

Advanced Medical Therapies in Cardiology

Pieter A. Doevendans

Chief of Cardiology UMCU

Utrecht NL

Representing the ESC

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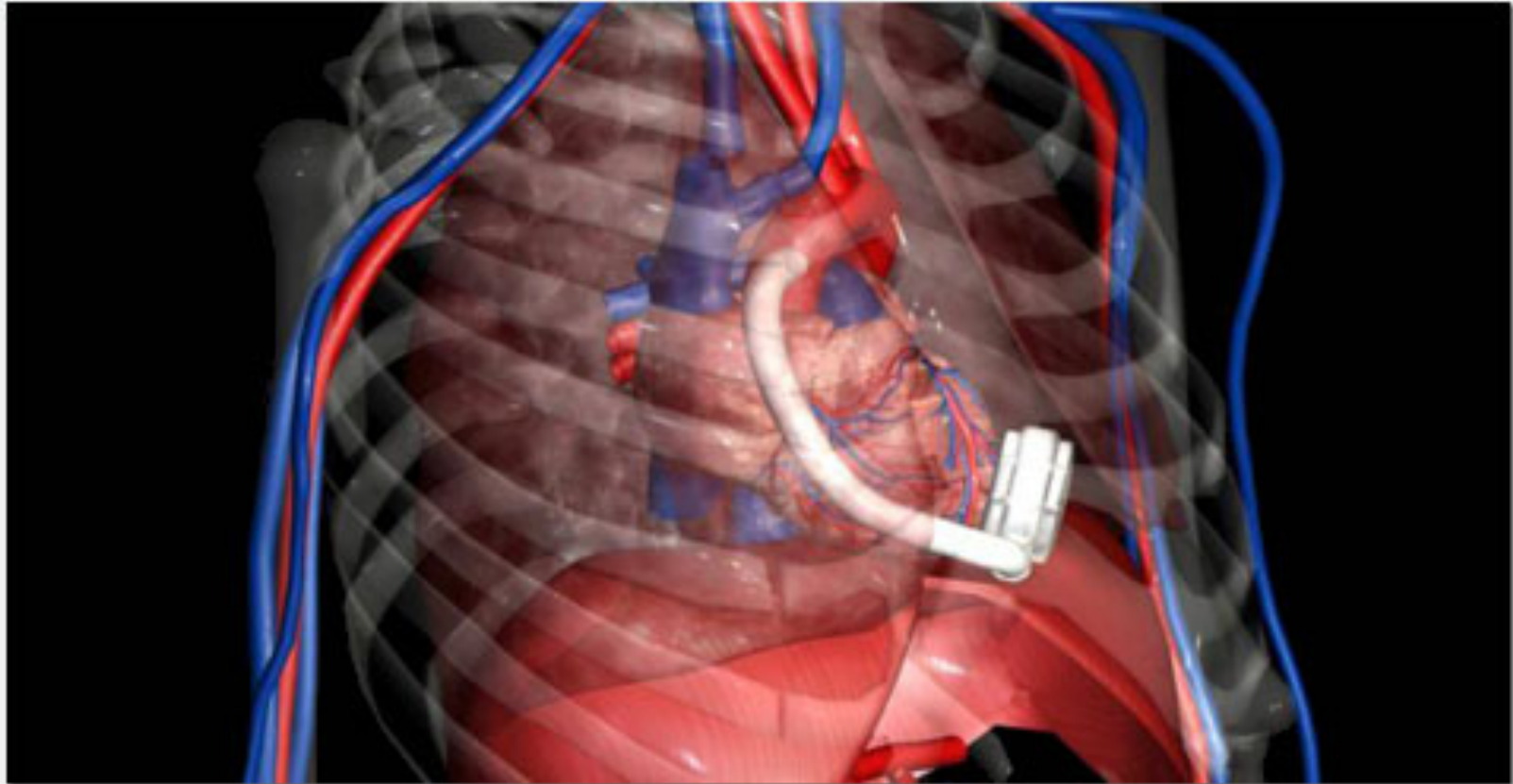


Improvement of Cardiac Function:

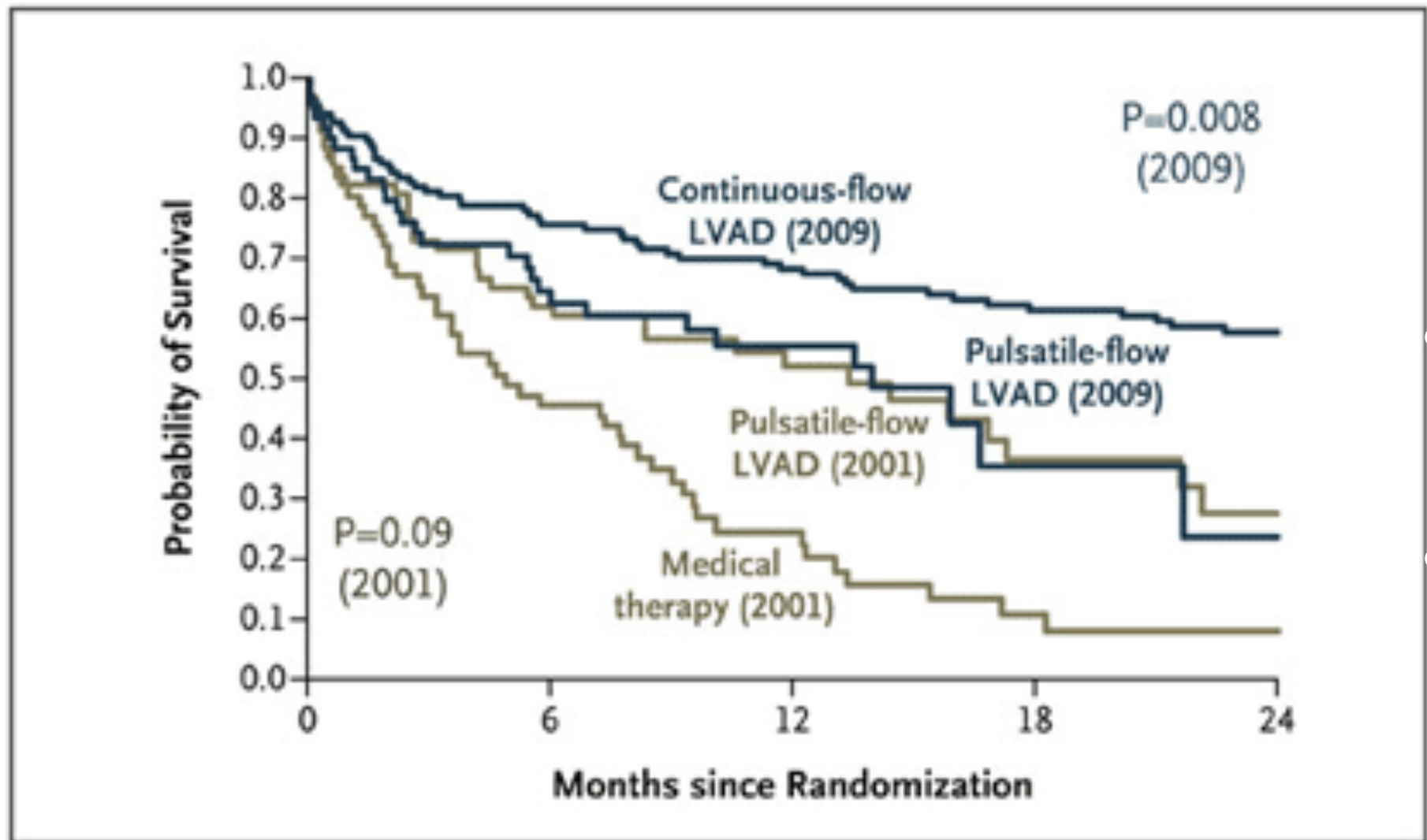
- Stem cells
 - Autologous Bone Marrow derived cells
 - Allogenic Mesenchymal stem cells
- Gene therapy
 - SERCA_{2a}



