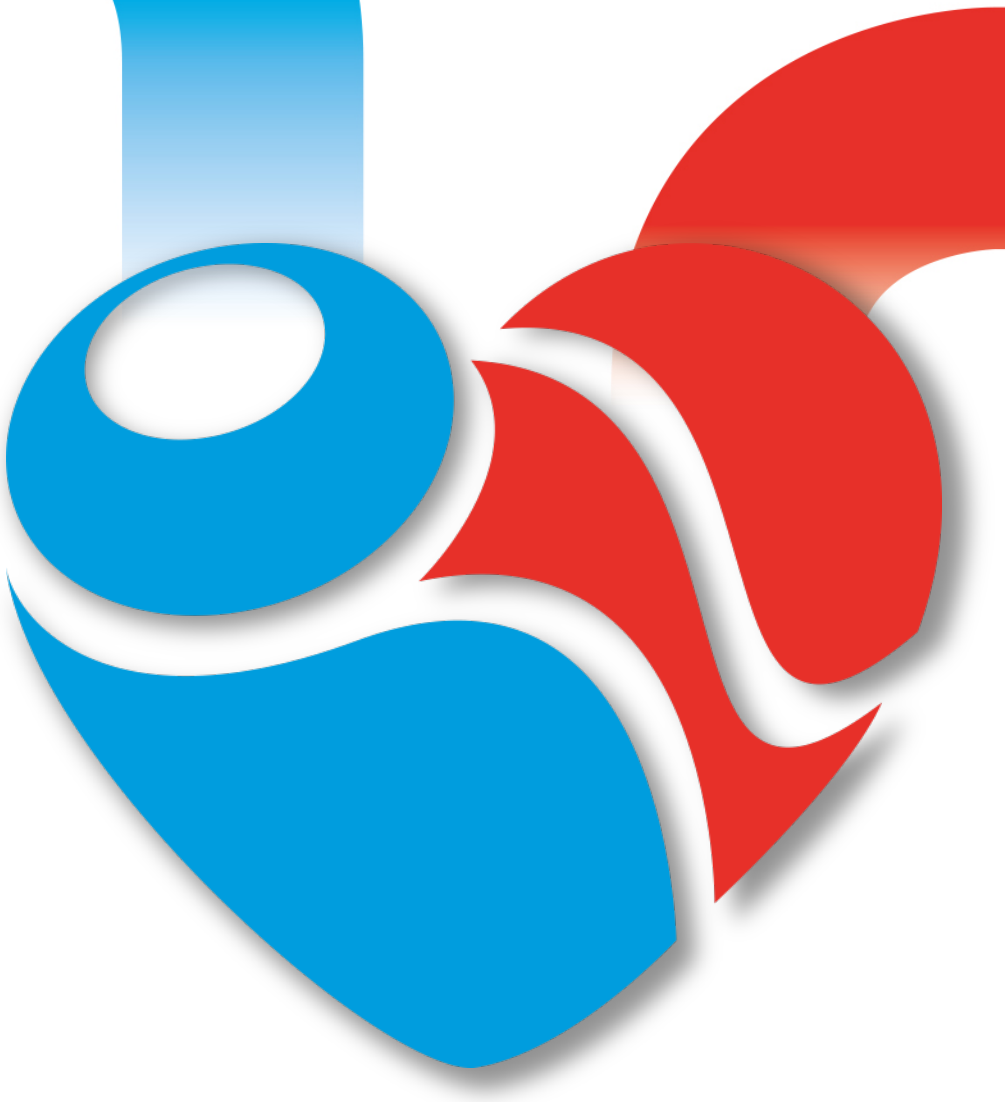
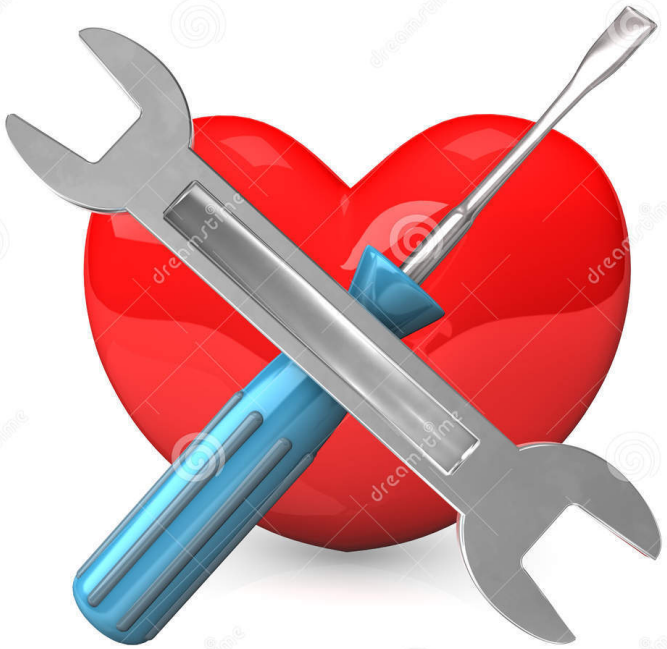
Barts Health NHS
NHS Trust

The ‘REGENERATE’ programme – results and future objectives



Professor Anthony Mathur
Barts Heart Centre
Queen Mary University of London
University College London

Regeneration vs repair



Cell Therapy Concepts

Cardiac Regeneration

- **production of new cardiomyocytes to replace damaged myocardium**
- **Magnitude >10^{12} cells**

Cardiac Repair

- **containment of myocardial injury**
- **optimisation of ischaemic environment**
- **Magnitude >10^{6} cells**

Cell Types

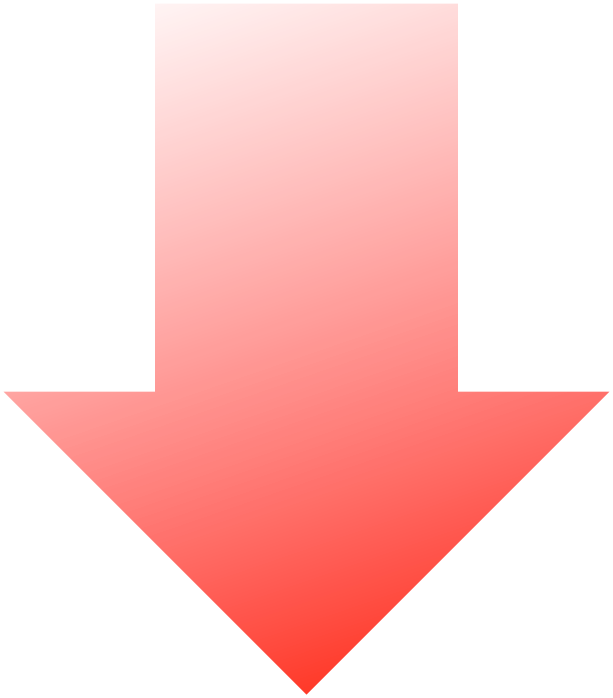
Autologous:

Bone marrow derived:
Mononuclear /CD34+ fraction
Mesenchymal stem cells (MSC)
Endothelial progenitor cells (EPC)
Multipotent adult progenitor cell (MAPC)
Skeletal myoblast
Cardiac stem cell
Adipose derived - MSC
Inducible Pluripotent stem cells

Allogeneic:

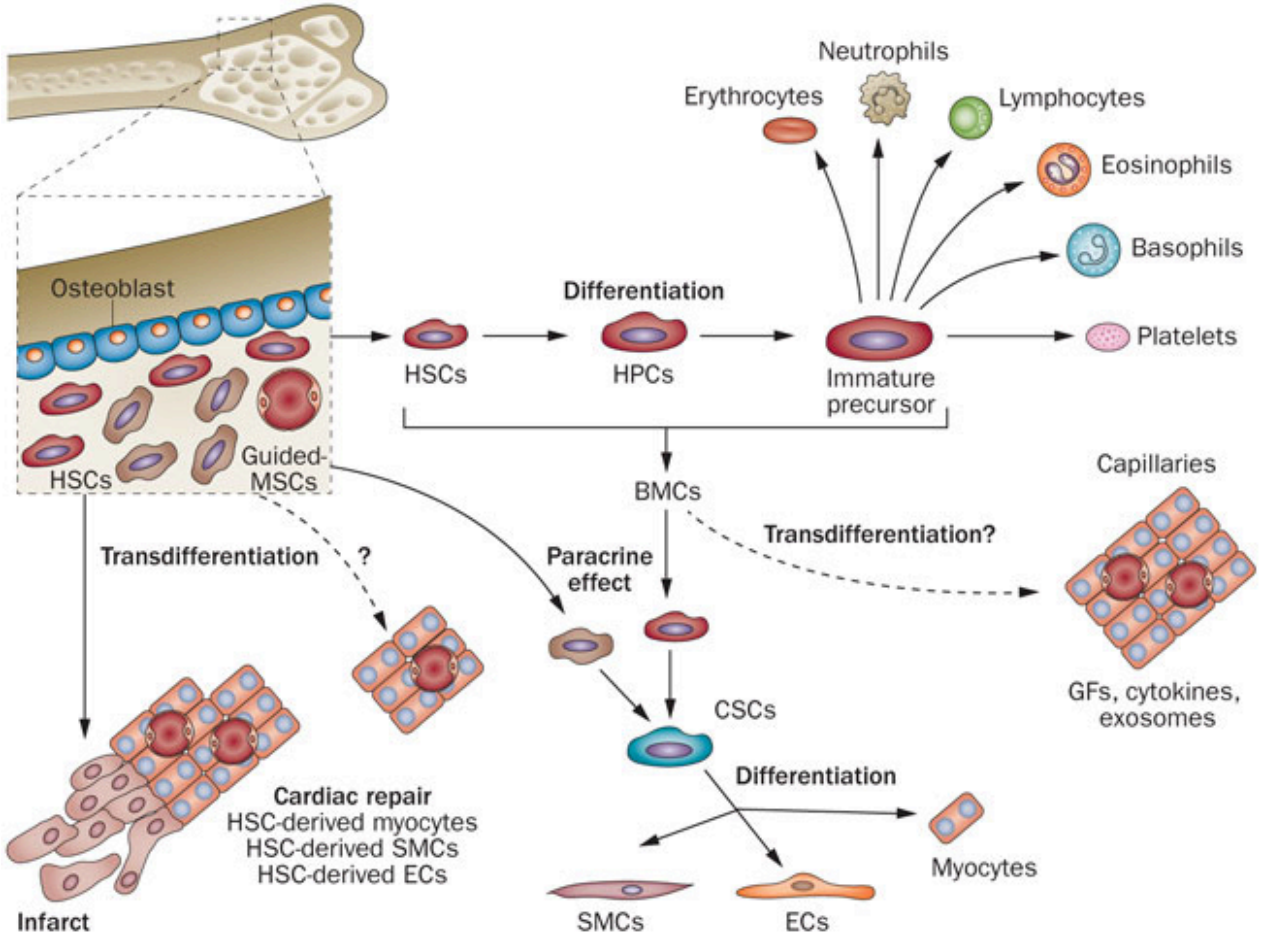
Bone marrow derived
Fetal Cardiomyocytes
Embryonic stem cells
Cord derived CD34+ cells
Amniotic fluid - CD34+/CD133+
Gonadal - menstrual/testicular

