Cardiac Stem Cells

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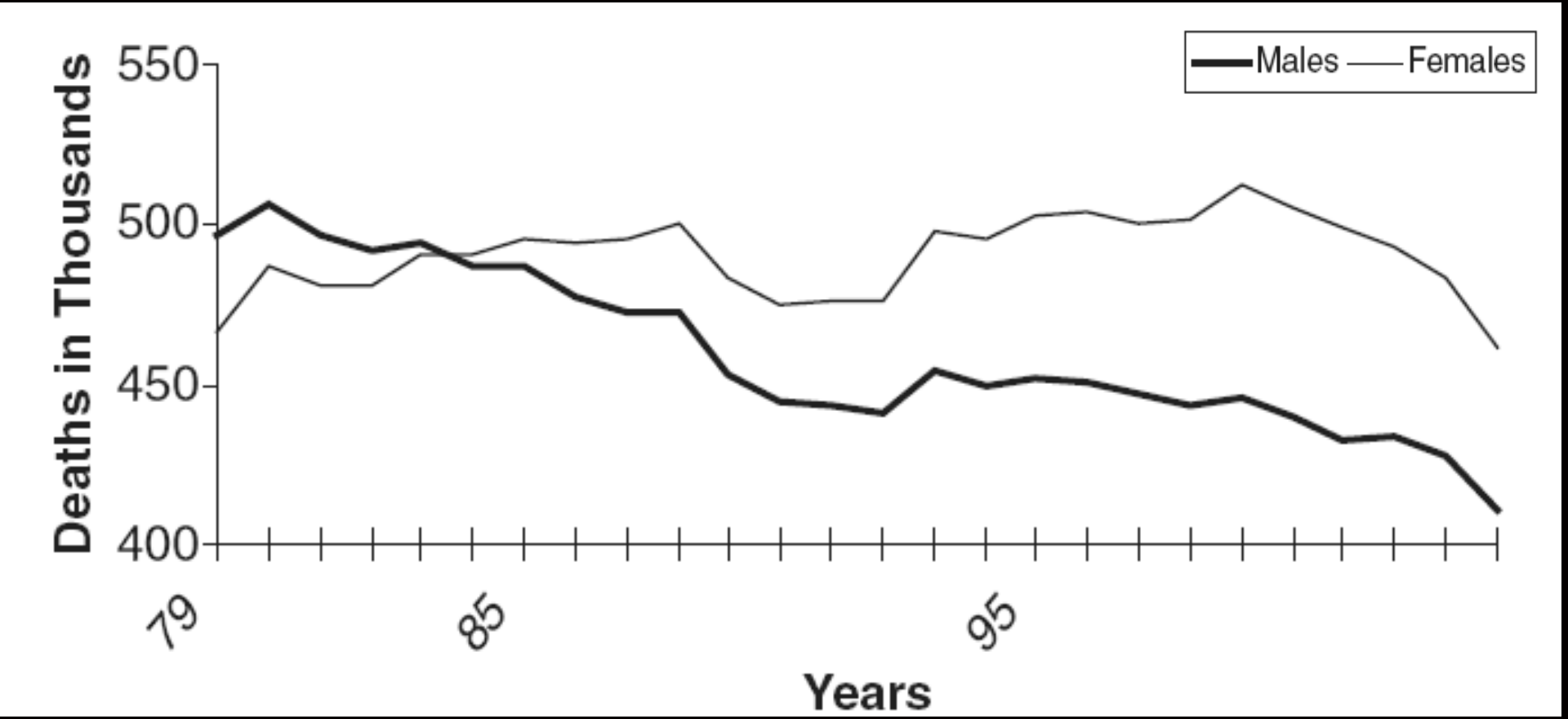
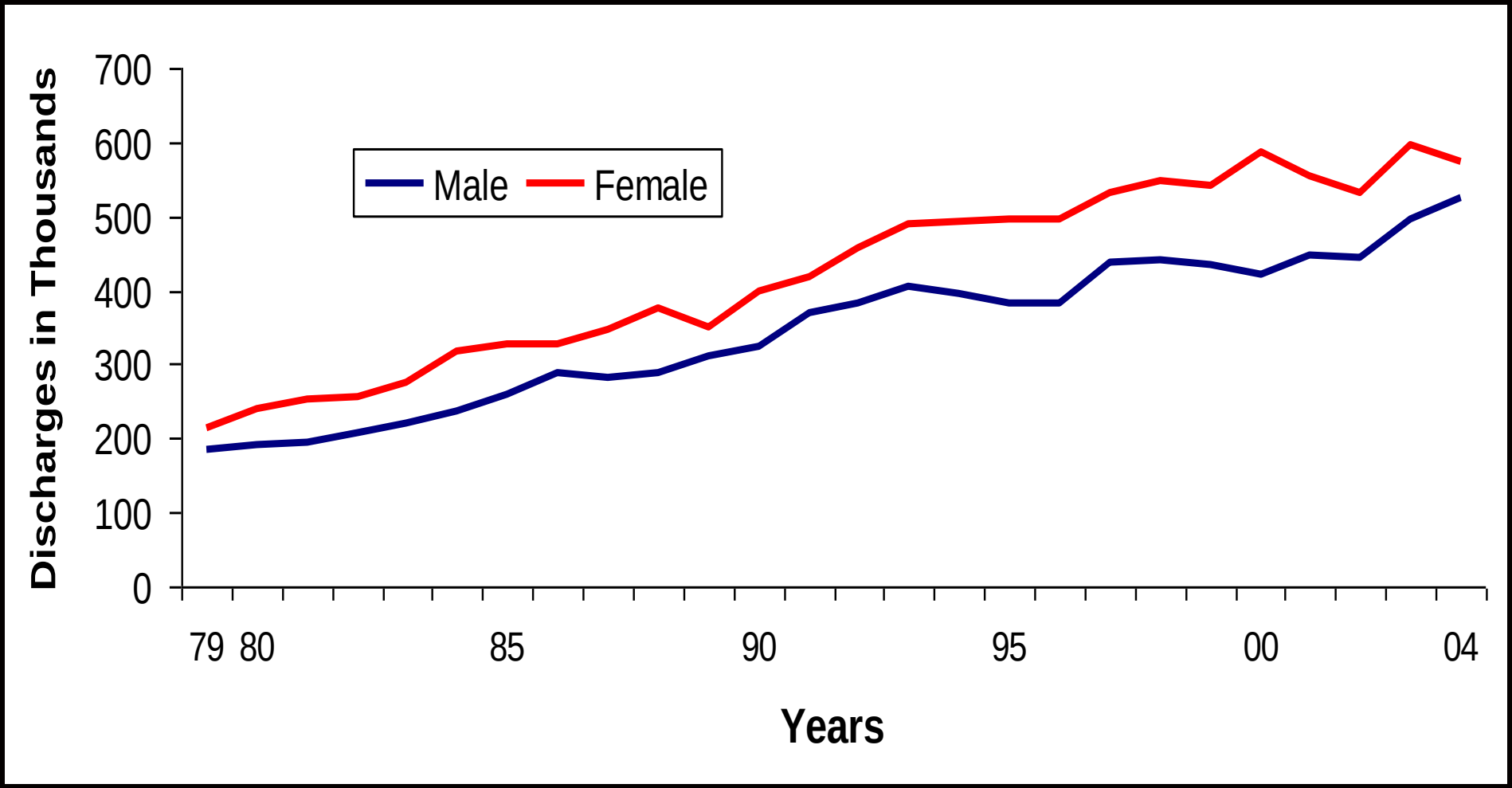
Rome: 31.01.2014