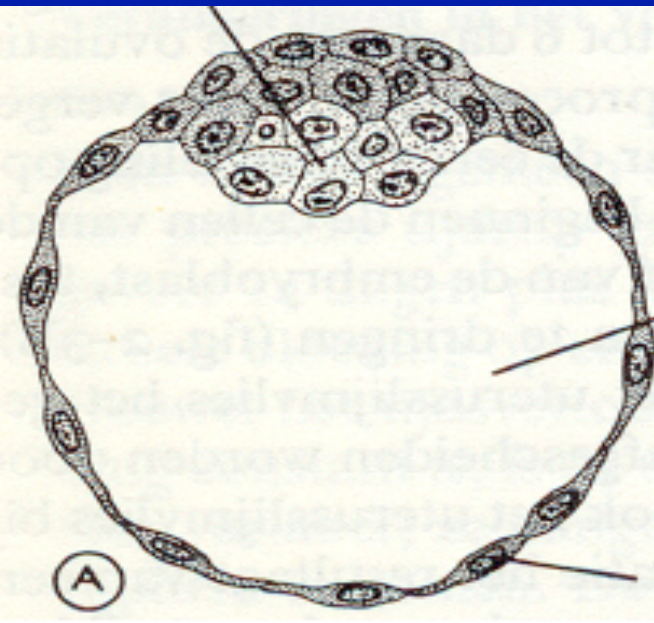
LVAD



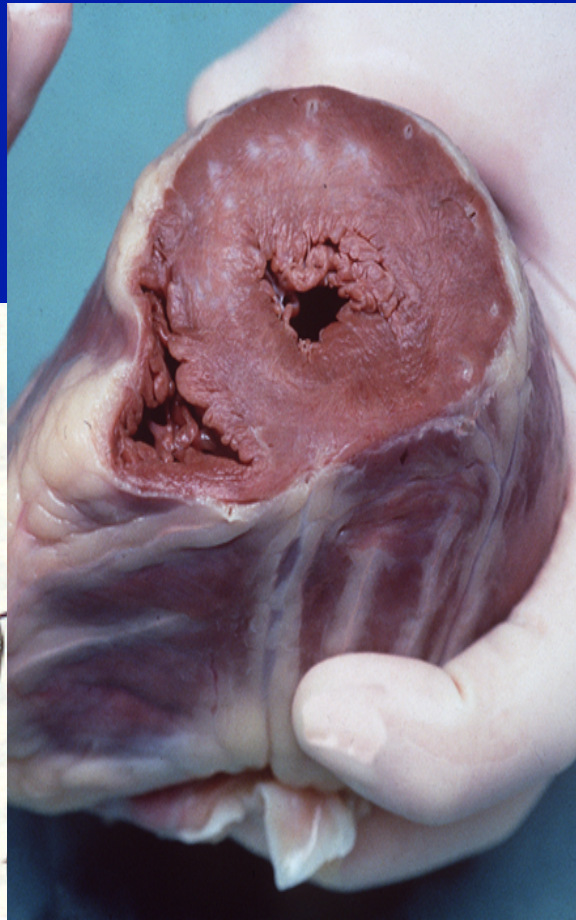
Assist device: Heartmate II



Embryo

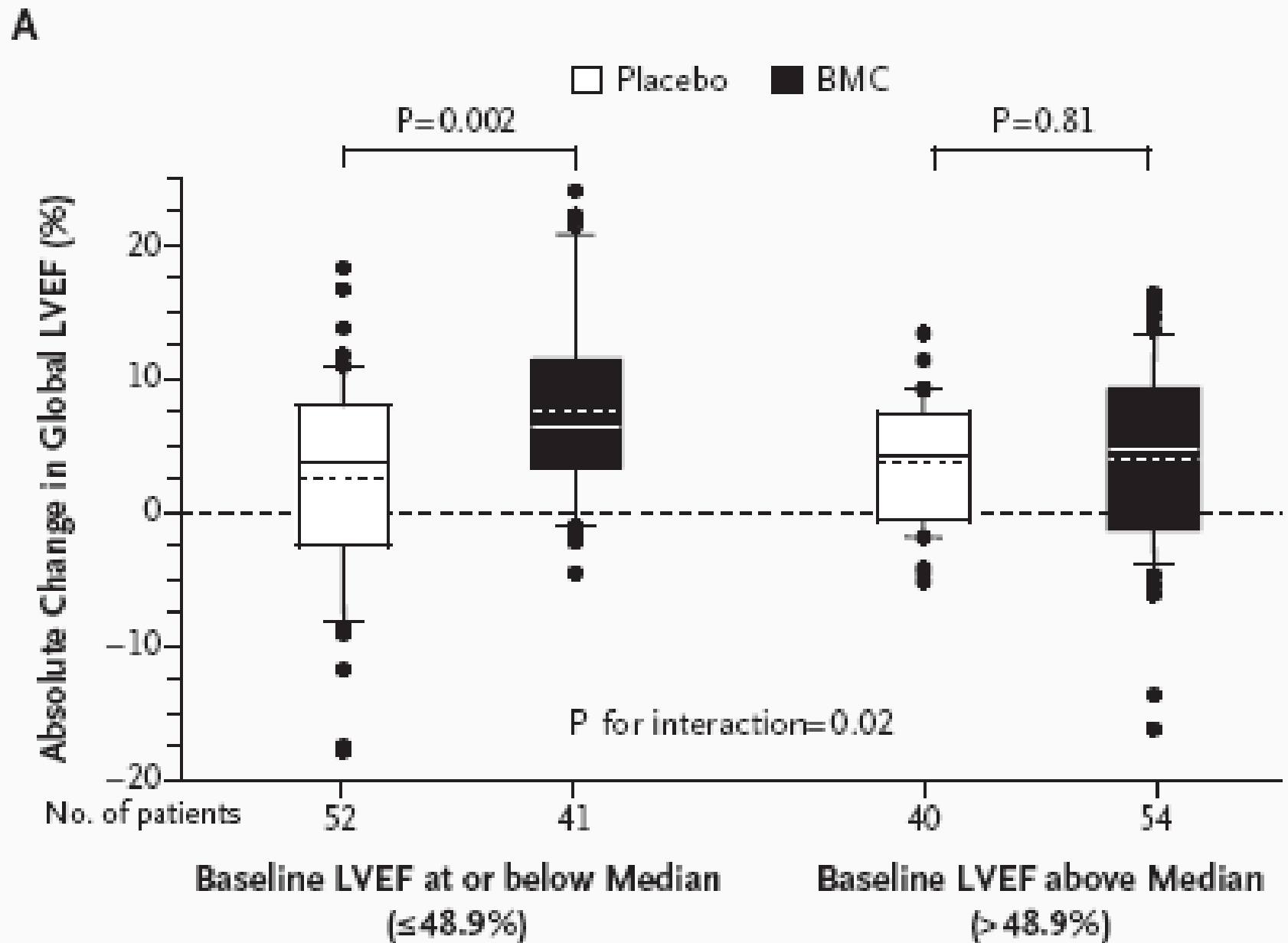


Heart