CARDIAC REPAIR

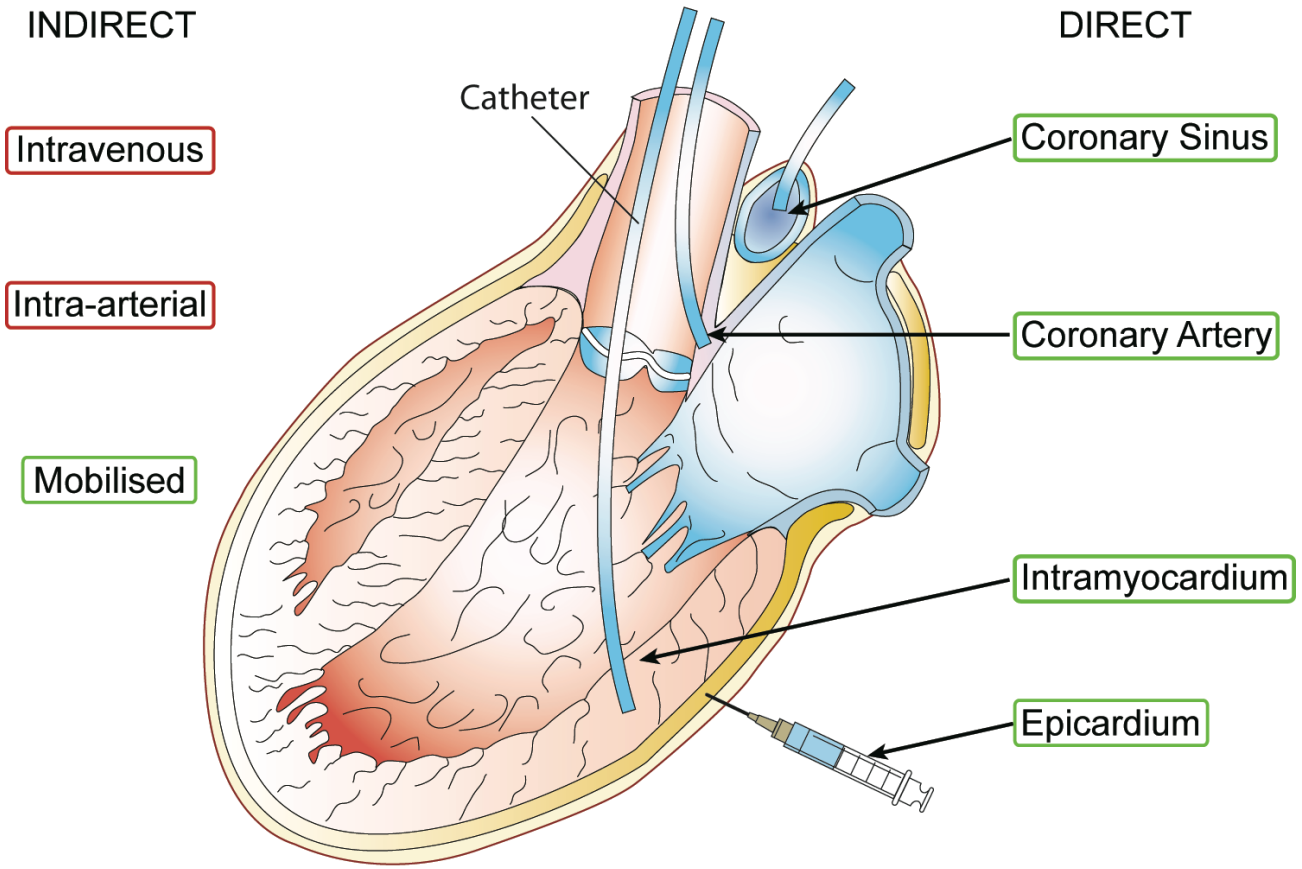


CARDIAC REGENERATION

Bone Marrow Mononuclear Cells

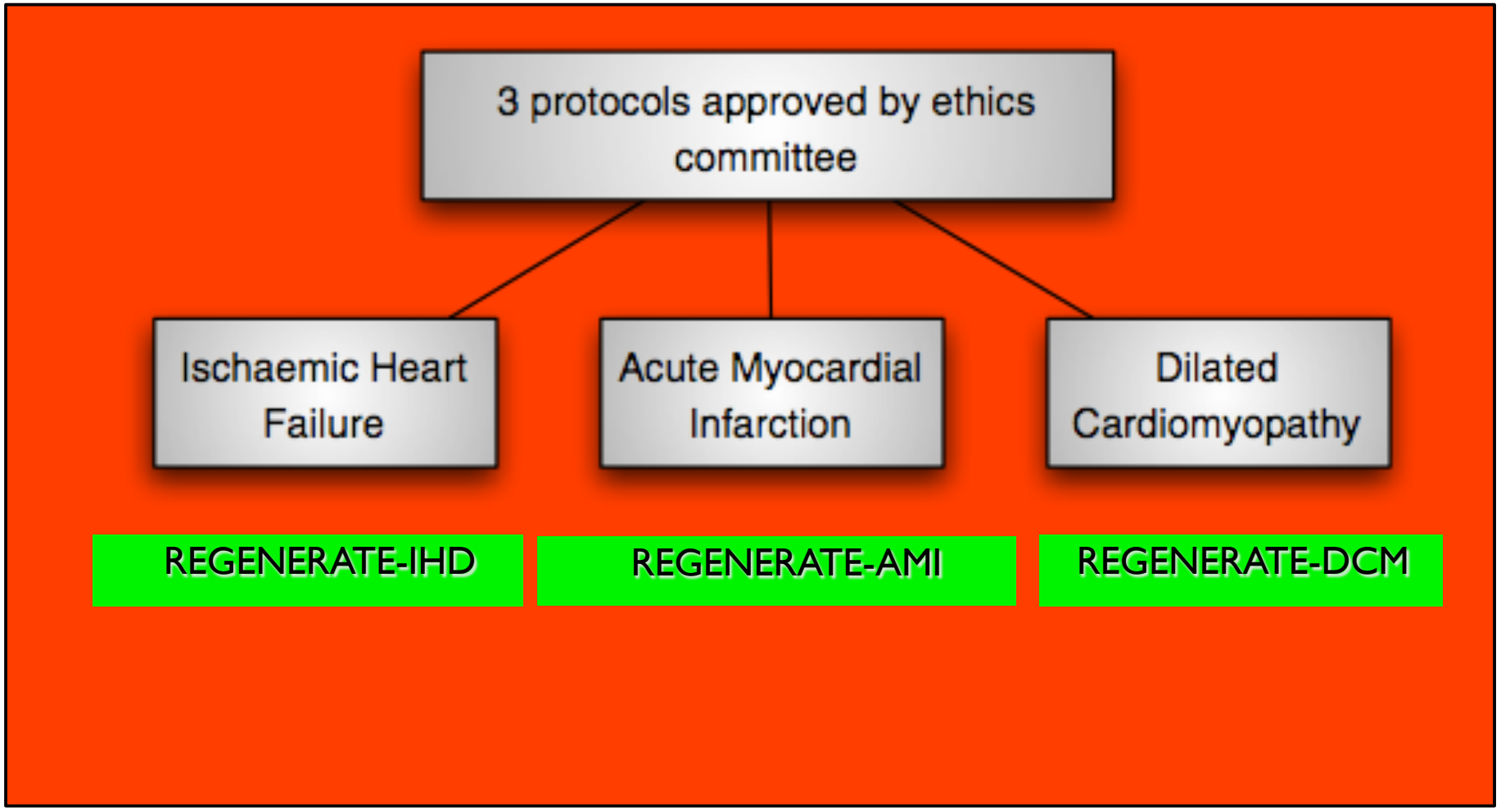


Delivery Routes

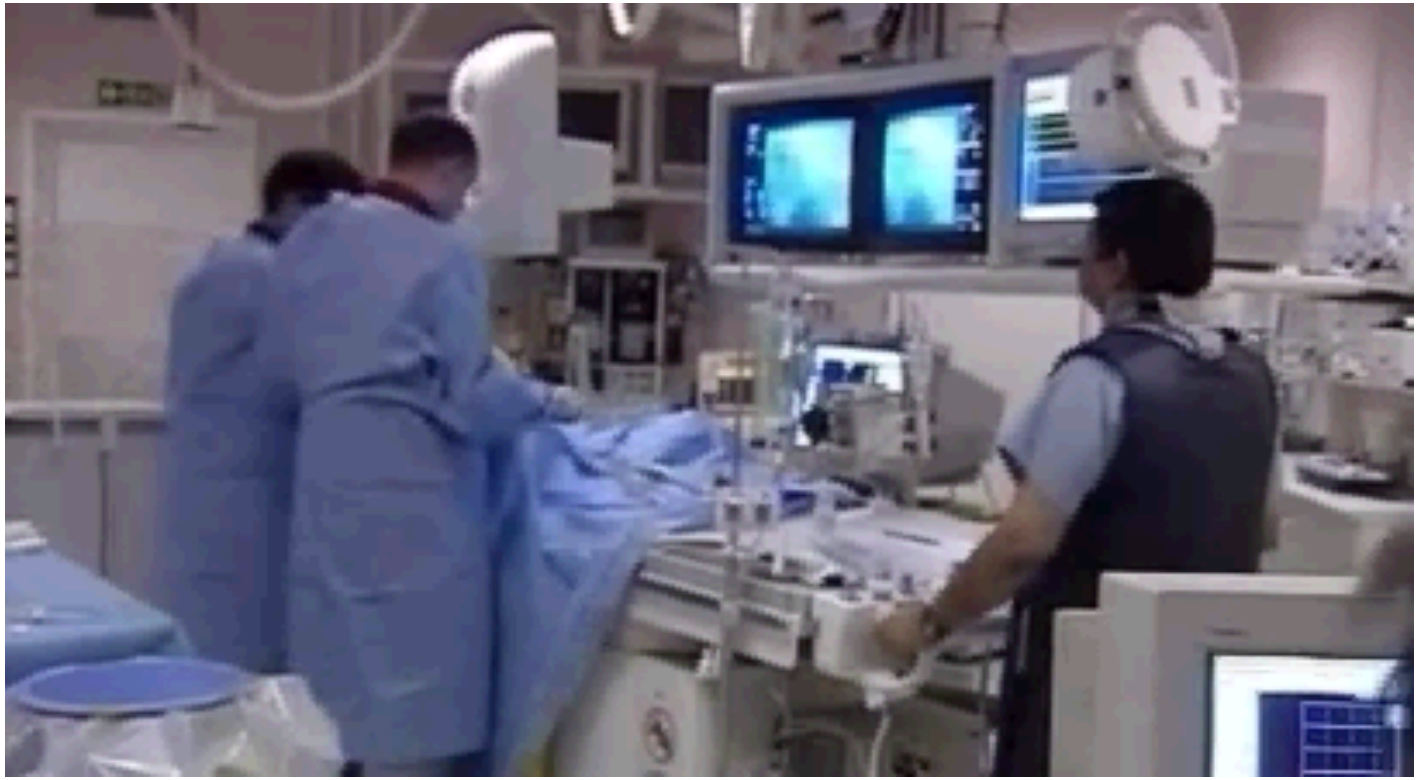


CLINICAL TRIALS

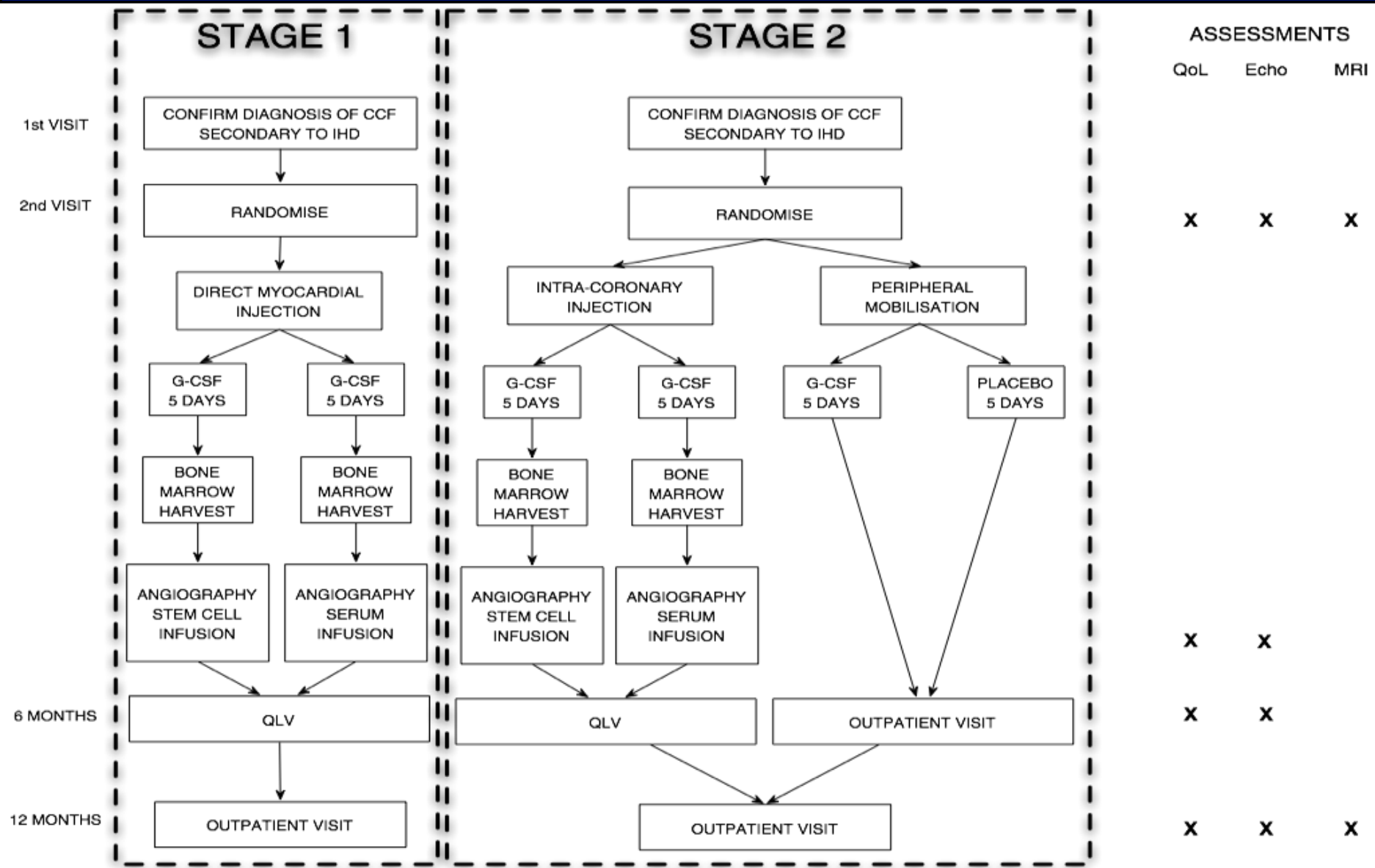
‘REGENERATE’


3 protocols approved by ethics committee
Ischaemic Heart Failure
Acute Myocardial Infarction
Dilated Cardiomyopathy
REGENERATE-IHD
REGENERATE-AMI
REGENERATE-DCM

