



# STEM-AMI Outcome

## STem cEll Mobilization in Acute Myocardial Infarction Outcome)

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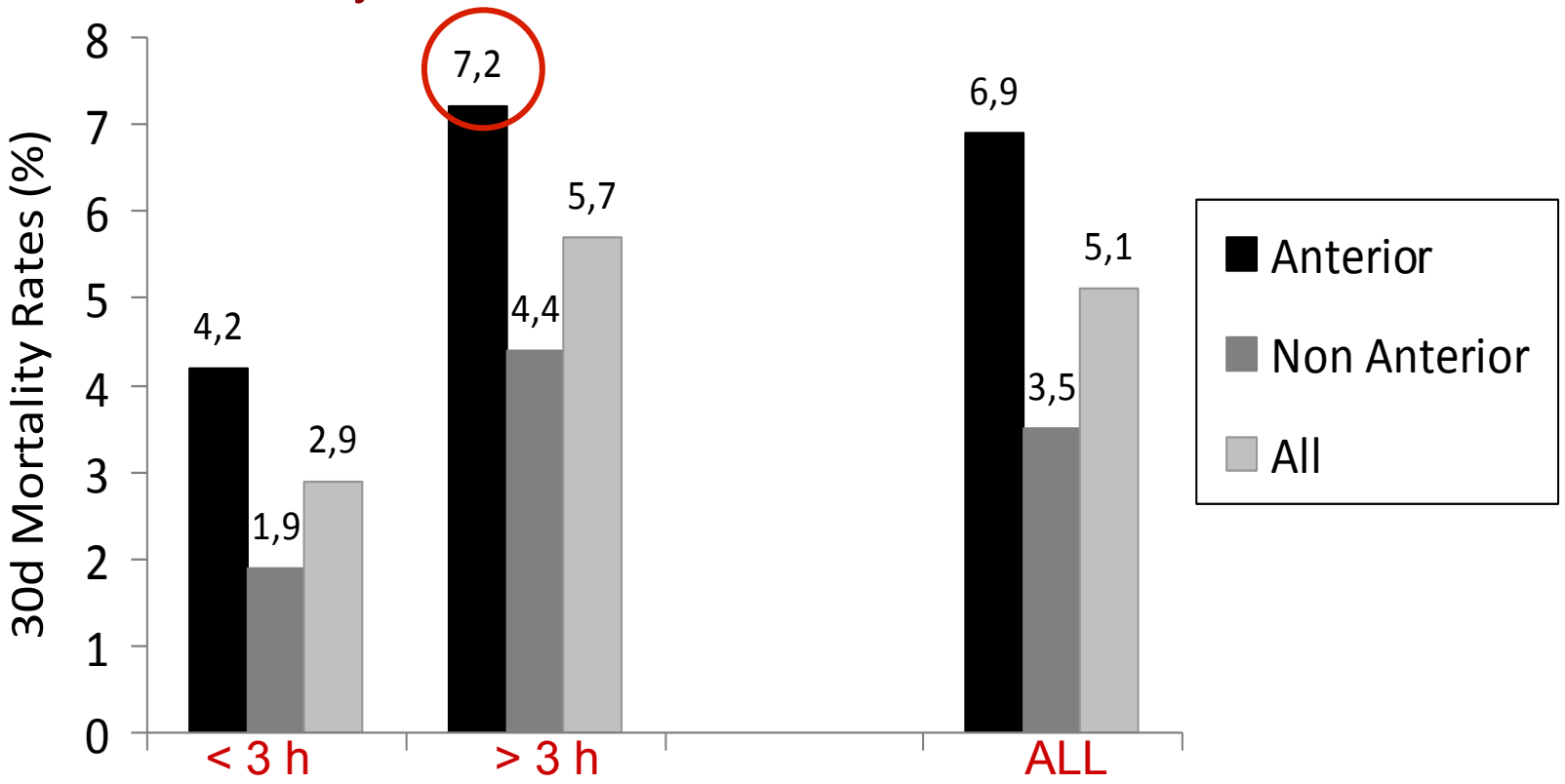
Azienda Ospedaliera San Gerardo

# STEM-AMI OUTCOME

## Clinical Background

Data from BLITZ 4

Mortality rates vs "ischemic time" and AMI location

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Int. J. Card. 2013

# STEM-AMI OUTCOME:Clinical Background

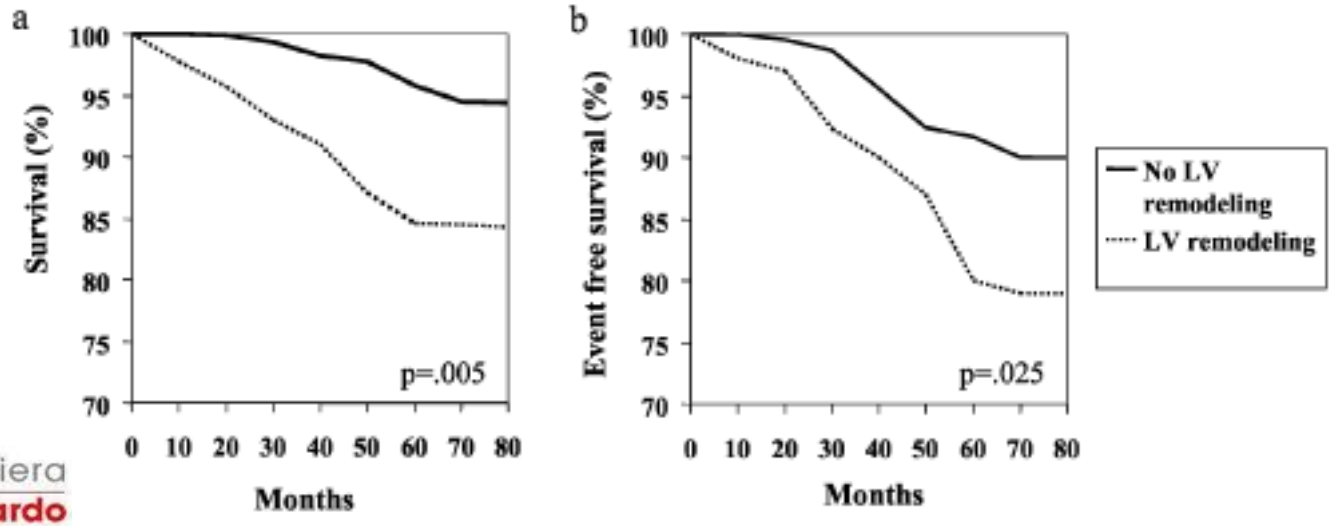
# LV Remodeling / Prognostic Implications