Myocardial Infarction Mortality in U.S.A.

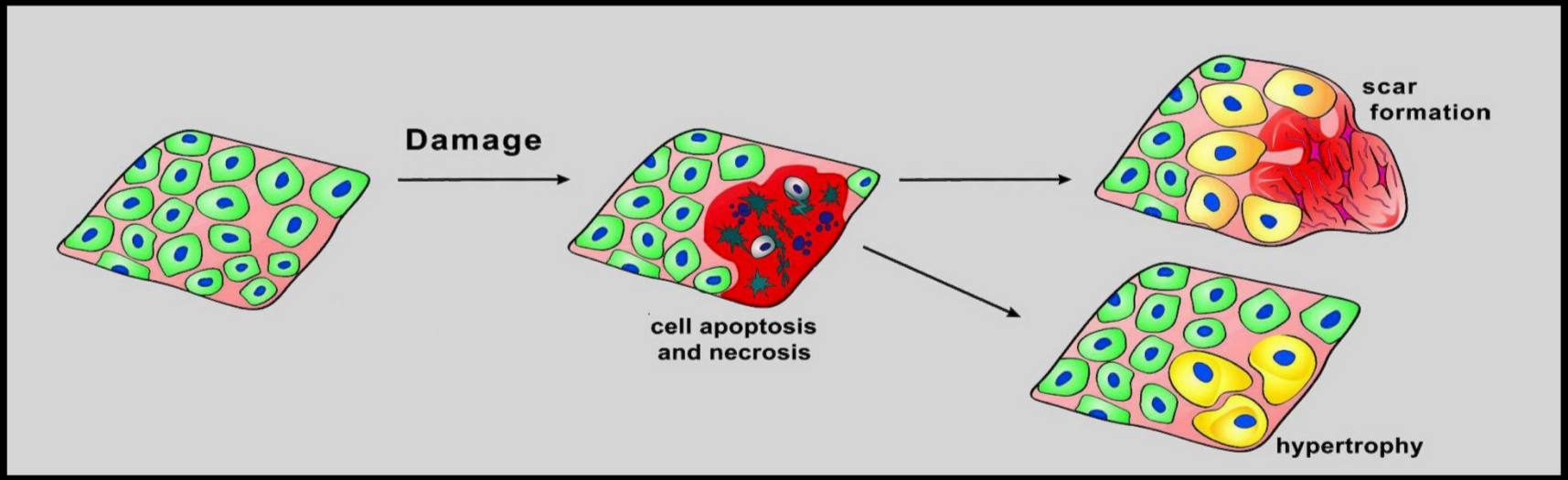


(Rosamund et al, Circulation 2007)

