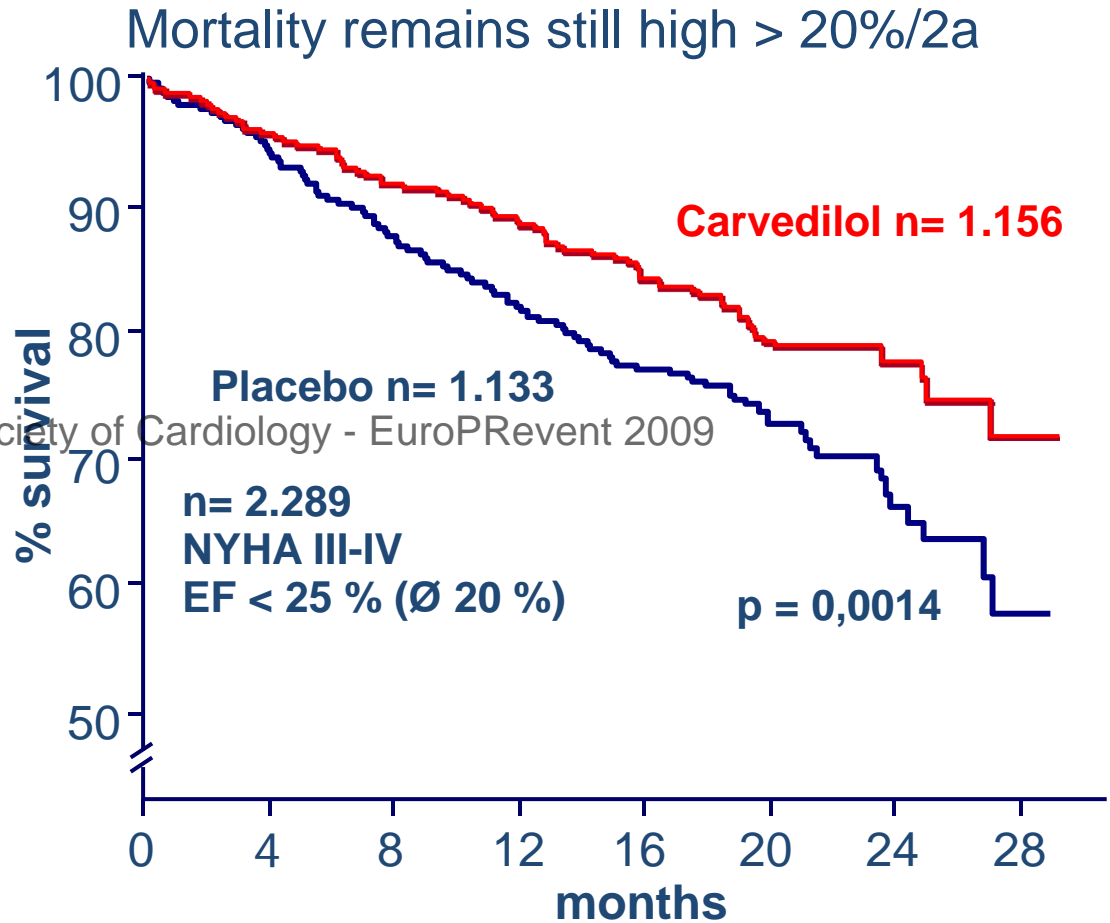
# COPERNICUS

## $\beta$ -Blocker Treatment in NYHA III-IV: The COPERNICUS Trial

2289 NYHA III-IV patients  
(LV-EF <25%) randomised to

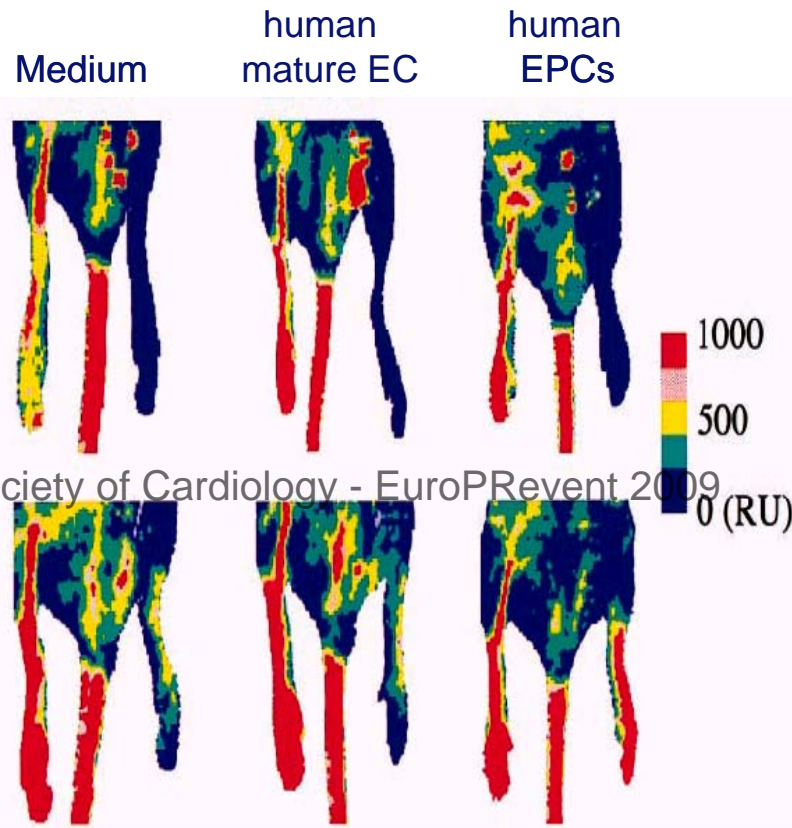
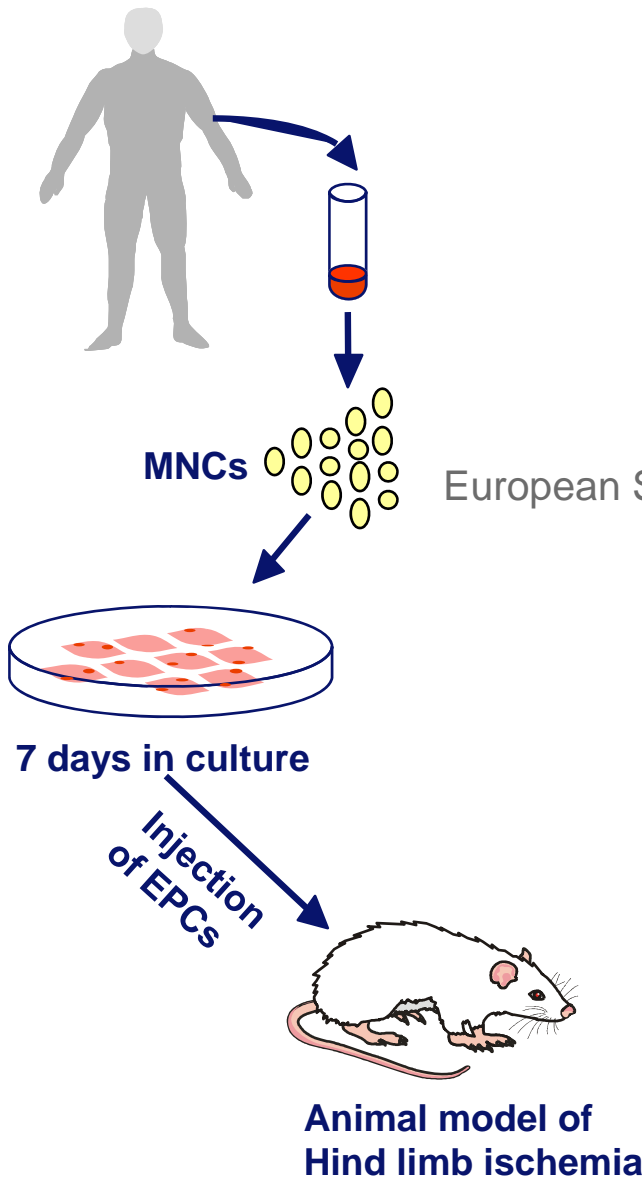


Initial dose 3.125 mg BID with  
doubling of dose every 2 wks  
until target dose of 25 mg BID  
was reached.

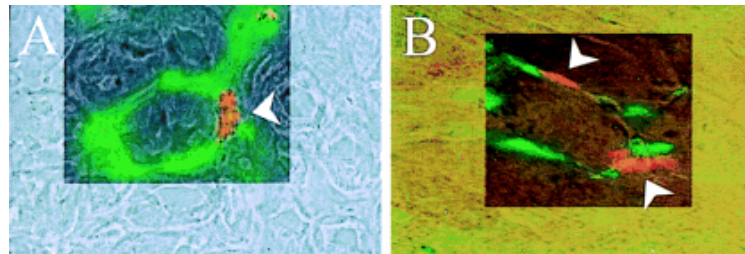


# Application of *ex vivo* cultivated EPCs

- Results from animal models -



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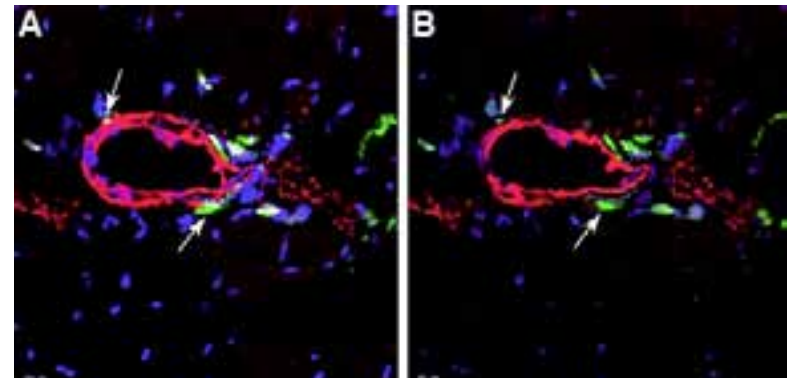
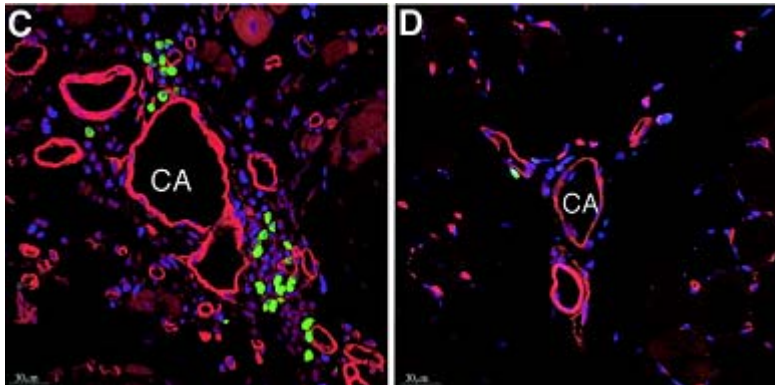
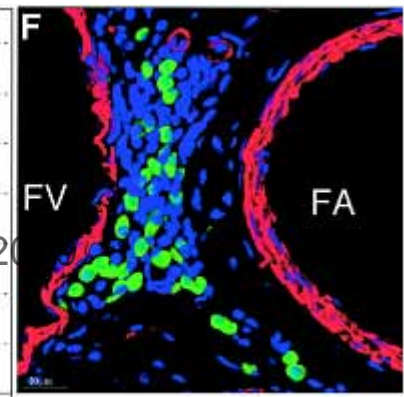
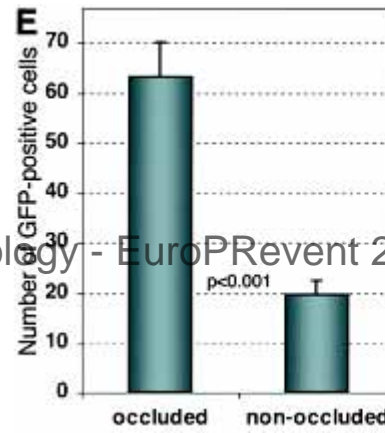
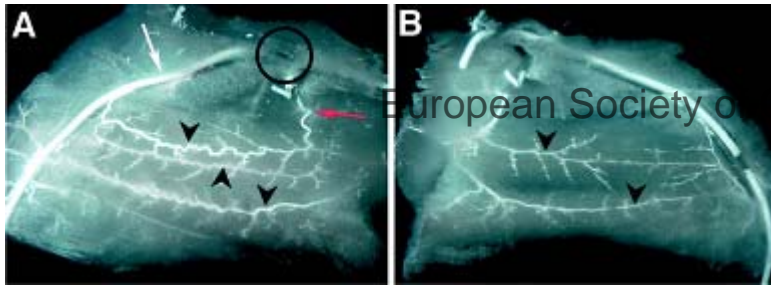