## Left Ventricular Remodeling After Primary Coronary Angioplasty

### Patterns of Left Ventricular Dilation and Long-Term Prognostic Implications

Leonardo Bolognese, MD, FESC; Aleksandar N. Neskovic, MD, PhD, FESC; Guido Parodi, MD; Giampaolo Cerisano, MD; Piergiovanni Buonamici, MD; Giovanni M. Santoro, MD, FESC; David Antoniucci, MD

*Conclusions*—LV remodeling after successful PTCA occurs despite sustained patency of the infarct-related artery and preservation of regional and global LV function. LV dilation at 6 months after AMI but not the specific pattern of LV dilation is clearly associated with worse long-term clinical outcome. (*Circulation*. 2002;106:2351-2357.)

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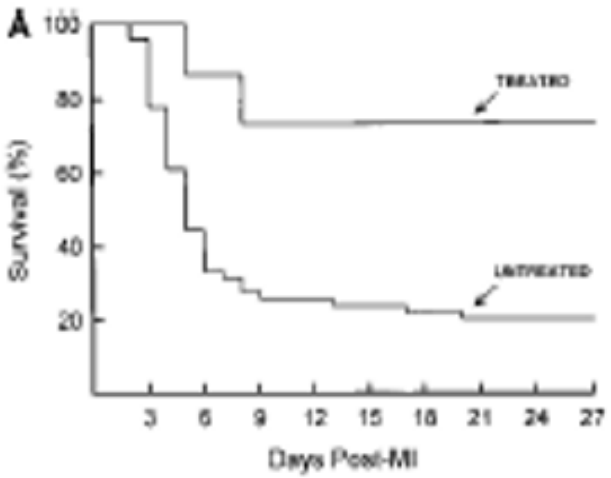
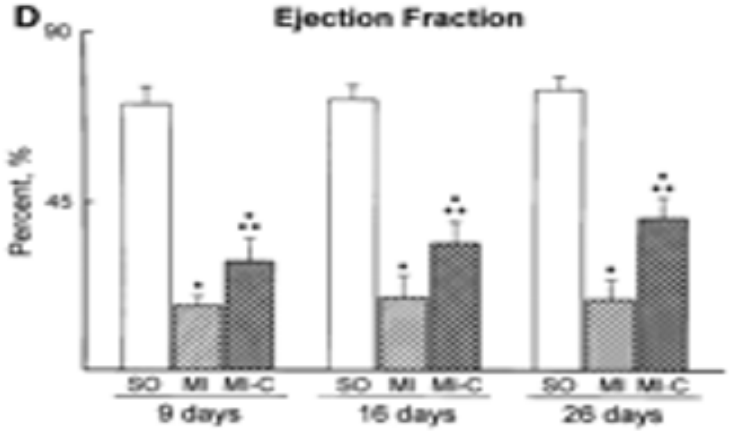
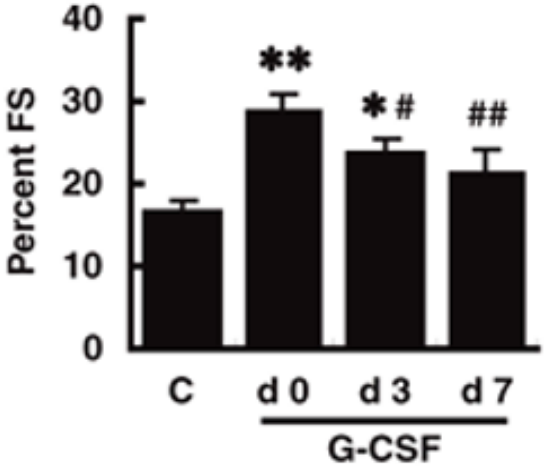
# Experimental Background - 1