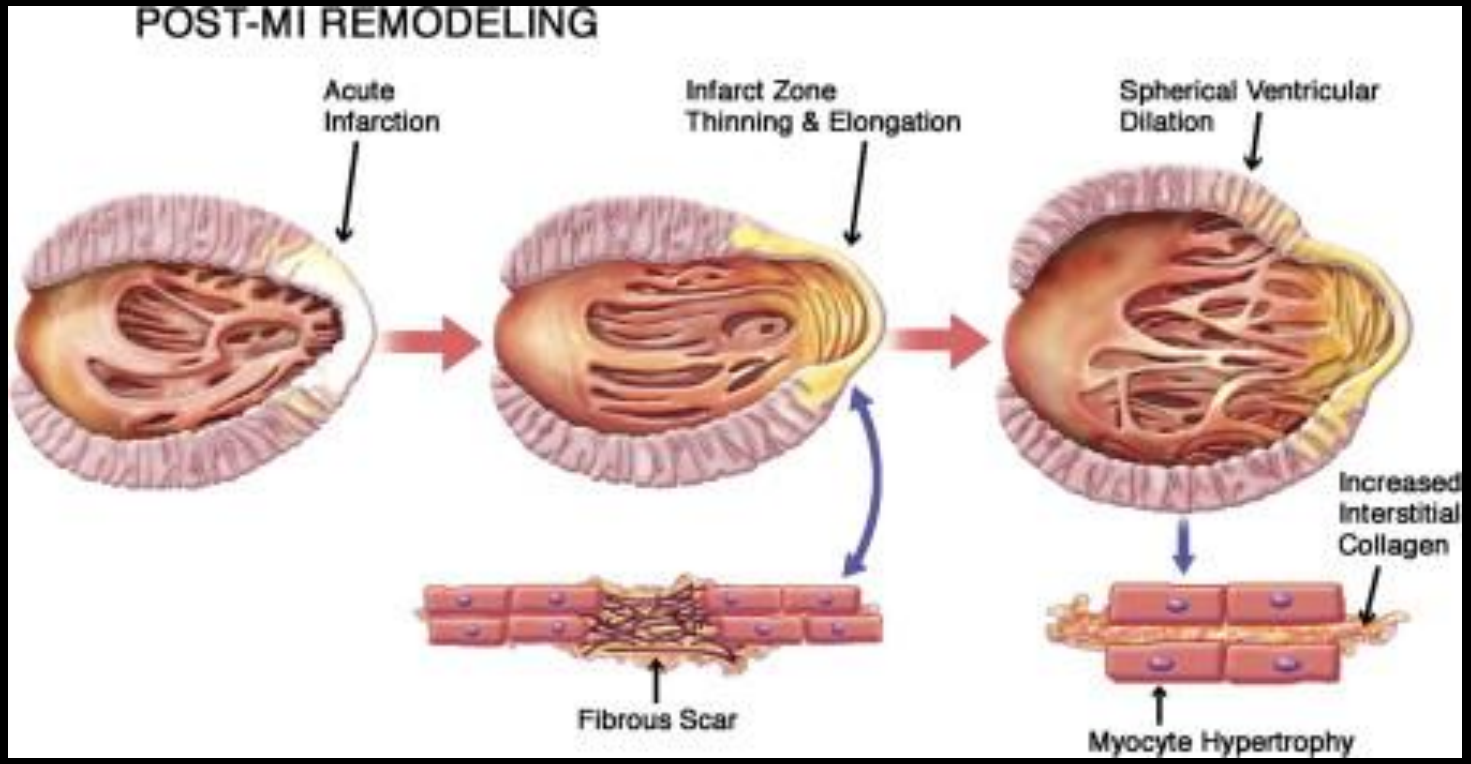
However…



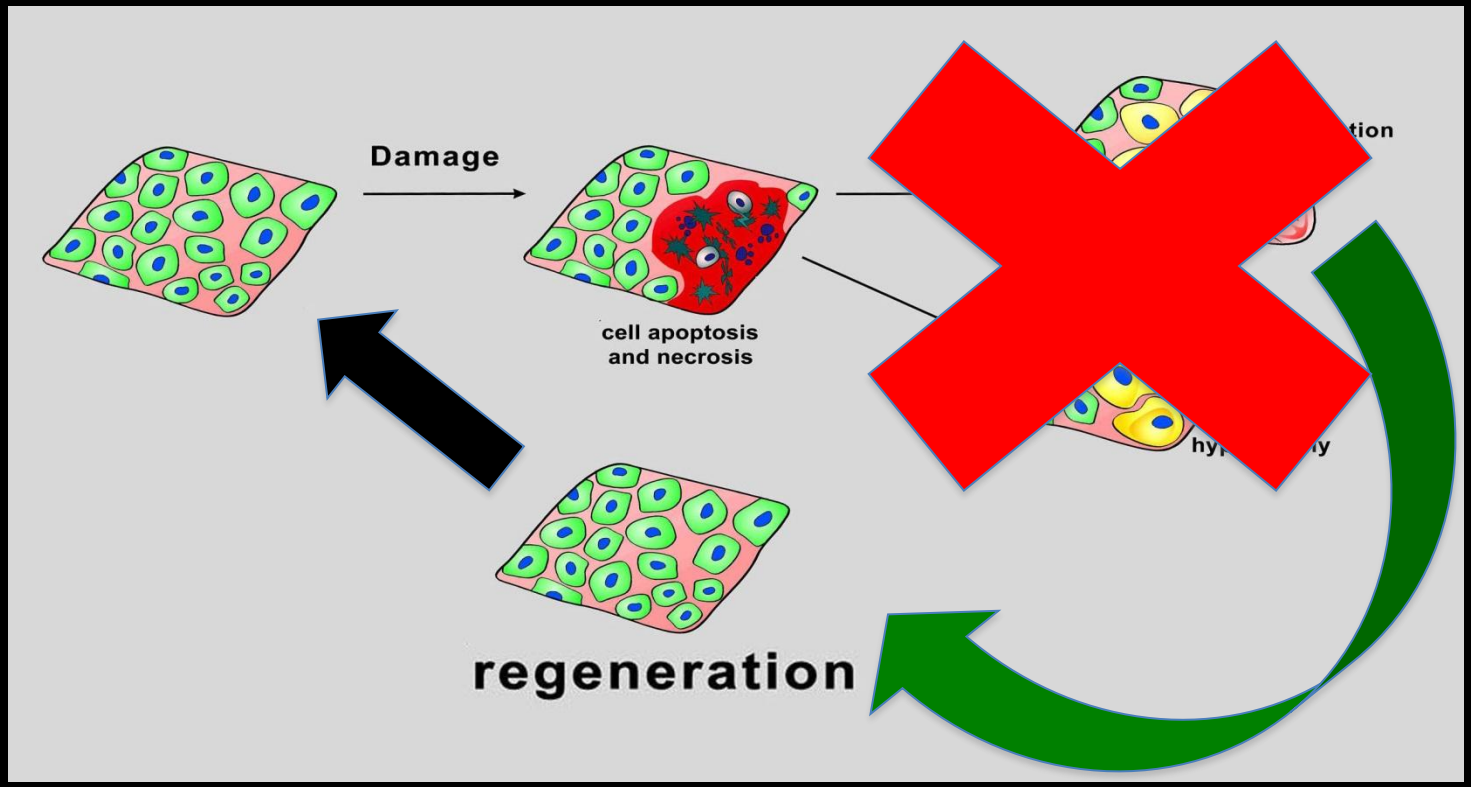
Hospital discharges for heart failure by sex
(United States: 1979-2004). Source: NHDS, NCHS and NHLBI)


