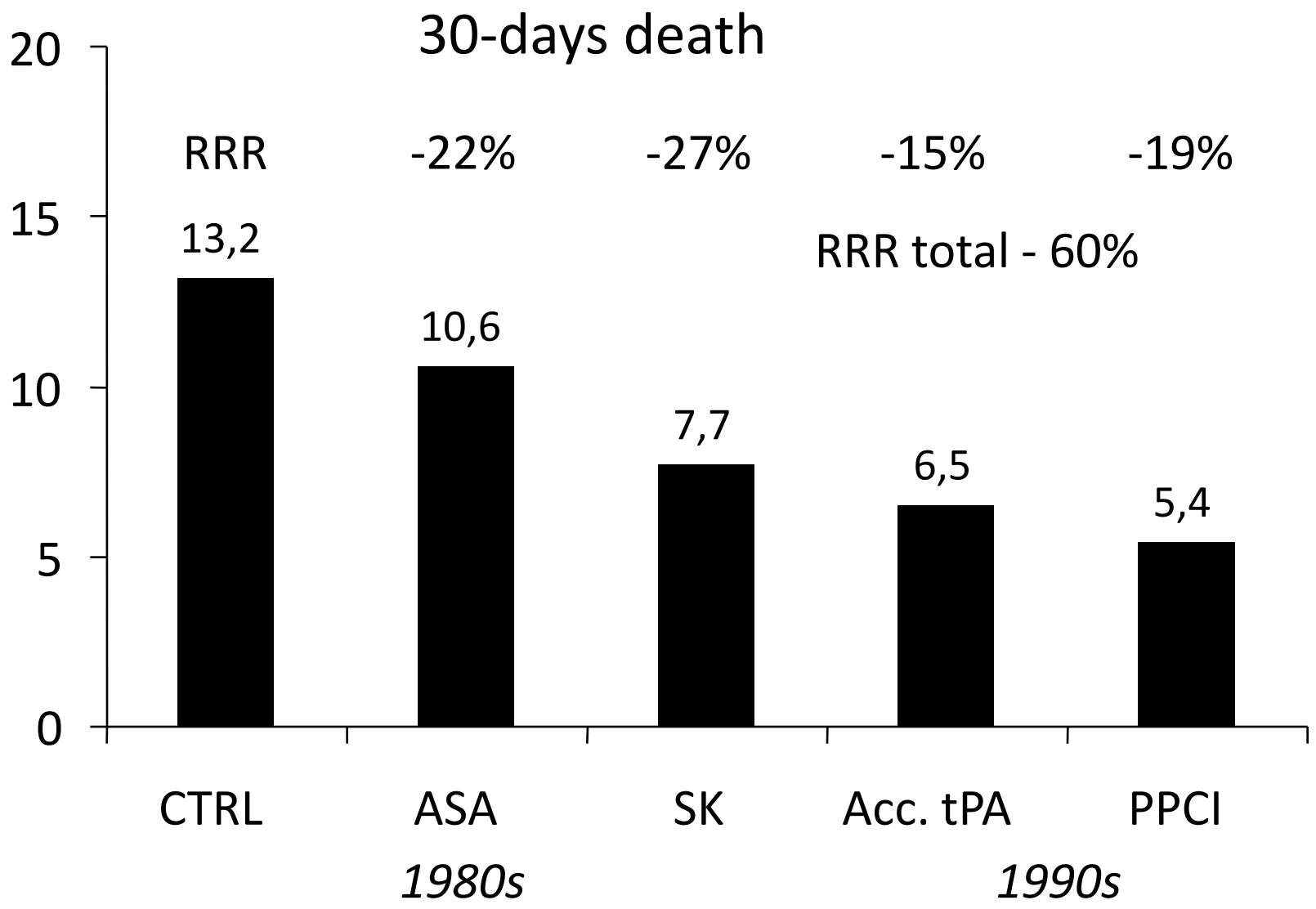
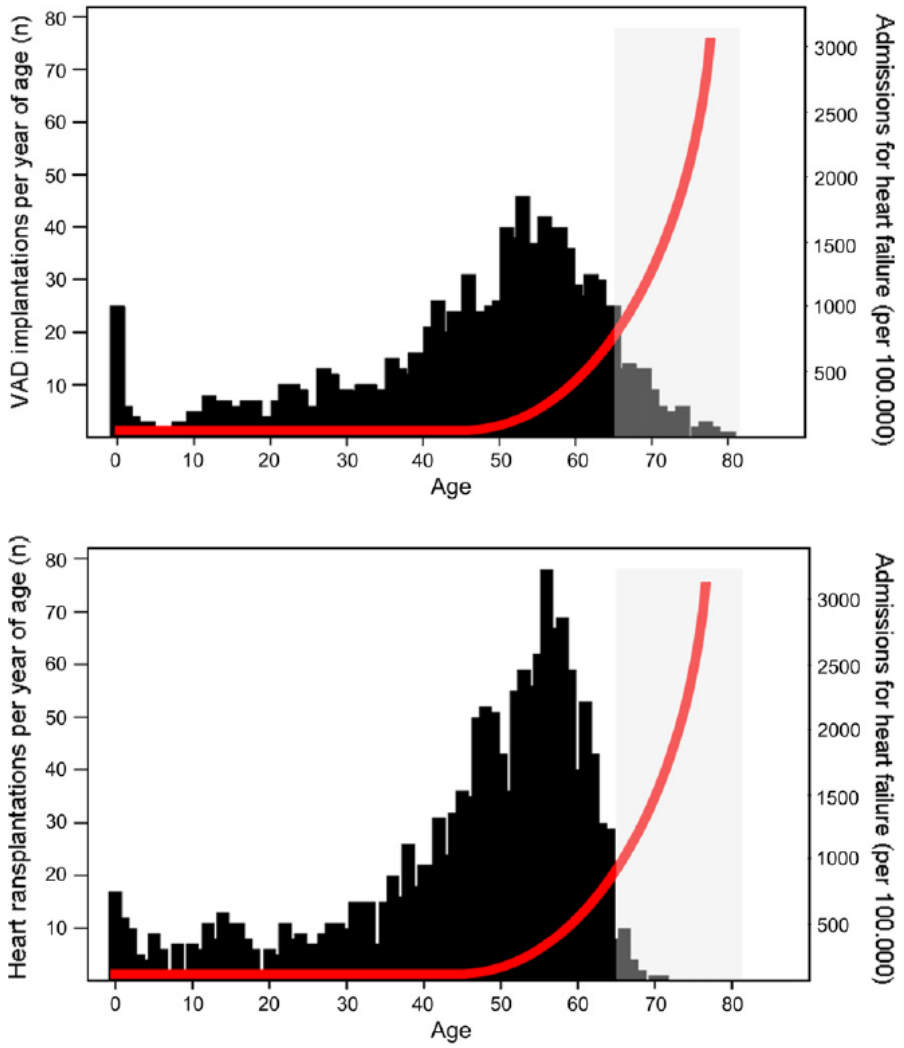
La medicina rigenerativa: Apparato Cardiovascolare

Giuseppe Rengo, MD, PhD
Fondazione Salvatore Maugeri -Istituto di Telese Terme IRCCS
Cattedra di Cardiologia – Università di Napoli "Federico II"

Myocardial infarction: Can we obtain more from drugs and PTCA ?



Current “curative” heart failure treatment options are limited in particular for old patients



Stamm et al. Experimental Gerontology 2008

Novel Therapies Are Much Needed

- Concept of “regenerative medicine” is clearly very attractive
- 1990’s Gene therapy was the novel therapy
- 2000’s Use of Stem Cells for cell-base therapies has become a very active area of Research
- But, what do we really know about this mode of therapy?

FACT vs. FICTION

Cardiac repair

- The majority of cardiac myocytes exit the cell cycle after a terminal round of cell division shortly after birth. On this basis, the postnatal heart has been viewed as a post-mitotic organ.

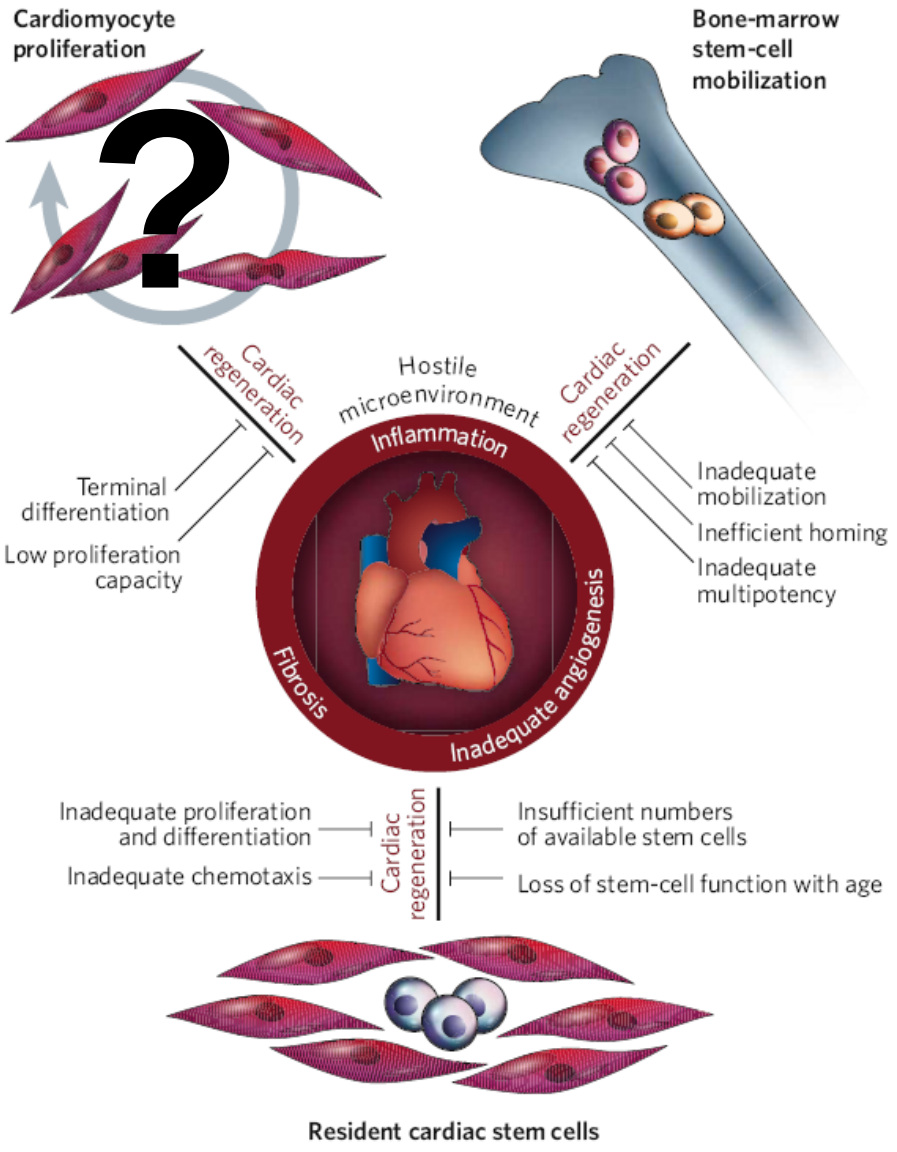
- During the past decade it has been recognized that organs considered postmitotic (e.g., brain or heart) have, in reality, regenerative potential.