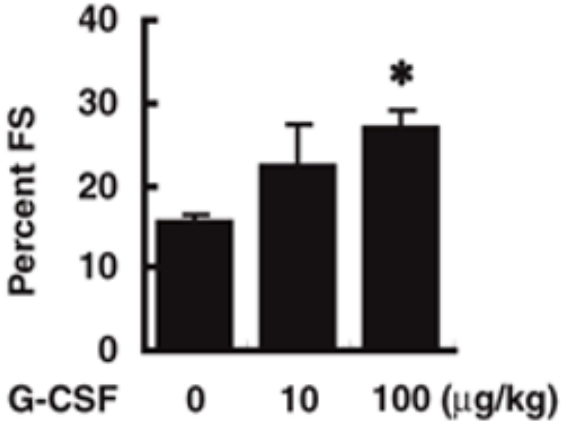

Mortality - 68%




EF+ 114%




TIME Dipendent




Dose Dipendent

# REMODELLING AND BONE MARROW STEM CELLS

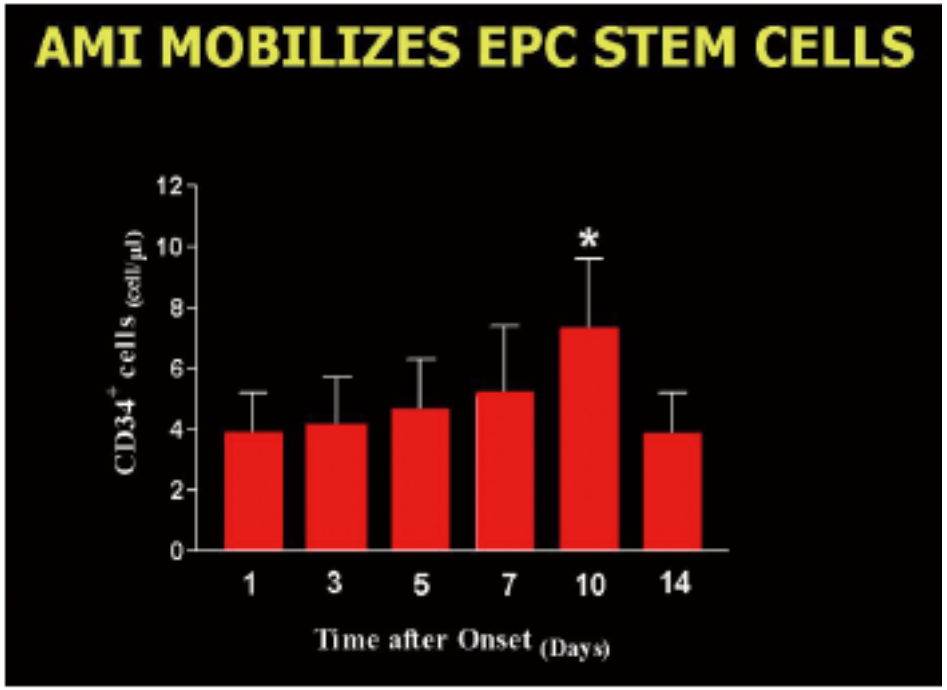
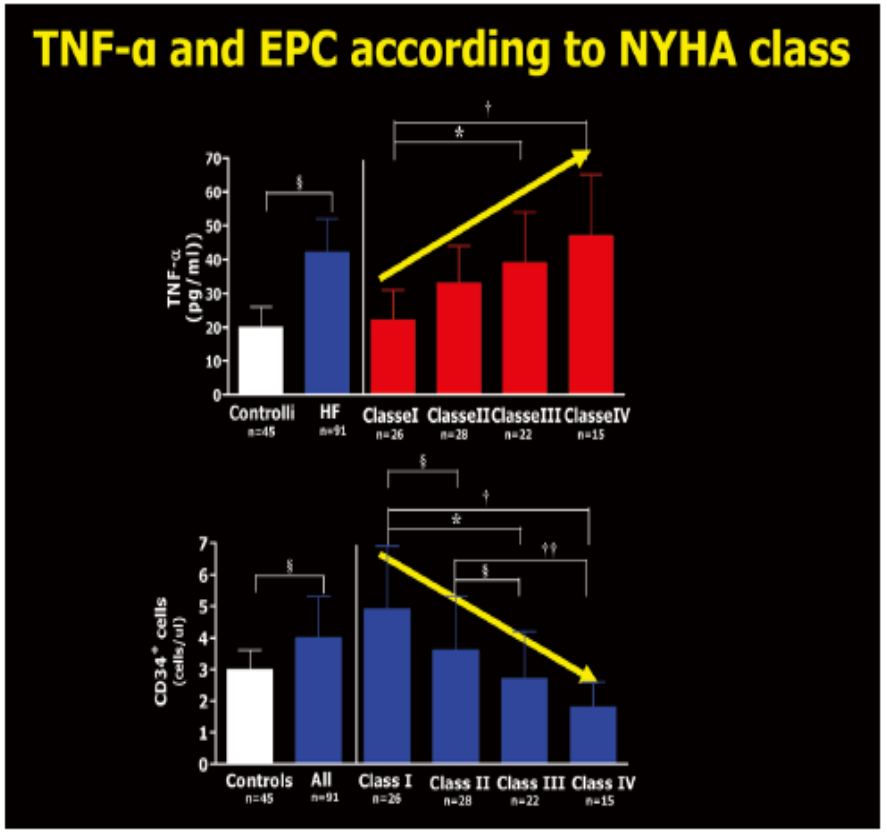
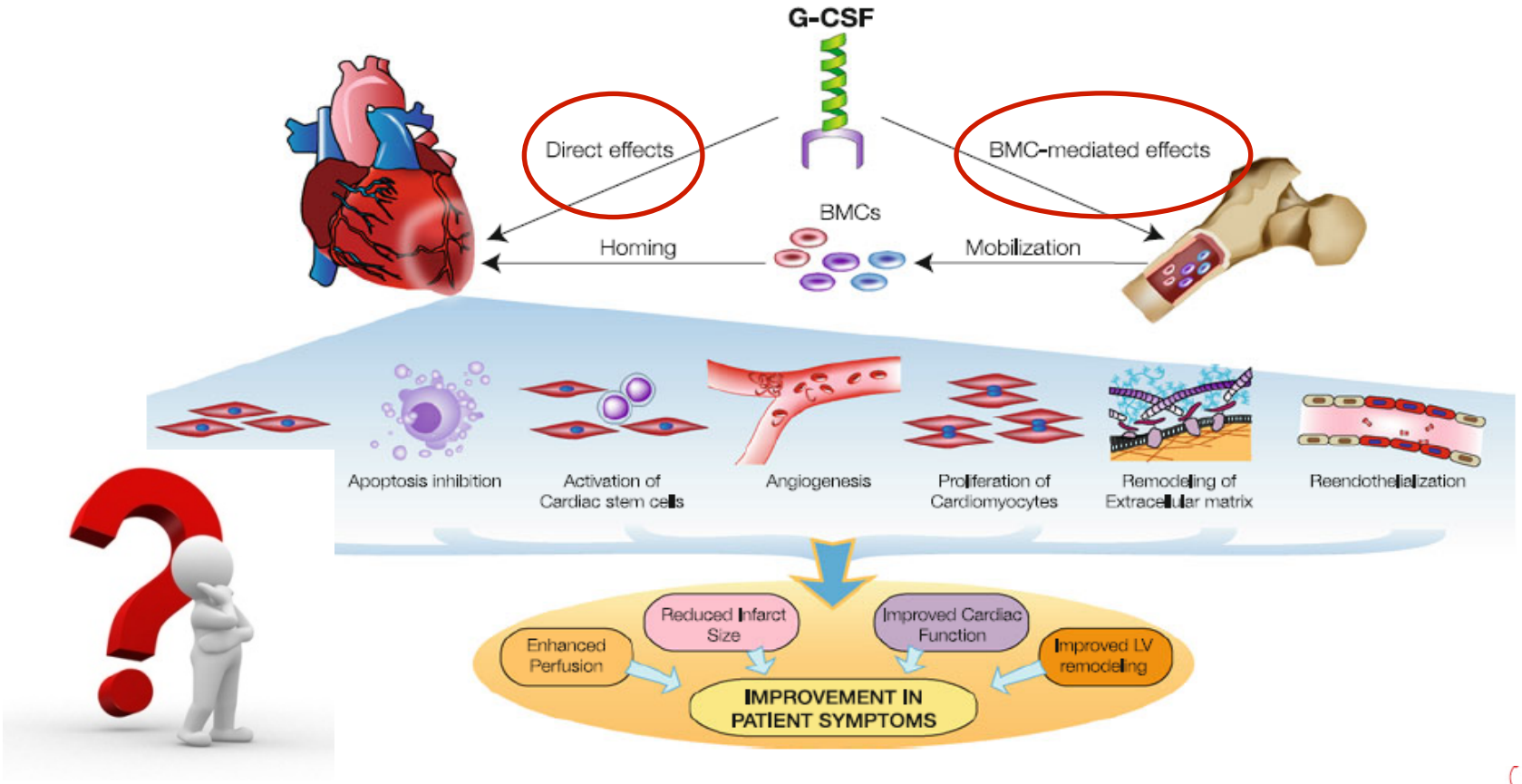