Damage
cell apoptosis
and necrosis
scar
formation
hypertrophy

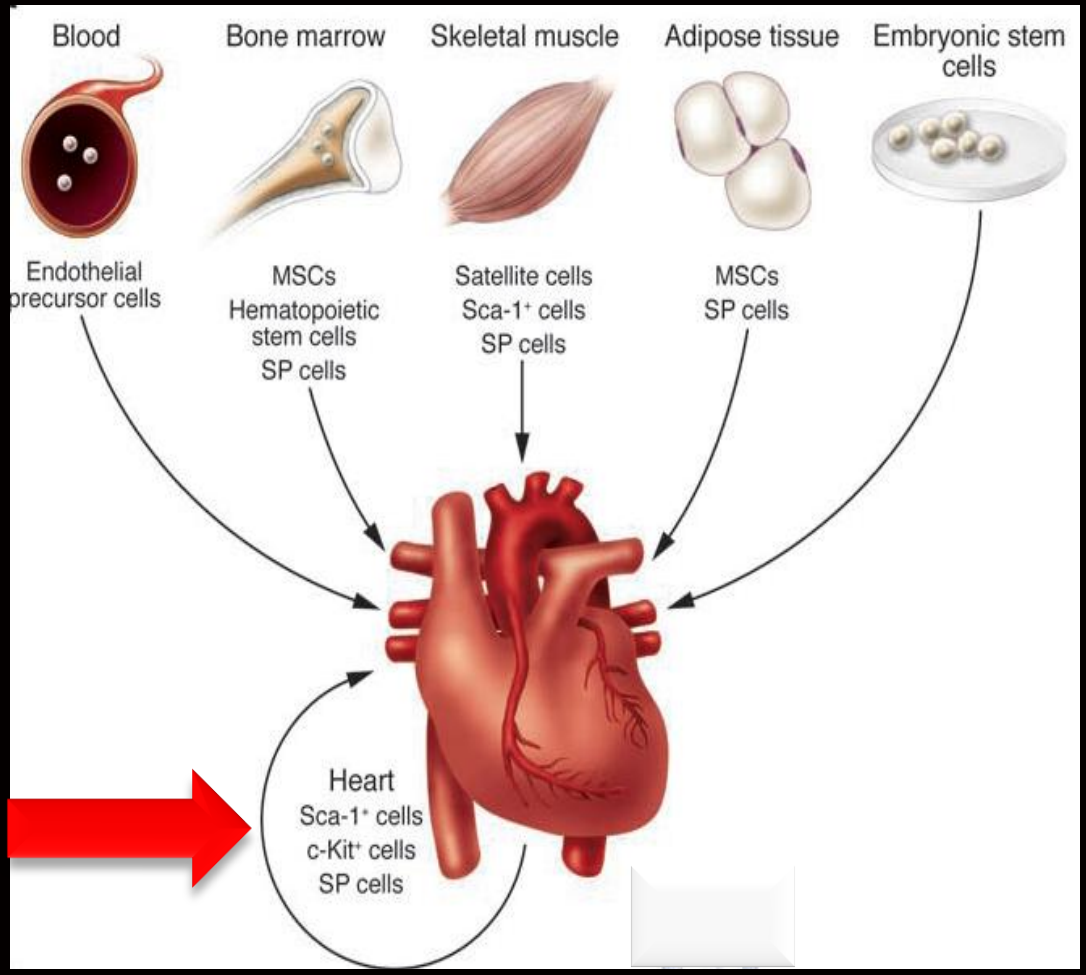
LEFT VENTRICULAR REMODELING



STEM CELL THERAPY

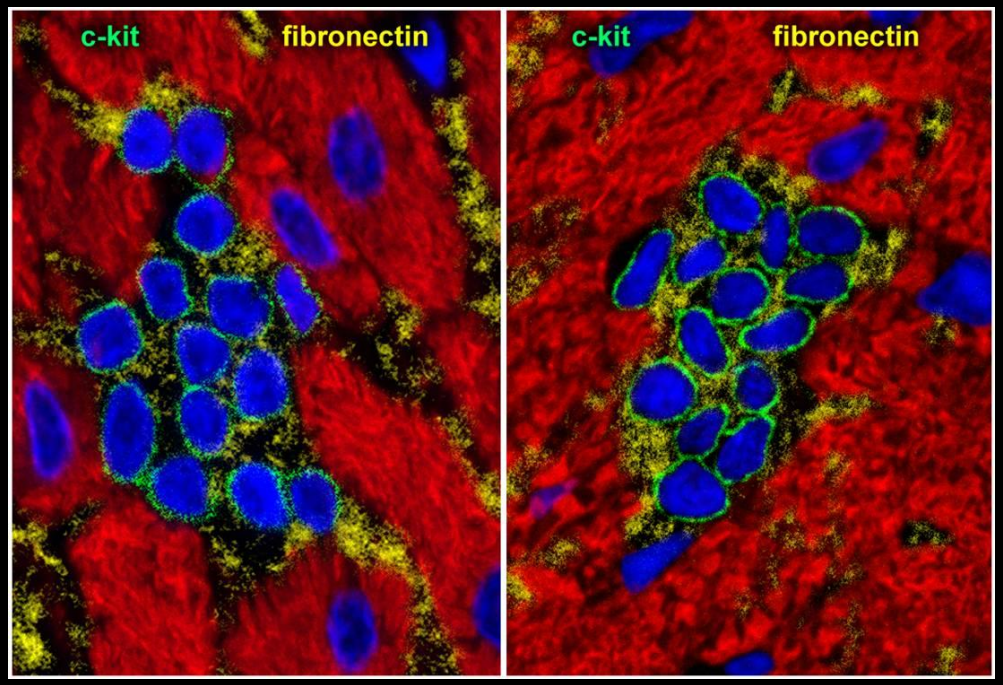


STEM CELL ORIGIN

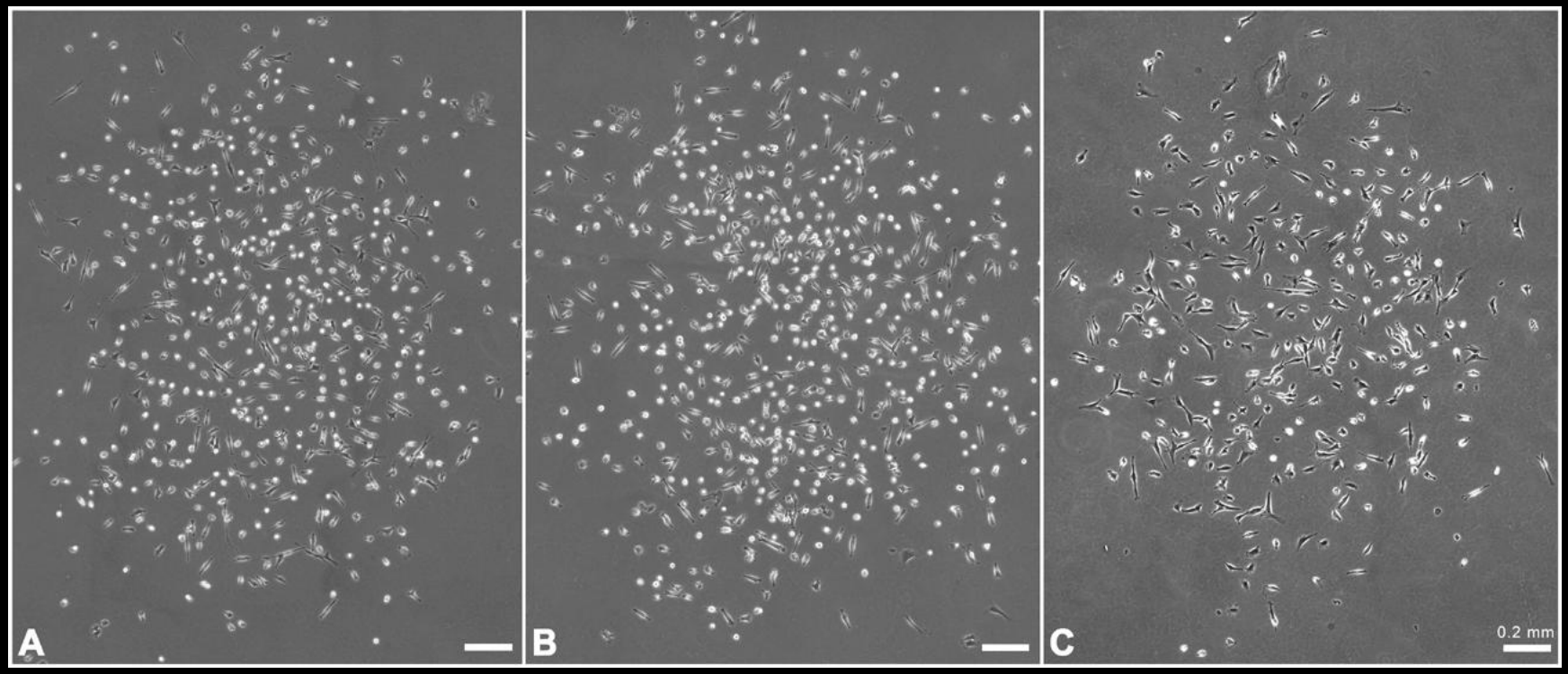


HUMAN CARDIAC STEM CELL

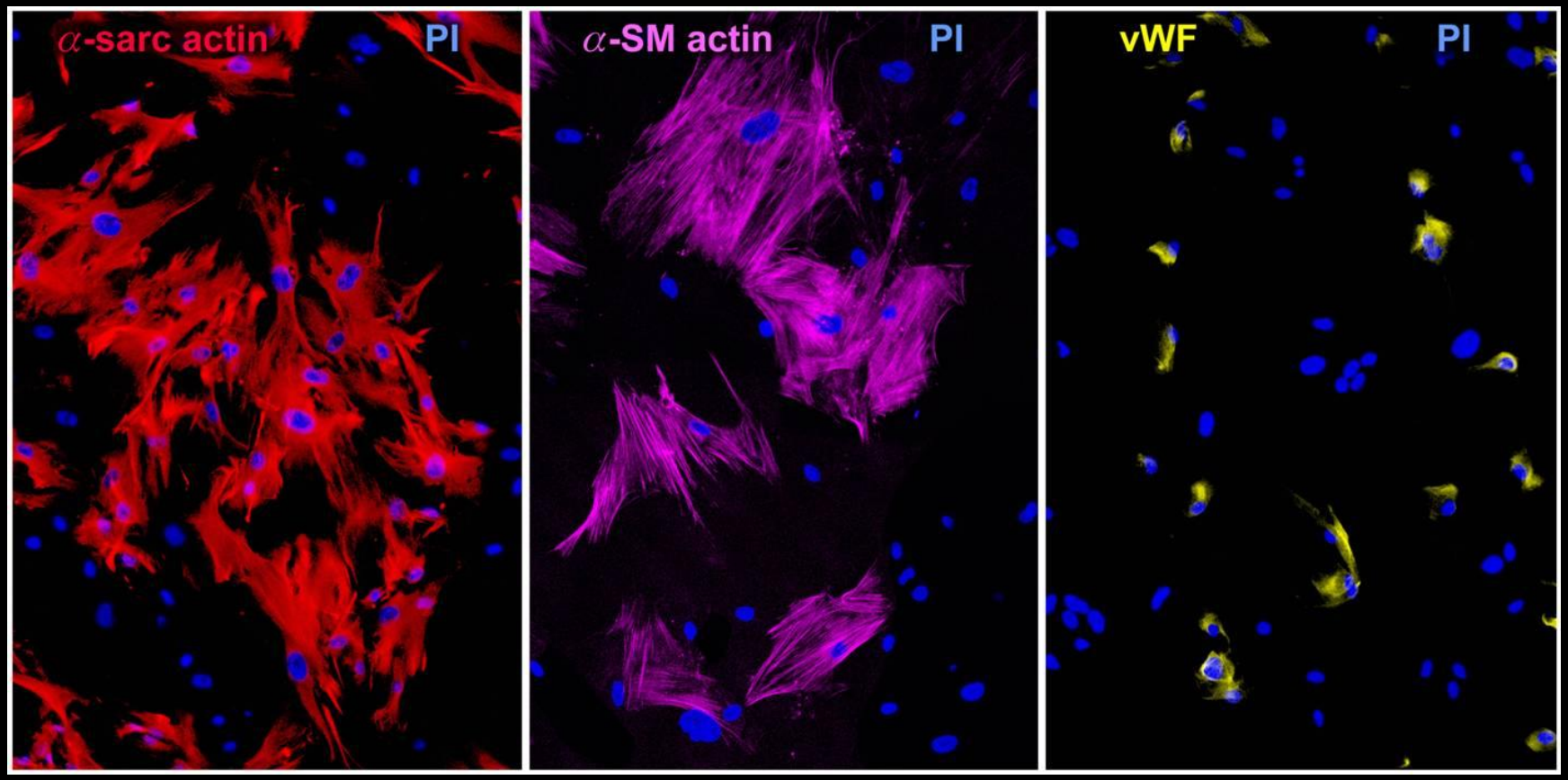
THE HEART AS A SELF-RENEWING ORGAN



Bearzi C., Hosoda T, D'Amario D. PNAS, 2007



Hosoda T, D'Amario D, Zheng H et al, PNAS, 2010



Hosoda T, D'Amario D., Zheng H et al., PNAS, 2010

SCIPIO

Stem Cell Infusion in Patients with Ischemic cardiomyOpathy

Bolli R, Chugh A, D'Amario D et al., Lancet 2011

Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial

Roberto Bolli, Atul R Chugh, Domenico D'Amario, John H Loughran, Marcus F Stoddard, Sohail Ikram, Garth M Beache, Stephen G Wagner, Annarosa Leri, Toru Hosoda, Fumihiro Sanada, Julius B Elmore, Polina Goichberg, Donato Cappetta, Naresh K Solankhi, Ibrahim Fahsah, D Gregg Rokosh, Mark S Slaughter, Jan Kajstura, Piero Anversa

www.thelancet.com **Published online November 14, 2011 DOI:10.1016/S0140-6736(11)61590-0**

Overview

- Phase I, prospective, randomized, open label, human study enrolling a maximum of 20 patients to the treated arm and 20 controls scheduled to undergo on-pump CABG surgery
- At the time of CABG, the right atrial appendage will be resected and harvested for CSCs
- At 4 ± 1 months after CABG surgery, treated patients will undergo selective intracoronary injections of CSC solutions. All patients will be followed clinically for up to 2 years
- Follow-up will include clinical assessment, laboratory studies, imaging and functional studies.