# No Evidence of Vasulogenesis by Progenitor Cells

- Results from animal experiments in hind limb ischemia -

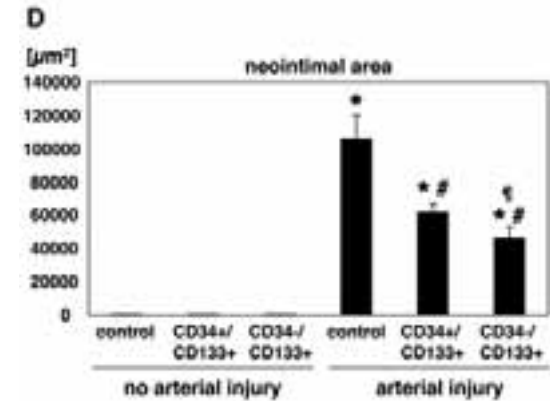
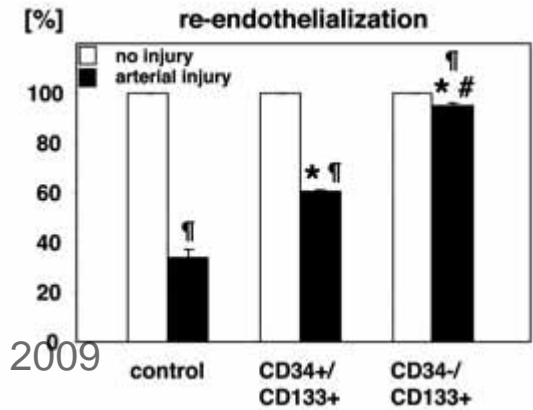
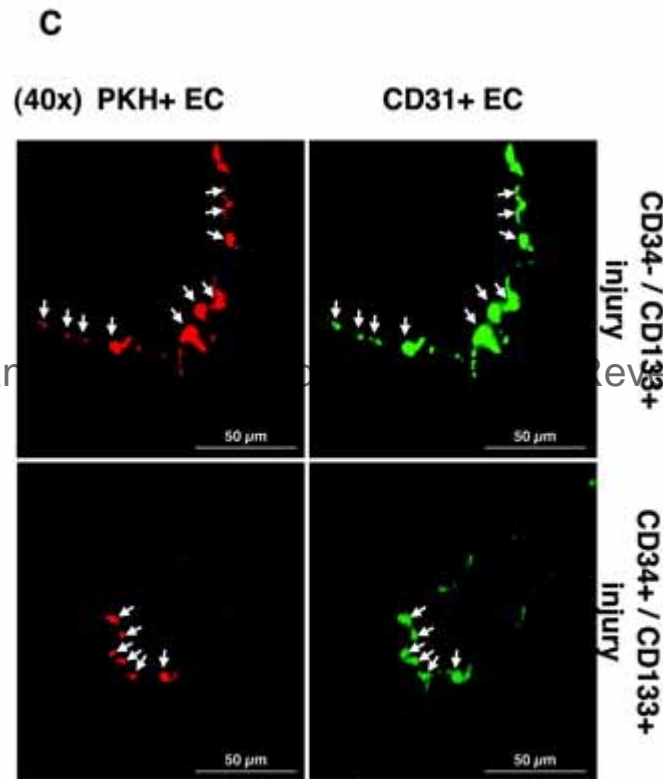
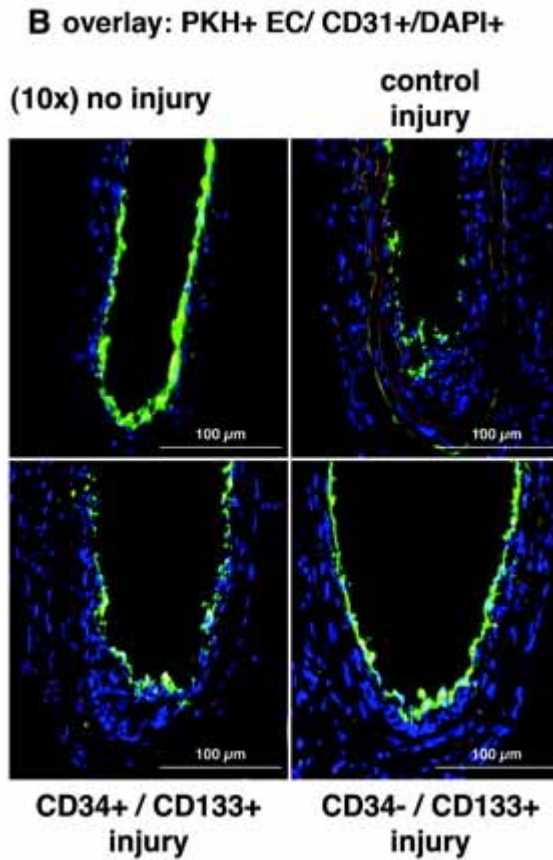
WT mice → Transplantation of GFP<sup>+</sup> BM → Ligation of femoral artery → Histolog. analysis of hind limb

↑  
lethal irradiation



# Progenitor Cells Regenerate Damaged Endothelium

## - Results from animal experiments -

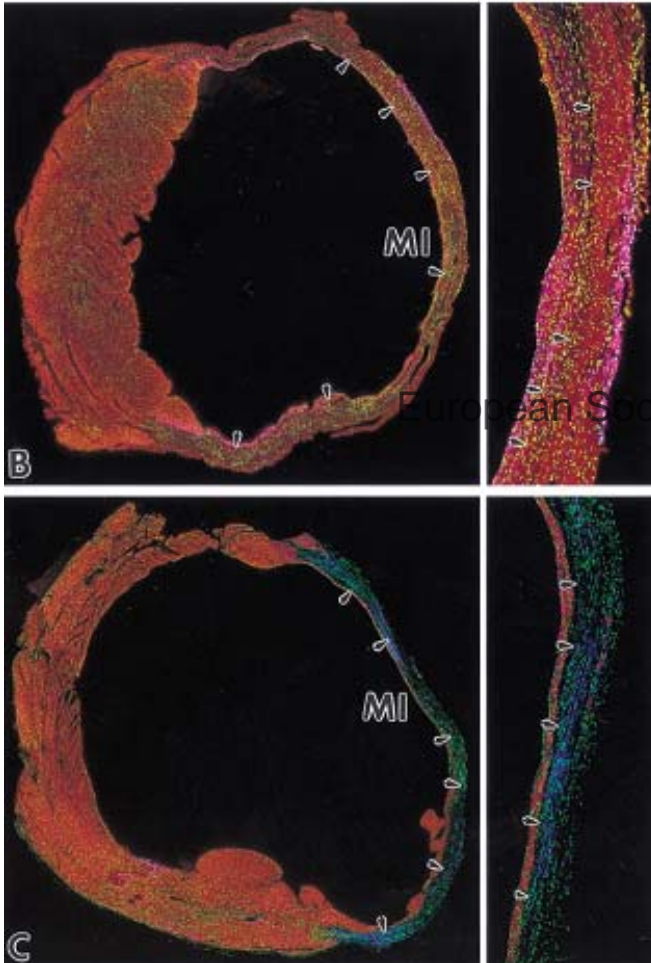




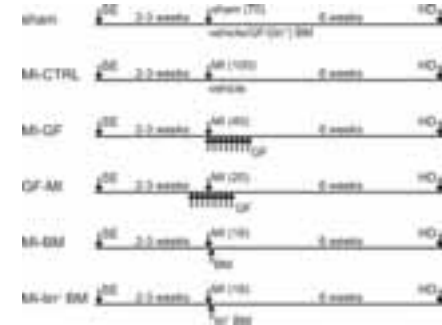
# G-CSF-induced Mobilization of Stem Cells

## - Results from animal experiments in myocardial ischemia -

### Cardiac Regeneration

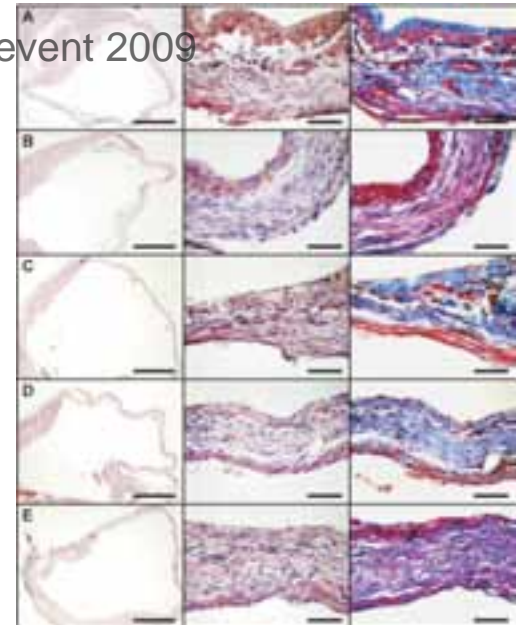


### No Cardiac Regeneration



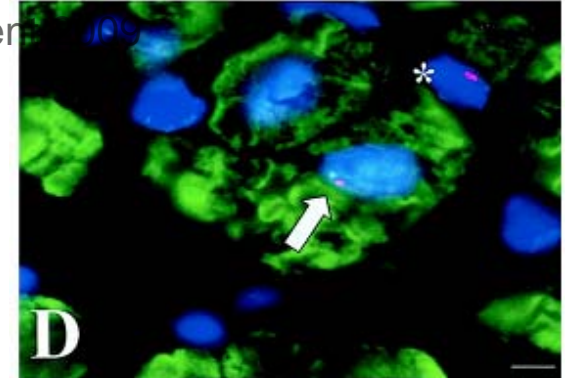
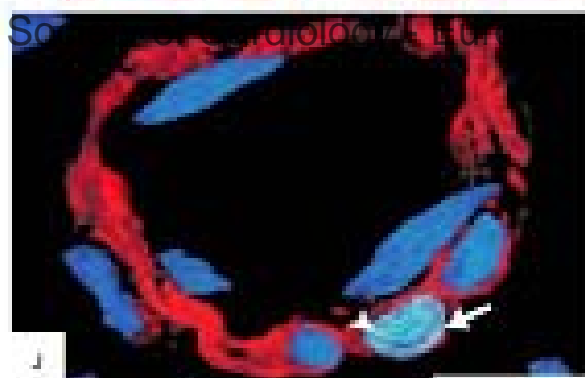
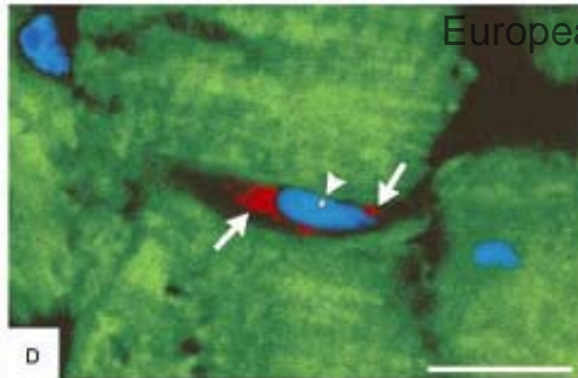
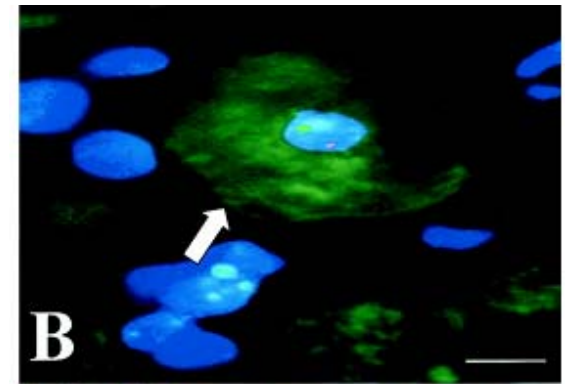
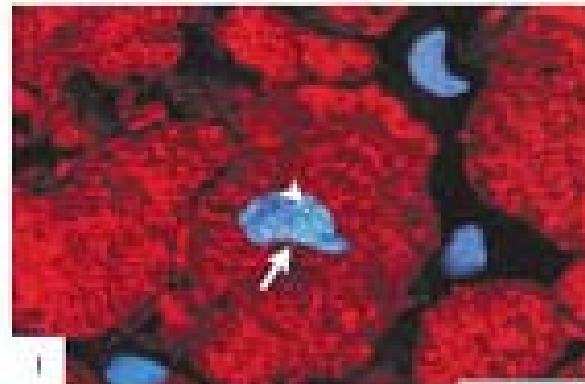
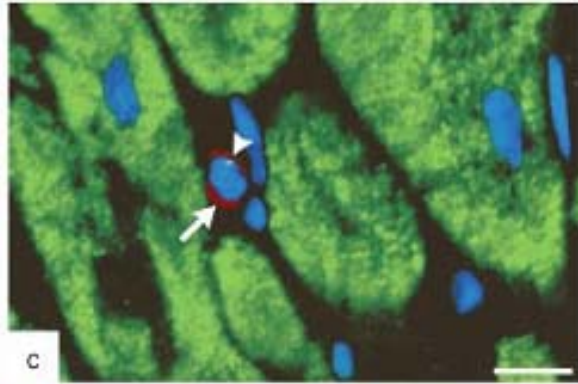
**G-CSF**

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# Contribution of Circulating Stem Cells to Myocardial Lineages - Results from humans after bone marrow transplantation -

## Endogenous Cardiac Regeneration



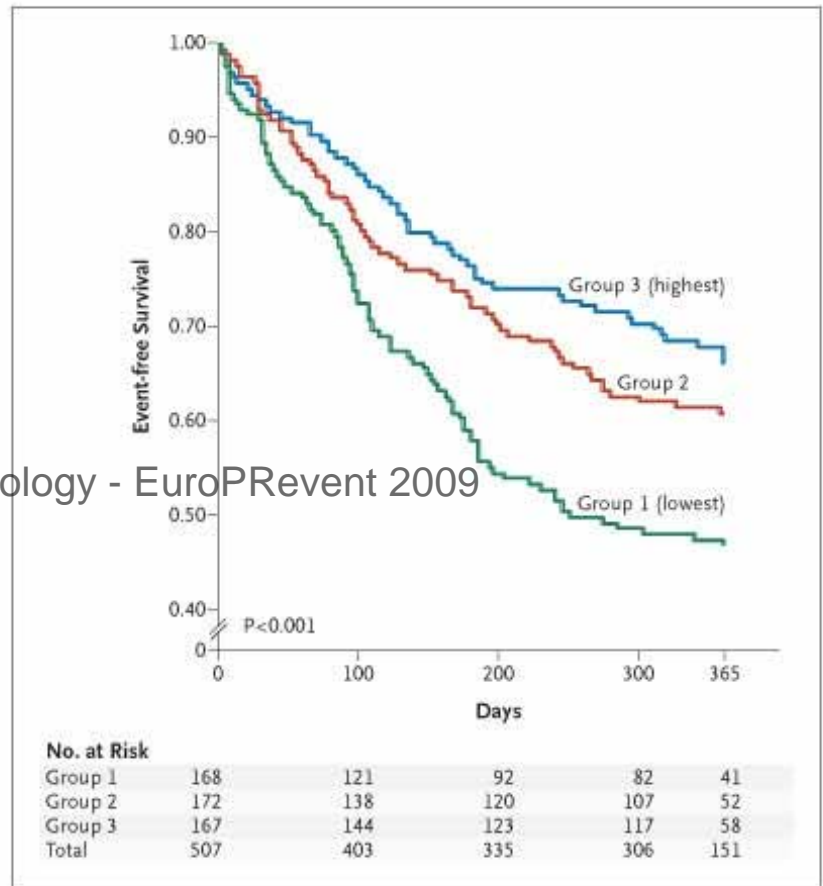
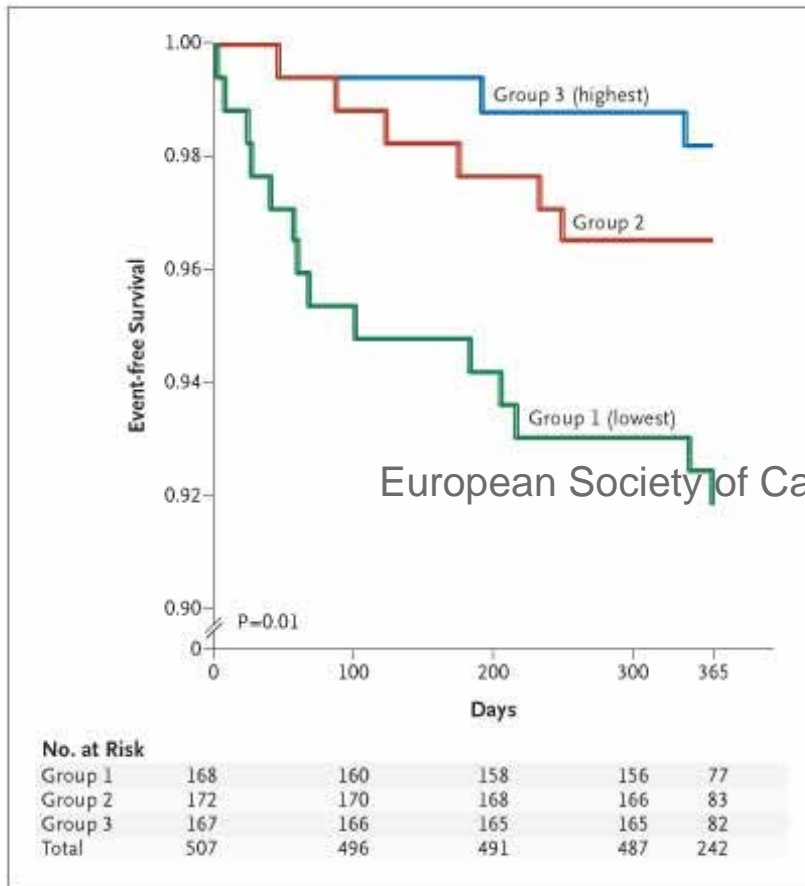
Lineage commitment:

cardiomyocytes  
smooth muscle cells  
endothelial cells

**Significance?**

# Circulating Progenitor Cells – Prognostic Implications

## - Results from humans with CAD-



Death from cardiovascular cause

Major cardiovascular events  
(MI, hospitalization, revascularization,  
death from cardiovascular cause)

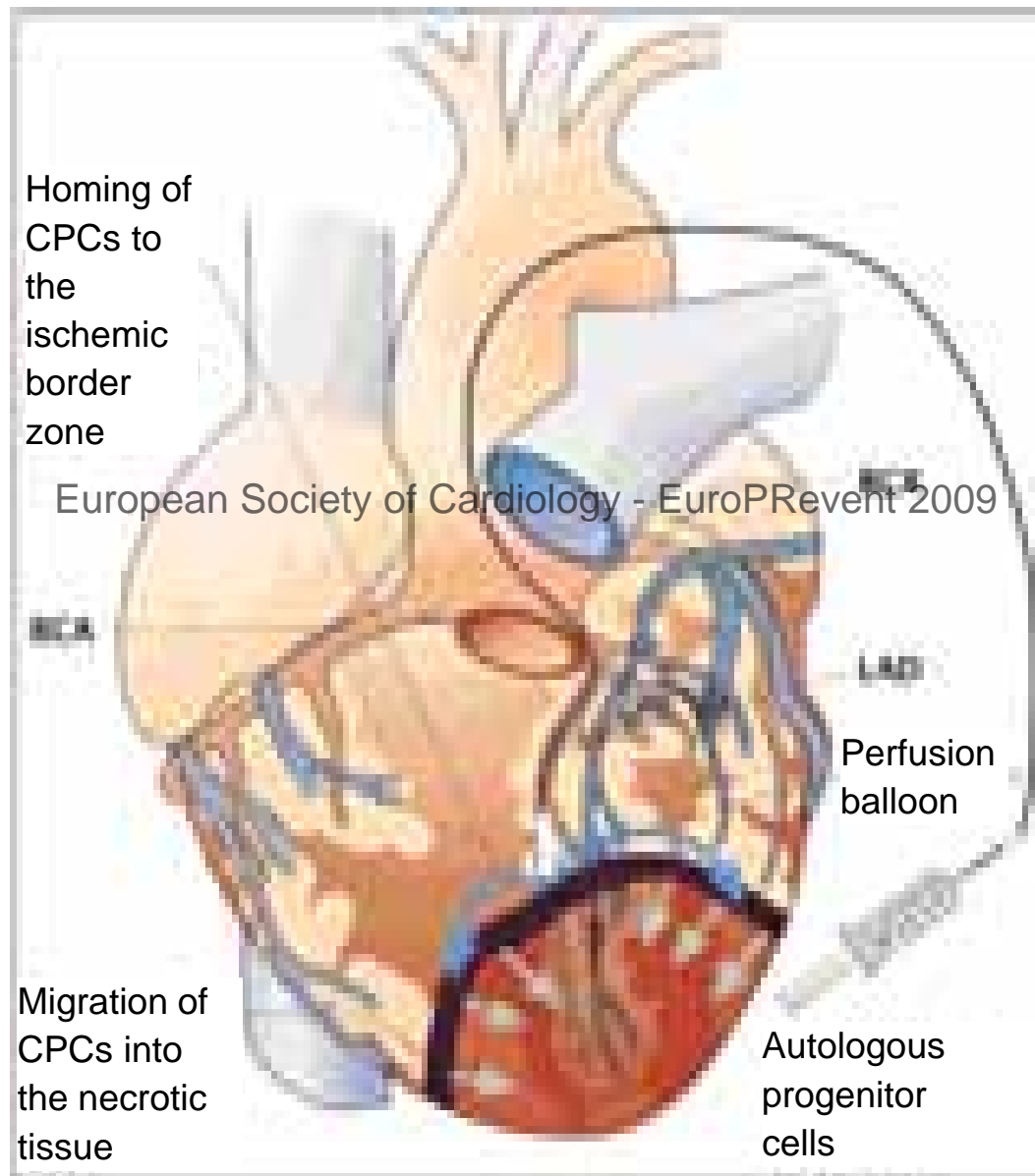
# What are the effects of intracoronary reinfusion of autologous stem cells in patients with acute AMI ?

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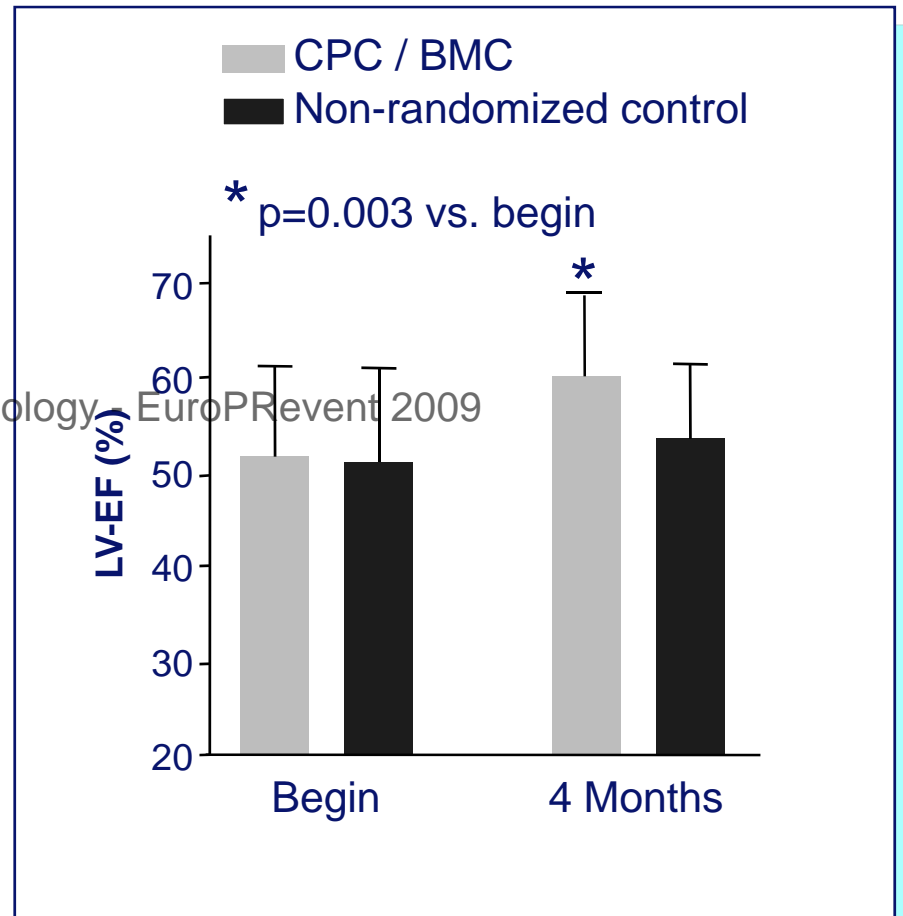
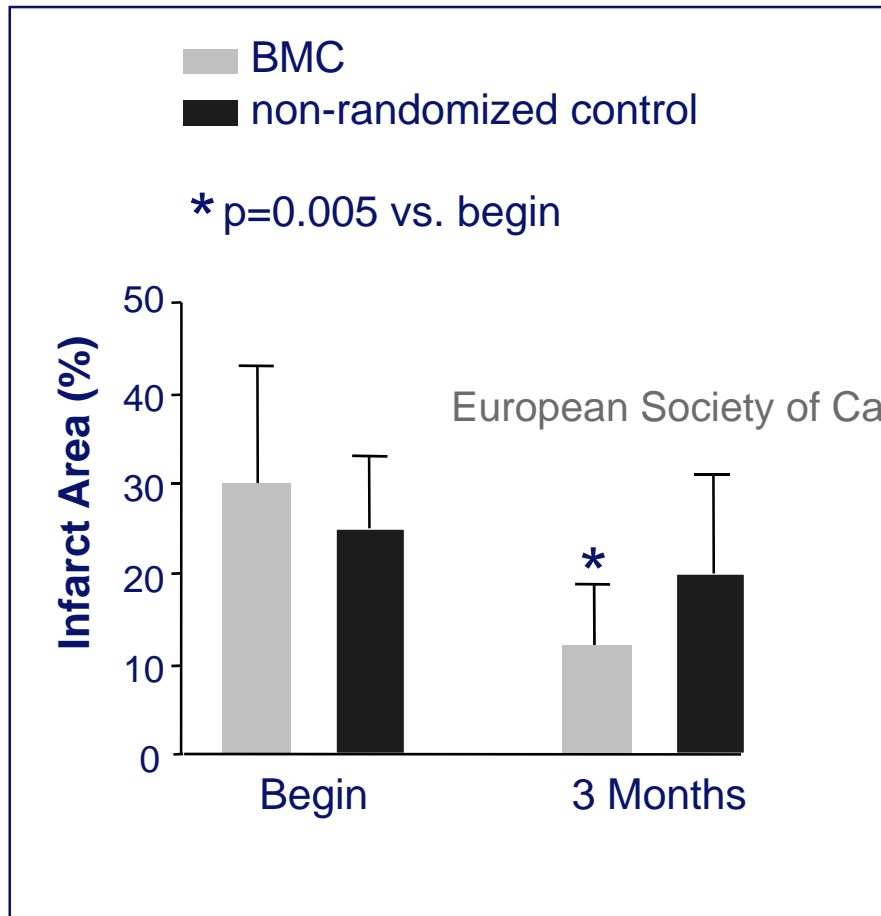
# Application of CPCs in ischemic heart disease

- A novel therapeutic concept in humans -



# Intracoronary Application of Autologous Stem Cells in AMI

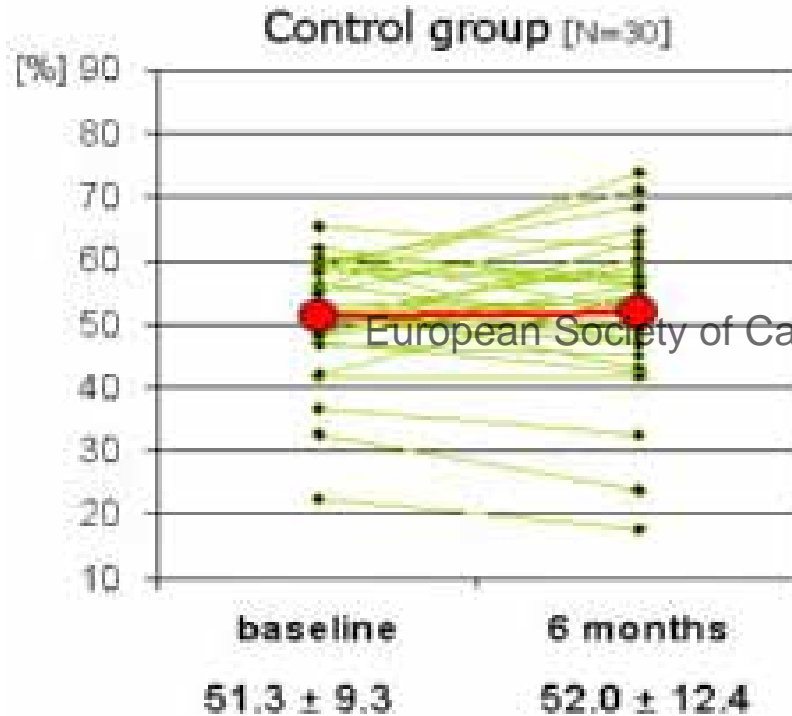
## - First results from non-randomized trials -