- However, less than 50% of cardiomyocytes are exchanged during a normal life span, and the repair system appears to be inadequate to the magnitude of an ischemic or heart failure insult

Cardiac repair can be considered as the outcome of 2 major processes:

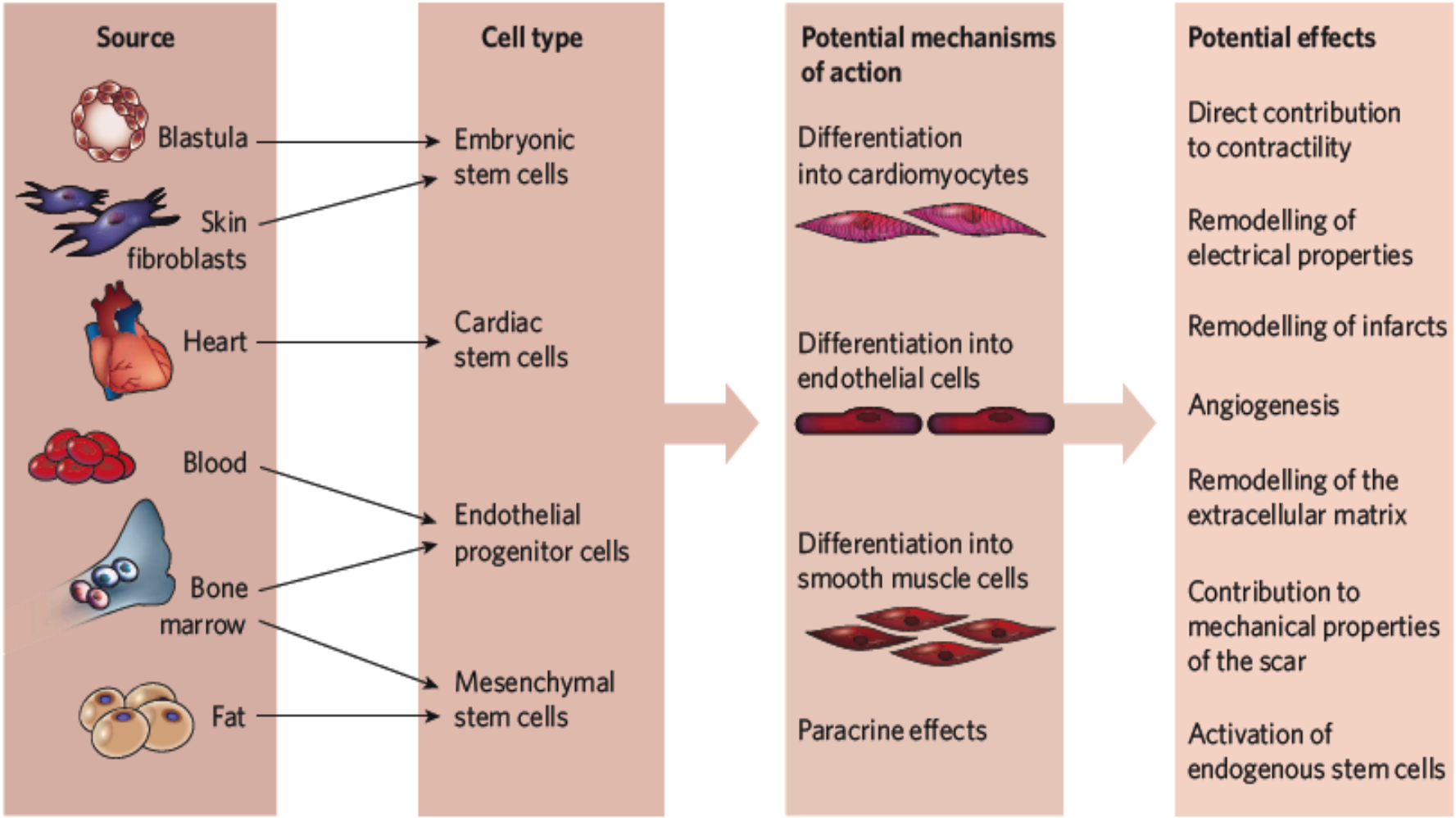
• Rejuvenation or restoration (activation of resident cardiac stem cells or other stem cells via paracrine or autocrine mechanisms; modulation of apoptosis, inflammation, angiogenesis, or metabolism)

• Regeneration (progenitor or stem cell engraftment forming differentiated myocytes)



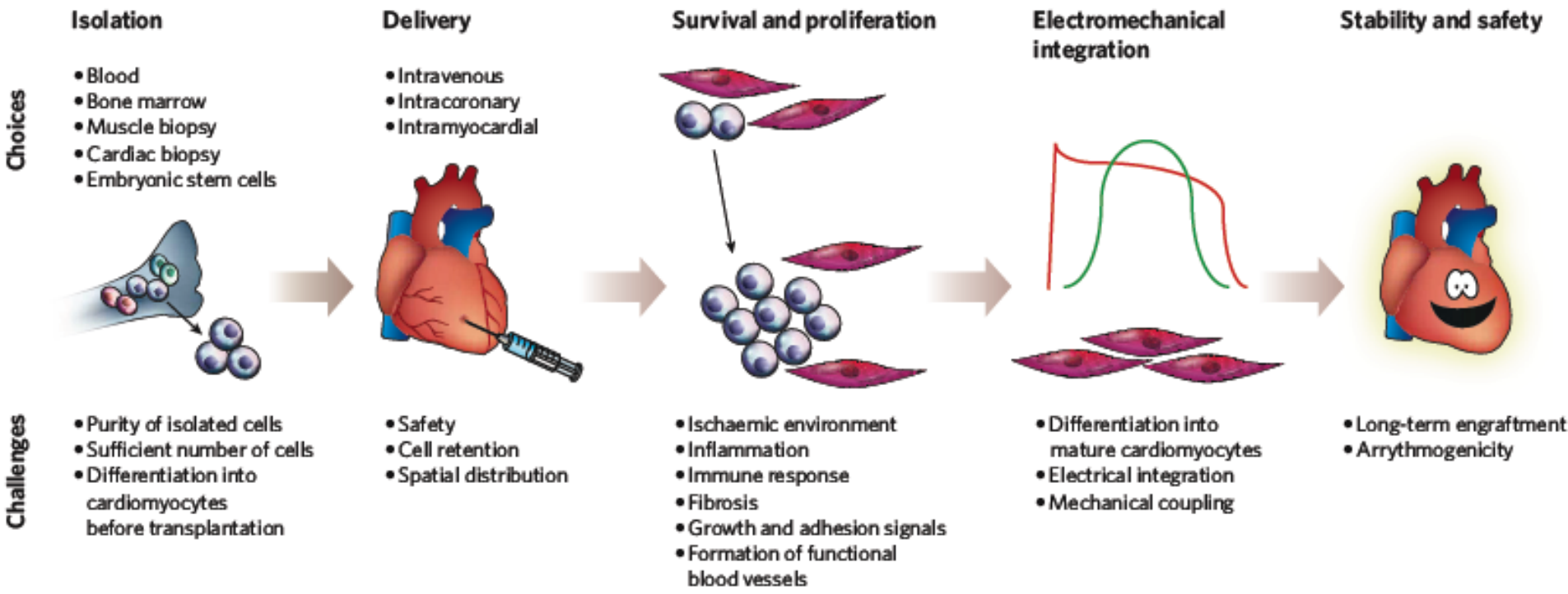
Segers VF et al, Nature, 2008; 451:937-42.

Which stem cells should be used for cardiac therapy?