**Figure 1.** Acute myocardial infarction (AMI) increases the production and release of bone marrow stem cells and in particular, endothelial progenitor cells (EPC). Peak production is within 7–10 days after AMI.




Ferrari R. Tavazzi L. Circulation 2009
Valgimigli et Al. Circulation 2004

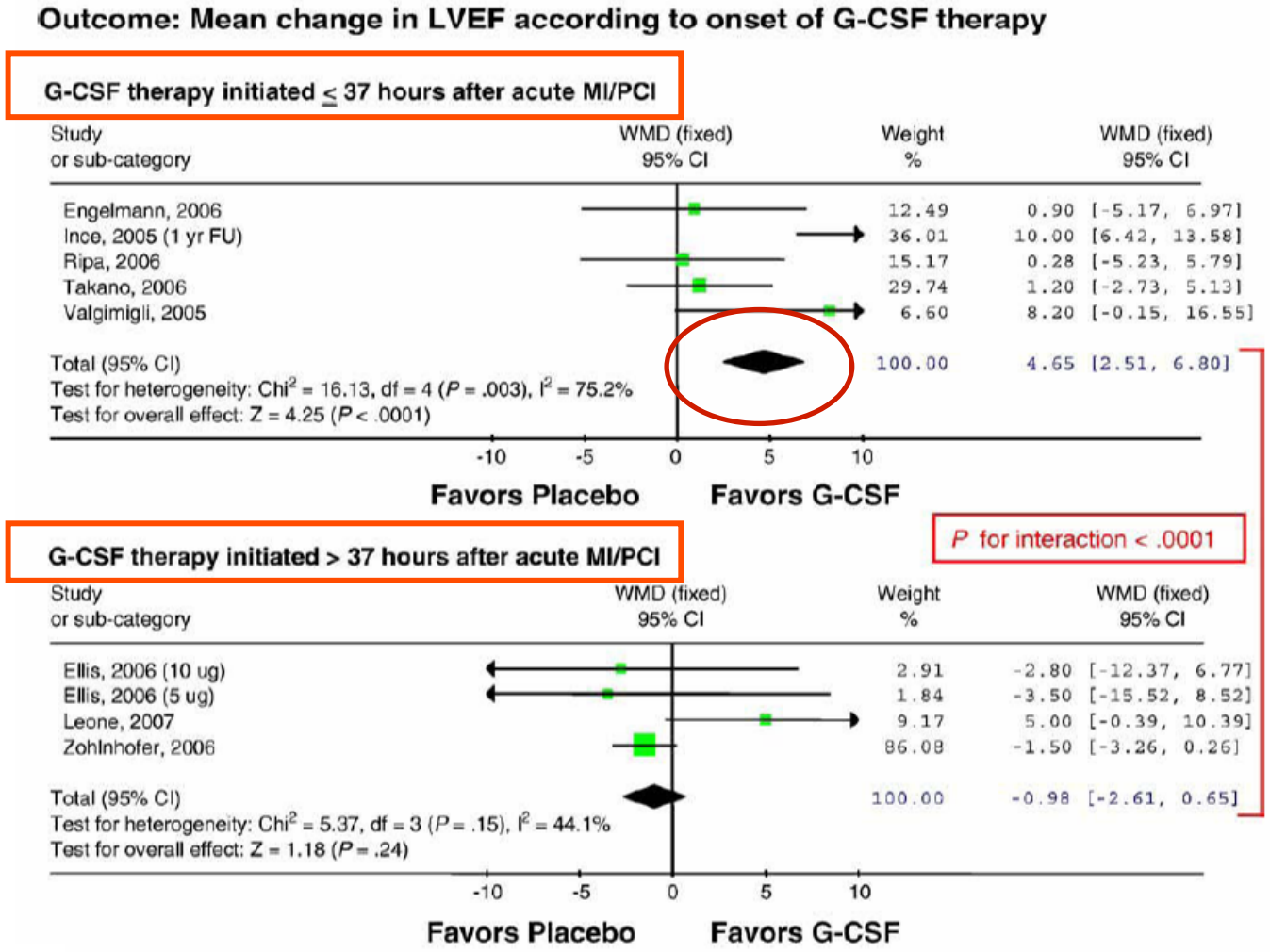
# What is GCS-F? – What has it to do with MI?