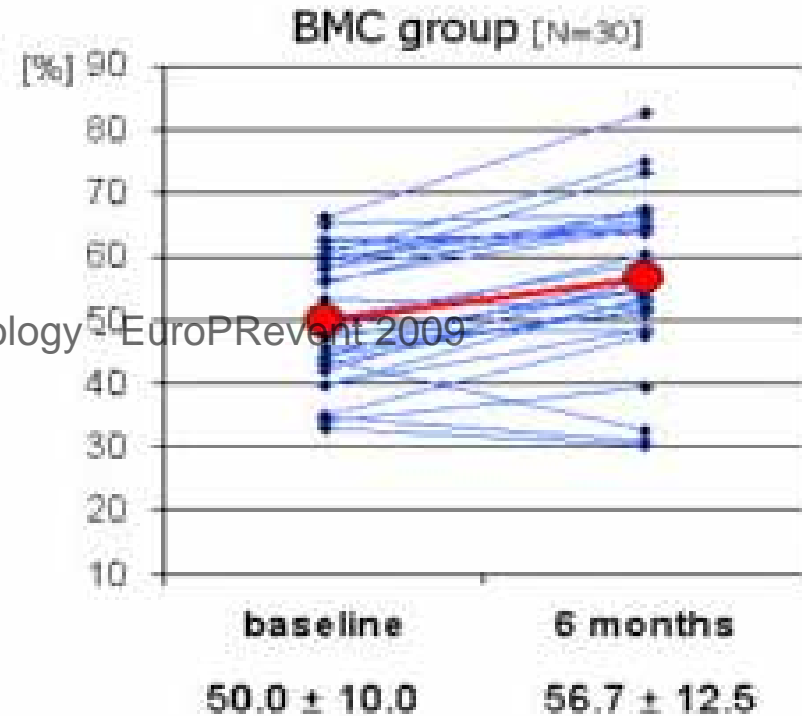
# Application of PCs in acute myocardial infarction

- First results from randomized trials -

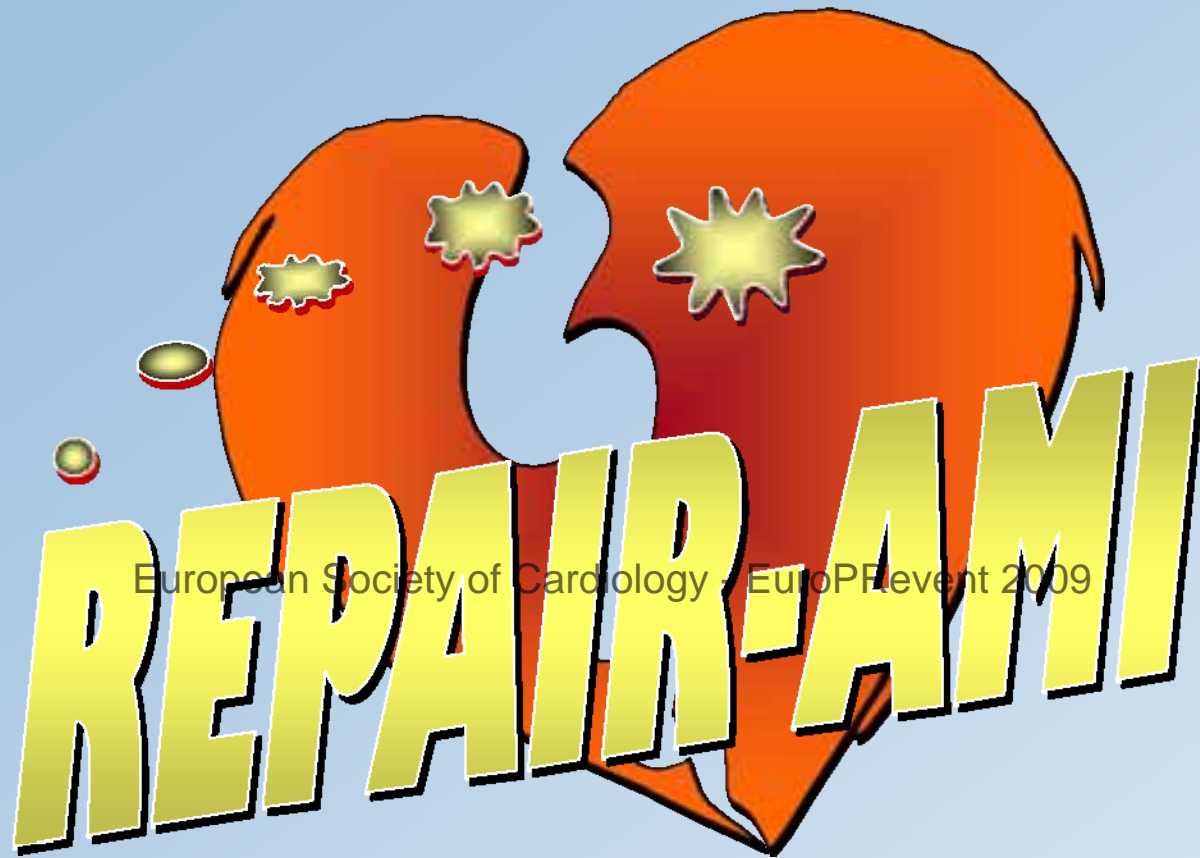
## LV-Ejection Fraction as Determined by MRI



**0.7 ± 8.1 %**



**6.7 ± 6.5 %**

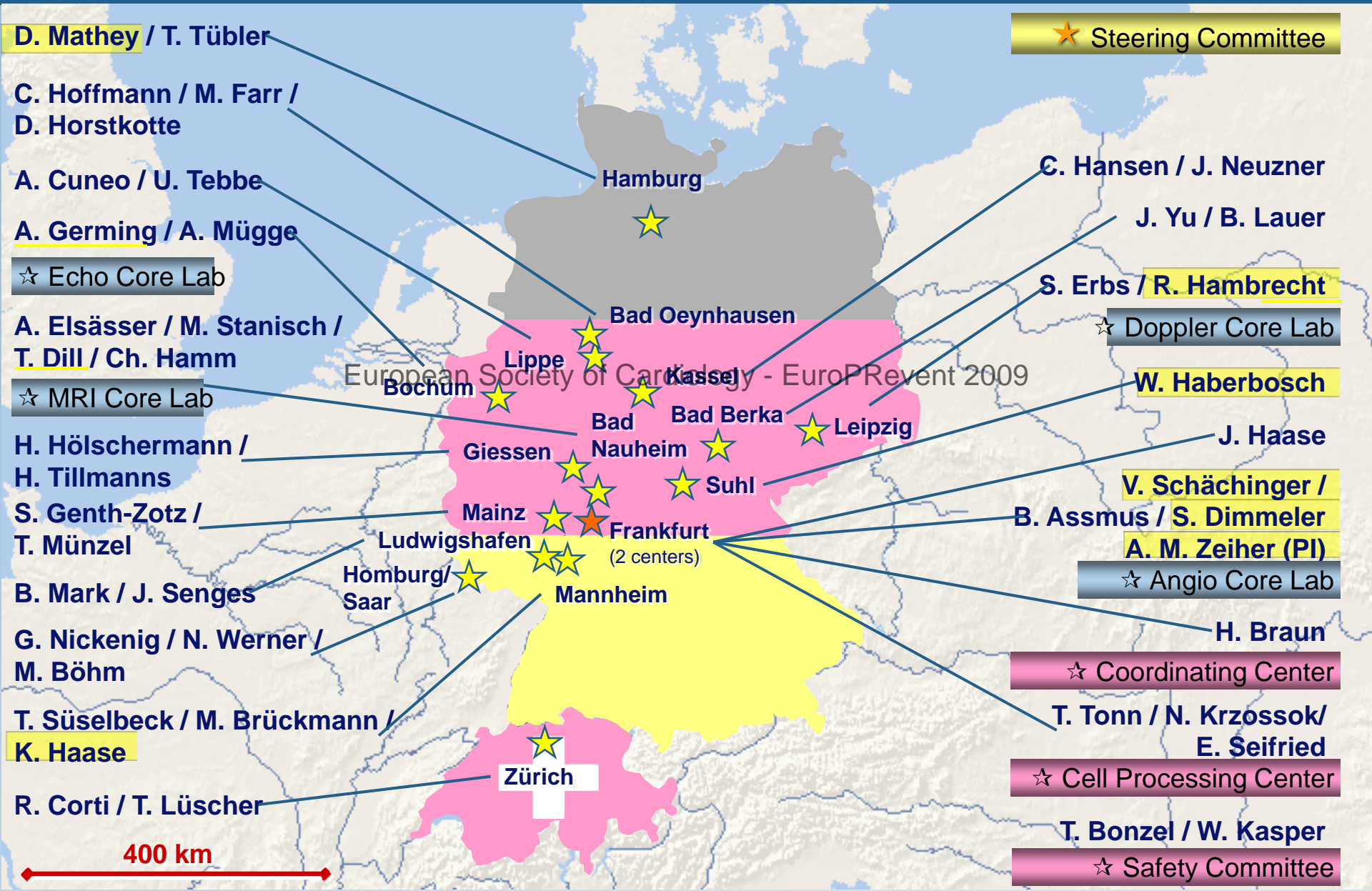


Reinfusion of Enriched Progenitor cells And Infarct Remodeling  
in Acute Mycocardial Infarction

**Double-blind, placebo-controlled, randomized multicenter trial**



# Study Centers and Core Facilities



D. Mathey / T. Tübler

C. Hoffmann / M. Farr /  
D. Horstkotte

A. Cuneo / U. Tebbe

A. Germing / A. Mügge

☆ Echo Core Lab

A. Elsässer / M. Stanisch /  
T. Dill / Ch. Hamm

☆ MRI Core Lab

H. Hölschermann /  
H. Tillmanns

S. Genth-Zotz /  
T. Münzel

B. Mark / J. Senges

G. Nickenig / N. Werner /  
M. Böhm

T. Süselbeck / M. Brückmann /  
K. Haase

R. Corti / T. Lüscher

Hamburg

Bad Oeynhausen

Lippe

Bochum

Kassel

Bad Nauheim

Bad Berka

Leipzig

Giessen

Frankfurt

Suhl

Ludwigshafen

Homburg/  
Saar

Mannheim

Frankfurt  
(2 centers)

Zürich

C. Hansen / J. Neuzner

J. Yu / B. Lauer

S. Erbs / R. Hambrecht

☆ Doppler Core Lab

W. Haberbosch

J. Haase

V. Schächinger /

B. Assmus / S. Dimmeler

A. M. Zeiher (PI)

☆ Angio Core Lab

H. Braun

☆ Coordinating Center

T. Tonn / N. Krzossok/  
E. Seifried

☆ Cell Processing Center

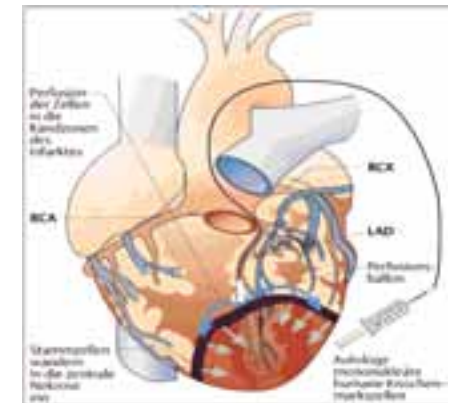
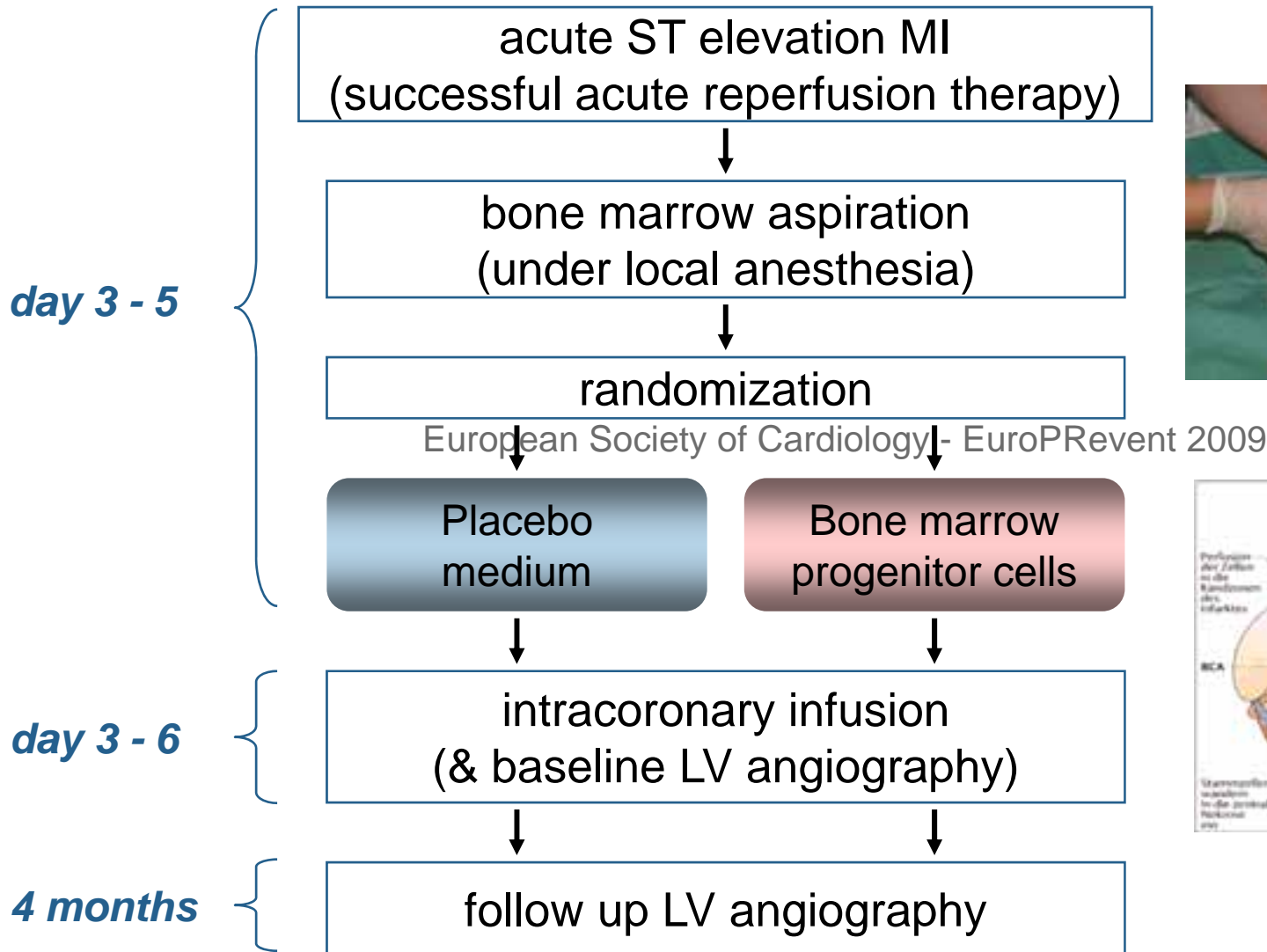
T. Bonzel / W. Kasper