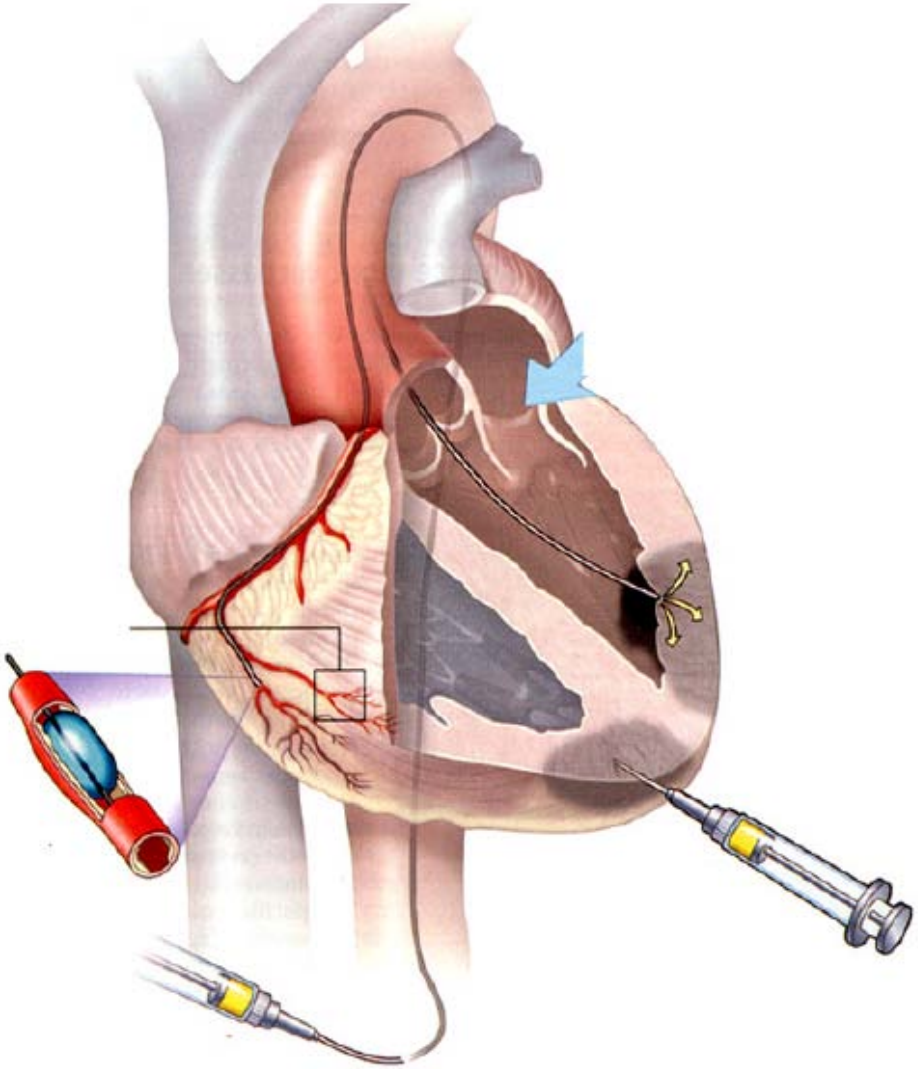
Segers VF et al, Nature, 2008; 451:937-42.

Challenges to stem-cell therapy for cardiac disease



Segers VF et al. Nature, 2008

Delivery Methods



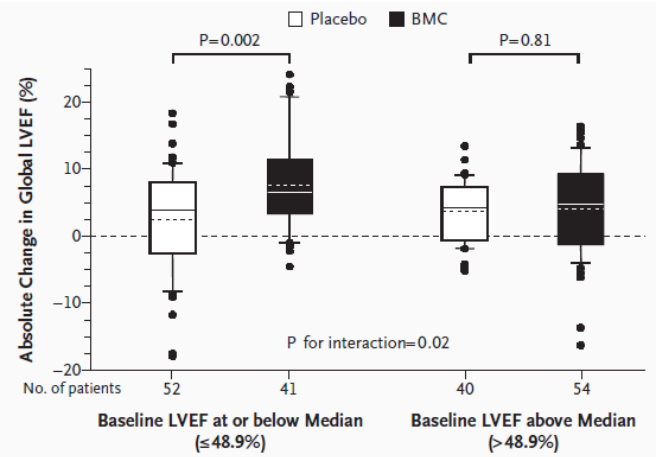
Stamm et al. Experimental Gerontology 2008

Intracoronary Bone Marrow–Derived Progenitor Cells 3 days after Acute Myocardial Infarction and successful PTCA

Variable	Placebo (N=92)	BMC (N=95)	P Value
Global LVEF (%)			
Baseline			
Mean	46.9±10.4	48.3±9.2	0.31
Median	47.5	50.6	
4 Mo			
Mean	49.9±13.0	53.8±10.2	0.02†
Median	53.2	54.7	
Absolute difference			
Mean	3.0±6.5	5.5±7.3	0.01‡
Median	4.0	5.0	
P value (baseline vs. 4 mo)	<0.001	<0.001	

At 4 months, LVEF was significantly higher (both global values and absolute difference) in the BMC group than in the placebo group

At 1 year, BMC infusion was associated with a reduction in the **combined** clinical end point of death, recurrence of MI, and revascularization procedure.



Patients with a baseline LVEF at or below the median value of 48.9% derived the most benefit

1-Yr follow-up (cumulative)§			
Death	6	2	0.28 †
Myocardial infarction	5	0	0.06†
Rehospitalization for heart failure	3	0	0.25 †
Revascularization	35	21	0.03‡
Target-vessel revascularization	24	16	0.18‡
Stent thrombosis	3	1	0.62†
Non–target-vessel revascularization	16	6	0.03‡
Cerebral infarction	1	1	1.0 †
Documented ventricular arrhythmia or syncope	5	5	1.0†
Combined events			
Death and recurrence of myocardial infarction	10	2	0.02 ‡
Death, recurrence of myocardial infarction, and any revascularization procedure	40	23	0.01 ‡
Death, recurrence of myocardial infarction, and infarct-vessel revascularization	29	18	0.08‡
Death, recurrence of myocardial infarction, and rehospitalization for heart failure	12	2	0.006‡

Schachinger V et al. N Engl J Med, 2006

Transendocardial, Autologous Bone Marrow Cell Transplantation for Severe Ischemic CHF

TABLE 5. Comparison of Baseline and 2-Month Follow-Up Values for the Treatment and Control Groups

	Treatment (n=14)	Control (n=7)	P*
ESV, cc			
Before treatment	146.78±53.46	89.42±26.23	
After treatment	123.21±47.88	98.85±20.52	0.041
P	0.026	0.36	
EDV, cc			
Before treatment	211.35±76.89	135.71±26.08	
After treatment	189.14±67.54	145±27.62	0.09
P	0.065	0.50	
EF, %			
Before treatment	30±5.56	36±11.73	
After treatment	35.5±7.85	31.85±7.55	0.029
P	0.027	0.31	

Perin et al. Circulation, 2003

Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of Acute Myocardial Infarction: Meta-Analysis of Controlled Clinical Trials (I)

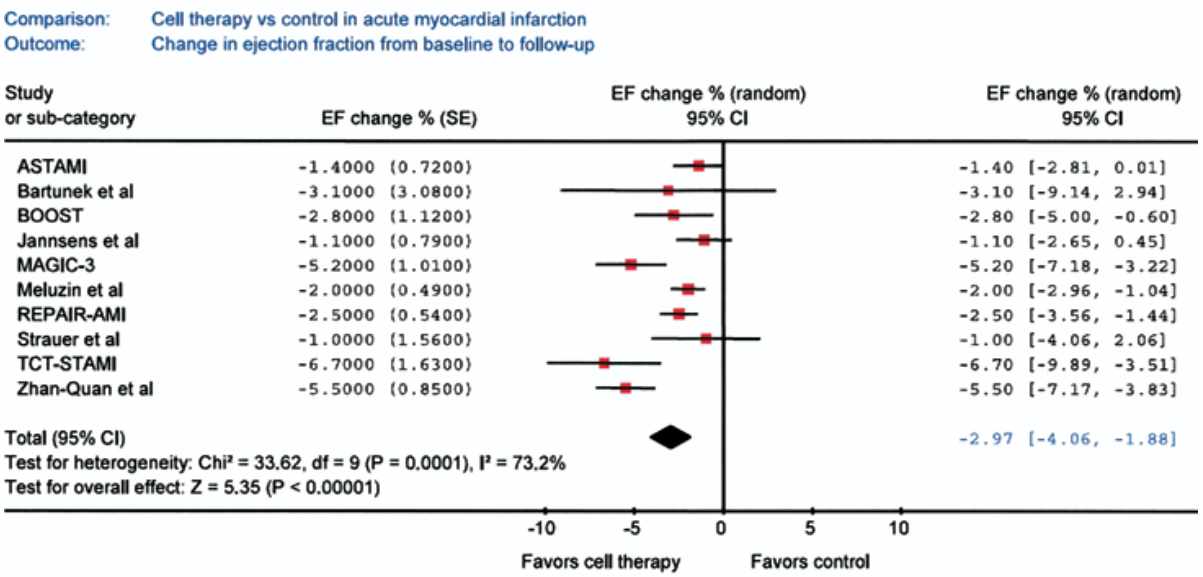
Table 1 Main Features of Included Studies

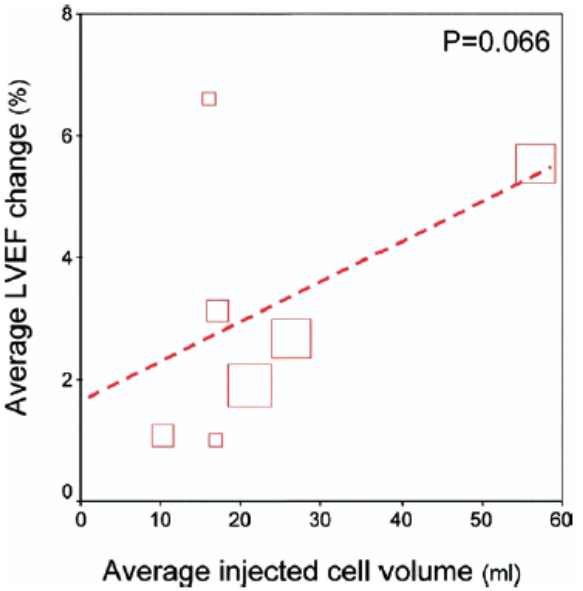
Study	Year	Design	Patients Enrolled (Patients at Follow-Up)	Cell Type	Follow-Up (Months)	Primary End Point	Imaging Modality for LVEF Assessment
Strauer et al. (10)	2002	Non-RCT	20 (20)	BMC	3	LVEF	LV angiography
Bartunek et al. (11)	2005	Non-RCT	35 (35)	BMC	4	Safety, LVEF	LV angiography, SPECT
Jannsens et al. (8)	2006	RCT	67 (66)	BMC	4	LVEF	Cardiac MRI
BOOST (7)	2006	RCT	60 (60)	BMC	18	LVEF, safety	Cardiac MRI
Zhan-Quan et al. (13)	2006	Non-RCT	70 (58)	PMC	6	LVEF, LV volumes, WMSI	Echocardiography
MAGIC CELL-3-DES (12)	2006	RCT	56 (50)	PMC	6	LVEF	Cardiac MRI
TCT-STAMI (15)	2006	RCT	20 (20)	BMC	6	LVEF	Echocardiography, SPECT
ASTAMI (2,4)	2006	RCT	100 (97)	BMC	6	LVEF, EDV, infarct size	SPECT, MRI, echo
REPAIR-AMI (5)	2006	RCT	204 (187)	BMC	12	LVEF	LV angiography
Meluzin et al. (16)	2006	RCT	66 (66)	BMC	3	Infarct zone systolic function	SPECT

BMC = bone marrow cells; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PMC = peripheral mononuclear cells; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; WMSI = wall motion score index.