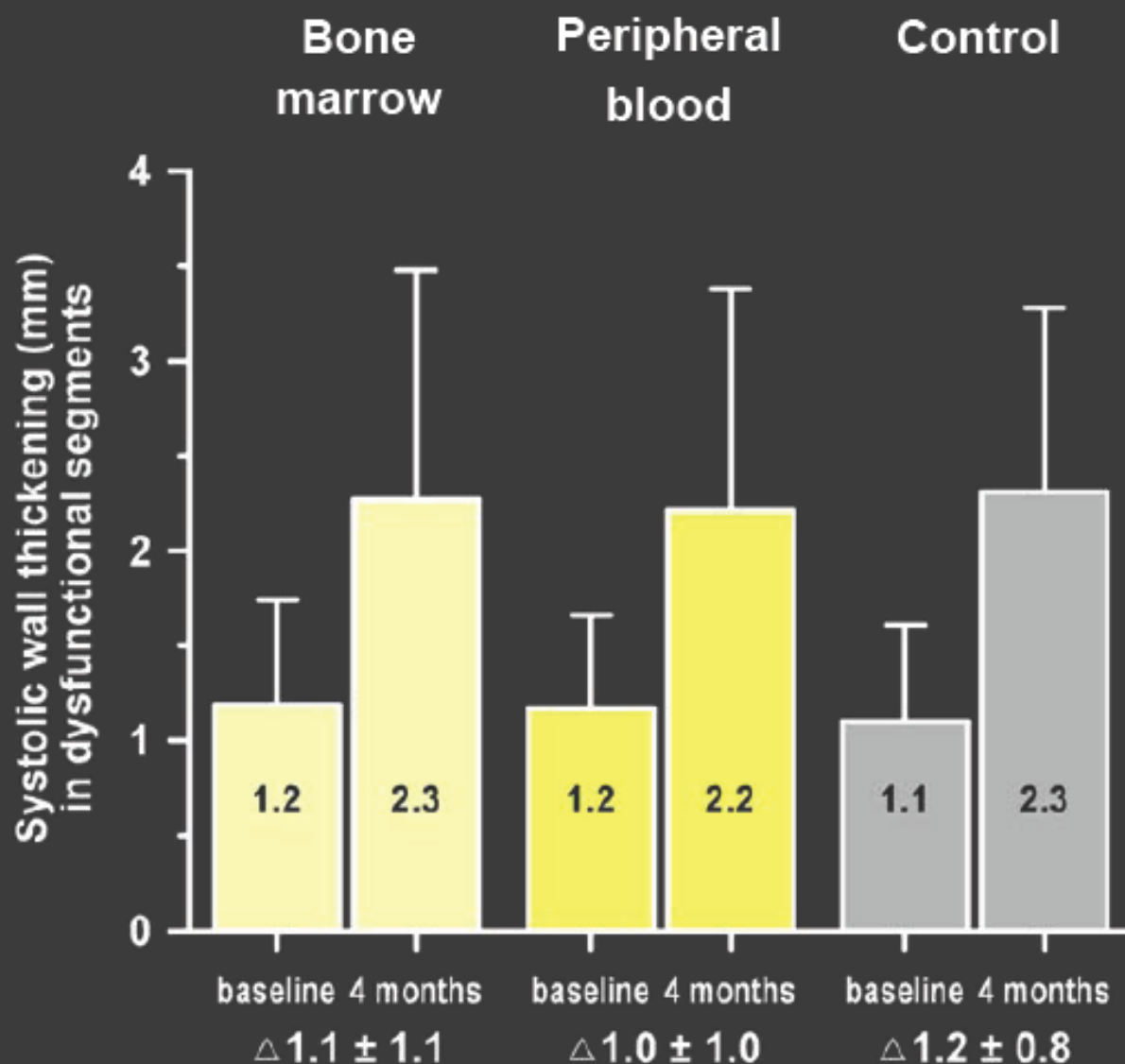


Bone marrow





Systolic wall thickening (SWT)



Bami

Supported by the EC
under the FP7 programme



The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