Sanganalmat SK, et al., Basic Res Cardiol 2011

# G-CSF THERAPY IN STEMI

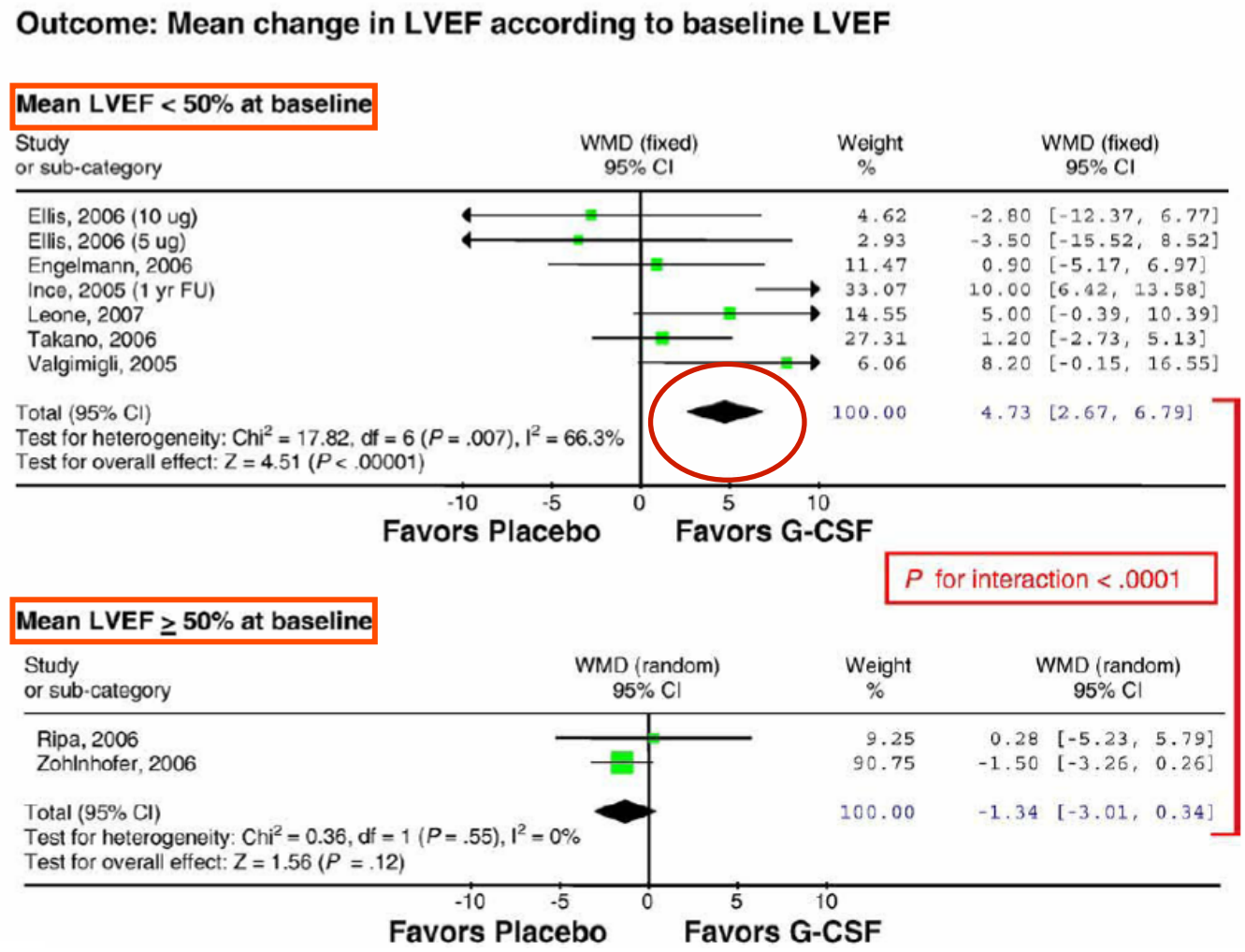
## Efficacy




Abdel-Latif et al. META-ANALYSIS - AM HEART J 2008

# G-CSF THERAPY IN STEMI

## Efficacy




Abdel-Latif et al. META-ANALYSIS - AM HEART J 2008

# Stem cEIls Mobilization in Acute Myocardial Infarction STEMAMI TRIAL

European Journal of Heart Failure

European Journal of Heart Failure (2010) **12**, 1111–1121
doi:10.1093/eurjhf/hfq150