Lipinski MJ et al. JACC, 2007

Meta-Analysis of Controlled Clinical Trials (II)



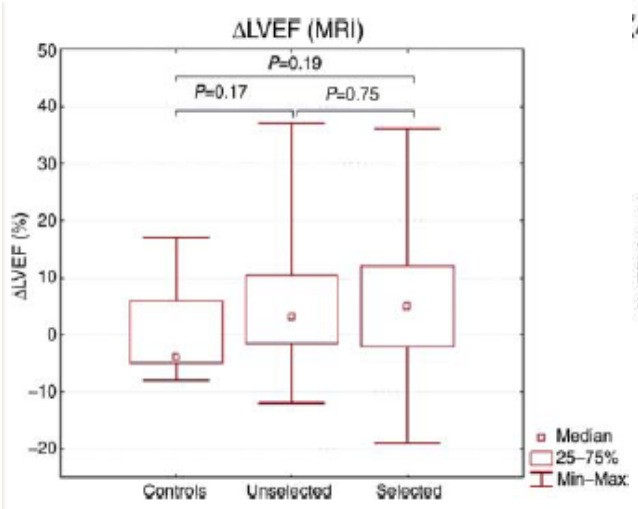


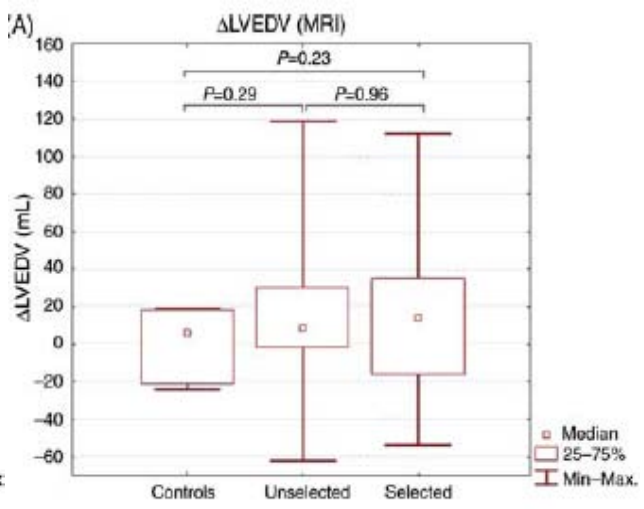
Left: Intracoronary cell therapy following PCI for MI appears to provide statistically and clinically relevant benefits on cardiac function

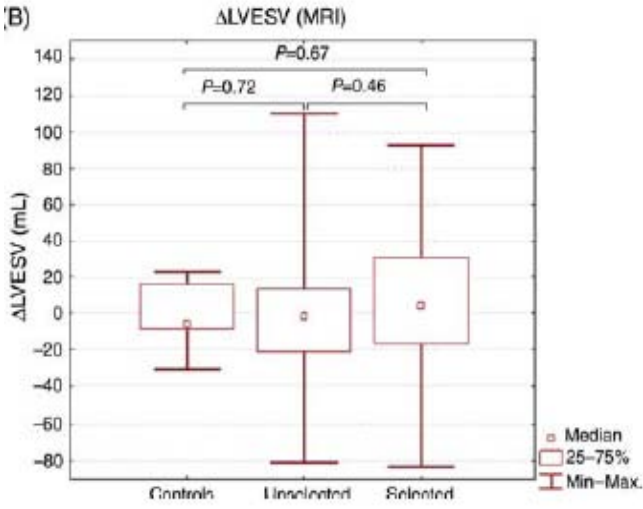
Meta-regression suggests the existence of a dose-response association between injected cell volume and LVEF change

Lipinski MJ et al. JACC, 2007

The REGENT trial







The main finding of the REGENT trial is that in patients with successfully reperfused anterior MI, the use of either selected BM-derived CD34+CXCR4+ cells or non-selected MNCs did not significantly improve the LVEF after 6 months follow-up.

Absolute changes of left ventricular end-systolic volume and left ventricular end-diastolic volume were not significantly different in all groups.

Table 2 Clinical follow-up

	Control (n = 40)	Non-selected MNC (n = 80)	Selected $CD34^+CXCR4^+$ cells (n = 80)	P-value
Death, n (%)	1 (2.5)	1 (1.25)	1 (1.25)	0.92
MI, n (%)	2 (5.0)	1 (1.25)	2 (2.5)	0.61
Stroke, n (%)	0	0	0	-
TVR, n (%)	7 (17.5)	13 (16.2)	12 (15.0)	0.87

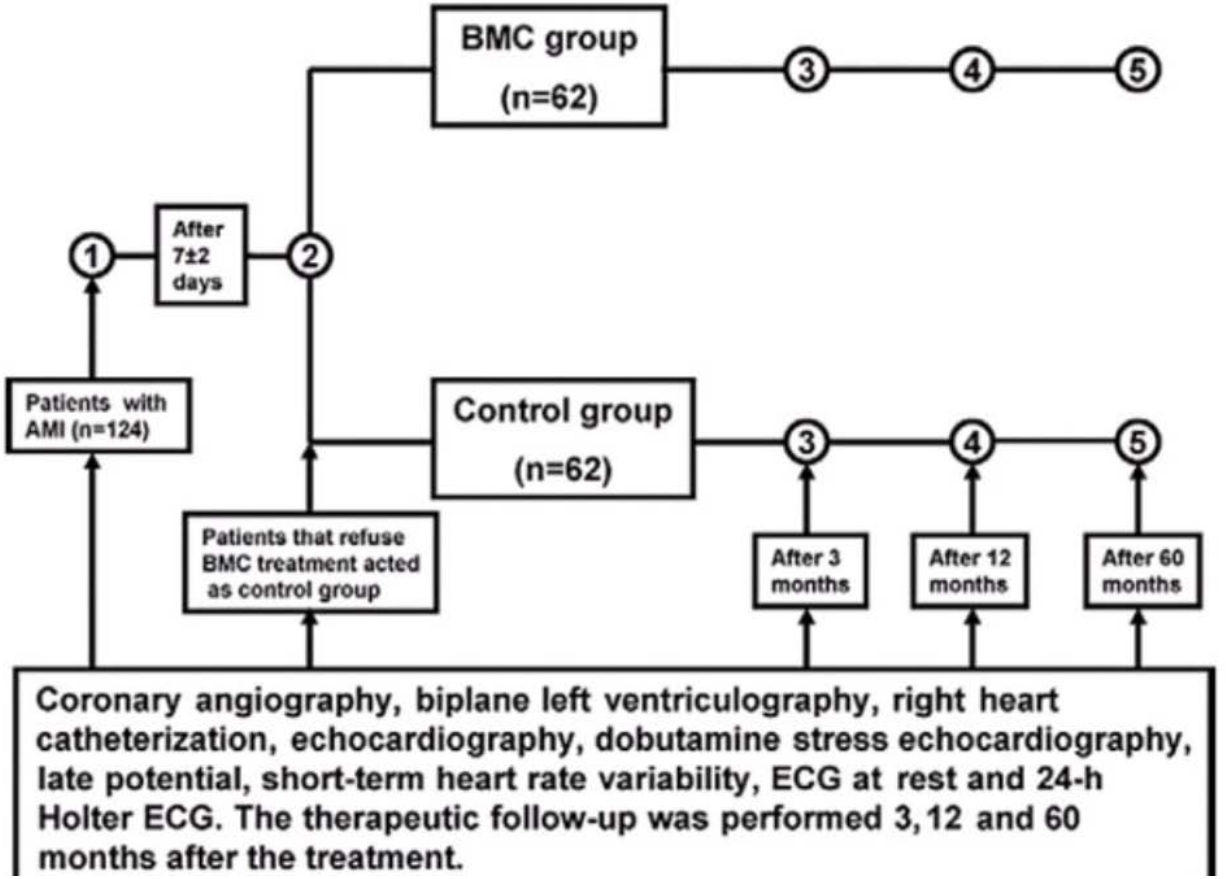
MI, myocardial infarction; TVR, target vessel revascularization.

There were no significant differences in the frequency of major cardiovascular adverse events as well as the composite endpoint between the groups.