all- cause mortality in acute myocardial infarction

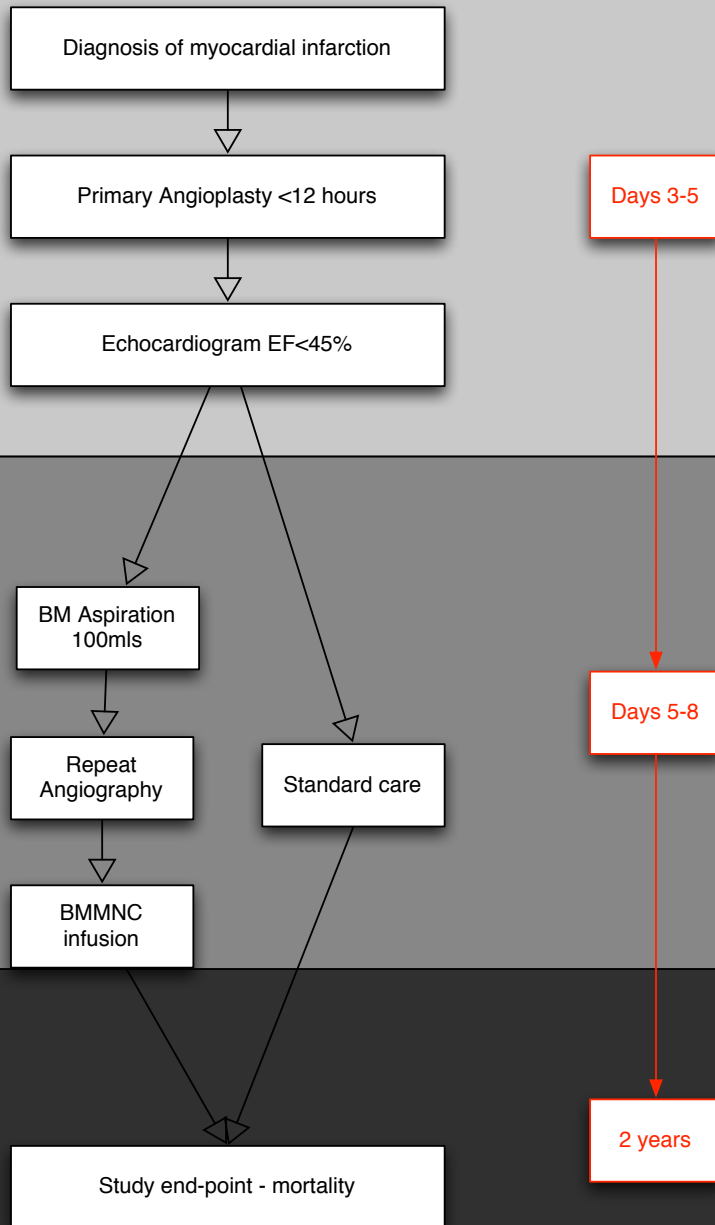
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BAMI protocol