REGENERATE IHD

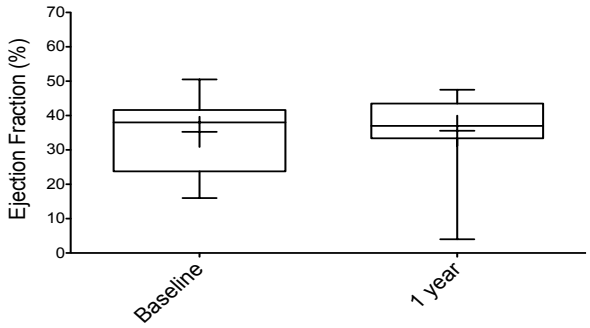


REGENERATE IHD

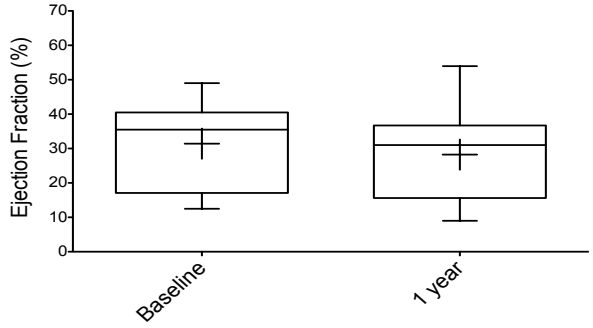


REGENERATE IHD

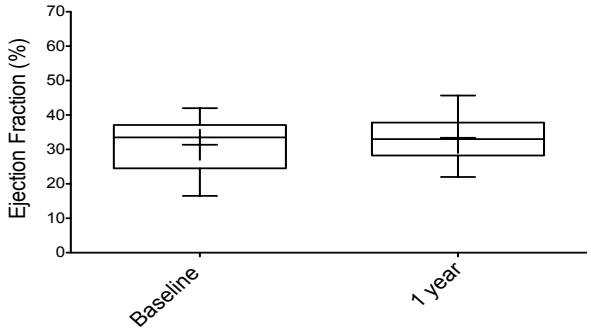
Peripheral placebo



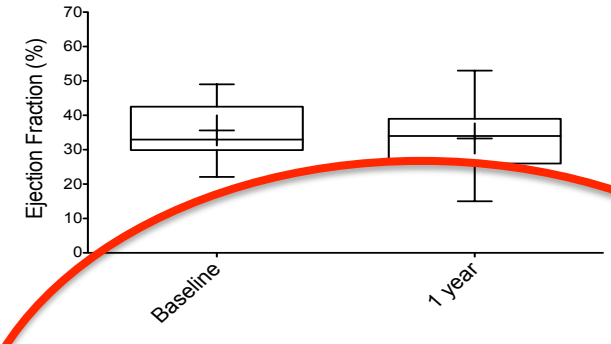
Peripheral G-CSF



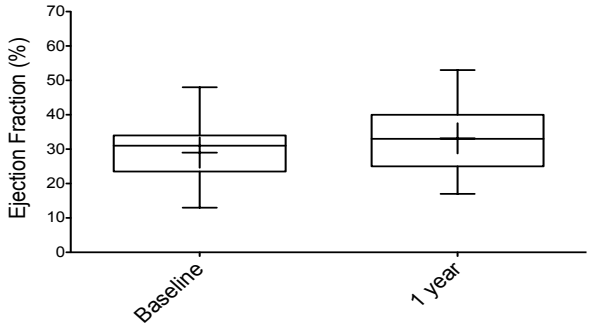
IC serum



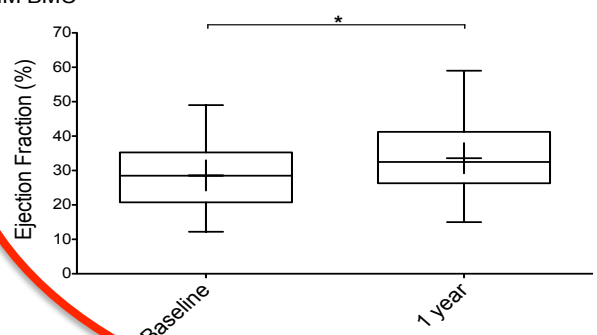
IC BMC



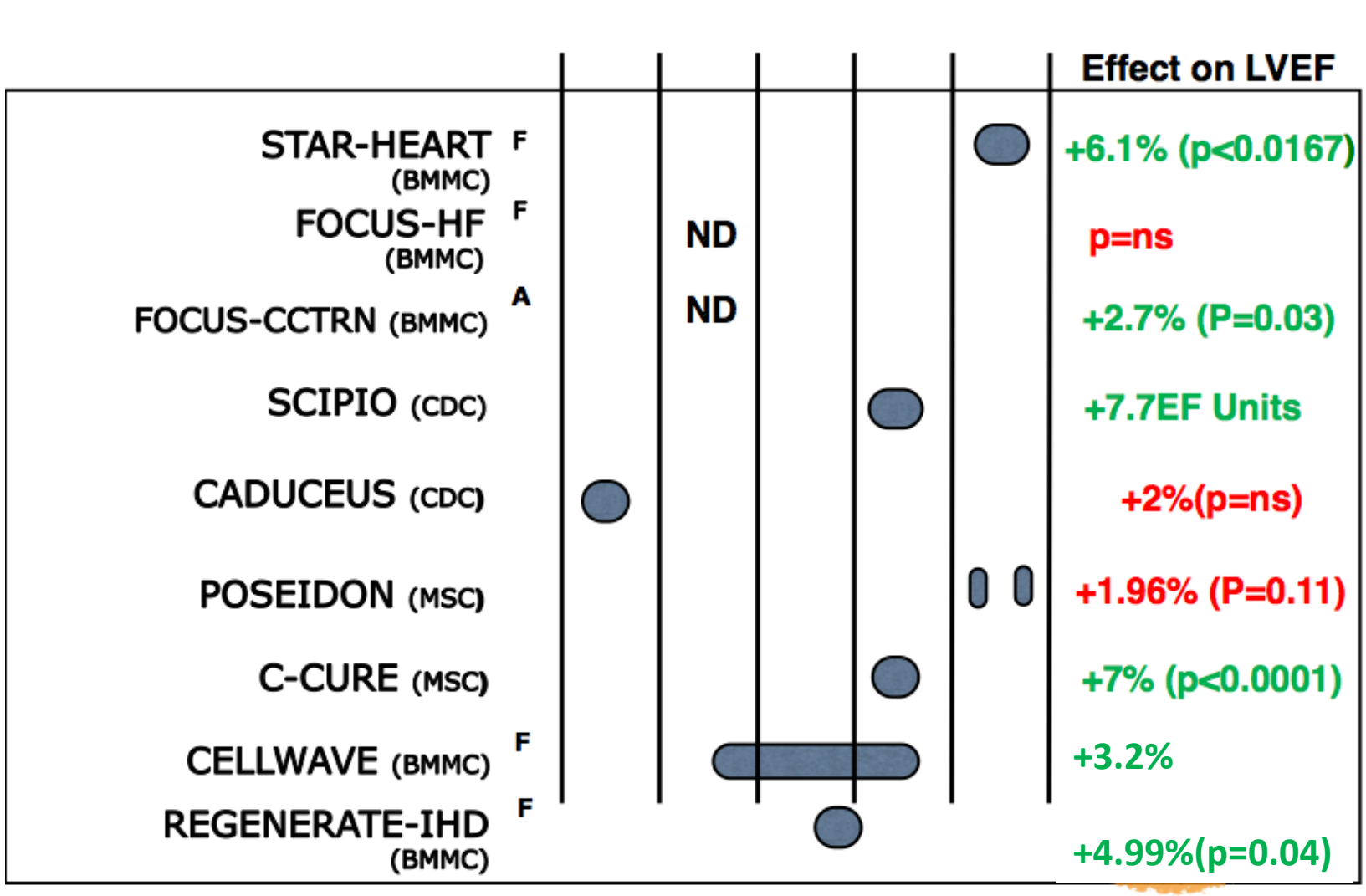
IM serum



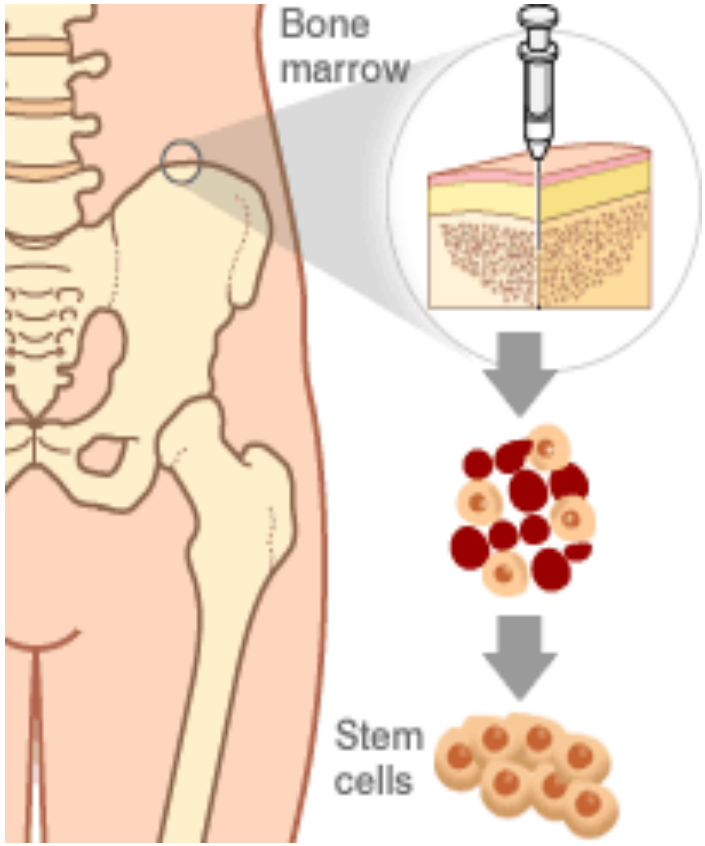
IM BMC

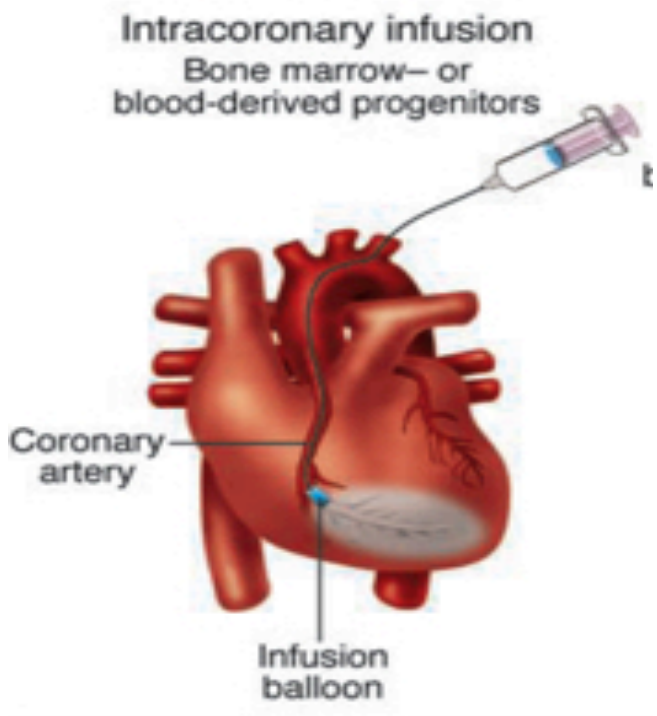


Recent Trials -CHF



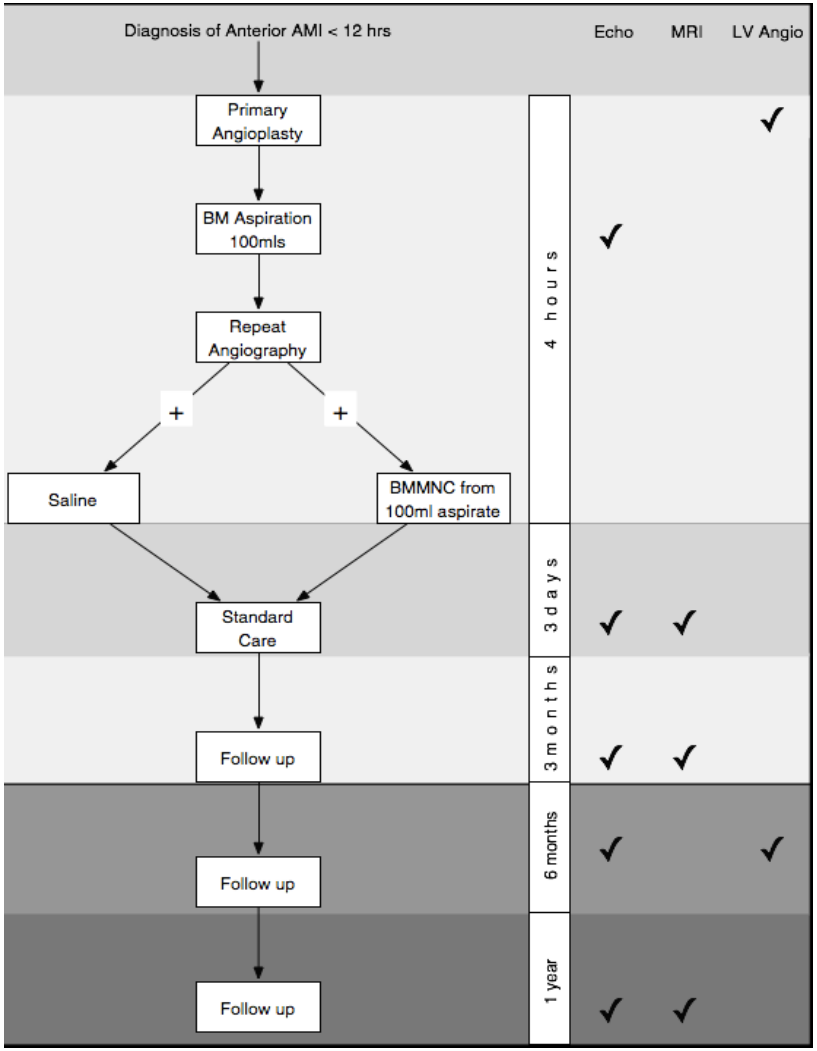
REGENERATE AMI





Dimmeler S, Zeiher AM, Schneider MD J Clin Invest 2005:115;572.