Tendera M. et al. European Heart Journal, 2009

The BALANCE Study

Clinical benefit and Long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction

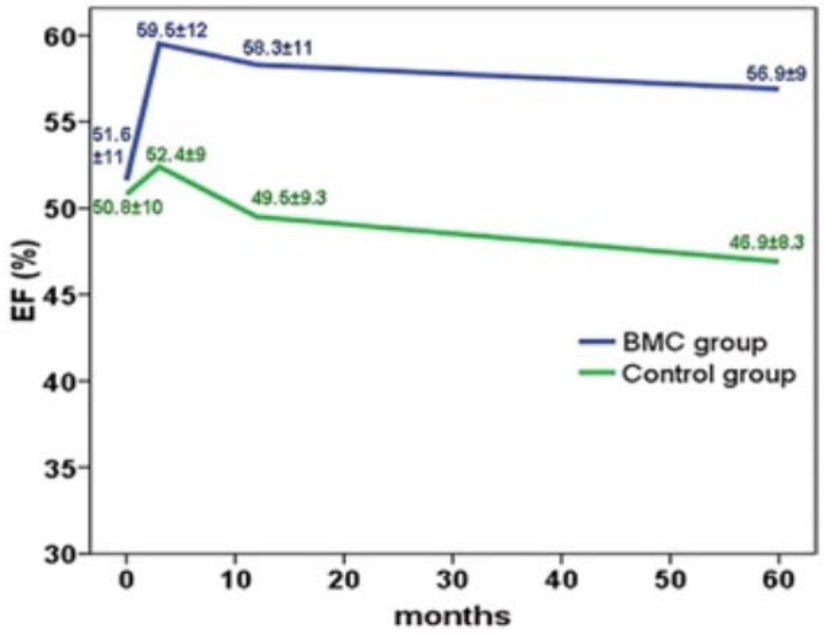


Yousef M et al J Am Coll Cardiol 2009

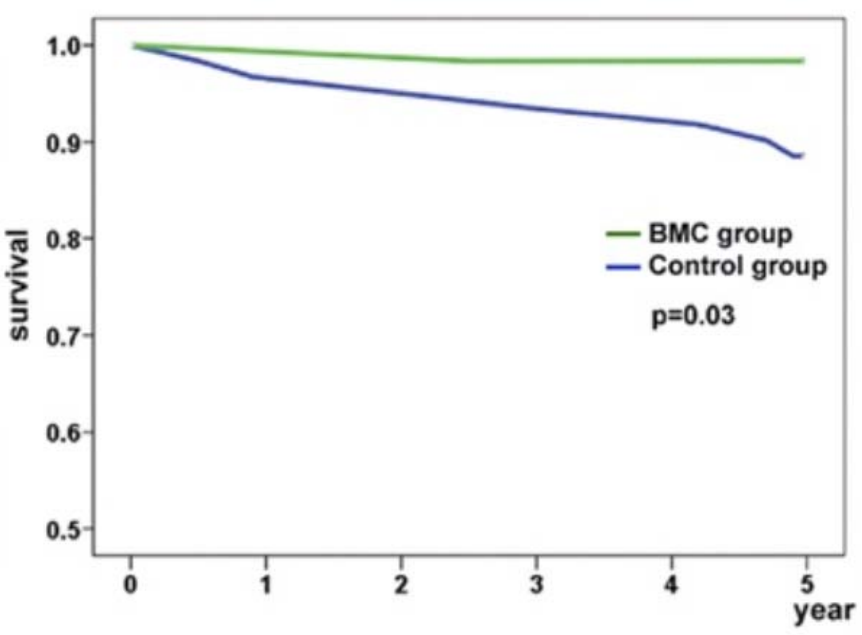
The BALANCE Study

Clinical benefit and Long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction

Ejection Fraction



Survival



Yousef M et al J Am Coll Cardiol 2009

European Journal of Heart Failure (2010) 12, 721–729
doi:10.1093/eurjhf/hfq095

The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-heart study

Bodo-Eckehard Strauer*, Muhammad Yousef, and Christiana M. Schannwell

From the Department of Medicine, Division of Cardiology, Pneumology and Angiology, Heinrich-Heine-University of Düsseldorf, Moorenstr 5, 40225 Düsseldorf, Germany

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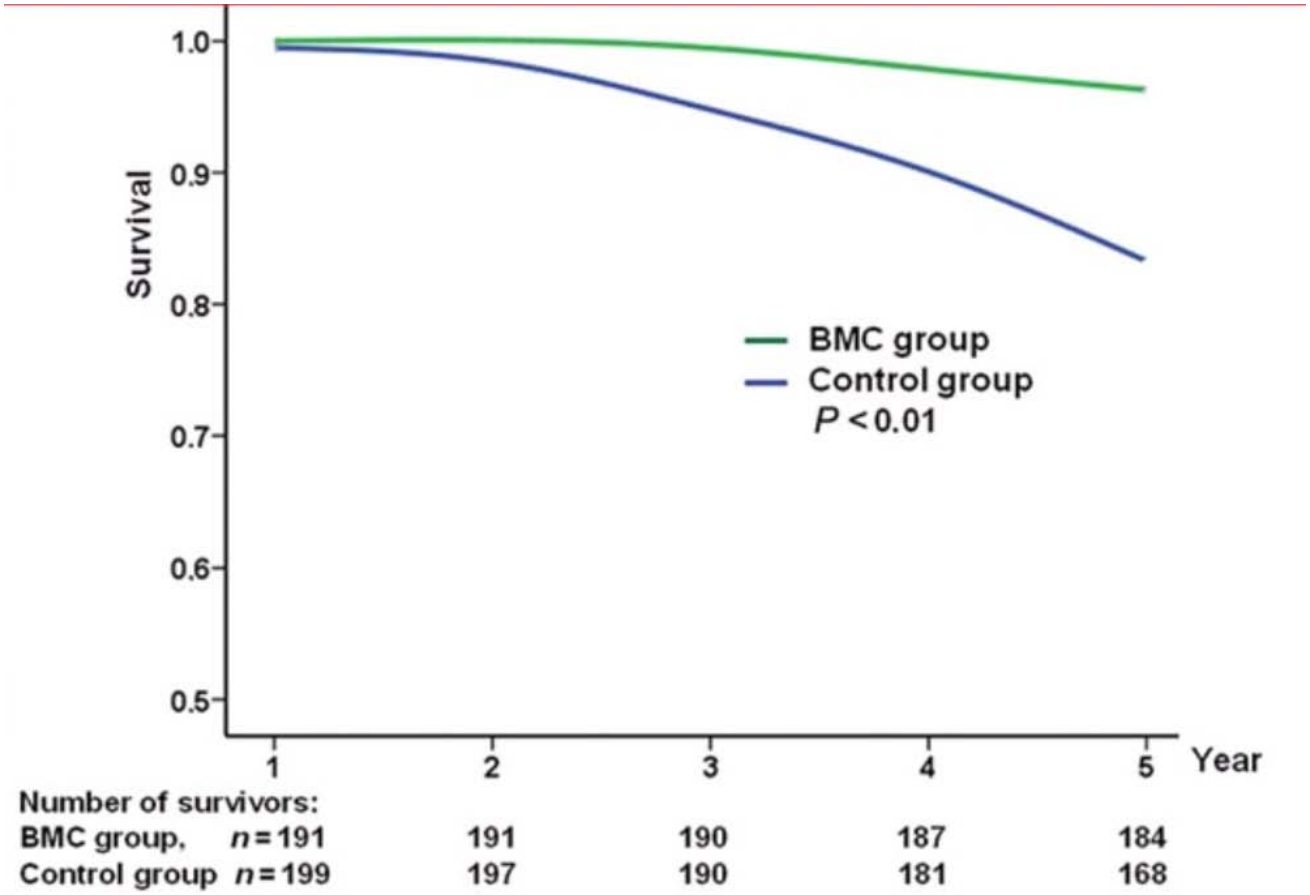
391 patients : 191 accepted cell therapy procedure
200 did not accepted the cell therapy but agreeded with a similar follow-up investigational agenda.
The time interval between the infarct intervention and inclusion In the protocol was 8.5+3.2 years.

Characteristics	Stem cell group ($n = 191$)	Control group ($n = 200$)	*P*-valu
Age	59 ± 12	60 ± 11	n.s.
BMI	30.1	30.2	n.s.
Sex (male %)	89	89	n.s.
EF (%)	29.4 ± 12.7	36.1 ± 13.8	n.s.
Number of injected cells ($\times 10^7$)	6.6 ± 3.3	–	–
Infarct-related coronary artery RCA/LAD/RCX (%)	33.4/49.1/17.5	31.2/50.7/18.1	n.s.
Number of stented coronary arteries until the time of BMC therapy	1.73 ± 0.72	1.7 ± 0.69	n.s.
Therapy during the acute infarct (%) (PTCA/PTCA + Stent/Primary stent)	0/84/16	0/79/21	n.s.

STAR Study

Mortality results



Eur J Heart Fail 2010

Conclusions

- Despite the positive results obtained in some clinical trials we have not to forget that the improvement in LVEF observed is not so huge and few data on long-term outcome are available.

- Until now, clinical trials have used cell types that are readily available (bone-marrow mononuclear cells and EPCs), but these cell types do not necessary reflect stem-cell populations that are most likely to regenerate myocardium. Which kind of cell to use?

- Cell Delivery Techniques and number of cells to deliver have to be standardized.

Gene Therapy Approach to Heart Failure

Manipulation of cardiac myocytes by exogenous DNA products that ultimately improve the function of the failing heart and/or reverse or attenuate the ventricular remodeling process.

Gene Therapy Approach to Heart Failure

2 parameters are needed for achieving success with HF gene therapy:

- clearly identified detrimental/beneficial molecular targets
- the means to manipulate these targets at a molecular level in a sufficient number of cardiac cells.

Vehicles for Myocardial Gene Therapy in HF

- Gene therapy in HF will certainly require efficient myocardial transduction and long-term transgene expression and only viral vectors appear to meet such a requirement.