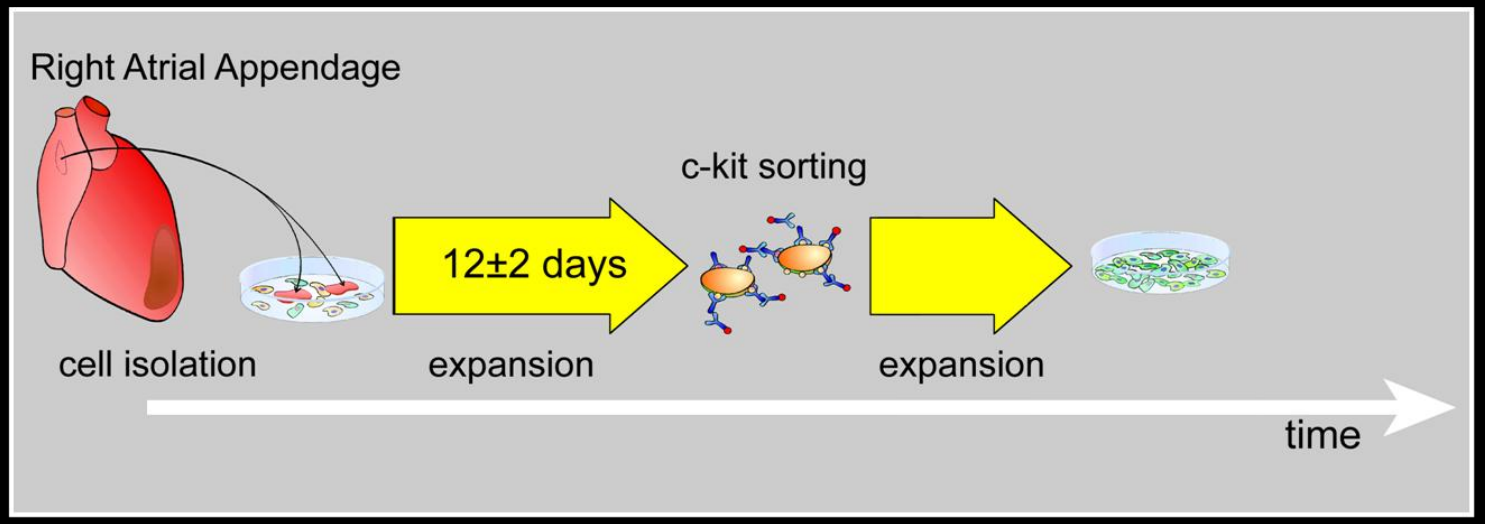
Bolli R, Chugh A, D'Amario D et al., Lancet 2011

Inclusion Criteria

- LVEF ≤ 40%
- A history of Q-wave (STEMI) MI with a residual akinetic and nonviable scar (as evidenced by a low-dose dobutamine stress echocardiogram and/or a thallium redistribution nuclear study for viability and/or an electrocardiogram and/or cardiac MRI and/or rest perfusion images on a sestamibi SPECT study)
- Patient scheduled for surgical revascularization within 2 weeks of the initial screening

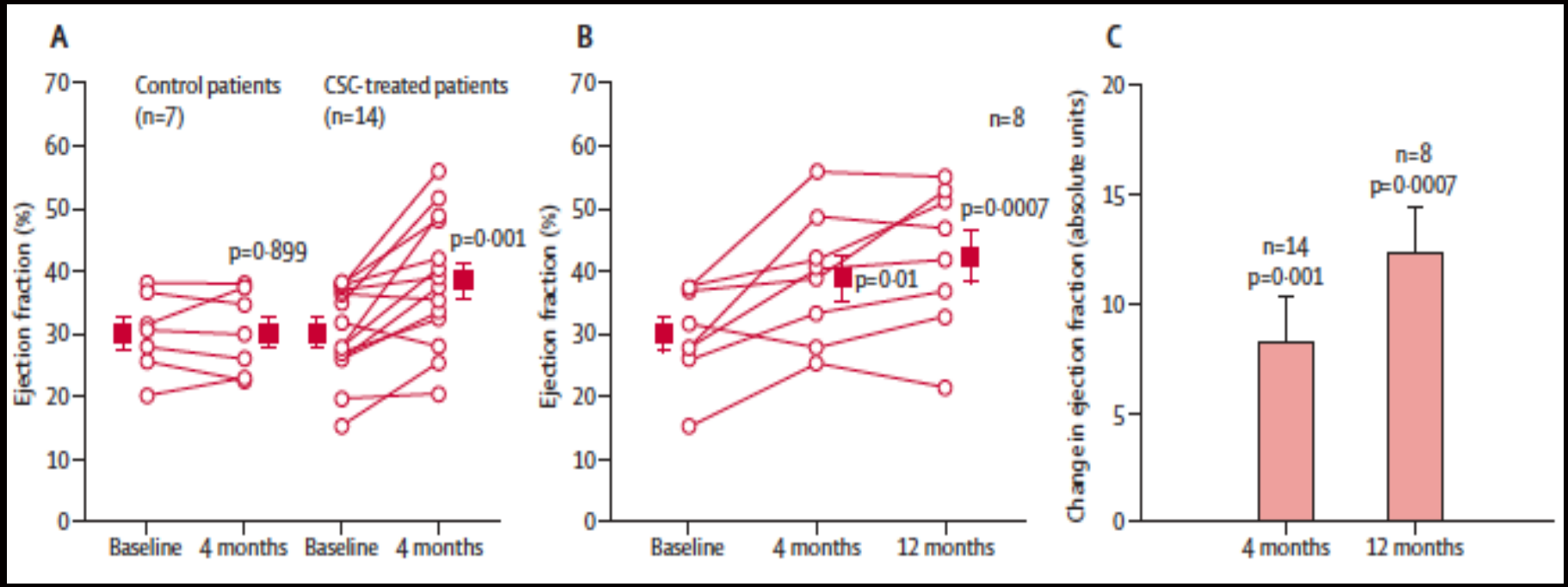
Bolli R, Chugh A, D'Amario D et al., Lancet 2011