REGENERATE AMI

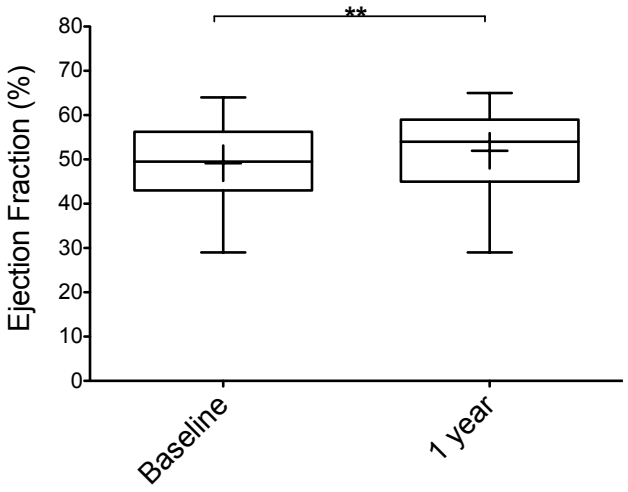


MRC Clinical Trials Unit

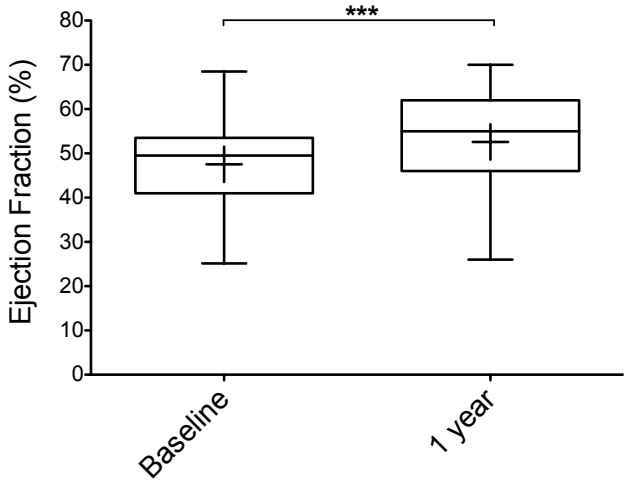
UK STEM CELL FOUNDATION

REGENERATE-AMI

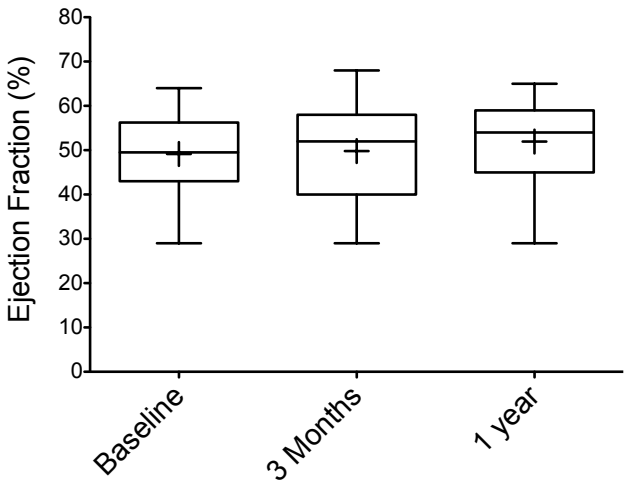
IC serum



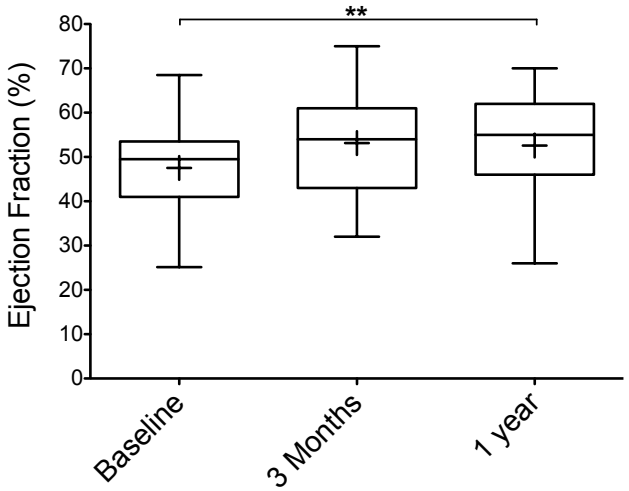
IC BMC



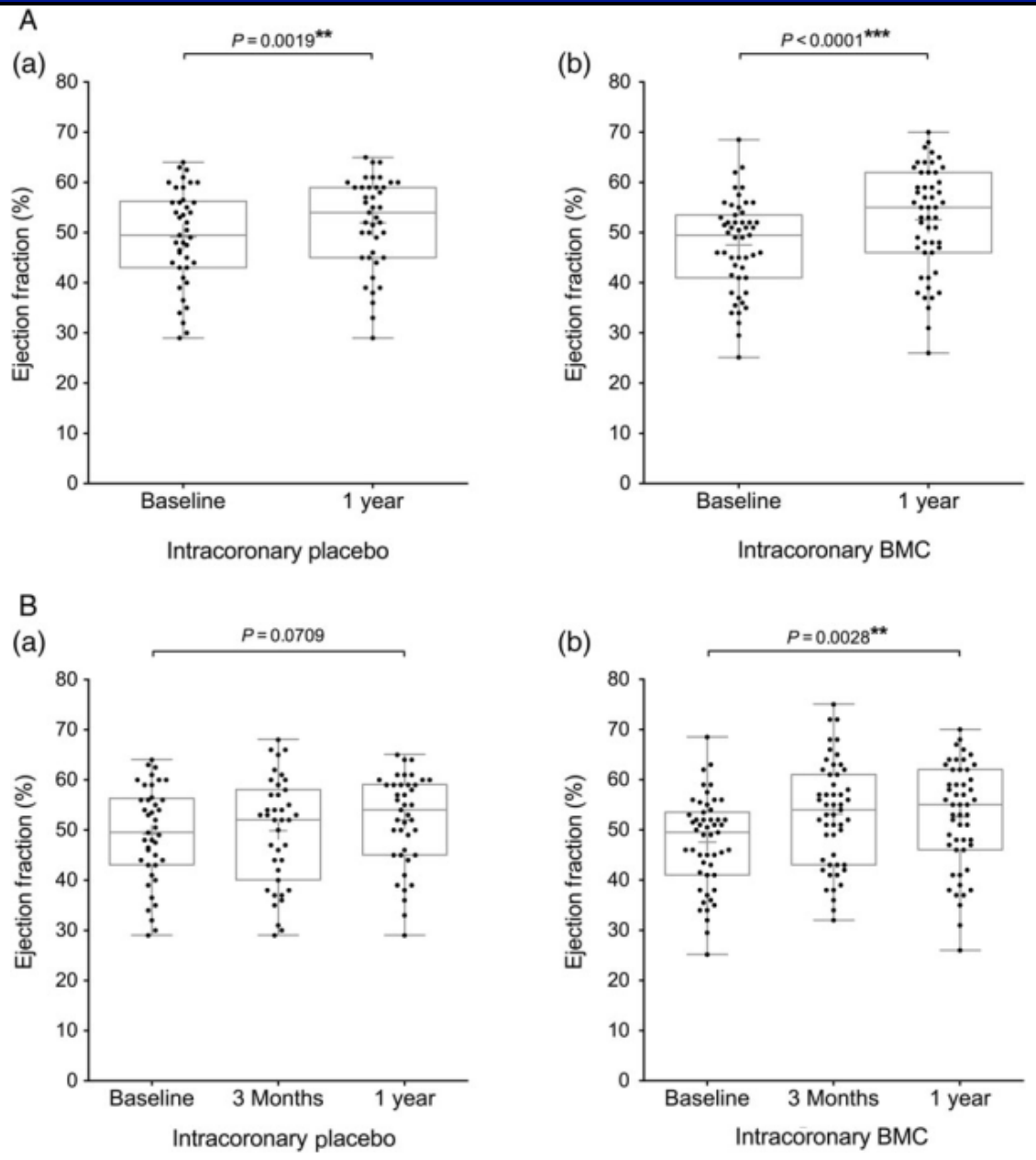
IC serum



IC BMC

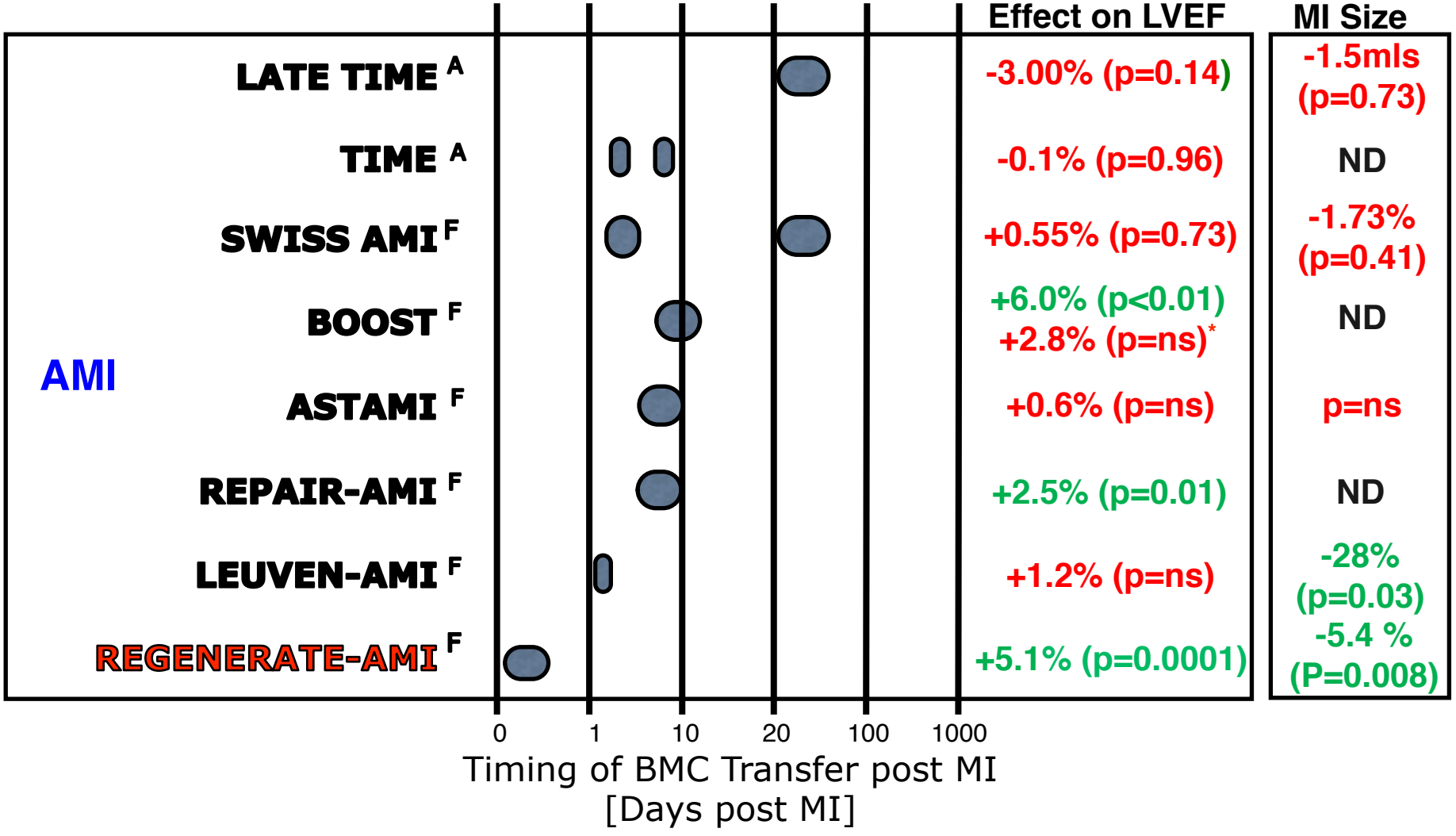


REGENERATE-AMI



F. Choudry et al., *European Heart Journal* , ehv493 (2015).

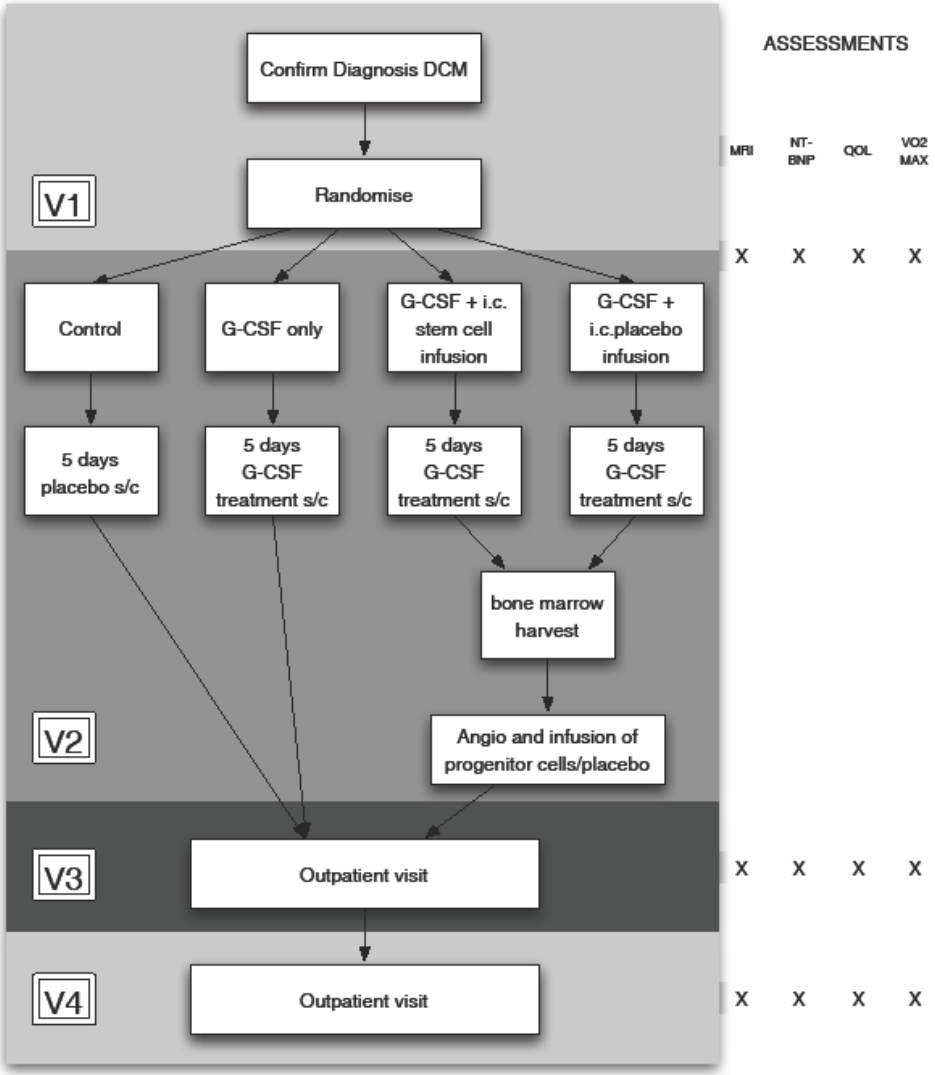
Recent Trials - AMI



REGENERATE DCM

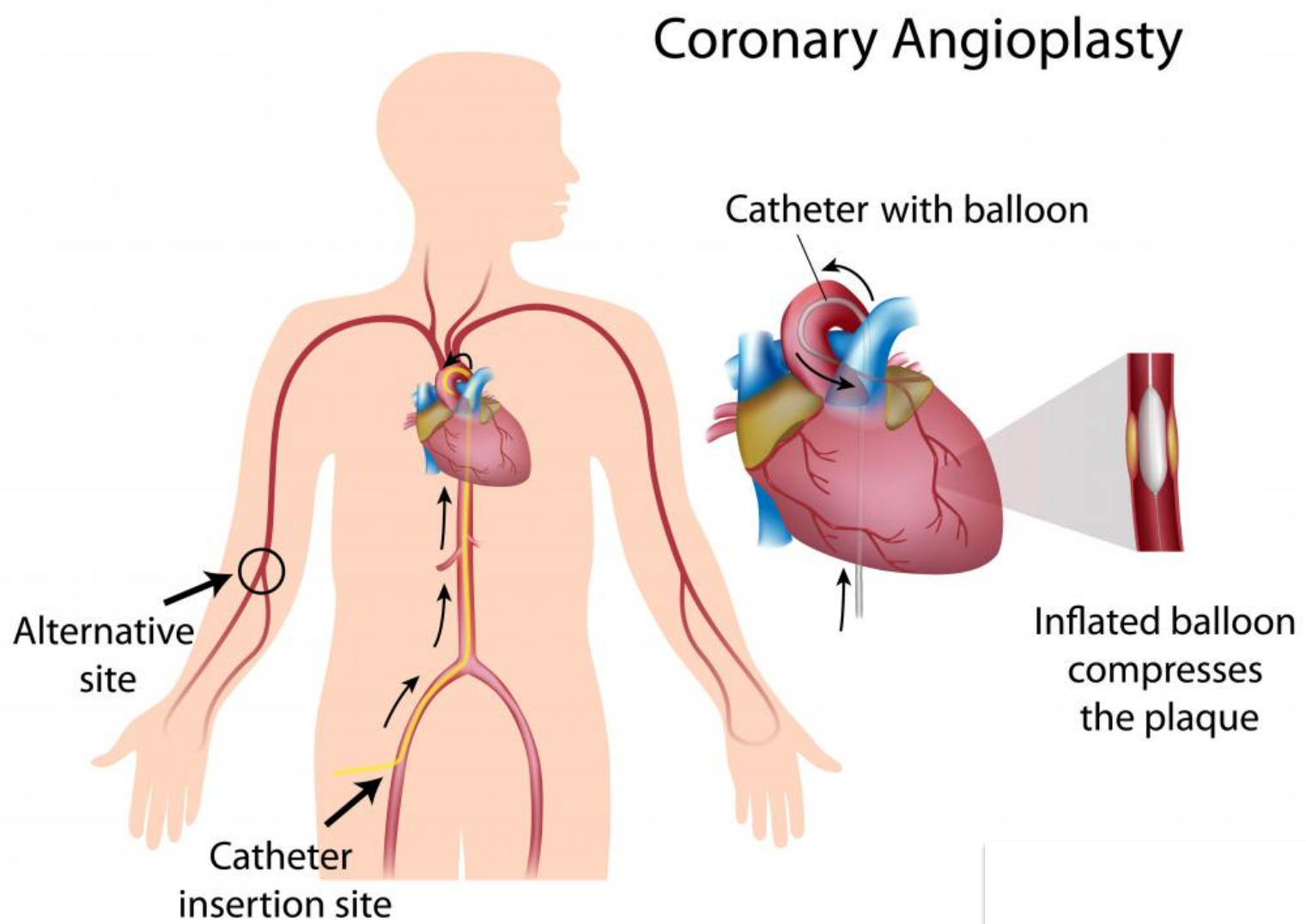
Pioneering UK Stem Cell Therapy

HEART CELLS FOUNDATION



S. Hamshere et al., *European Heart Journal* **36**, 3061-3069 (2015).

Coronary artery injection

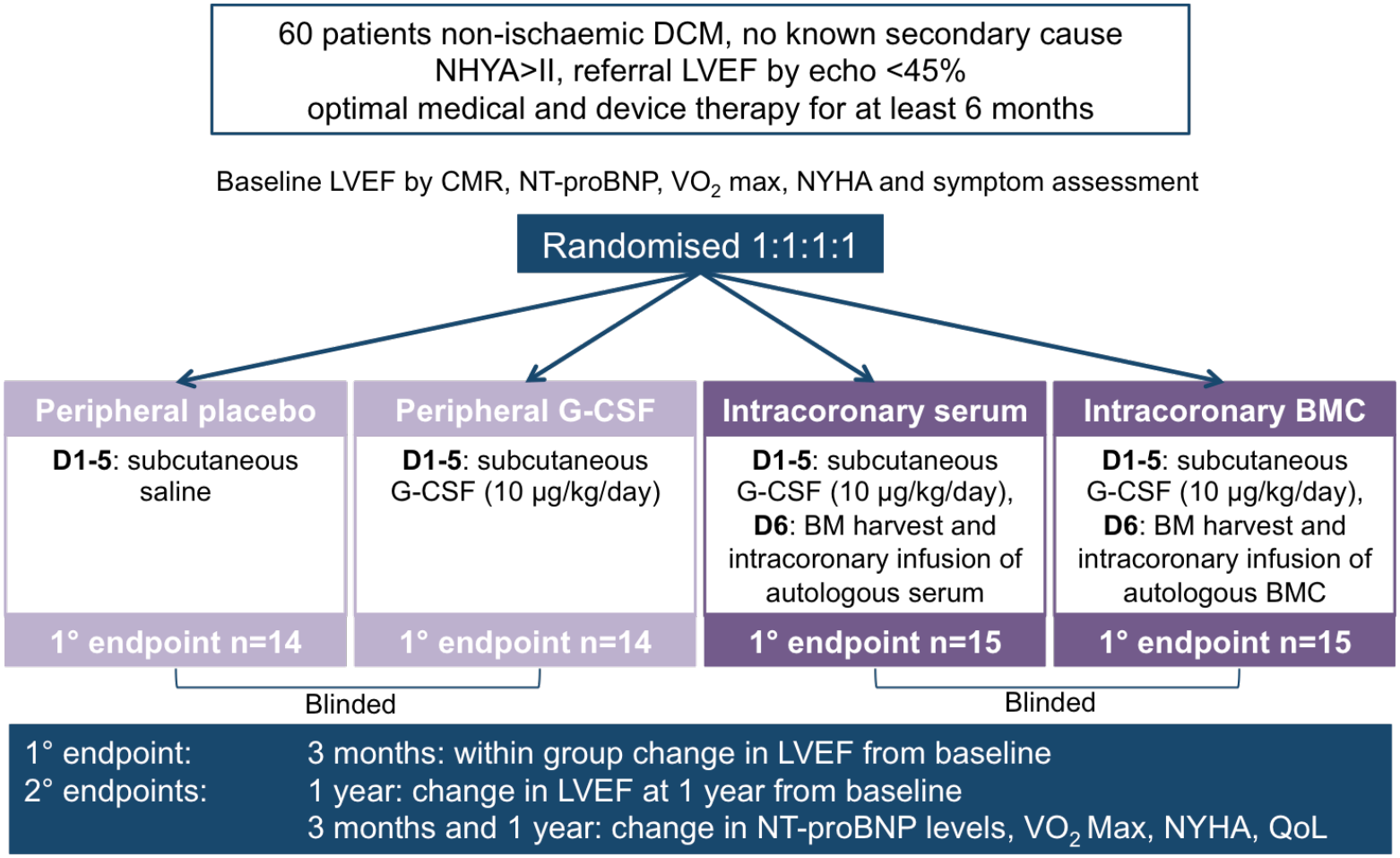


Baseline characteristics

	Peripheral Placebo (n = 14)	Peripheral G-CSF (n=14)	Intracoronary Serum (n = 15)	Intracoronary BMC (n = 15)
Age (years), mean (SD)	56·79 (9·84)	54·57 (9·76)	54·87 (10·86)	57·67 (12·32)
Sex (M/F)	12/2	10/4	9/6	10/5
BMI (kg/m^2), mean (SD)	29·15 (4·48)	29·19 (5·19)	28·26 (9·10)	27·23 (4·33)
Hypertension, No. (%)	2 (14·2%)	1 (7·1%)	1 (6·6%)	2 (13·3%)
Hypercholesterolemia, No. (%)	3 (21·4%)	2 (14·2%)	1 (6·6%)	0 (0%)
Diabetes mellitus, No. (%)	2 (14·2%)	1 (7·1%)	1 (6·6%)	2 (13·3%)