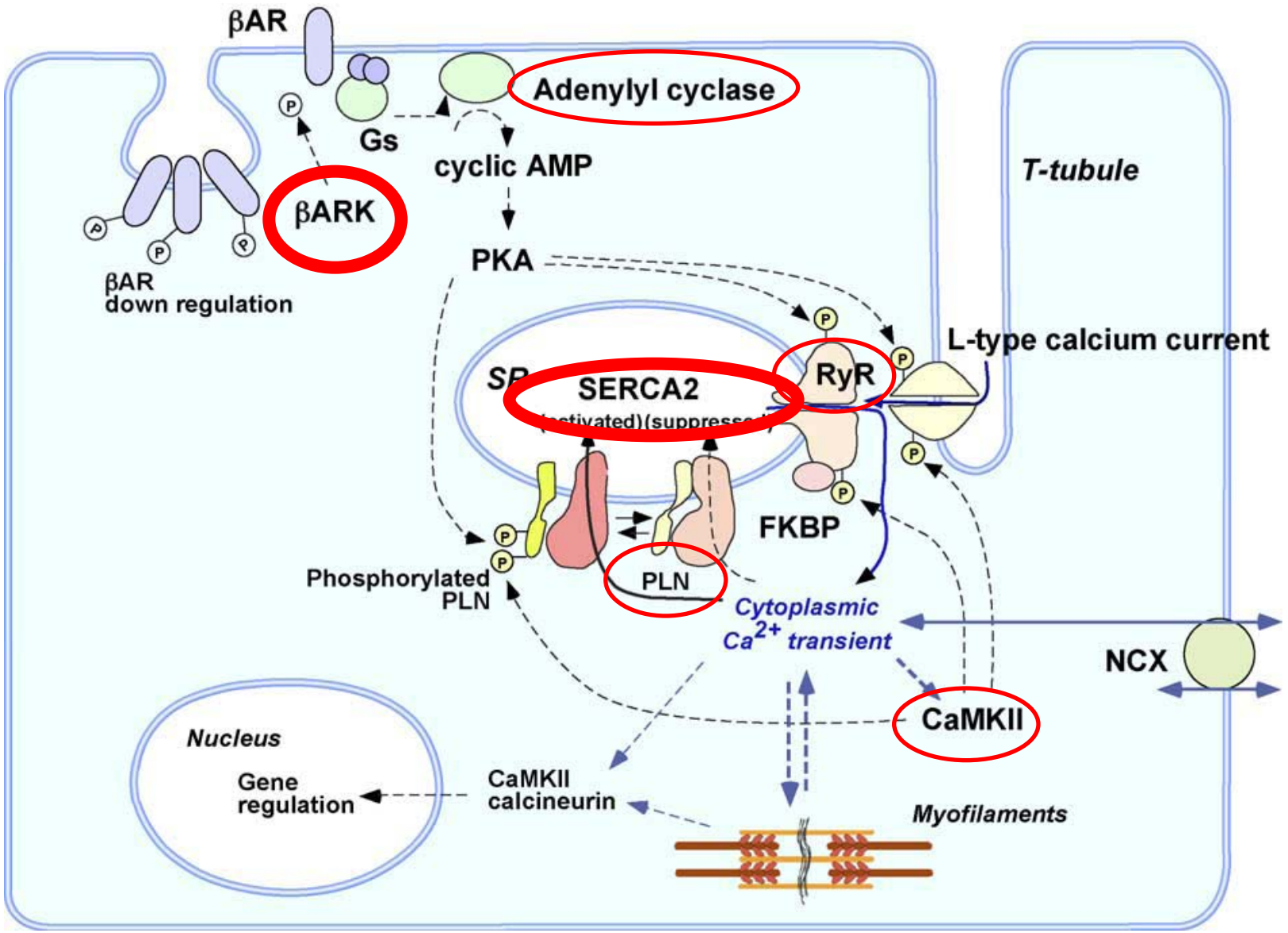
Adenovirus
-easily manipulated
-large transgene cloning capacity (7 to 8 kb)
-high production titers
-global heart trasduction

Disadvantages: in vivo inflammatory response, transient transgene expression and a secondary immune response if attempting to intervene again

AAVs
-produce stable and long-term transgene expression
-much less immunogenic
-some serotypes display tropism toward cardiac tissue

Disadvantages: low packaging capability (4 to 5 kb), the presence of naturally occurring antibodies against some AAVs in the human population may limit their value.

Molecular targets for gene therapy in HF



SERCA2A gene therapy

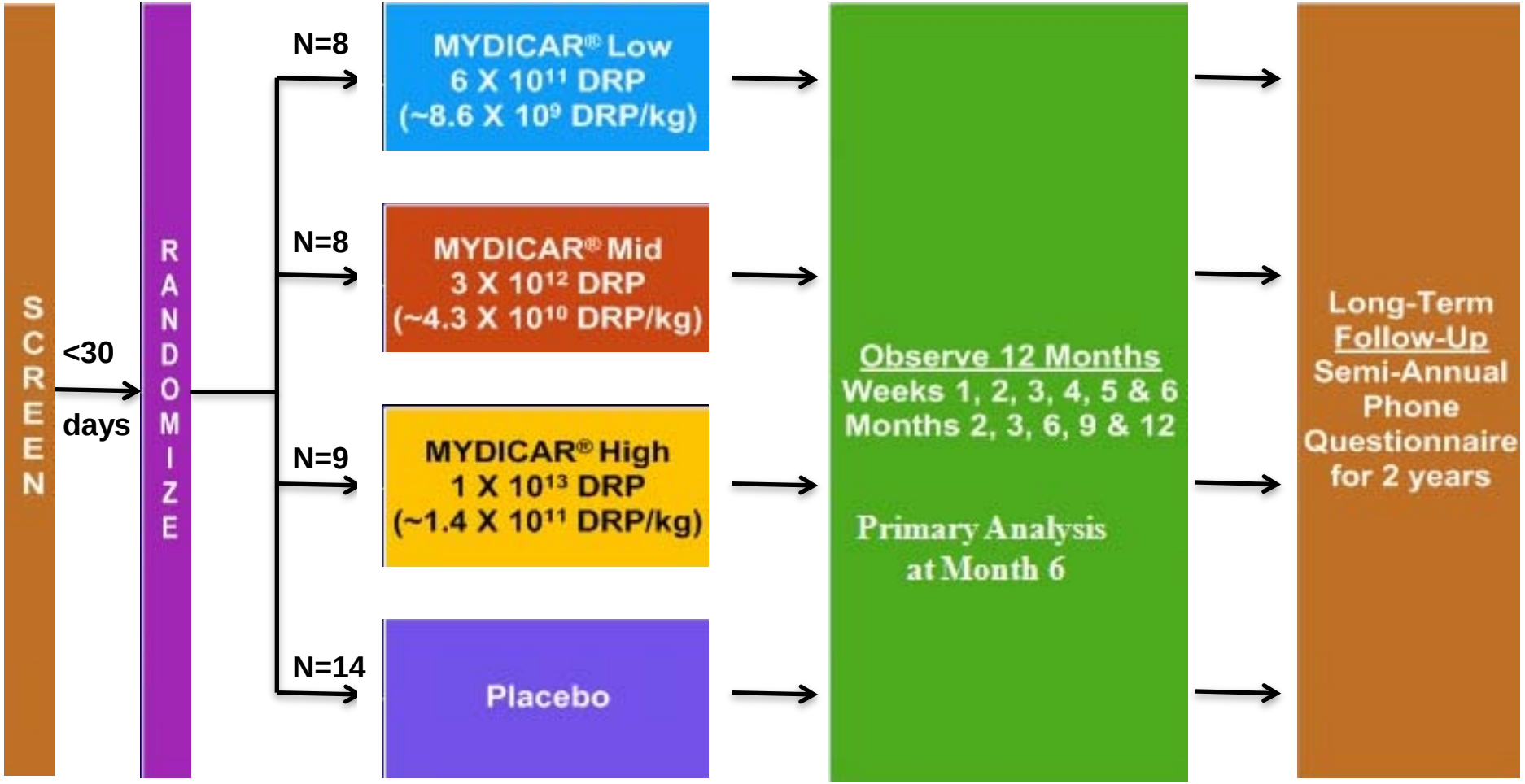
- SERCA2a is the cardiac isoform of this family of Ca2-ATPases, and a loss of its activity and resultant decrease in SR Ca2 uptake is a feature of the failing cardiomyocyte including in human HF
- Conceptually, SERCA2a gene therapy in HF is a rational venture as it would remove cytosolic Ca2 faster in diastole and increase contractile reserves by increasing SR Ca2 concentration

SERCA2a Gene Therapy Trials: CUPID

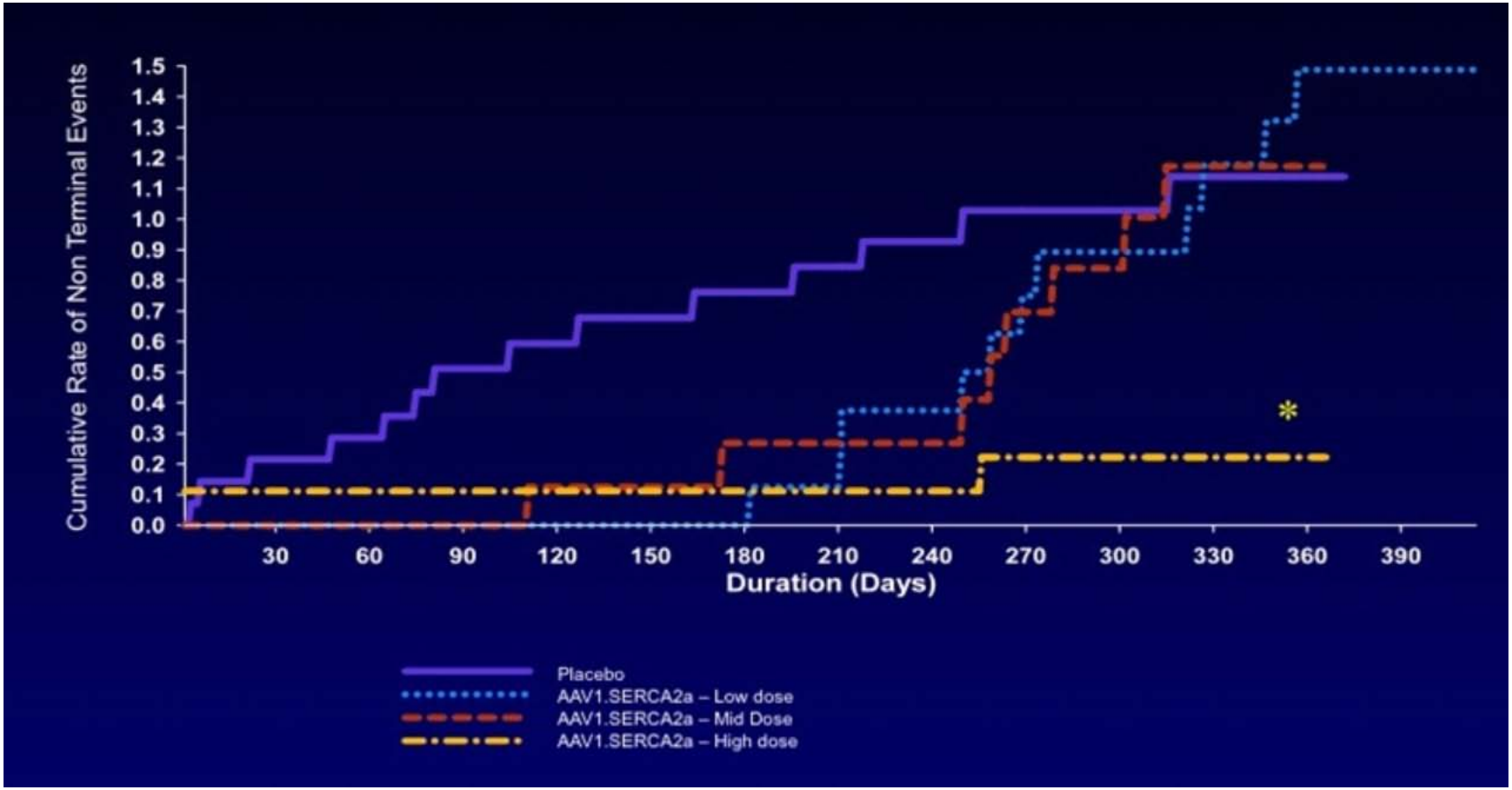
Intracoronary delivery of AAV1- SERCA2a (denominated MYDICAR) in HF patients (III/IV Class):