☆ Safety Committee



# Study Design

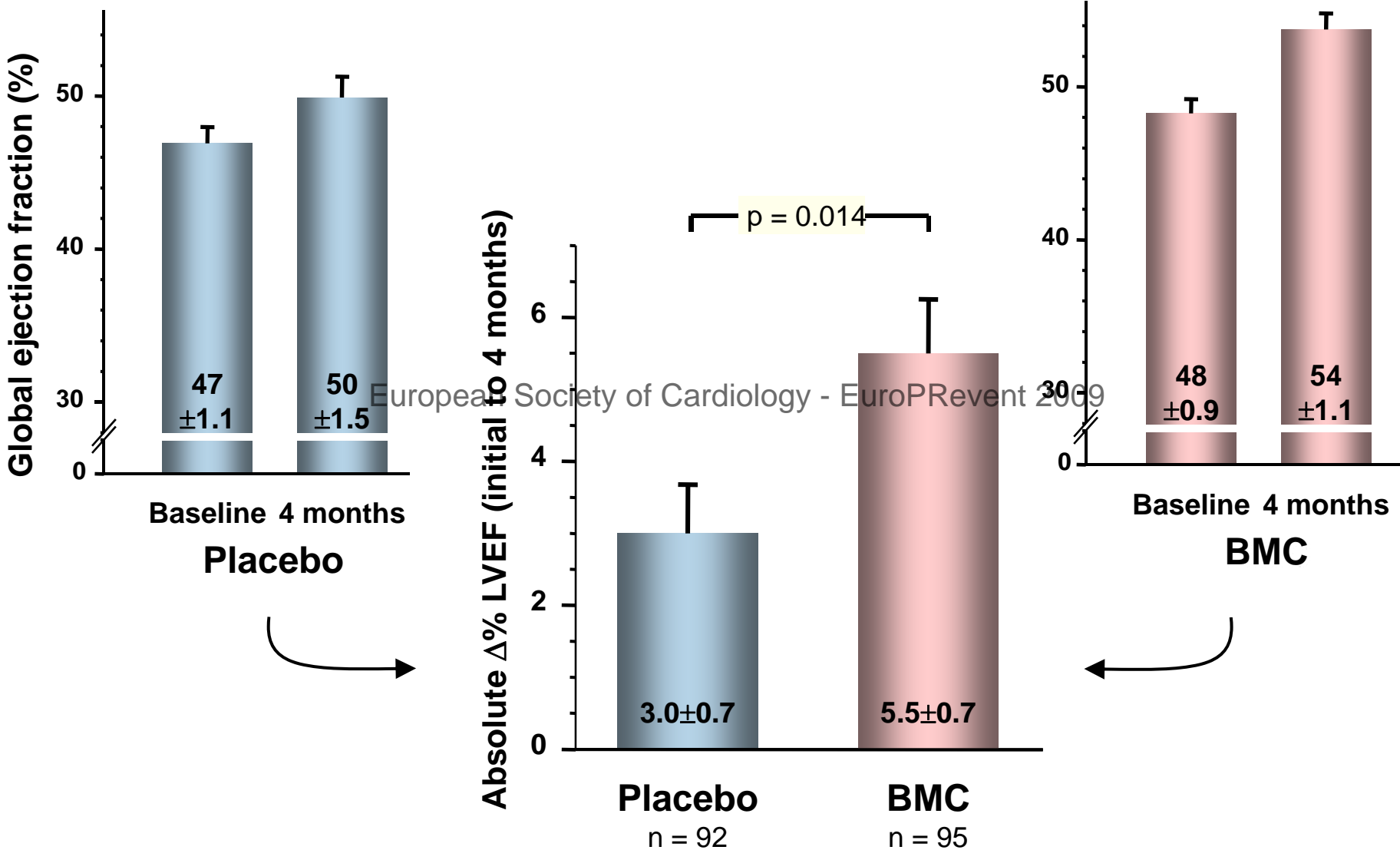
- Double-blind, Placebo-controlled, Randomized, Multicenter Trial -





# Change of global LV ejection fraction

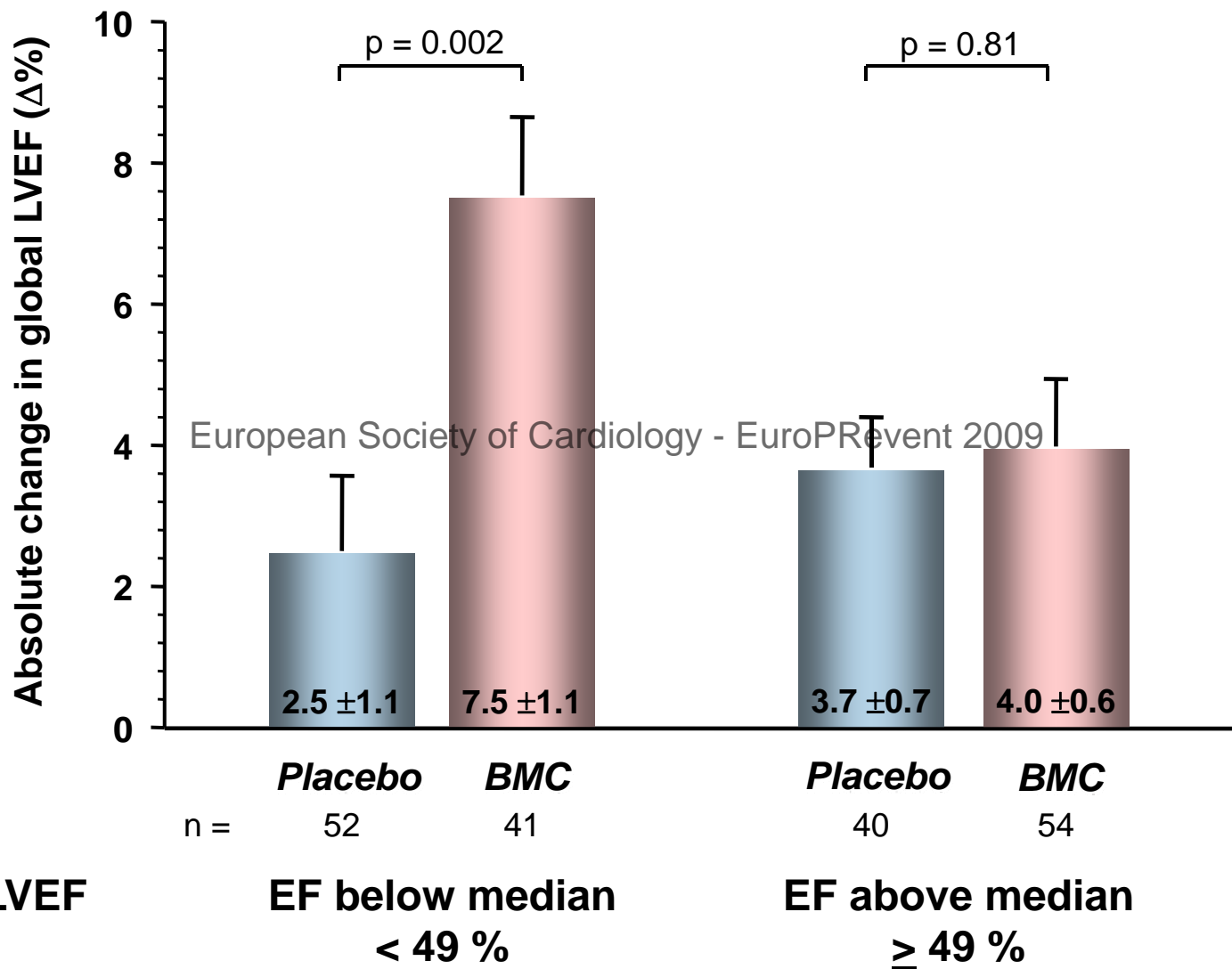
- primary endpoint -





# Interaction with baseline ejection fraction

- secondary endpoint -



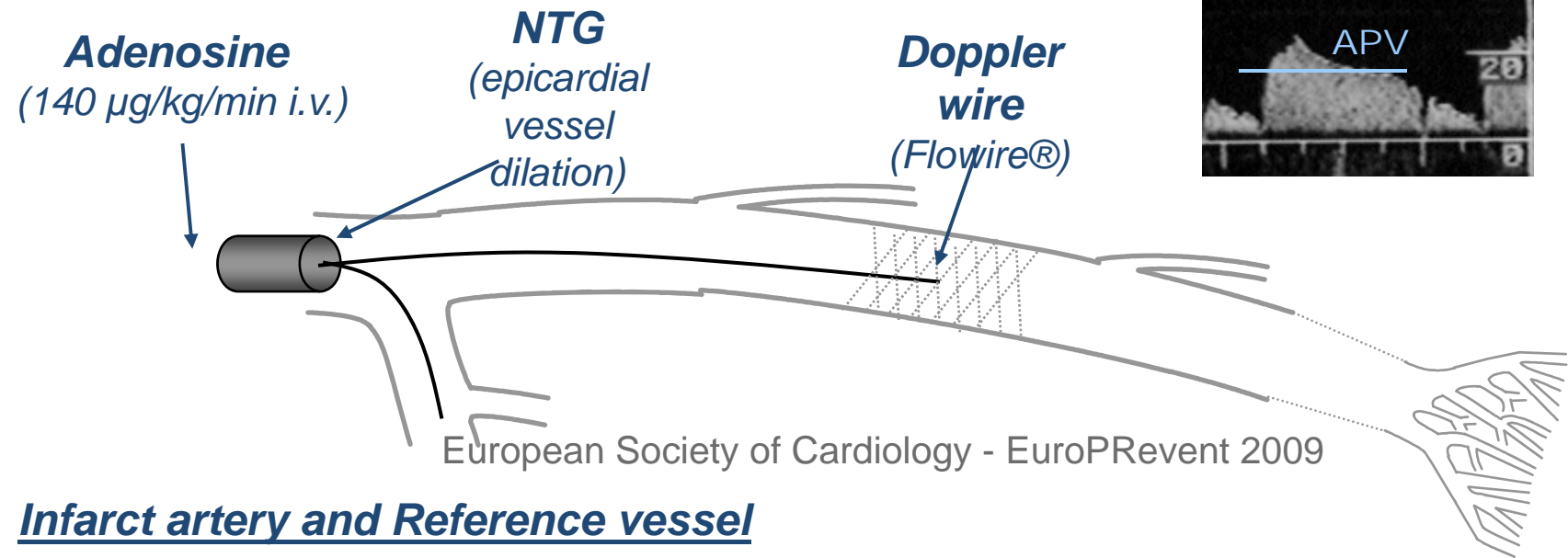
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Baseline LVEF by QLVA:



# Doppler Substudy

- Mechanistic Insights from Coronary Flow Assessment -



## Infarct artery and Reference vessel

- Coronary flow reserve:  $CFR = APV_{\text{adenosine}} / APV_{\text{basal}}$
- Relative flow reserve:  $rCFR = CFR_{\text{target vessel}} / CFR_{\text{reference vessel}}$

## Core Lab:

Sandra Erbs / Rainer Hambrecht (Herzzentrum Leipzig)