Active smoker, No. (%)	2 (14·2%)	1 (7·1%)	2 (13·3%)	2 (13·3%)
Family history of heart disease,No. (%)	2 (14·2%)	1 (7·1%)	2 (13·3%)	2 (13·3%)
Diagnosis to enrolment (y),mean (SD)	5·43 (0·98)	7·6 (2·09)	8·00 (1·61)	4·9 (0·96)
Therapy				
ACEi/ARB, No. (%)	13 (92·9%)	14 (100%)	15 (100%)	15 (100%)
B-Blockers, No. (%)	14 (100%)	12(83·7%)	13 (86·6%)	13 (86·6%)
Diuretics, No. (%)	8 (57·1%)	8 (57·1%)	8 (53·3%)	9 (59·9%)
Aldosterone Antagonists, No. (%)	11 (78,6%)	7 (50·0%)	12 (79·9%)	10 (66·6%)
ICD, No. (%)	3 (21·4%)	5 (35·7%)	4 (26·6%)	4 (26·6%)
Biventricular Pacemaker, No. (%)	1 (7·1%)	0 (0%)	2 (13·3%)	2 (13·3%)
CRT-D, No. (%)	6 (42·9%)	4 (28·6%)	3 (19·9%)	7 (46·6%)
LVEF; mean (95%CI)	29·75 (24·61 – 34·89)	36·5 (28·64 – 44·36)	41·70 (33·25 – 50·15)	32·93 (23·82 – 42·05)
NT-proBNP (pg/ml); mean (95%CI)	1374 (652·4 – 2095)	1558 (394·3 – 2721)	1379 (228·8 – 2528)	1031 (500·7 – 1562)
VO2 Max (ml/kg/min); mean (95%CI)	18·99 (17·03 – 20·96)	18·83 (15·82 – 21·83)	19·55 (15·65 0 23·44)	17·67 (14·48 – 20·87)

Objective & design

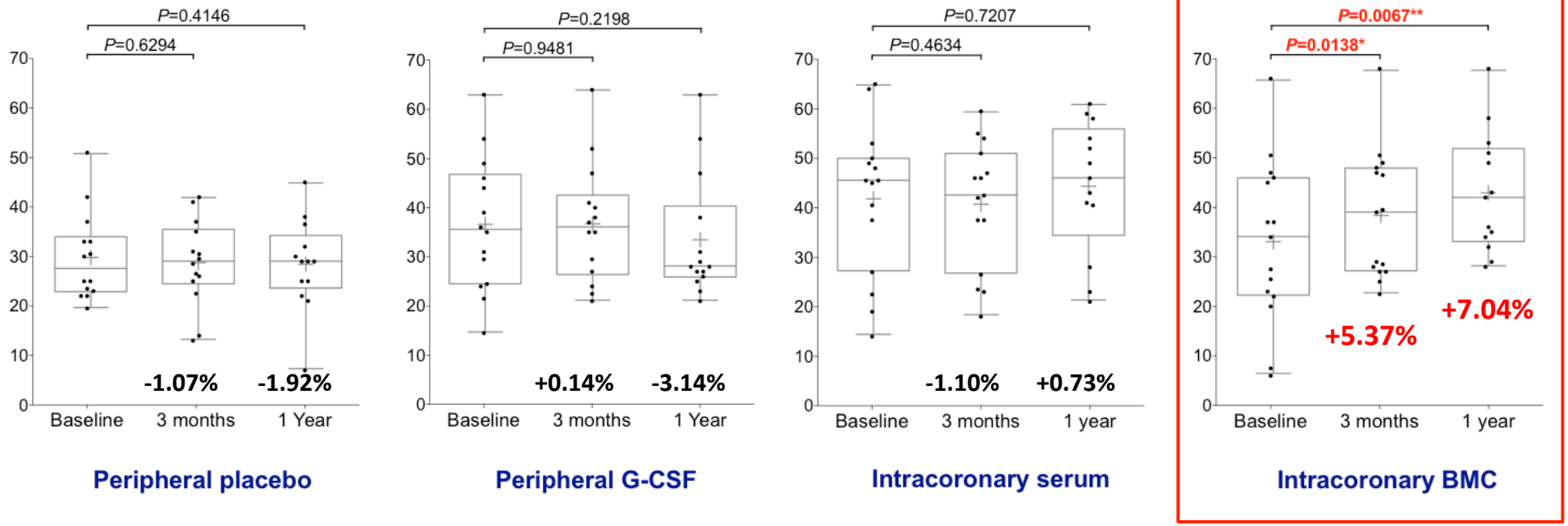
Objective: to determine if G-CSF alone or in combination with intracoronary autologous bone marrow progenitor cells leads to an improved outcome in DCM.