- Phase I: is a dose-escalation study (4 doses per patient appropriately spaced in time) aimed at identifying safe and efficient dose of AAV1-SERCA2a delivered by antegrade epicardial coronary artery infusion to patients with ischemic or nonischemic dilated cardiomyopathy (12pts).
- Phase 2: is a placebo-controlled randomized trial. Importantly, patients receiving AAV1- SERCA2a are required to also receive an implantable intracardiac defibrillator. Thus, the potential occurrence of ventricular arrhythmias discussed above will be addressed (39 pts).

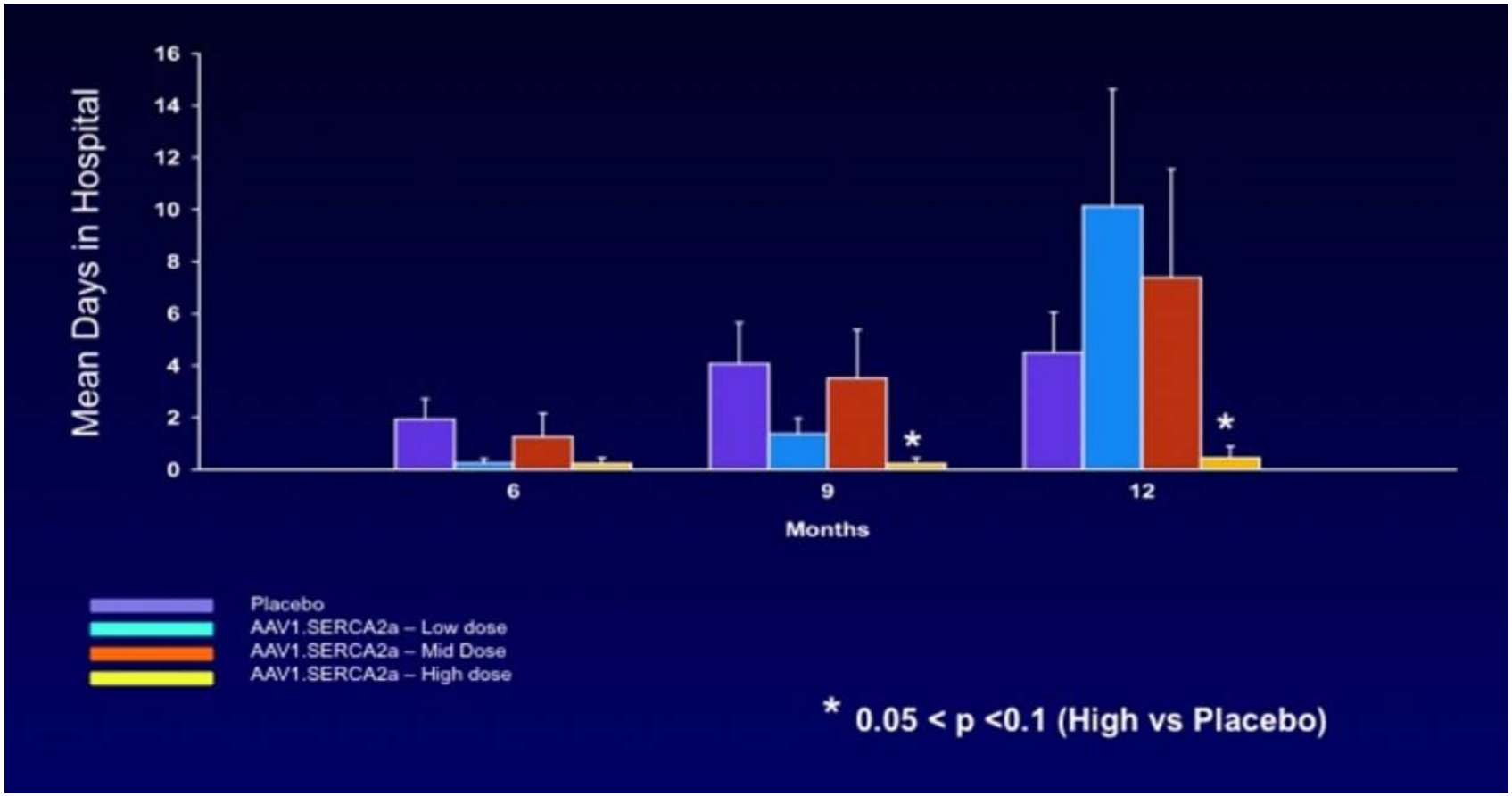
Study Schema



Cumulative Clinical Event Rate



Days of CV-Related Hospitalization



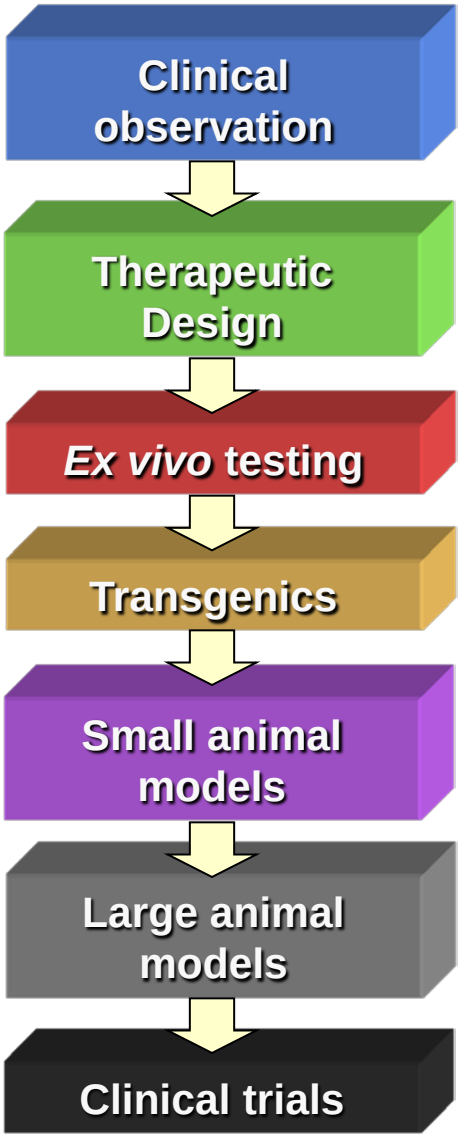
Safety

	Placebo N=14	MYDICAR Low N=8	MYDICAR Mid N=8	MYDICAR High N=9
Any Adverse Event (Post-Infusion), n (%)	13 (93)	8 (100)	8 (100)	8 (89)
Any Serious Adverse Event, n (%)	9 (64)	5 (63)	4 (50)	3 (33)

- No findings for changes over time between groups for:
  - Troponin, CK, CK-MB
  - Serum Chemistries and Hematology
  - Vitals
  - Heart Rate
- No new findings compared to baseline for ICD interrogation and ECG