## Granulocyte colony-stimulating factor attenuates left ventricular remodelling after acute anterior STEMI: results of the single-blind, randomized, placebo-controlled multicentre STem cEll Mobilization in Acute Myocardial Infarction (STEM-AMI) Trial

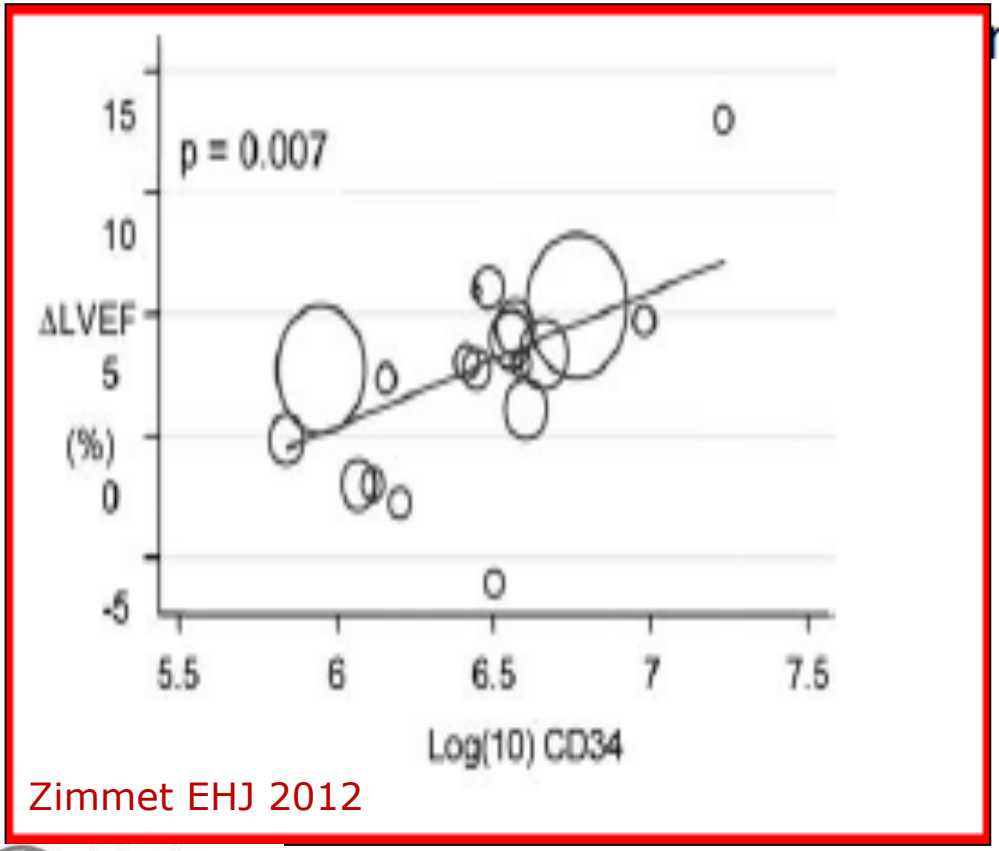
Felice Achilli[1]*, Cristina Malafronte[1], Laura Lenatti[1], Francesco Gentile[2], Viola Dadone[2], Giuseppe Gibelli[3], Stefano Maggiolini[4], Lidia Squadroni[5], Claudio Di Leo[6], Ilaria Burba[7], Maurizio Pesce[7], Luca Mircoli[1], Maurizio C. Capogrossi[8], Alessandro Di Lelio[9], Paola Camisasca[10], Alberto Morabito[11], Gualtiero Colombo[12], and Giulio Pompilio[13] for the STEM-AMI Investigators†

- Randomised, blinded, placebo controlled
- 60 Pts (30T/30C)
- PRIOR ANTERIOR AMI treated with Primary PTCA
- >2 hours by symptoms onset
- EF ≤ 45%
- GCSF s.c. 10γ/die for 5 days (1-5 day) vs placebo

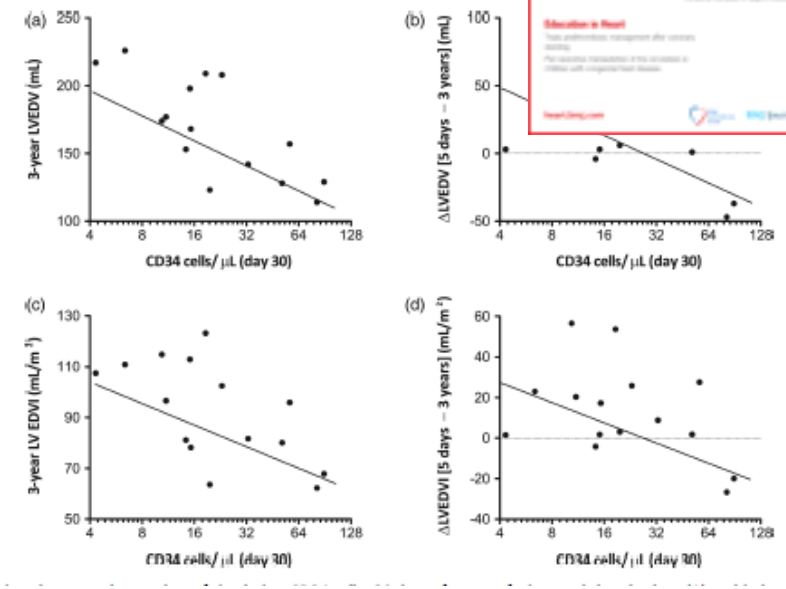
# Stem cEIls Mobilization in Acute Myocardial Infarction: STEMAMI TRIAL