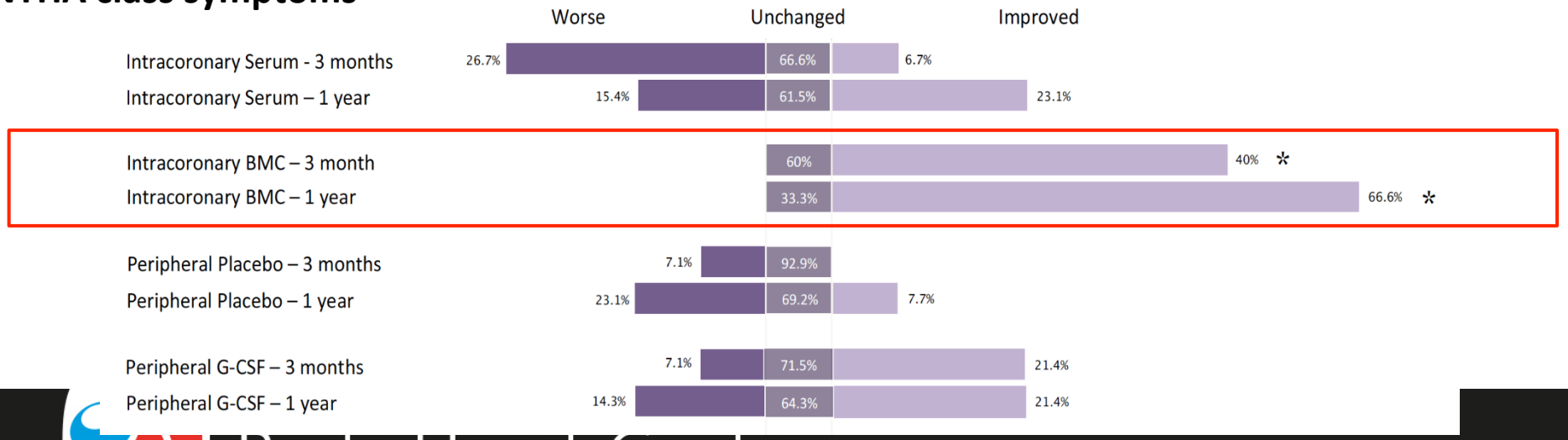
REGENERATE DCM

Character	Range	Mean
CD34+ (/uL)	1.358-13.30	4.911
EPC (CD133+/VEGFR2+) (/uL)	13.95-382.5	90.27
Total MNC ($x10^9$/L)	10.80-825.0	216.0
Plts ($x10^9$/L)	54.00-4700	858.5
Neutrophils ($x10^9$/L)	6.750-132.1	63.45
RBC ($x10^{l2}$/L)	450.0-6300	2433

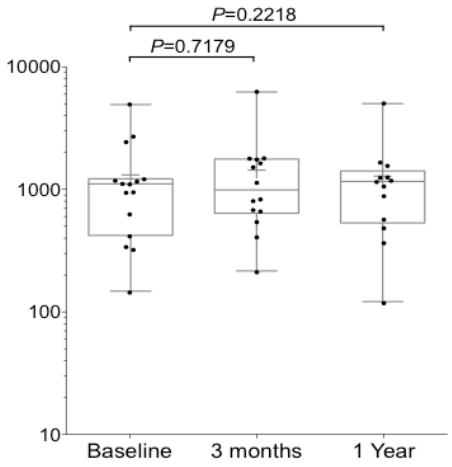
Ejection Fraction (%)



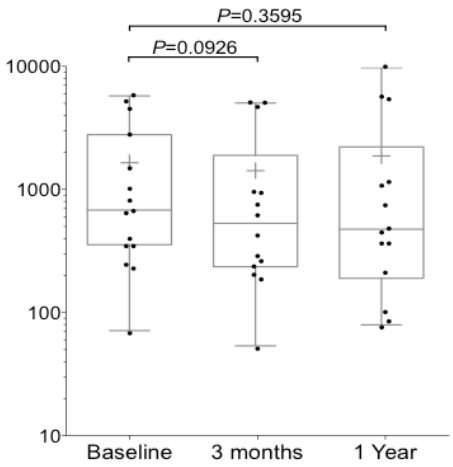
NYHA class symptoms



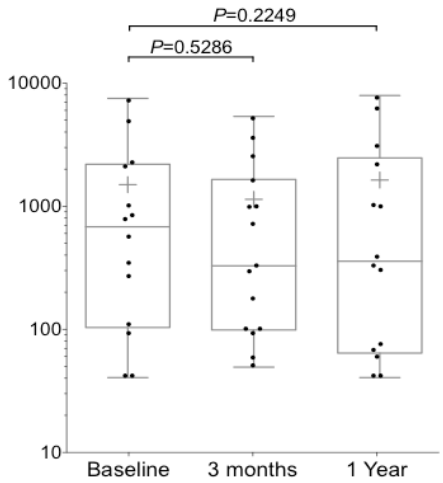
NT-proBNP (pg/ml)



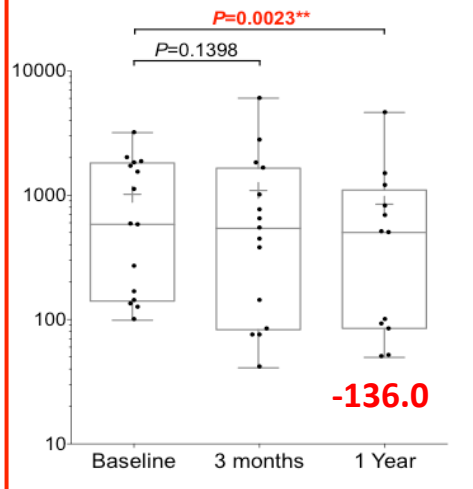
Peripheral placebo



Peripheral G-CSF

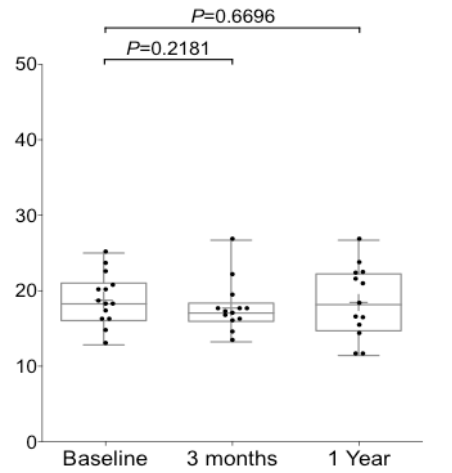


Intracoronary serum

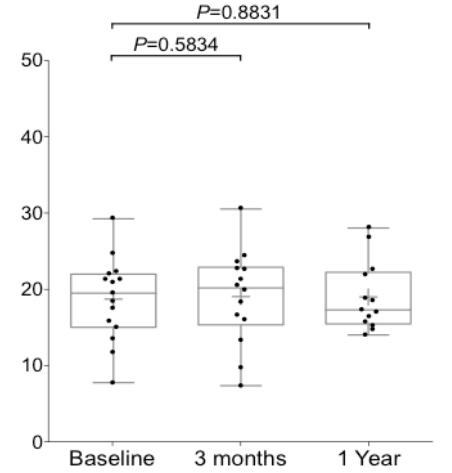


Intracoronary BMC

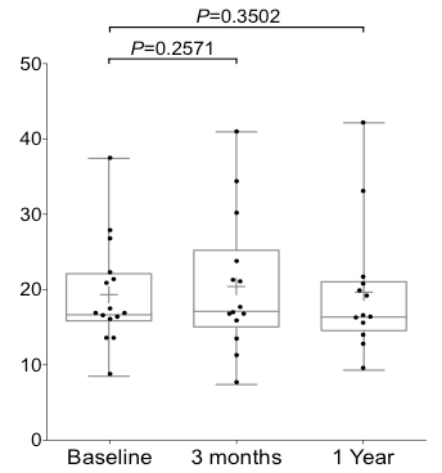
VO_2 Max (mL/kg/min)



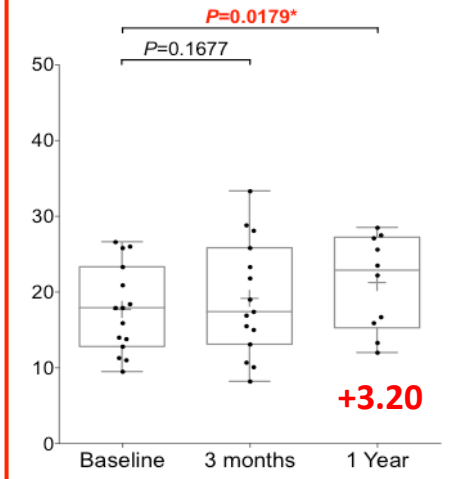
Peripheral placebo



Peripheral G-CSF



Intracoronary serum



Intracoronary BMC

Safety/MACE

- Up to 3 months: peripheral placebo n=1, peripheral G-CSF n=1
- Up to 1 year: IC serum n=3, IC BMC n=2

Limitations

- Small study size
- Not completely blinded across all groups

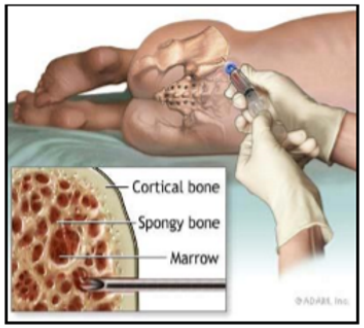
Conclusions

- 1st blinded placebo controlled trial in DCM
- IC infusion of autologous BMC in combination with G-CSF is safe
- It is associated with an increase in LVEF of 5.37% at 3 months which is maintained to 1 year
- And is accompanied by improvement in a panel of biochemical and symptom related outcomes supporting clinical benefit

CONTEXT

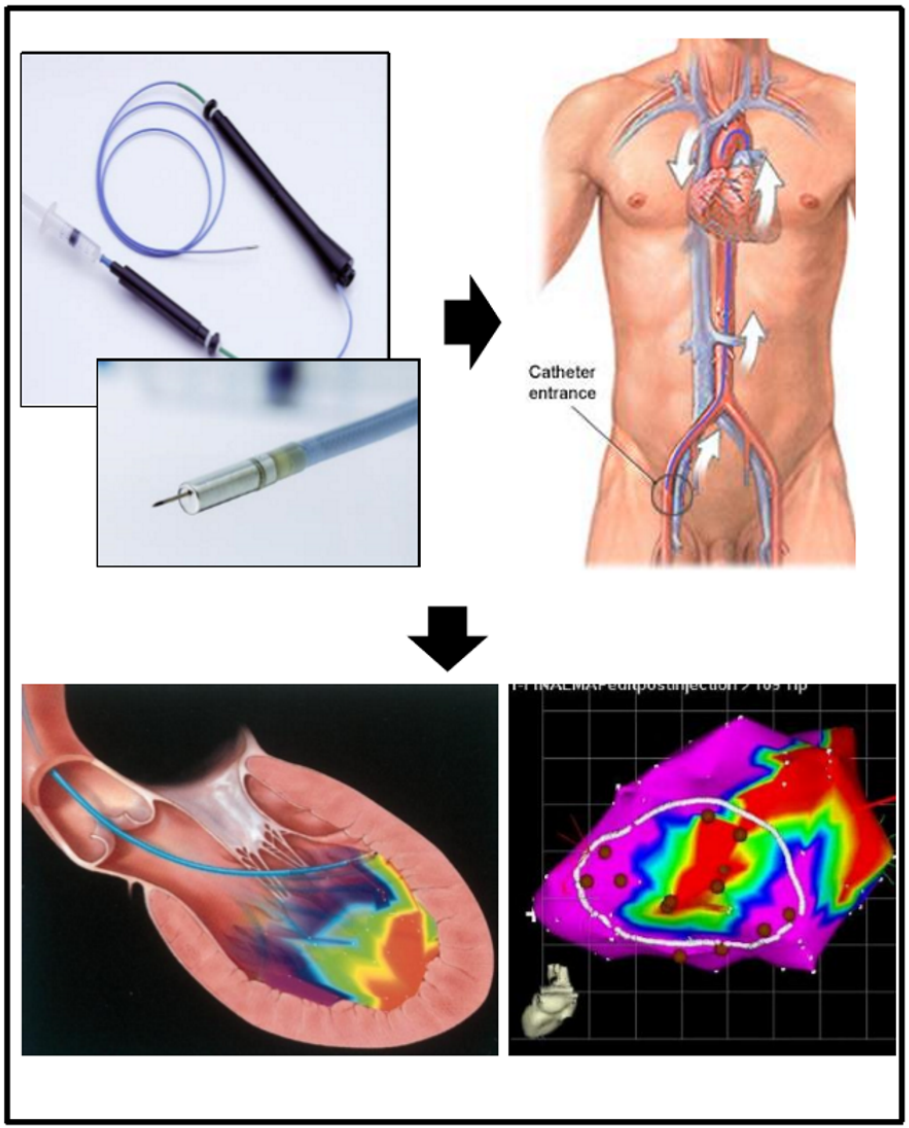
The MSC-HF trial

- 59 patients
  - 65.5 ± 8.77 years
  - Severe ischemic heart failure
  - Ejection fraction 28.1 ± 8.8 %
  - NYHA Class II-III
  - No further treatment options
- Intramyocardial Injection
  - Placebo (20)
  - Mesenchymal Stromal Cells (MSCs) (39)