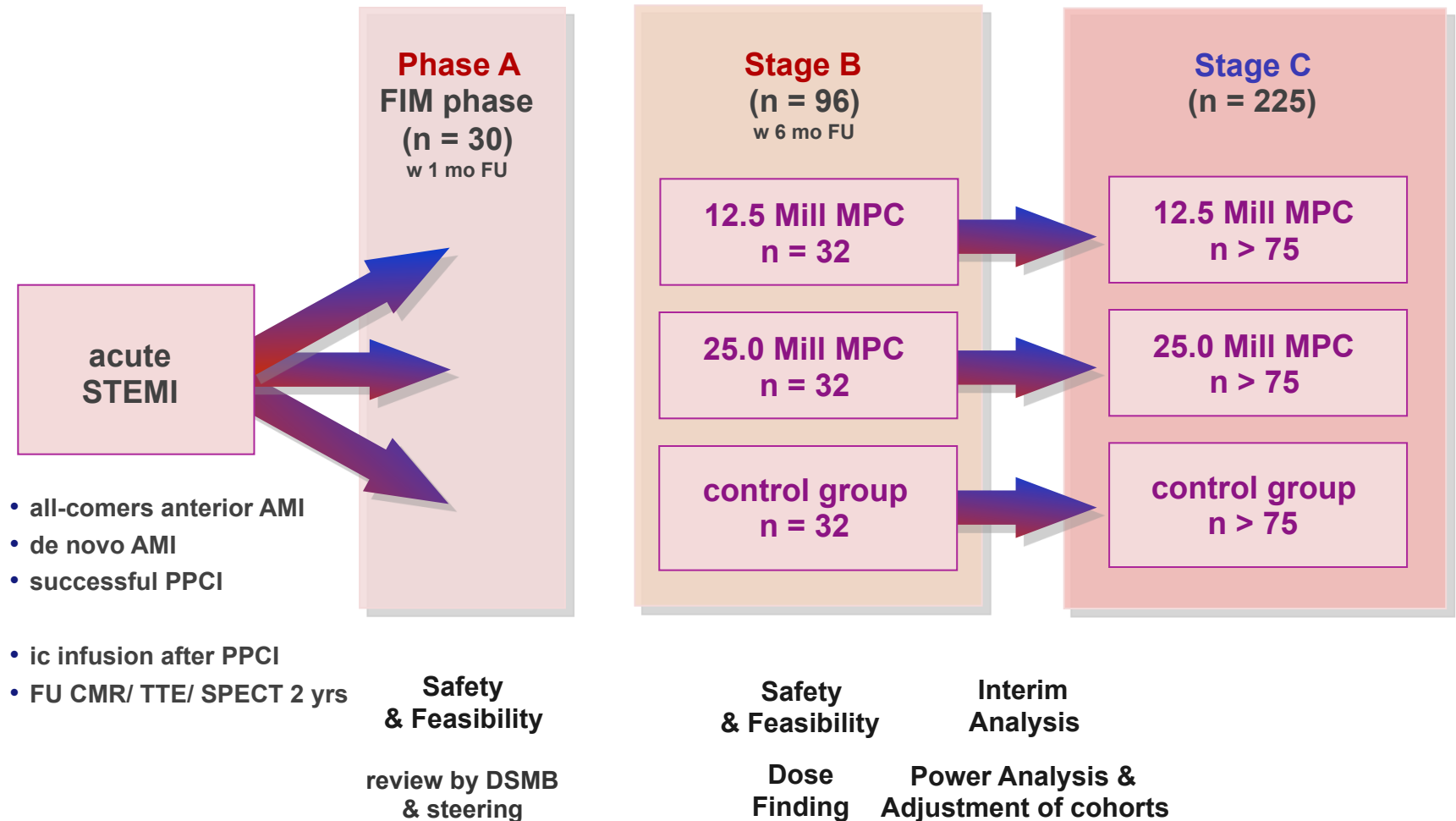
- 3000 patient outcome study
- End-point = 25 % reduction in death (all cause at 2 years)
- STANDARDISATION of cell processing technique