ORIGINAL ARTICLE

## G-CSF treatment for STEMI: final 3-year follow-up rolled STEM-AMI




Zimmet EHJ 2012


Achilli F. et Al. Heart 2014

European Journal of Heart Failure (2010) **12**, 1021–1023
doi:10.1093/eurjhf/hfq153

**EDITORIAL**

Basic Res Cardiol (2011) 106:709–733
DOI 10.1007/s00395-011-0183-y

REVIEW

# Hematopoietic cytokines for cardiac repair: mobilization of bone marrow cells and beyond

Santosh K. Sanganalmath · Ahmed Abdel-Latif · Roberto Bolli · Yu-Ting Xuan · Buddhadeb Dawn

## THE FINAL VERDICT ON G-CSF THERAPY

will emerge not from meta-analyses, but from adequately powered randomized controlled trials with optimized study parameters, i.e., dose, duration, timing, patient population, and outcome parameters".

# STEMAMI OUTCOME :

## The first Phase III growth factor study in STEMI

### STUDY OBJECTIVES

To demonstrate that G-CSF in addition to state of the art treatment **is safe** and significantly **improves clinical outcome** in patients with reduced left ventricular EF (≤45%) after successful reperfusion for large anterior acute myocardial infarction

# STEM-AMI OUTCOME

## DESIGN

Phase III, randomized, open label.

**1530** Patients will be randomized to **standard therapy + G-CSF** or **standard therapy alone** in 1:1 ratio.

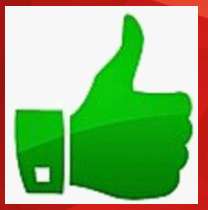
**Accrual time 3 years. Follow-up time 2 years.**

## TREATMENT

**FILGRASTIM 5 µ/kg** will be administered **subcutaneously bis in die** for 6 days (**from Day 0 to Day 5**), starting **within 24 h** after PCI and reperfusion.

# STEM-AMI OUTCOME

## Inclusion Criteria



- Patients affected by **acute anterior STEMI** undergoing **primary PCI** (or **PCI-rescue** with persistent occlusion of coronary artery)
- Time symptom-to-balloon **≥3 h and ≤12h** (or ≤24 h if symptoms persist)
- **TIMI flow** post PCI **≥2**
- Evidence of LV dysfunction **(EF biplane ≤ 45%)** ≤ 24 h after revascularization
- Men and women aged ≥18 years and ≤ 75 years,
- Informed consent must be signed before proceeding with any study procedure.

# STEM-AMI OUTCOME

## Endpoints

### PRIMARY EFFICACY END POINT

Clinical outcome will be assessed by the composite endpoint of:

- **Death** or
- **Recurrence of MI** or
- **Hospitalization** due to **Heart Failure**

### SAFETY ENDPOINTS

- Incidence and severity of **Bleeding** complications
- Incidence of **Malignancy**
- Incidence and intensity of **AEs and SAEs**

# STEM-AMI OUTCOME

## RMN Sub-study

**Enrollment**

- 120 pts with anterior STEMI undergoing primary PCI with EF ≤ 45% with symptoms-to reperfusion time ≥ 3hours ≤24 hours. Subjects already randomized for the main study in centers equipped with CMR laboratories as described above

**Therapy**

- Granulocyte colony-stimulating factor (Lenograstim) 5 μg/kg or placebo will be administered subcutaneously bis in die (b.i.d.) for 6 days (from Day 0 to Day 5), starting within 24 h after PCI and reperfusion. Placebo group will receive saline (white blood cells count > 50.000/mm3 is the cut-off for the discontinuation of treatment).

**CMR at day 7 and 180**

- **Assessment of myocardial volumes, mass and function.**
- **Quantitative evaluation of the myocardium at risk (edema imaging).**
- **Quantitative evaluation of infarct size with late Gadolinium enhanced MRI.**

# STEM-AMI OUTCOME

## Up to Date


42 Italian Cardiology Units
First Patient: 8/11/2013
Effective time of enrollment 20m

**532 Patients enrolled to 08/02/2016**

**MRI SubStudy: completed**

# STEM-AMI OUTCOME TRIAL

## Baseline characteristics: 532 Patients

| | CONTROL | TREATMENT | TOT | P |
|---|---|---|---|---|
| **Population** | 265 (49,8) | 267 (50,2) | 532 (100) | - |
| **Age** | 62,1 | 61,5 | 61,8 | O,49 |
| **Male** | 222 (83,8) | 227 (85) | 449 (84,4) | - |

# STEM-AMI OUTCOME TRIAL

## CLINICAL HISTORY

| | CONTROL 265 | TREATMENT 267 | TOT 532 |
|---|---|---|---|
| **AOCP** | 8(3) | 16(5,9) | 24(4,5) |
| **CKD** | 6(2,3) | 9(3,4) | 15(2,8) |
| **COPD** | 5(1,9) | 15(5,6) | 20(3,8) |
| **Previous Angina** | 15(5,7) | 19(7,1) | 34(6,4) |
| **Previous MI** | 13(4,9) | 9(3,4) | 22(4,1) |
| **Previous CABG** | 2(0,7) | 1(0,4) | 3(0,6) |

# STEM-AMI OUTCOME TRIAL

## STEMI: BLOOD TESTS ADMISSION

| | CONTROL 265 | TREATMENT 267 | TOT 532 | P |
|---|---|---|---|---|
| **ProBNP** | 1637 | 1560 | - | 0,81 |
| **CKMB max** | 192 | 204 | - | 0,58 |
| **WBC peak** | | 52,07 x 103 | | |