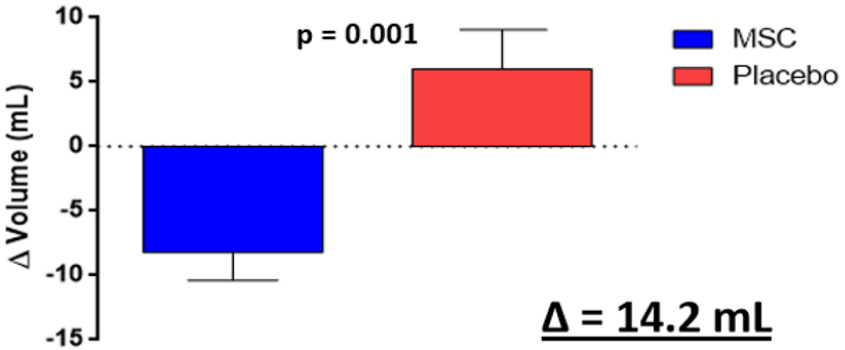
Bone-Marrow

Culture expanded



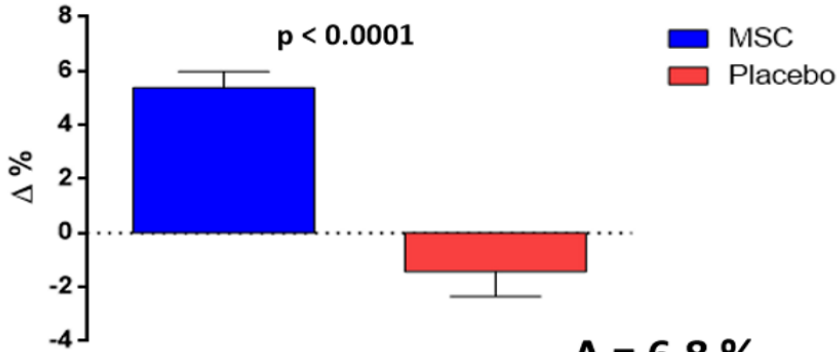
Results I

End systolic volume



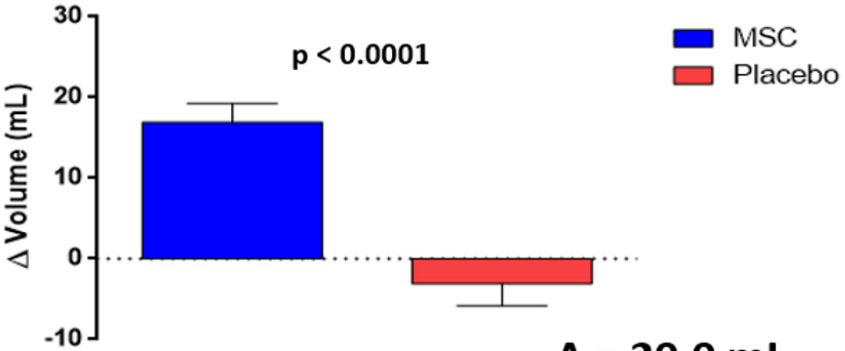
Δ = 14.2 mL

Ejection fraction



Δ = 6.8 %

Stroke volume



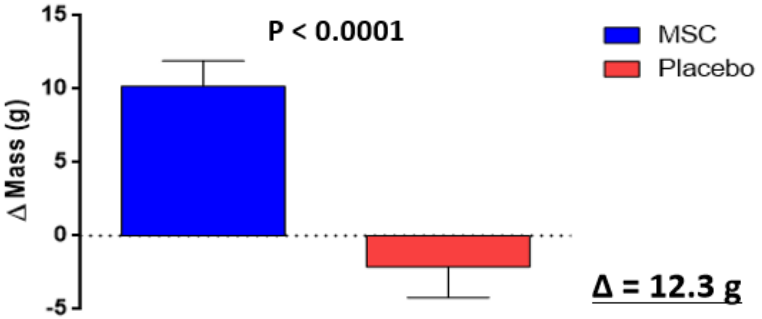
Δ = 20.0 mL

Improved heart pump function

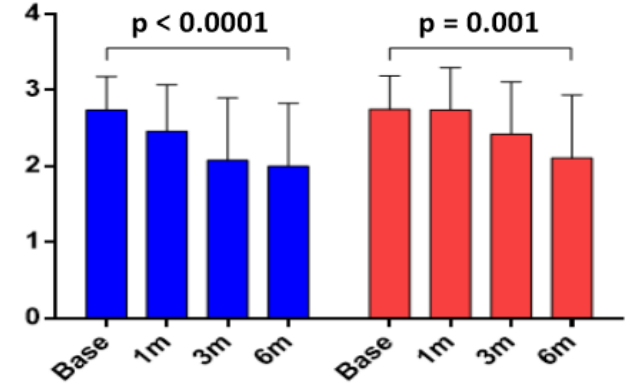
(Mean + SEM)

Results II

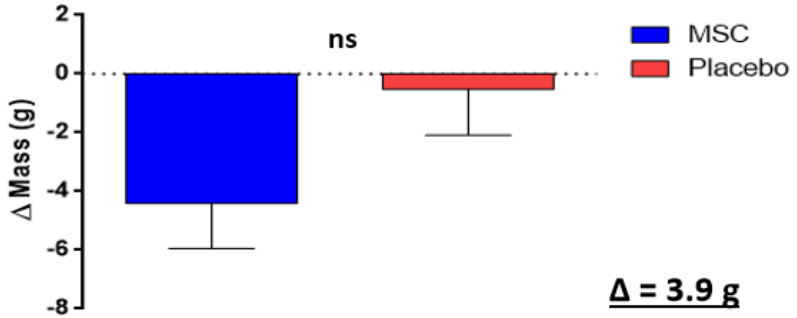
Myocardial mass (end systolic)



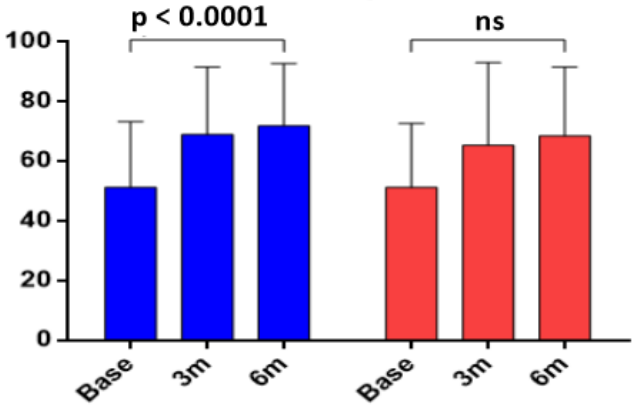
NYHA Class



Scar tissue mass (n=17)



KCCQ – Quality of Life



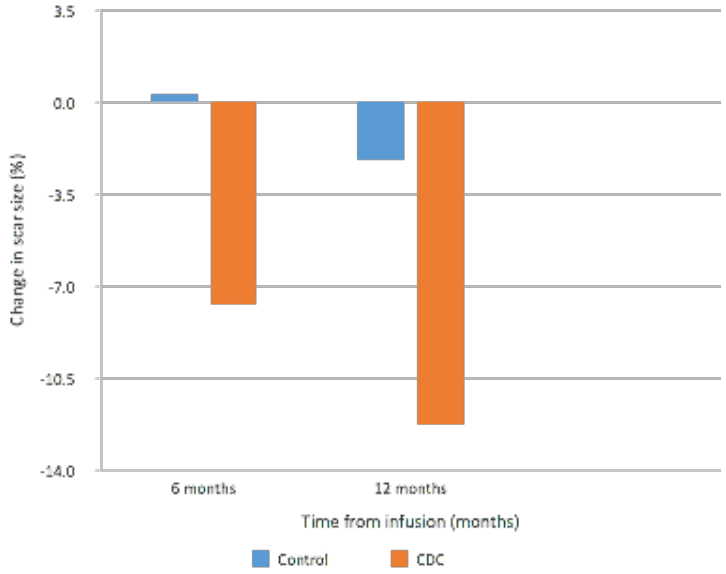
New heart muscle tissue

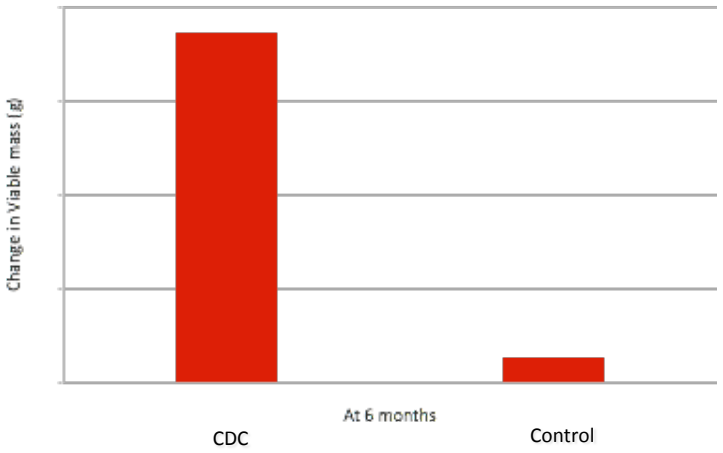
Fewer symptoms, better quality of life

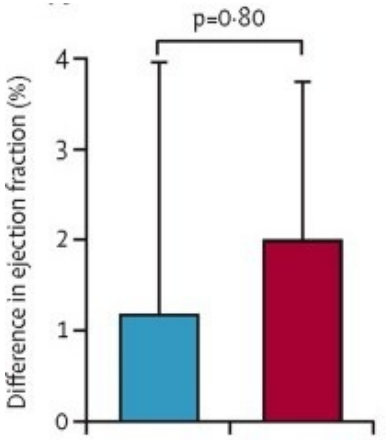
(Mean + SEM)

CADUCEUS

- Prospective, randomised, phase 1 trial using cardiosphere-derived cells via intracoronary administration



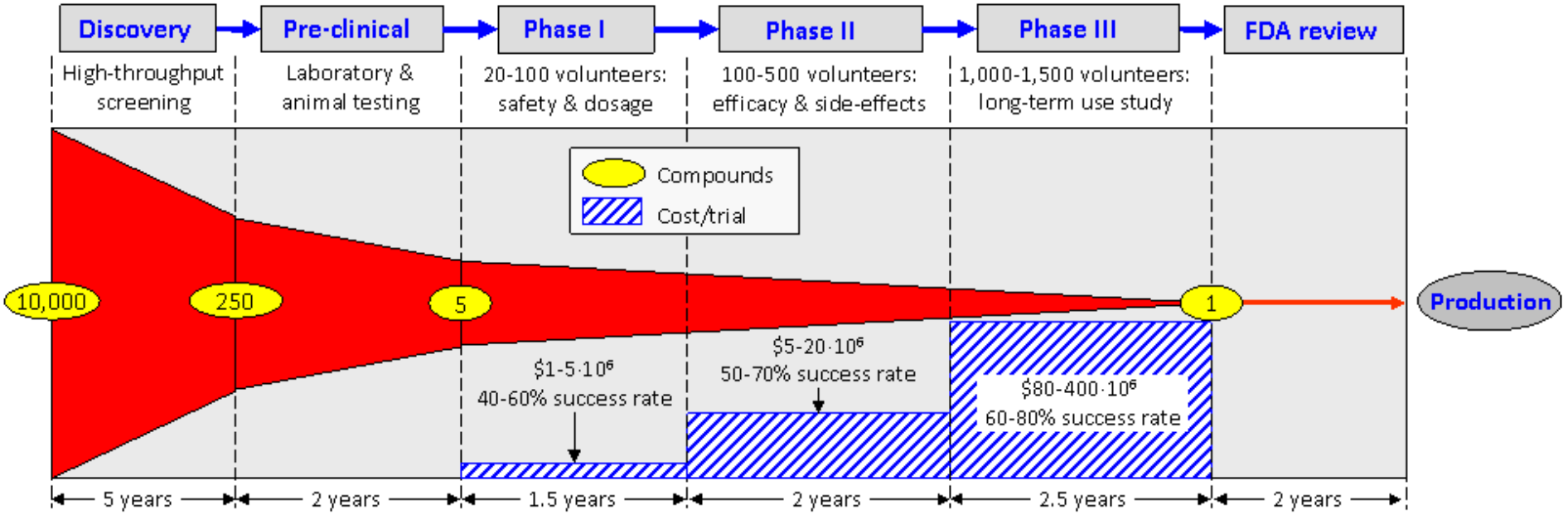




R. R. Makkar et al., *The Lancet* **379**, 895-904 (2012).

WHAT NEXT……

Innovation pipeline



Next generation cell therapy

Table 2 | Studies of purified and next-generation cell-based regenerative therapies in ischaemic heart disease

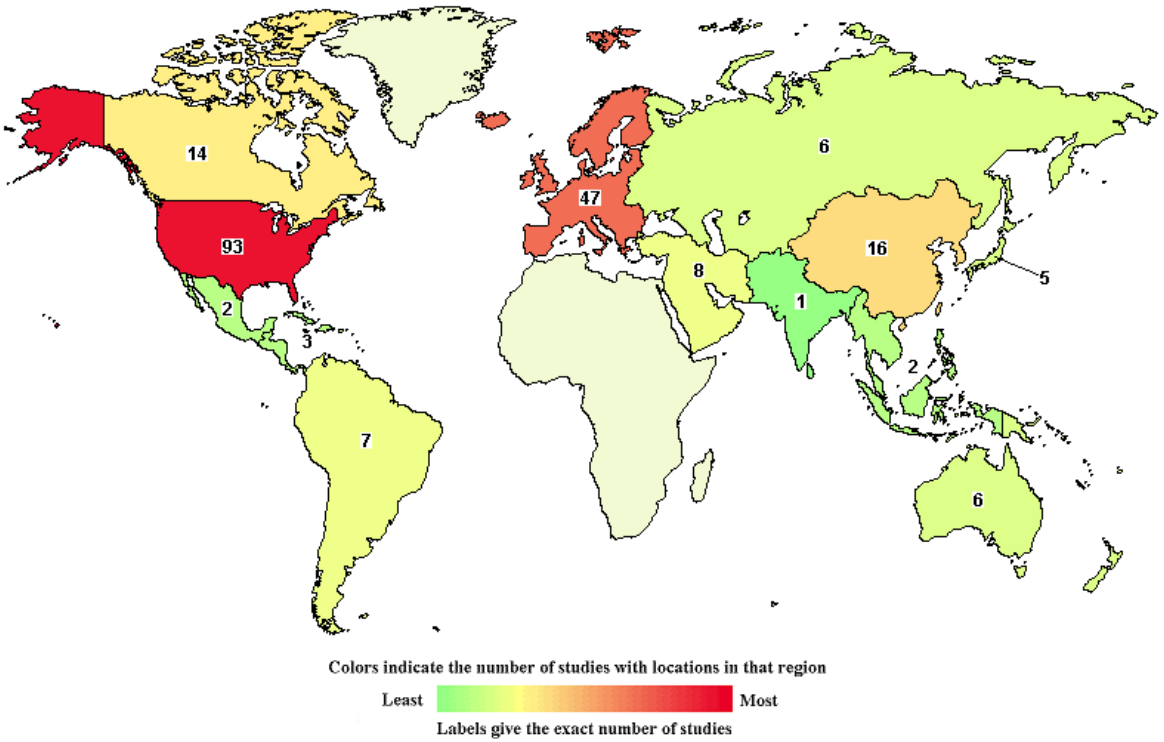
Study	*n*	Cells delivered	Cell harvesting and manipulation			Cell delivery			Method of follow-up	Clinical effects (next phase)
			Cell processing	Mode of purification	Incubation time	Vehicle	Route	Number of cells		
Studies using purified cell populations										
ACT34-CMI (2011)[63]	168	Circulating $CD34^+$ EPCs	5 days treatment of patients with GCSF	Isolex 300i magnetic cell selection system	1 day or ND	Normal saline and 5% autologous plasma	NOGA® cardiac navigation technology (Cordis Corporation, USA)	1.0×10^5 to 5.0×10^5 cells per kg	IVRS	Reduced frequency of angina
POSEIDON (2012)[53]	31	BM-derived hMSCs	4–5 weeks in culture	Cell culture	Frozen	PBS and 1% HAS	Biocardia™ Helical Infusion Catheter (Biocardia, Inc., USA)	2.0×10^7 to 2.0×10^8	Cardiac CT	Neutral effect on ejection fraction
Studies using 'next-generation' stem cell isolation methods										
SCIPIO (2011)[73]	16	$SCFR^+$ CSCs	Infused at 4 months after CABG surgery	Magnetic immunosorting	ND	Plasma-Lyte® A (Baxter International Inc., USA)	Intracoronary (OTW balloon); four injections lasting 3 min	5.0×10^5 to 1.0×10^6	Echo	Positive
CADUCEUS (2012)[77]	31	Cardio-spheres	Within 36 days of tissue sampling	3D cardio-spheres	ND	Normal saline, heparin (100 U/ml) and nitroglycerin (50 μg/ml)	Intracoronary (OTW balloon); three injections lasting 15 min	1.3×10^7 to 2.5×10^7	cMRI	No change (ALLSTAR[85] and RECONSTRUCT[84])
C-CURE (2013)[88]	45	Cardiopoietic hMSCs	4–6 weeks culture and guidance of BM-derived hMSCs	Cardiopoietic lineage specification	3 days	5% HAS in LR	NOGA® guided; 9–26 injections of 4.5–12.7 ml	6.0×10^8 to 1.2×10^9	Echo	Positive (CHART-1[94] and CHART-2)