## 3 Centers (54 patients):

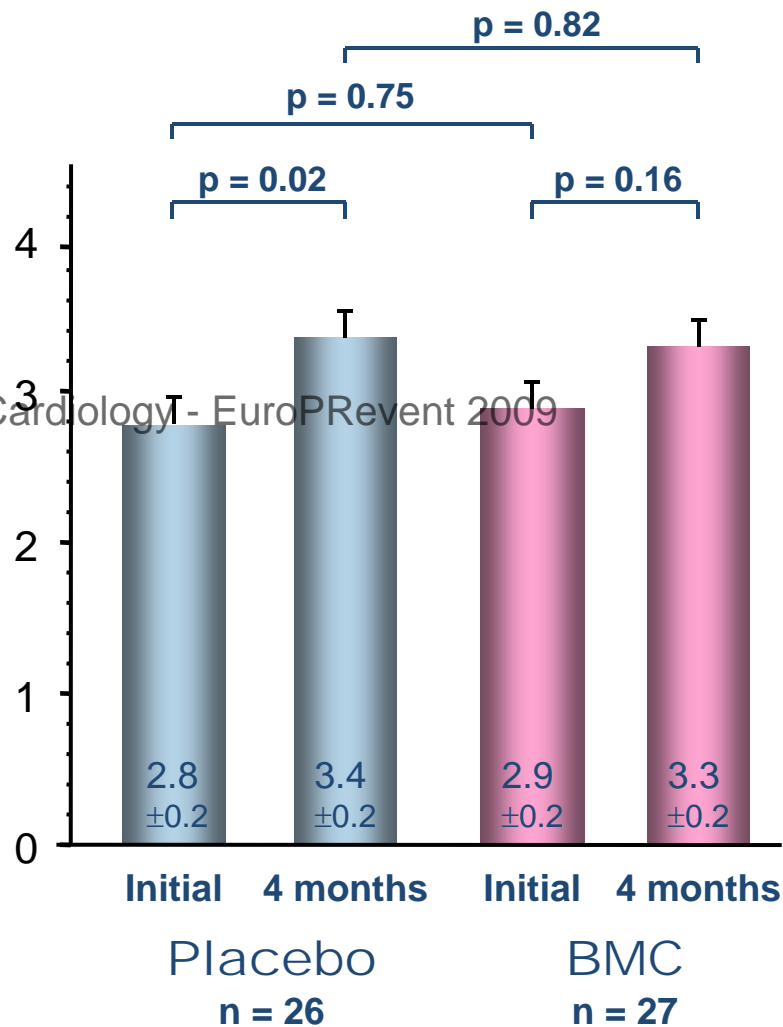
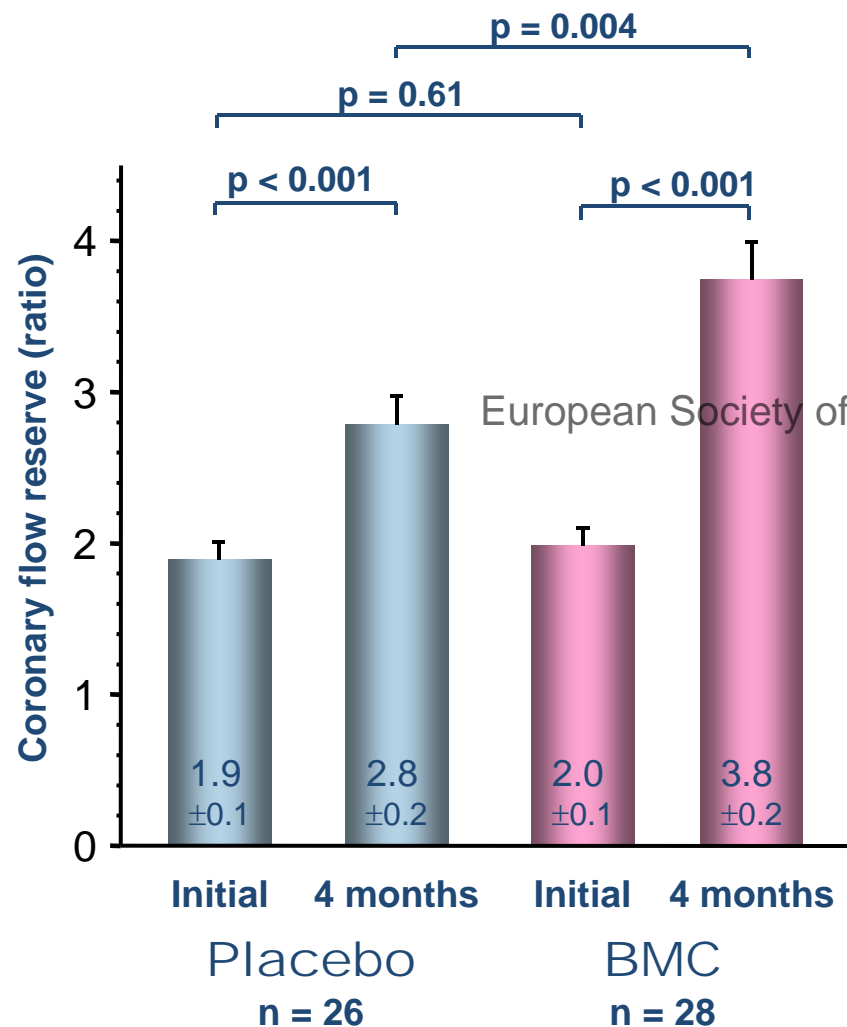
- Herzzentrum Leipzig (32),
- J. W. Goethe University Frankfurt (20),
- Herz- u. Diabeteszentrum Bad Oeynhausen (2)



# Coronary Flow Reserve

## Infarct vessel

## Reference vessel



# What are the effects of intracoronary reinfusion of autologous progenitor cells in patients with chronic CAD?

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# Application of CPCs following successful recanalisation of chronic coronary occlusions (EPACCO)

**Study Design:** Randomised, double-blind and placebo controlled

**Primary End Point:** Coronary flow reserve (CFR)  
European Society of Cardiology - EuroPRevent 2009

**Sec. End Points:** Endothelium-dependent vasodilation,  
Hibernating segments,  
Regional wall motion abnormality,  
Left ventricular function

# Application of CPCs following successful recanalisation of chronic coronary occlusions (EPACCO)

***Inclusion Criteria:*** Successful recanalisation of  
chron. coronary occlusions (> 4 wks.)  
Myocardial ischemia (ergometry)  
Regional wall motion abnormality

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***Exclusion Criteria:*** Unstable angina pectoris  
Indication for CABG  
Malignant disease  
Diabetic retinopathy

# Study Protocol

Recanalisation of chronic coronary occlusions



Echo, MRT, PET



Stimulation with G-CSF for 4d (2 x 300 µg s.c. / d)



Blood sampling (400 ml) and ex.vivo cell culture (4d)



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Intracoronary flow measurement



Treatment Group  
CPC-application



Control Group  
NaCl/serum-application



Clinical control of patients 1x per week

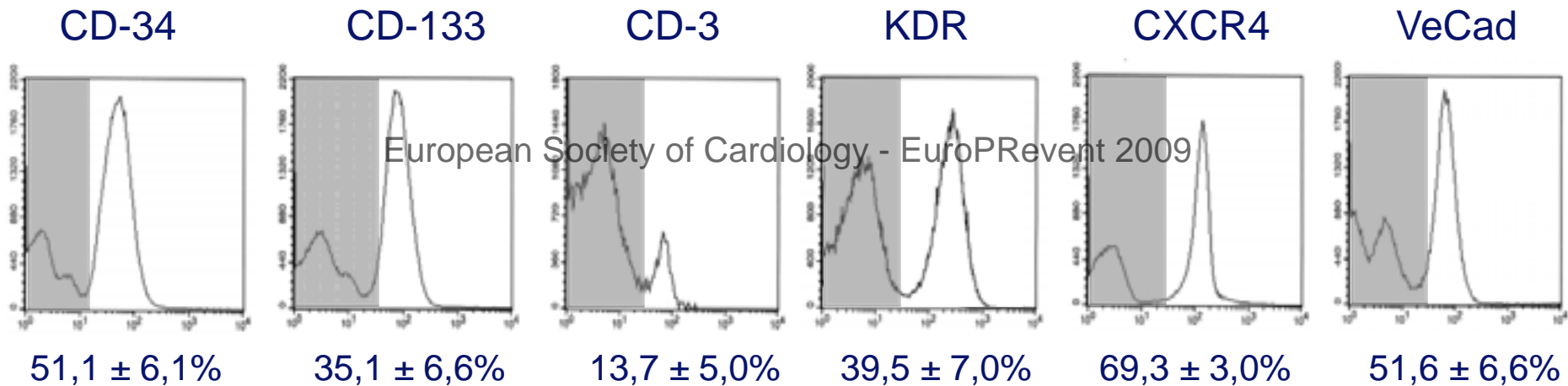


Echocardiography, MRT, PET, and intracoronary flow measurement  
12 weeks after CPC application

# Cell Culture Characterization

**Cell culture:** Ficoll-density gradient centrifugation,  
4 days of cell culture in endothelium-specific medium

**Cell characterisation:** FACS-analysis of cultured CPCs

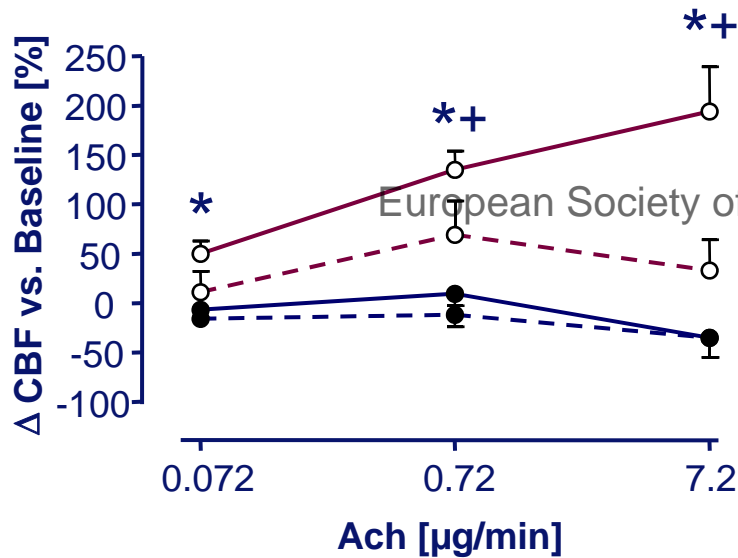


**Cell Viability:** Trypan-blue exclusion 94± 1%.

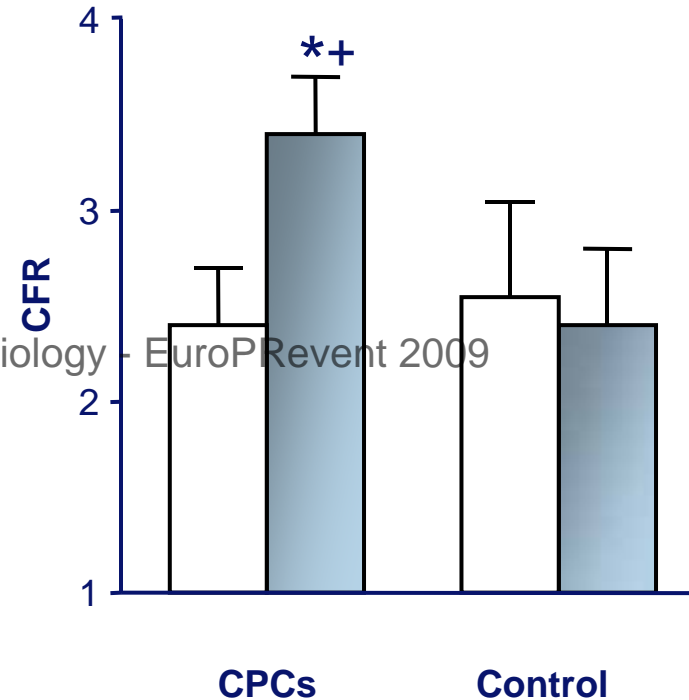
**Cell Application:** Catheter-directed infusion (stop-flow technique)  
of 69±14x10<sup>6</sup> CPCs.

# Effects of CPC Application on Coronary Blood Flow and Coronary Flow Reserve

## Endothelium-dependent Coronary Flow



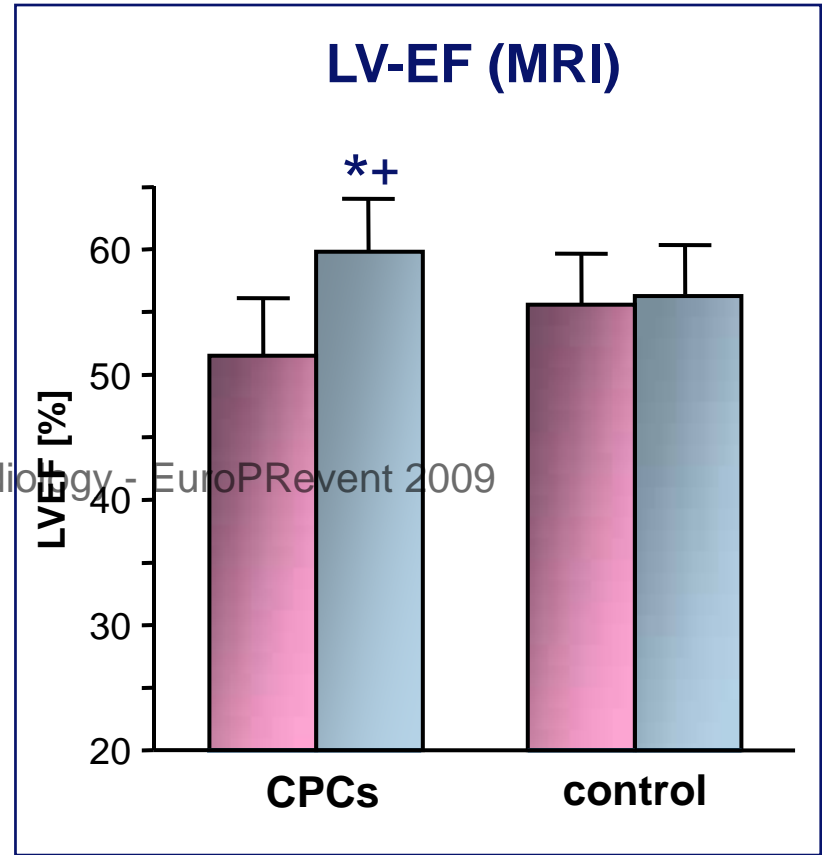
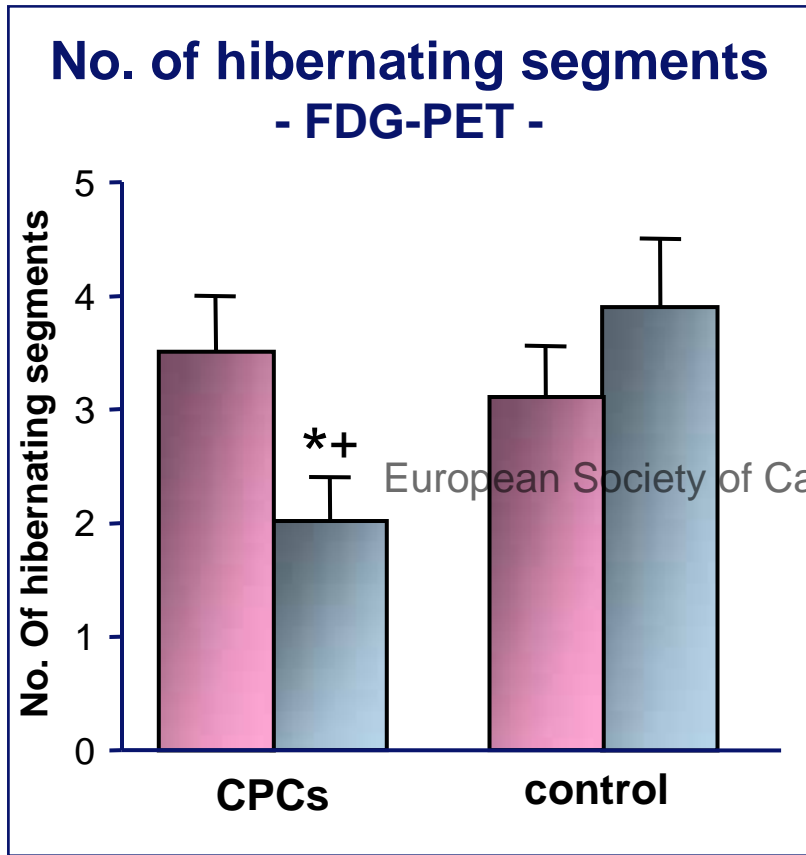
## CFR (Adenosine)