# STEM-AMI OUTCOME TRIAL

## STEMI: ECHO ADMISSION

| | CONTROL 265 | TREATMENT 267 | TOT 532 | P |
|---|---|---|---|---|
| **EF** | 38,9 % | 38,4 % | 38,7% | 0,30 |
| **EDV** | 99 | 104 | 101 | - |
| **ESV** | 59 | 63 | 61 | - |

# STEM-AMI OUTCOME

## STEMI: Cath Lab

| | CONTROL 265 | TREATMENT 267 | TOT 532 |
|---|---|---|---|
| **Symtomps to Ballon** | 316’ | 323’ | 320’ |
| **Multivessel** | 122(46) | 127(47,6) | 249(46,8) |
| **TIMI 0 pre PCI** | 192(72,4) | 206(77,1) | 398(74,8) |
| **TIMI 3 post PCI** | 245(92,45) | 245(91,8) | 490(92,2) |
| **PCI to G-CSF** | - | 909’ (15h) | - |

# STEM-AMI OUTCOME TRIAL

## DRUGS AT DISCHARGE

| | CONTROL 265 | TREATMENT 267 | TOT 532 |
|---|---|---|---|
| **Diur** | 99(37,4) | 115(43,1) | 214(40,2) |
| **BB** | 237(89,4) | 240(89,9) | 477(89,7) |
| **ACE-I / All Ant** | 218(82,2) | 216(80,9) | 434(81,5) |
| **Statins** | 253(95,5) | 255(95,5) | 508(95,5) |
| **ASA** | 254(95,8) | 257(96,2) | 511(96,1) |
| **Clopidogrel** | 35(13,2) | 43(16,1) | 78(14,7) |
| **Prasugrel** | 103(38,9) | 106(39,7) | 209(39,3) |
| **Ticagrelor** | 122(46) | 112(41,9) | 234(44) |
| **Warfarin** | 15(5,7) | 14(5,4) | 29(5,45) |

# STEM-AMI OUTCOME

## Discharge

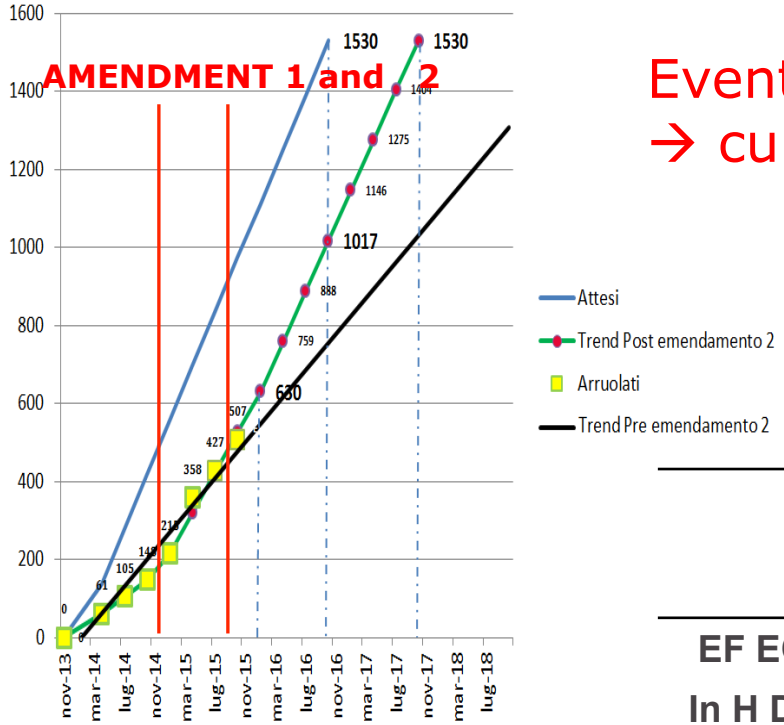
| | CONTROL 265 | TREATMENT 267 | TOT 532 | P |
|---|---|---|---|---|
| **EF ECHO** | 44,1±7.8% | 44,3±7.9% | 44,2% | 0.83 |
| **In H Death** | 3 (1,1) | 3 (1,1) | 6 (1,1) | |
| **6 Months MACE** | 8 (3%) | 6 (2.2%) | 14 (2.6% | |
| **LOS** | 7,1 | 10,5 | 8,8 | 0,001* |

# STEMAMI OUTCOME

## February 2016: discussion with sponsors for trial continuation

Enrollment rate lower than expected
→ STEMI epidemiology has changed

Event rate lower than expected
→ current STEMI standard of care very high




| | CONTROL 265 | TREATMENT 267 | TOT 532 | P |
|---|---|---|---|---|
| EF ECHO | 44,1±7.8% | 44,3±7.9% | 44,2% | 0.83 |
| In H Death | 3(1,1 %) | 3(1,1%) | 6(1,1) | |
| 6 months MACE | 8 (3%) | 6 (2,2 %) | 14 (2,6 %) | |

# STEMAMI OUTCOME: Conclusions

- The low accrual and event rates increased the study budget, with unpredictable consequences for an investigator-driven study

HOWEVER

- 532 Pts enrolled, 2-year follow-up ongoing (largest regenerative therapy trial so far).

- G-CSF therapy is safe in a large cohort of randomized STEMI Pts

- MRI Substudy completed in 137 Pts (expected 120): follow-up will close in July 2016, results ready before December 2016

# STEMAMI OUTCOME:

Thank you to all 42 centers involved in the study