Abbreviations: BM, bone marrow; CABG, coronary artery bypass grafting; cMRI, cardiac MRI; CSC, cardiac stem cell; Echo, echocardiography; EPC, endothelial progenitor cell; GCSF, granulocyte colony-stimulating factor; HAS, human serum albumin solution; hMSC, human mesenchymal stem cell; IVRS, interactive voice response system; LR, lactated Ringer's solution; NA, not available; ND, not disclosed; OTW, over the wire; PBS, phosphate-buffered saline; SCFR, mast/stem cell growth factor receptor Kit (also known as c-Kit).

Behfar, A. *et al.* (2014)
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2014.9

nature REVIEWS CARDIOLOGY

Phase II is over……



……Phase III is beginning

mesoblast
the regenerative medicine company

Phase III - Heart Failure

MPC-150-IM: Phase 3 Trial Design Targets Patients with High Risk of HF-MACE

- The Phase 3 CHF trial is recruiting well across multiple North American sites
- Double-blinded, 1:1 randomized, sham-procedure-controlled, in approximately 1,730 patients, evaluating a single dose of MPC-150-IM delivered via endomyocardial injection into the left ventricle
- The enrolled patient population in the Phase 3 trial is enriched for patients at high risk of HF-MACE. This is achieved by using the following inclusion criteria:
  - High baseline NT-proBNP levels
  - HF-related hospitalization within the past 9 months
- Expected near-term Phase 3 milestones
  - Complete enrollment for the first interim analysis during the second quarter 2015
  - First interim analysis for safety and efficacy (left ventricular remodeling) after 6 months of follow-up
  - A subsequent second interim analysis of the primary endpoint will be used for possible resizing or early trial termination based on efficacy

Celyad
we care · we cure

Phase III - Heart Failure

C-Cure

CHART-1
EMA Approved

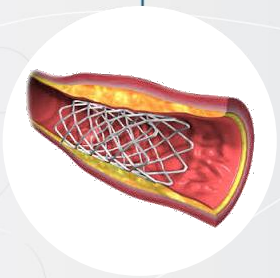
- NYHA class IIb-III-Iva
  FU @ 9mths
- Composite endpoint: Mortality, WHF, 6MWT, QoL, EF, ESV
- Currently ongoing in 30 sites, 12 countries

CHART-2
FDA Approved

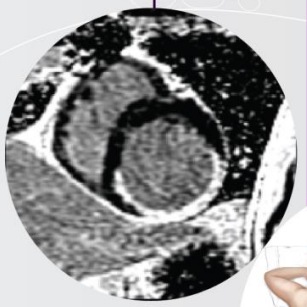
- NYHA class IIb-III-Iva
  FU @ 9mths
- Clinical enpdoint;
  6MWT
- Will start in Q2 2015 in US and Europe

Phase III – AMI

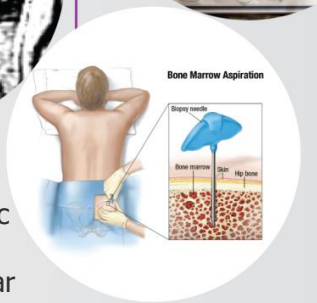
DAY 1 DAY 2 DAY 3 DAY 4 DAY 5 DAY 6 DAY 7 DAY 8 DAY 9 DAY 10 DAY 11



DAY 1:
Patient comes to emergency room with heart attack and receives stent

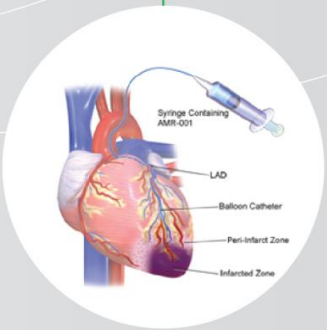


DAY 4:
Cardiac magnetic resonance to assess ventricular function



DAY 4-9:
Mini bone marrow procedure to harvest cells

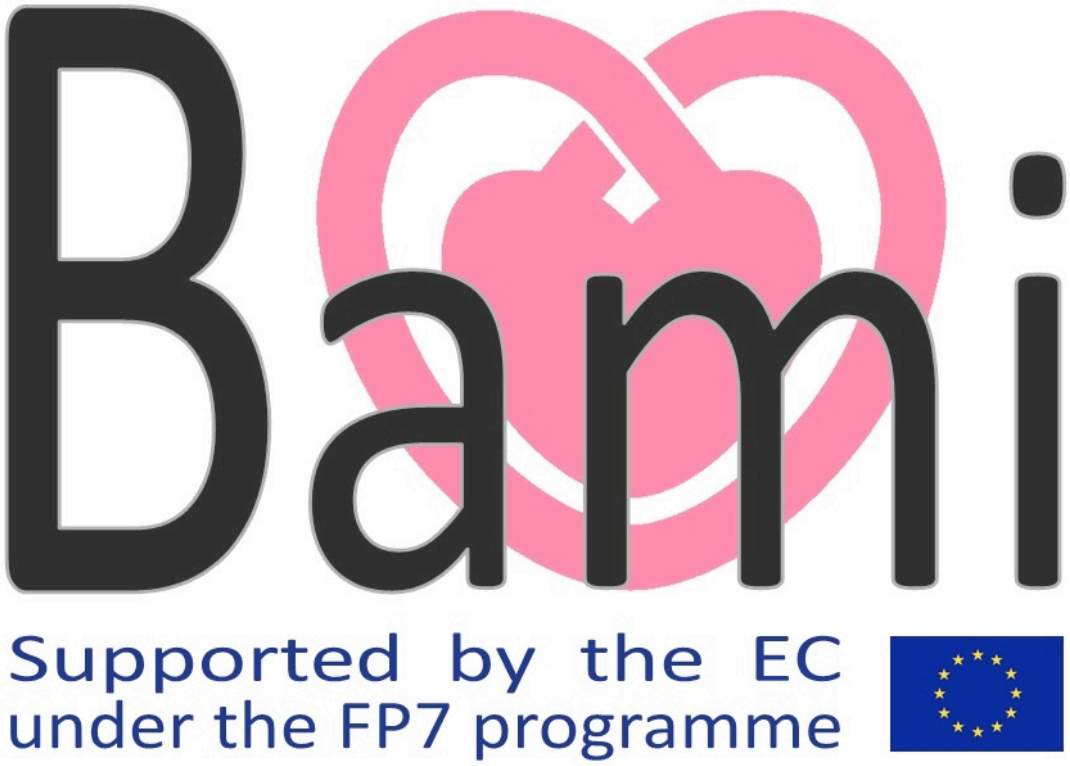
DAY 5-9:
6-8 hour cell separation process to isolate CD34/CXCR4 cells



DAY 6-11:
Injection of cell therapy into the infarct-related artery

*Process as per protocol for PreSERVE Phase 2 study

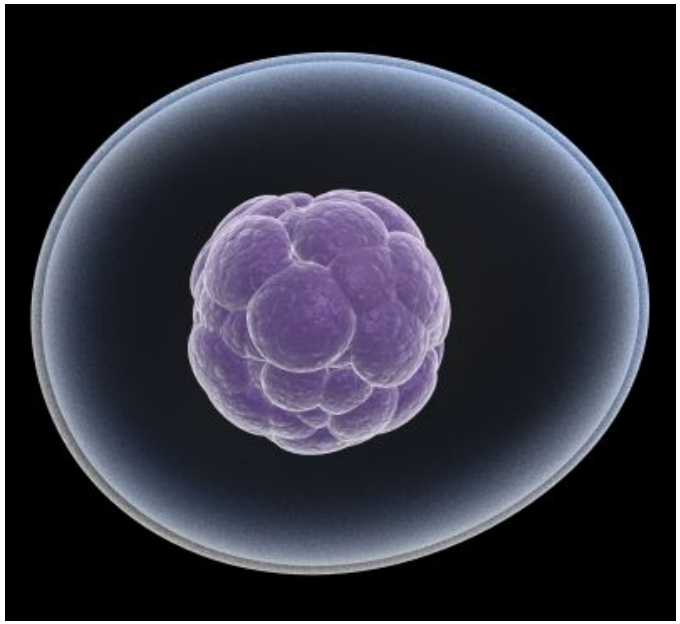
Phase III - AMI



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

REGENERATE – IHD/DCM

The largest randomised, placebo-controlled trial in the UK investigating the use of G-CSF and autologous bone marrow-derived stem / progenitor cells to improve cardiac function and symptoms in heart failure patients

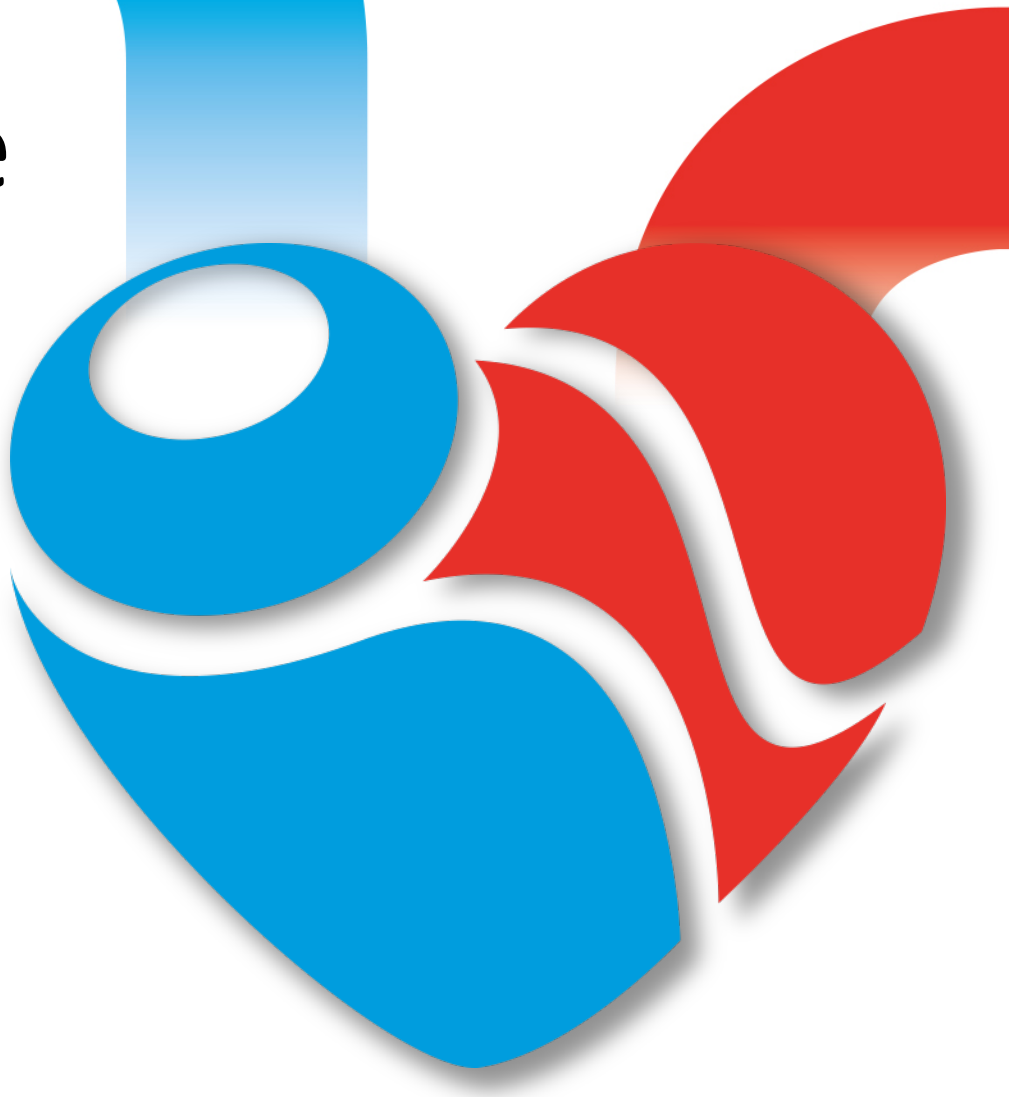


REGENERATE
LIFE SCIENCE

Barts Health NHS
NHS Trust

Compassionate Therapy Unit

Barts Heart Centre



Pioneering UK Stem Cell Therapy

HEART CELLS FOUNDATION

Conclusions

- REGENERATE –Phase II Trials - safety/activity
- Autologous cells may be beneficial in the treatment of heart failure (IHD/DCM)
- In chronic ischaemic heart failure im route indicated, intracoronary for DCM
- Early autologous cell infusion in AMI 'safe' & evidence of efficacy
- Phase III trials of autologous cells needed

Thank you