The AMICI trial

- Allogeneic Stro-3^{bright} Mesenchymal Precursor Stem Cells
- in the treatment of patients with an acute STEMI
 - FIM australia Q2 2013
 - PI Eric Duckers UMC Utrecht

The AMICI clinical trial

- Multi-center, prospective, randomized, double-blinded phase IIa/IIb study with a sequential design, with 3 parallel arms and blinded core lab analyses
- 1:1:1 randomization: 12.5/25.0 Mill allogeneic MPC vs placebo control



Improvement of Cardiac Function:

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 - SERCA 2a

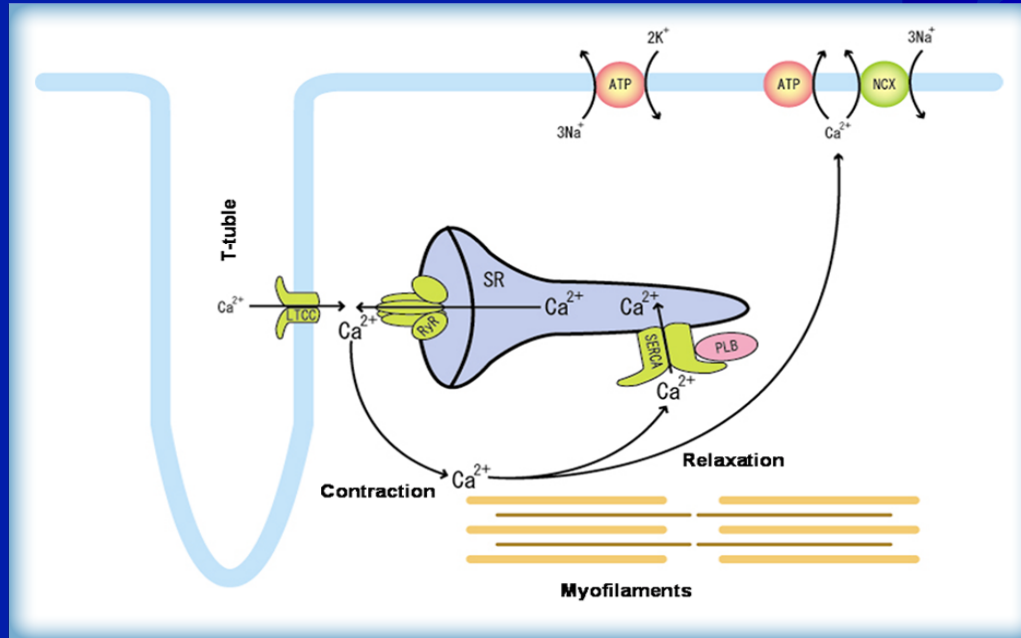
Central to failure



on deficiency results in

ne transfer rescues

M, et.al. Gene Ther. (24 Jul 2008);



- SERCA2a transfers 75% of Ca^{2+} from cytosol to SR lumen
- In both experimental models and human HF, SERCA2a deficiency results in abnormal Ca^{2+} handling and a deficient contractile state
- In animal models, restoration of SERCA2a activity via gene transfer rescues contractile deficit
 - J Am Coll Cardiol. 2008;51:1112-1119; J Mol Cell Cardiol. 2007;42:852-861; Byrne M, et.al. Gene Ther. (24 Jul 2008); [DOI: 10.1038/gt.2008.120]

Phase 2
**Myocardial Delivery of AAV1/
SERC A_{2a} (MYDICAR[®]) in
Subjects with Advanced Heart
Failure**