- begin
- 12 weeks
- CPC group
- - - Control group

- \* p < 0.05 vs. begin
- + p < 0.05 vs. Control

# Effects of CPC Application on Myocardial Hibernation (FDG-PET) and LV-EF



begin  
12 weeks

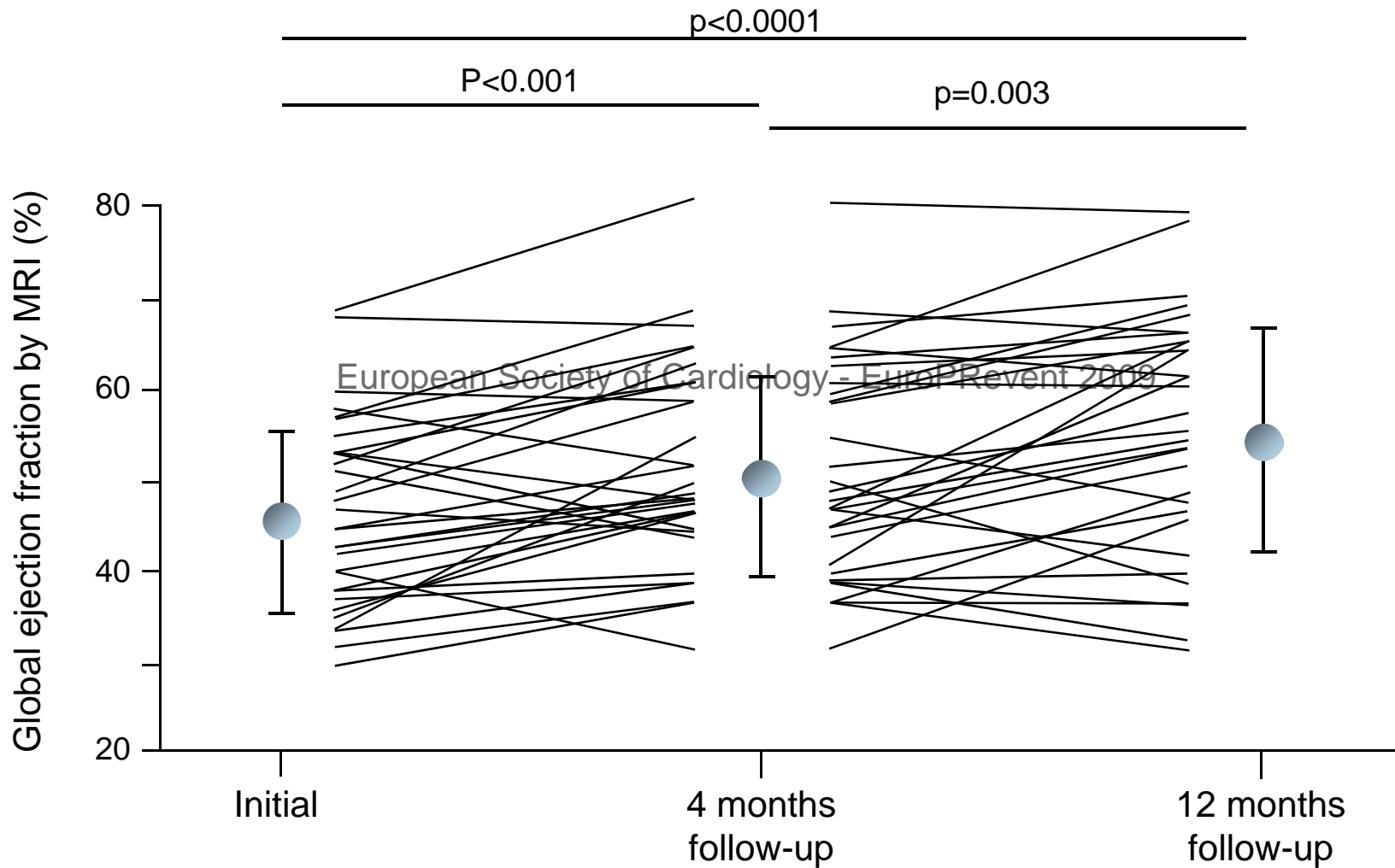
\*  $p < 0.05$  vs. begin  
+  $p < 0.05$  vs. control

# What are the long-term results ?

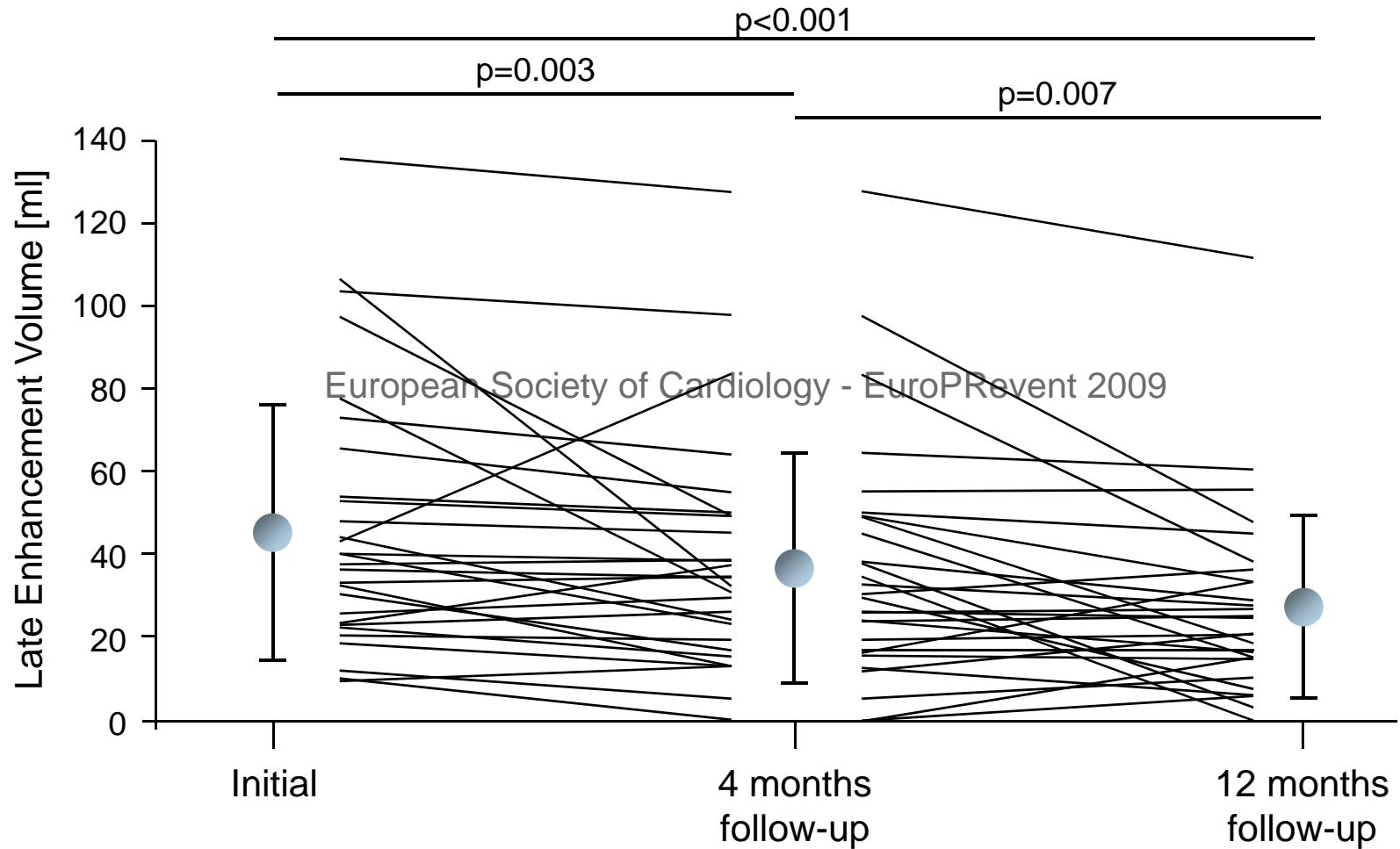
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# Results of the TOPCARE-AMI Trial - Improvement of LVEF -



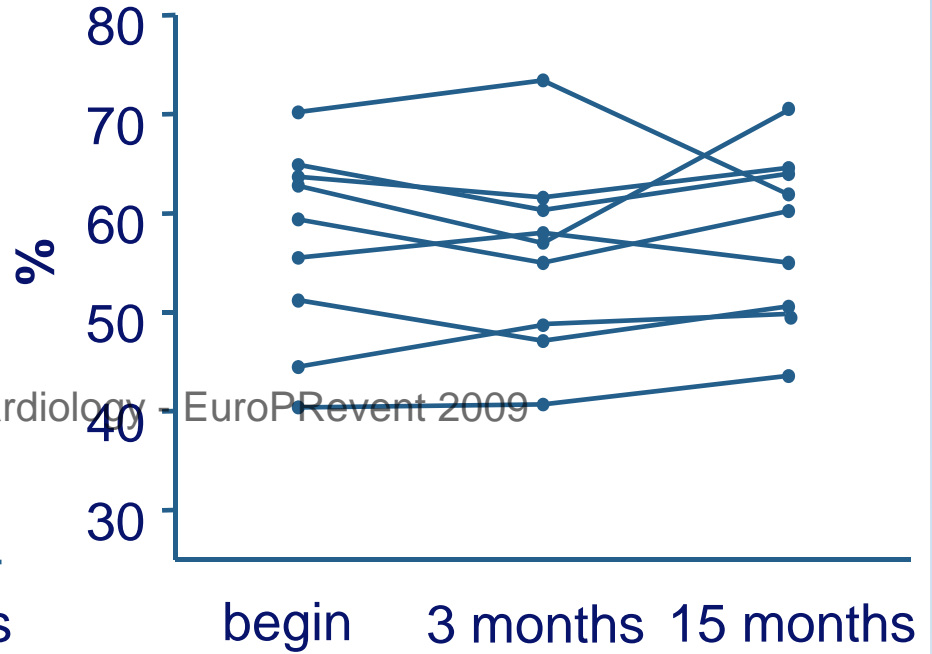
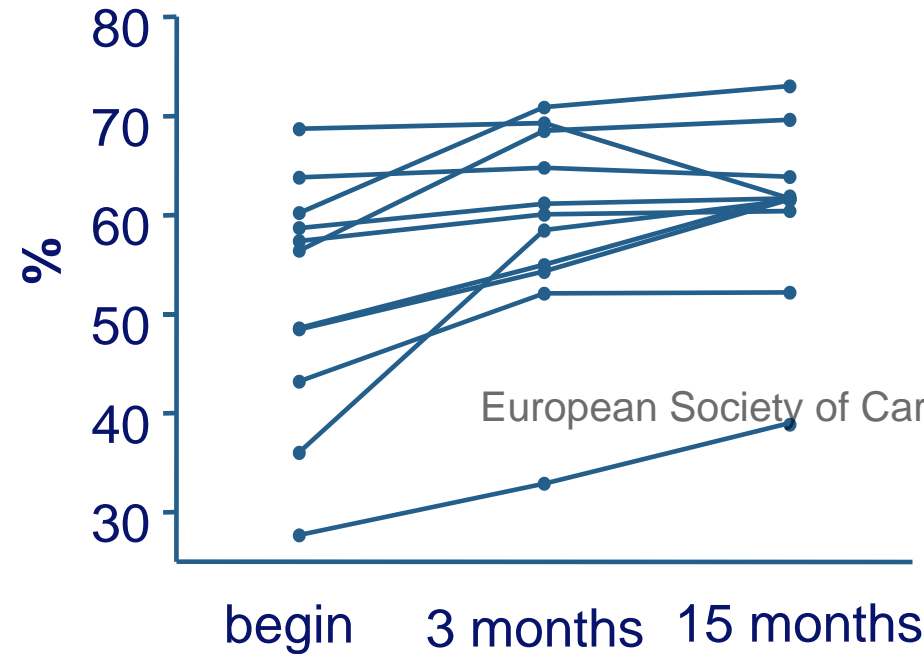
# Results of the TOPCARE-AMI Trial - Reduction of late enhancement volume -



# Long-term Follow-up: Left-ventricular Ejection Fraction (EPACCO)

## CPC

## Control



mean  
±SEM:

52±4%

59±3%

60±3%

56±3%

55±3%

57±3%

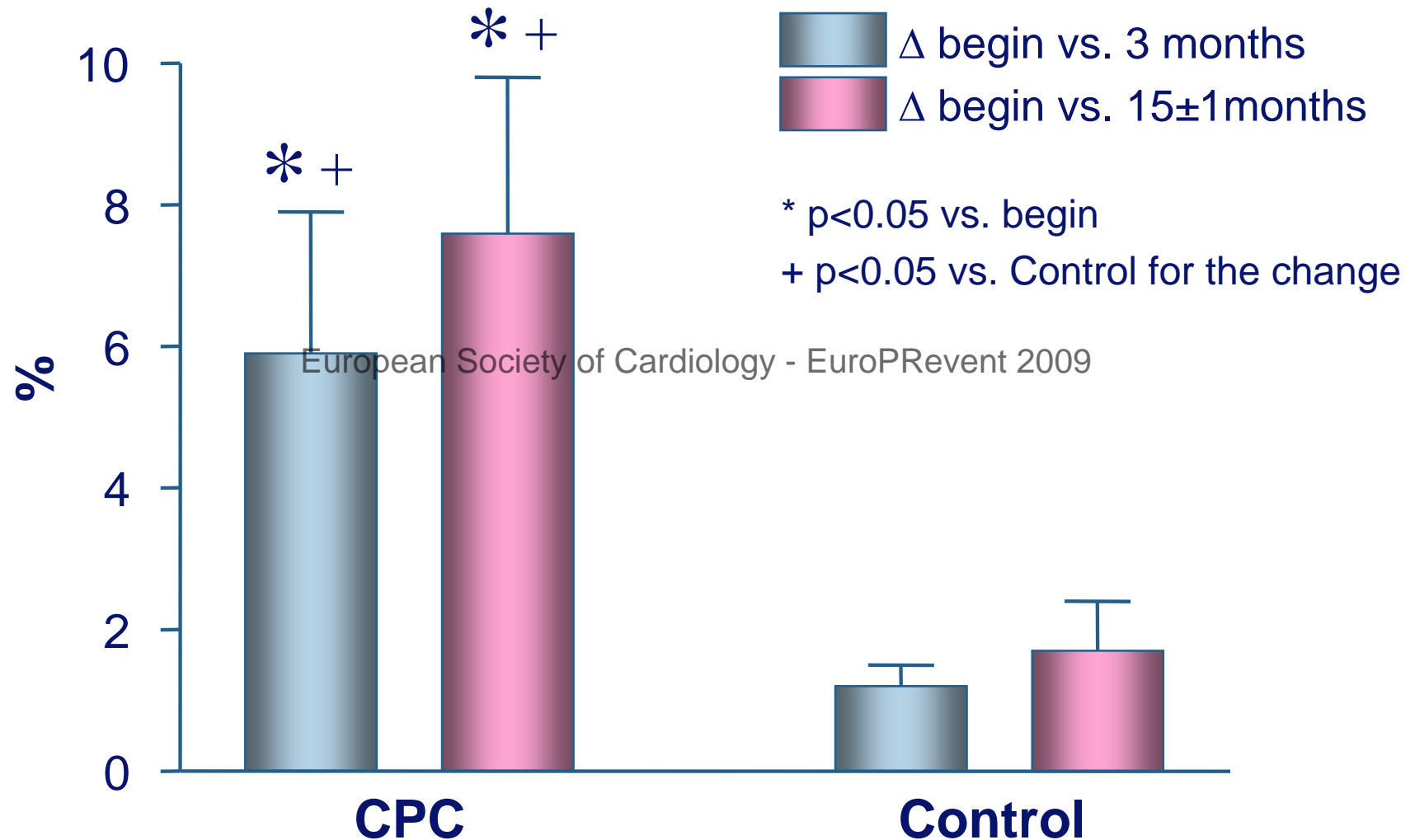
\* +

\* +

\* p<0.05 vs. begin

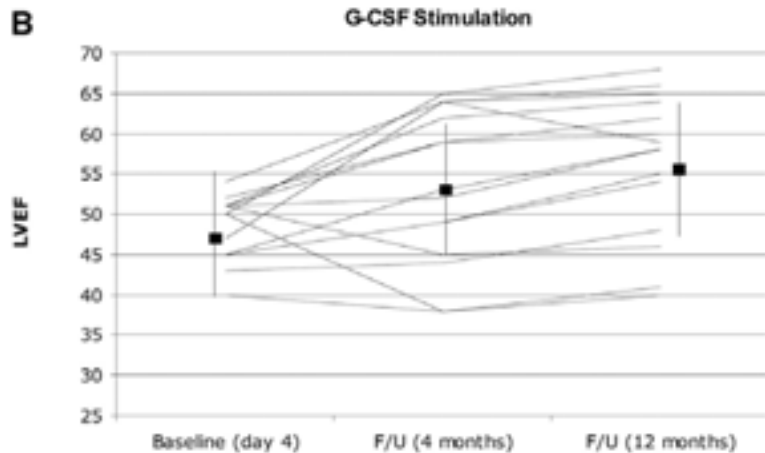
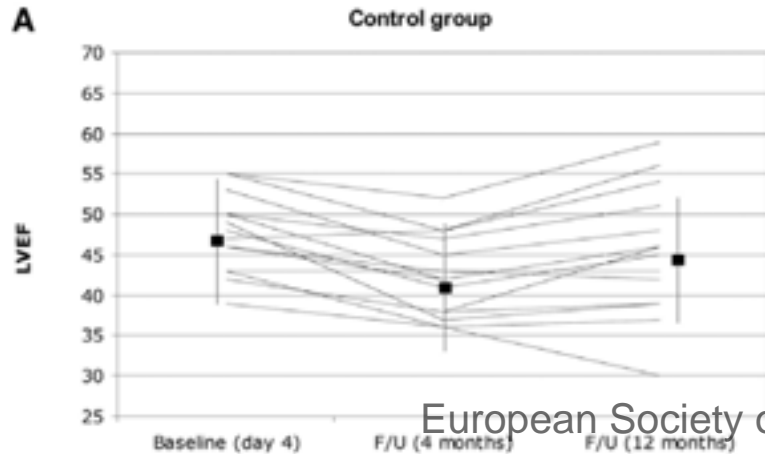
+ p<0.05 vs. control for the change

# Long-term Follow-up: Change in Regional Wall Motion Score



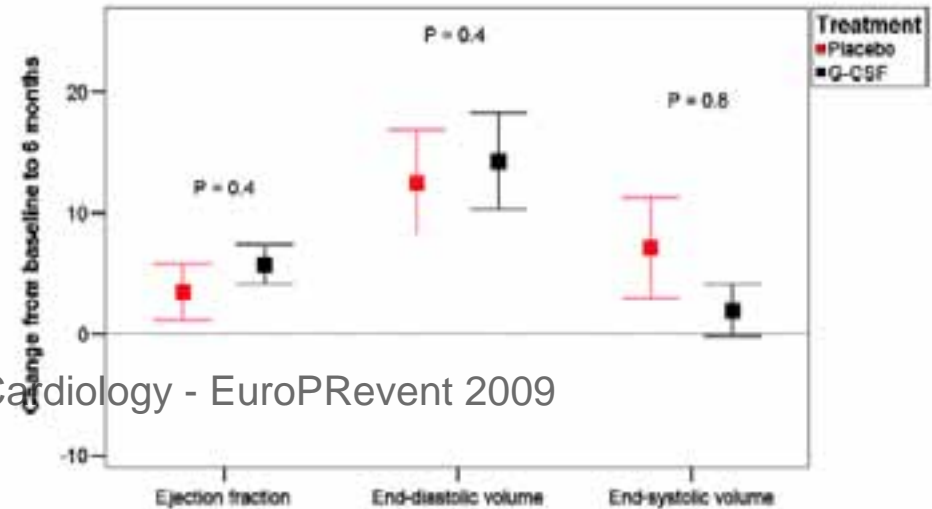
# Potential of Circulating Progenitor Cells Mobilized By G-CSF

## Improvement



**FIRSTLINE-AMI (n=30)**

## No Improvement



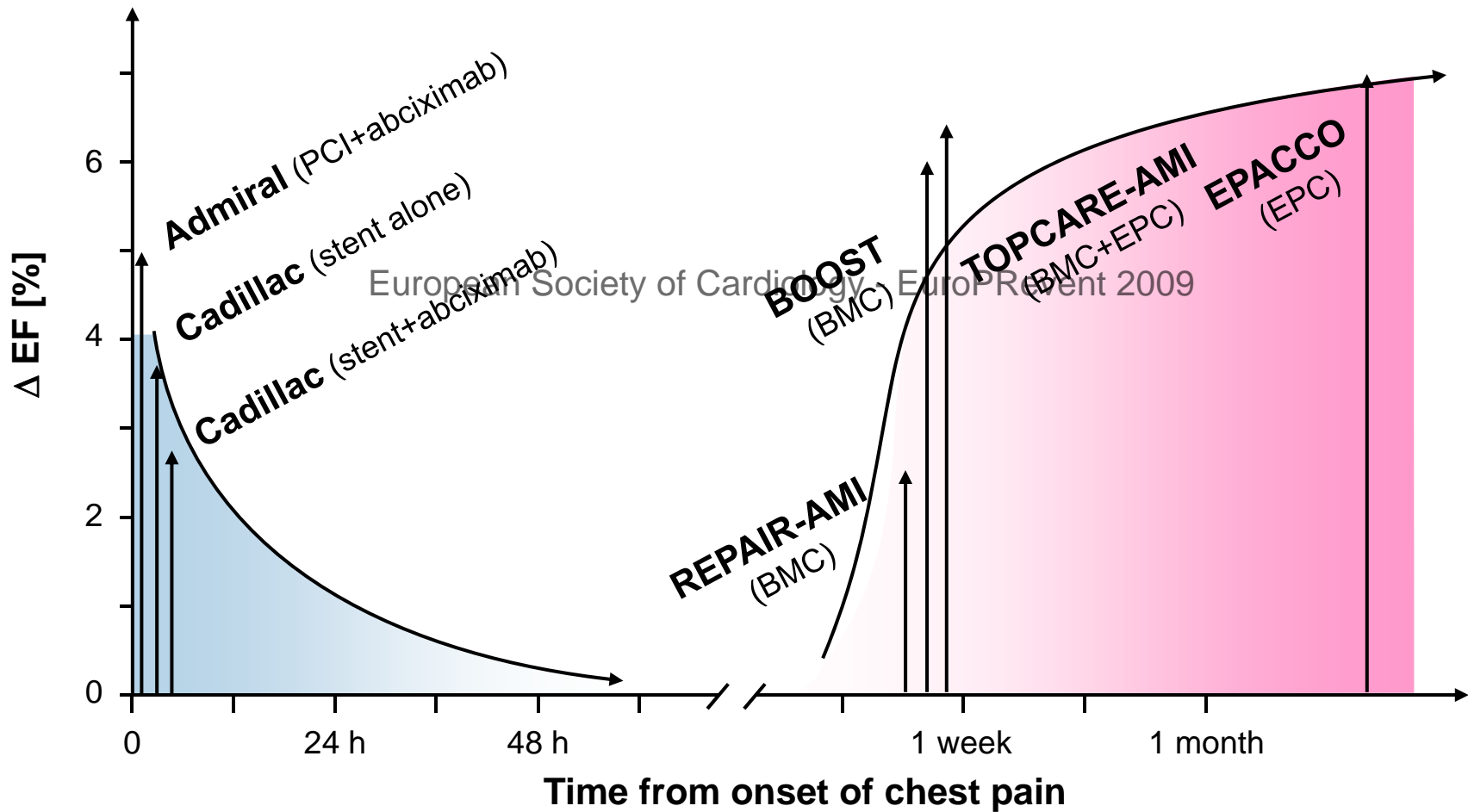
**STEMMI Trial (n=78)**

**REVIVAL-2 (n=114)**

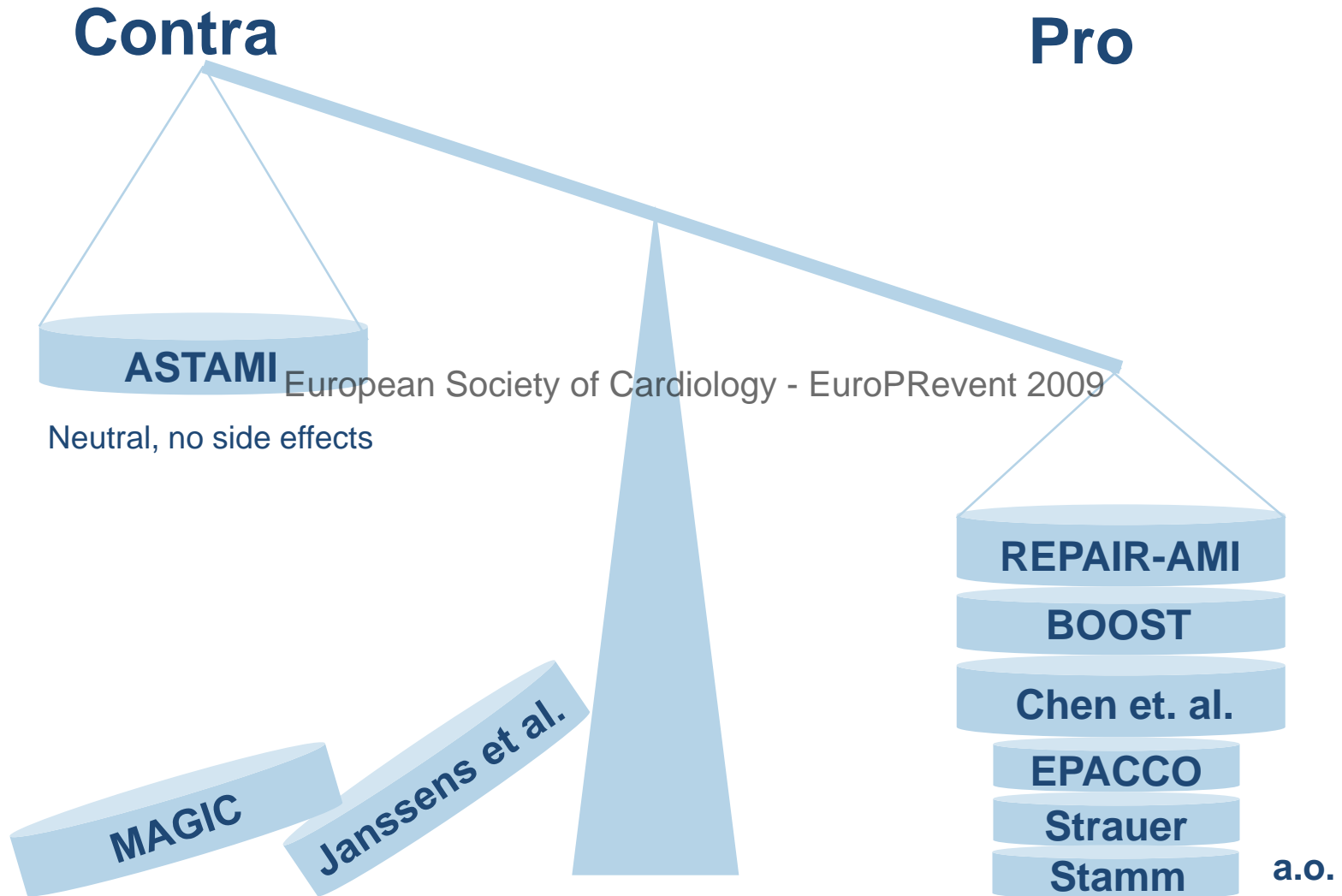
# Change in LV-EF Induced by Primary PCI and Progenitor Cells

Golden time for reperfusion

Golden time for regenerative therapy



# Pro / Contra: Autologous Transplantation of Progenitor Cells



A black and white photograph of the interior of Grand Central Terminal in New York City. The image captures the iconic vaulted ceiling and the four massive, arched skylights that allow natural light to stream into the space. The light rays are captured in a long-exposure style, appearing as bright, diagonal beams that create a sense of depth and grandeur. In the foreground and middle ground, numerous people are seen walking through the terminal, their figures slightly blurred, suggesting movement and the busy atmosphere of the location. The overall composition is dramatic, emphasizing the architectural scale and the play of light and shadow.

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