GRK2 inhibition in HF

Effective Model of Translational Research



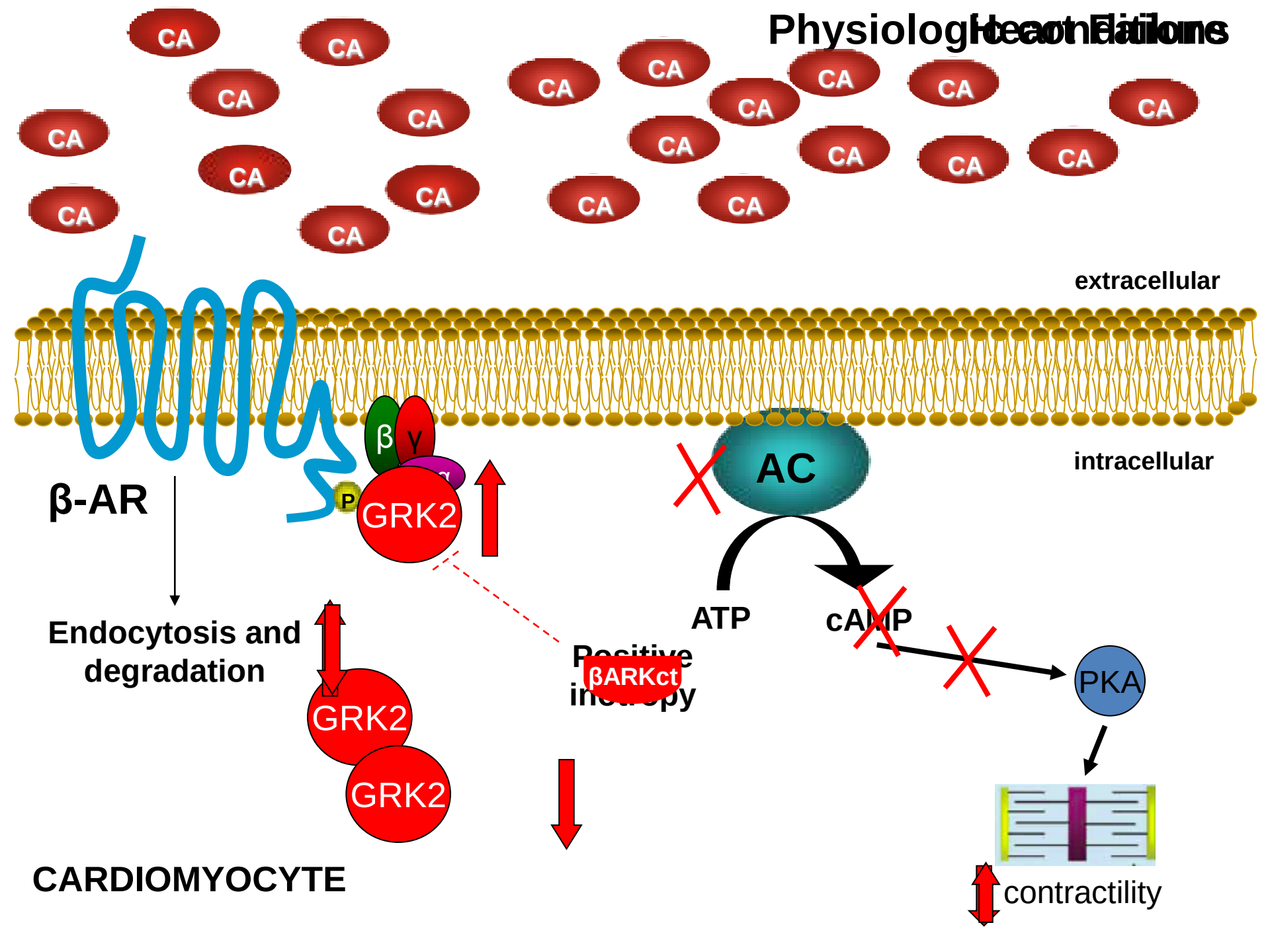
Circulation 1993

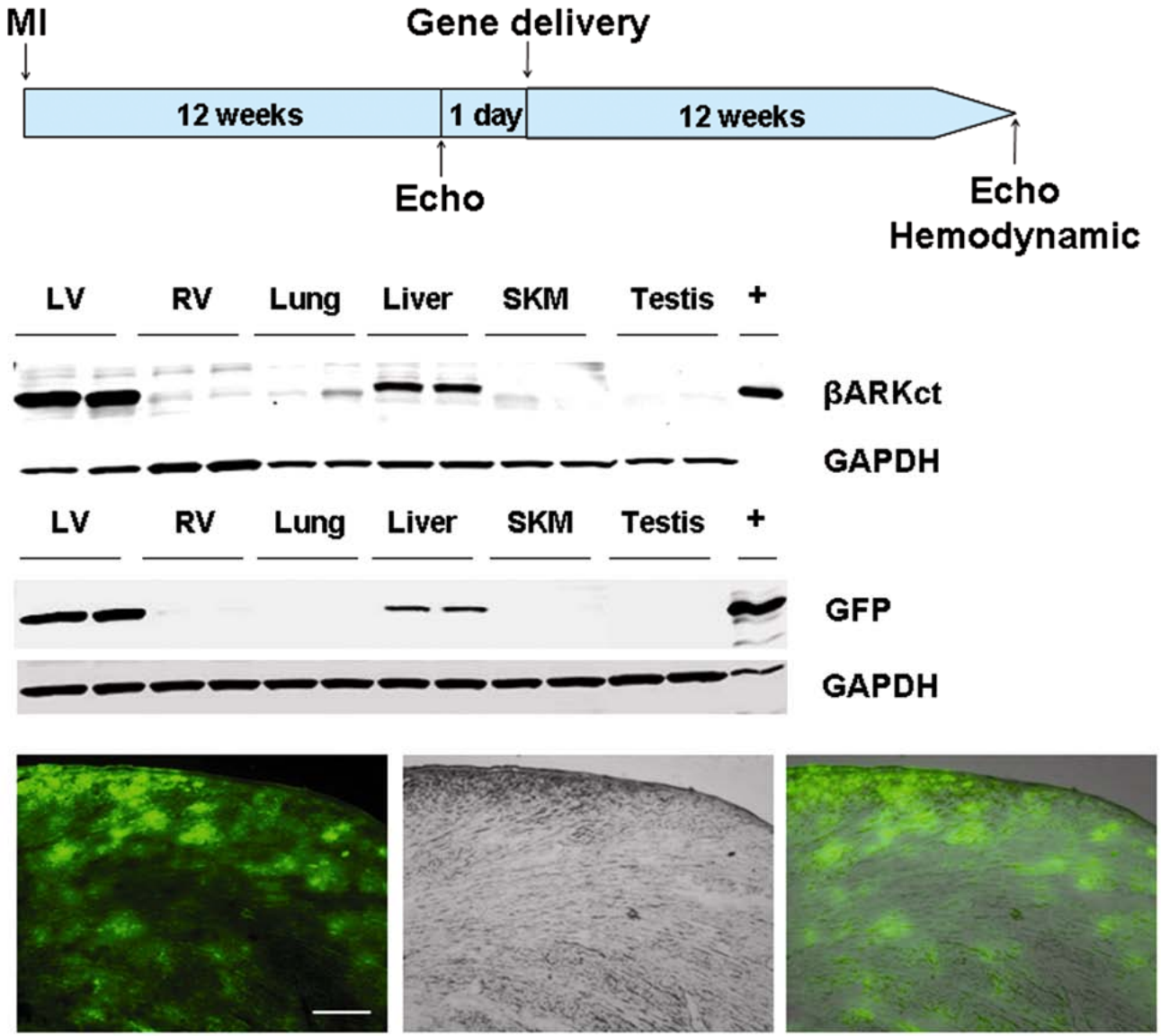
Circulation 2004

Science 1995, PNAS 1998, 2001, JACC 2002, Circ. Res 2008

Circulation 2000, 2001, 2009

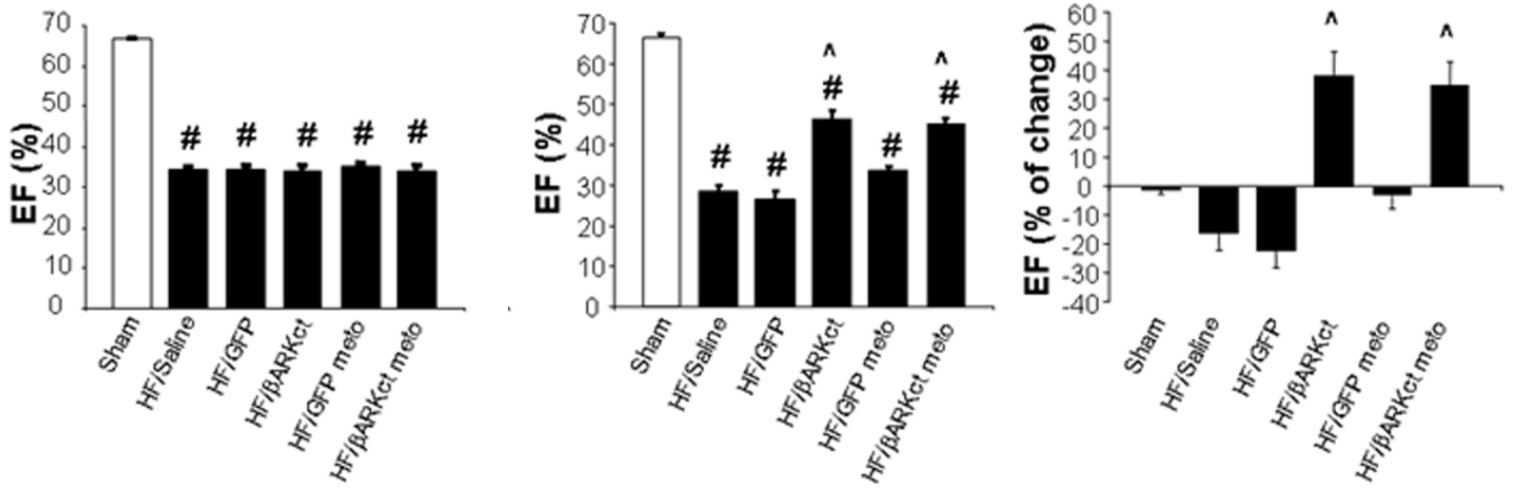
Work in progress


CA
extracellular
intracellular
β-AR
β
γ
P
GRK2
AC
ATP
cAMP
PKA
Endocytosis and degradation
GRK2
GRK2
βARKct
Positive inotropy
contractility
CARDIOMYOCYTE



Rengo et al. Circulation. 2009;119:89-98

Long-term rAAV6-mediated βARKct gene therapy improves cardiac function in chronic HF



^*P*<0.05 vs HF/saline, HF/GFP, or HF/GFP-metoprolol groups; #*P*<0.05 vs sham; ANOVA analysis and Bonferroni test among all groups; n= 12-14 for each group

Rengo et al. Circulation. 2009;119:89-98

Conclusions

- Despite gene therapy is still in its infancy, it holds great promise in the aspect of improving survival and quality of life for HF patients
- Importantly, a few of the potential targets are in preclinical stages with the goal of clinical trials in the near future.
- The initial safety and outcomes of the human trials ongoing with AAV-SERCA2a will be extremely valuable to fuel the journey of other targets and keep the momentum going for HF gene therapy

(Time to Market, 4 Years)

(Time to Market, 10 Years)