clinicaltrials.gov Identifier
NCT00454818

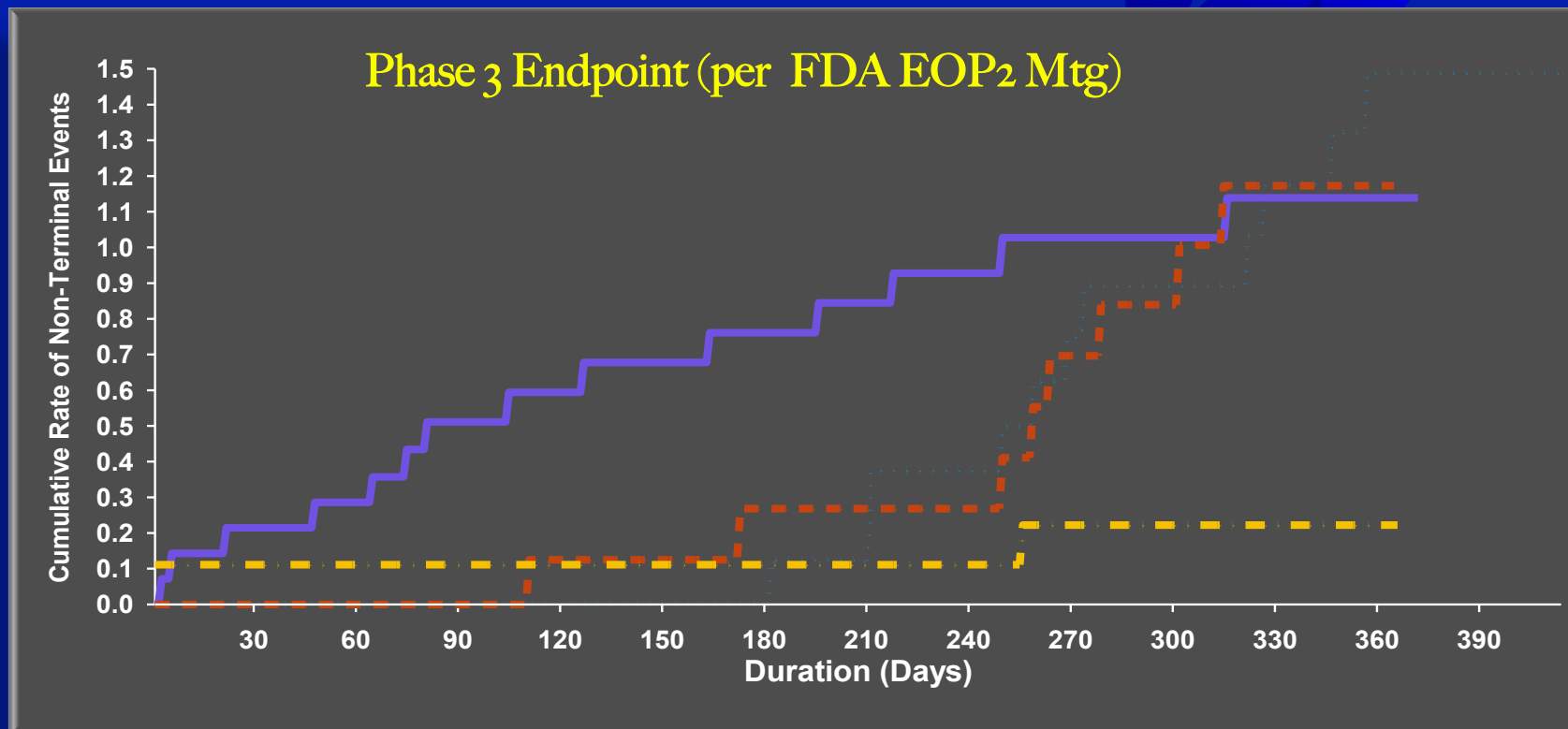
Protocol: J Card Fail. 2008;14:355-367

**Phase I: J of Cardiac Fail 2009;15(3):
171-181**

**Phase 2: Circulation. 2011 Jul 19;124(3):
304-313.**

Phase 2: Time-to-Recurrent HF-related Hospitalizations

Adjusted for Competing Risk of Terminal Event (CV Death, Transplant, LVAD)



—	P (N=14)	
·····	L (N=8)	HR(CI)=0.40 (0.13, 1.21), p = 0.11
- - -	M (N=8)	HR(CI)=0.44 (0.16, 1.24), p = 0.12
- · - · -	H (N=9)	HR(CI)=0.12 (0.03, 0.49), p = 0.003

*Biometrics 2000;56(2):554-62;
Circulation 2009; 119(7): 969-977*

ACC 2015

CUPID₂

The CUPID Phase 2b trial randomized 250 patients in 56 clinical sites worldwide. On April 26, 2015, we announced that the CUPID Phase 2b trial did not meet its primary or secondary endpoints.

Conclusions

- Stem cell studied to date have a limited effect on cardiac function.
- We have to await the outcome of AMICI and BAM1
- SERCA2a Gene therapy for heart failure has failed in a phase 2b trial
- We need to improve:
 - Standardization: preclinical work, clinical end-points
 - Complete publication of all pre-clinical work