CM
1
2
3


Right Atrial Appendage
c-kit sorting
12±2 days
cell isolation
expansion
expansion
time

SCIPIO: Results

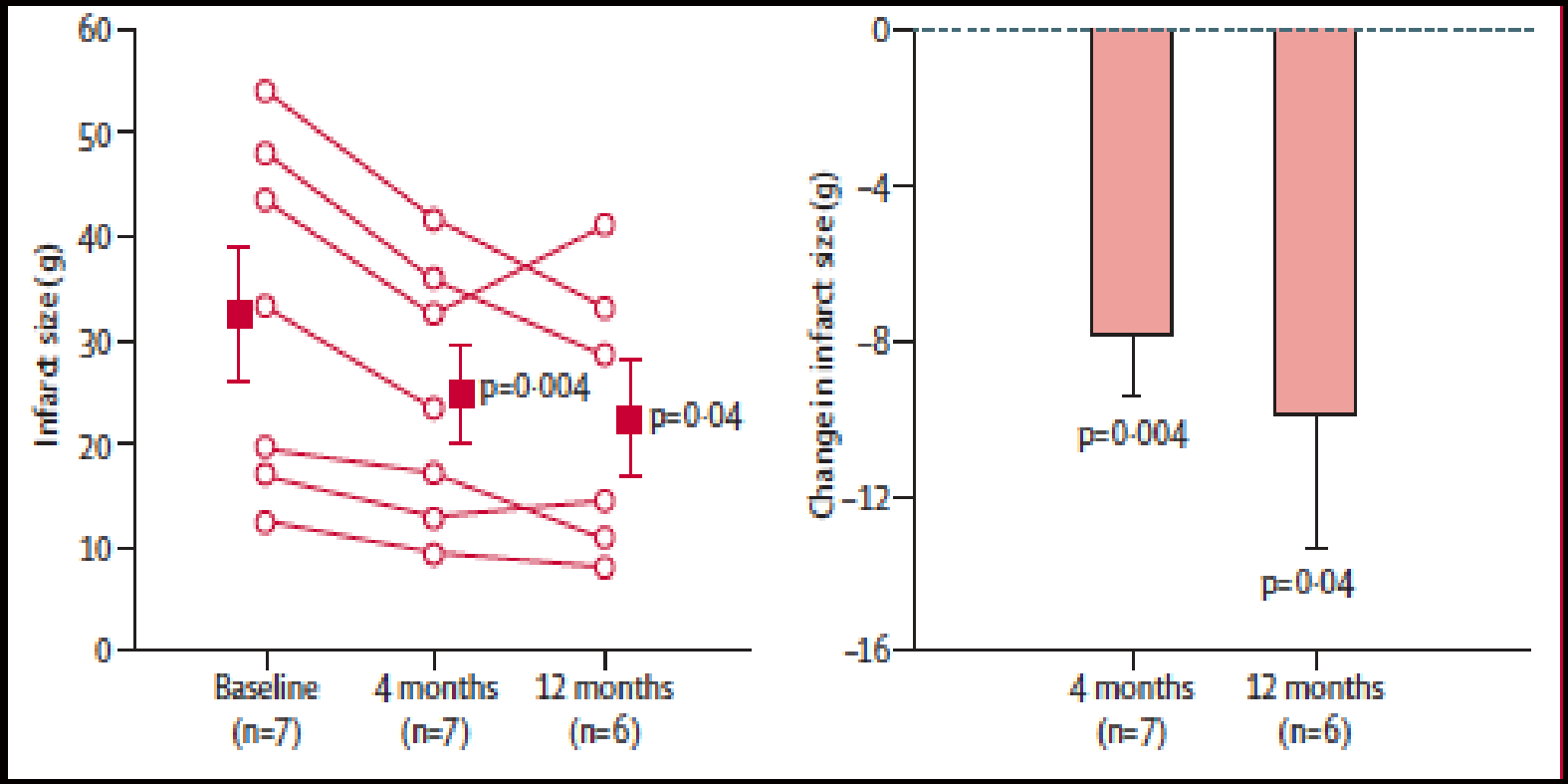
Ejection Fraction



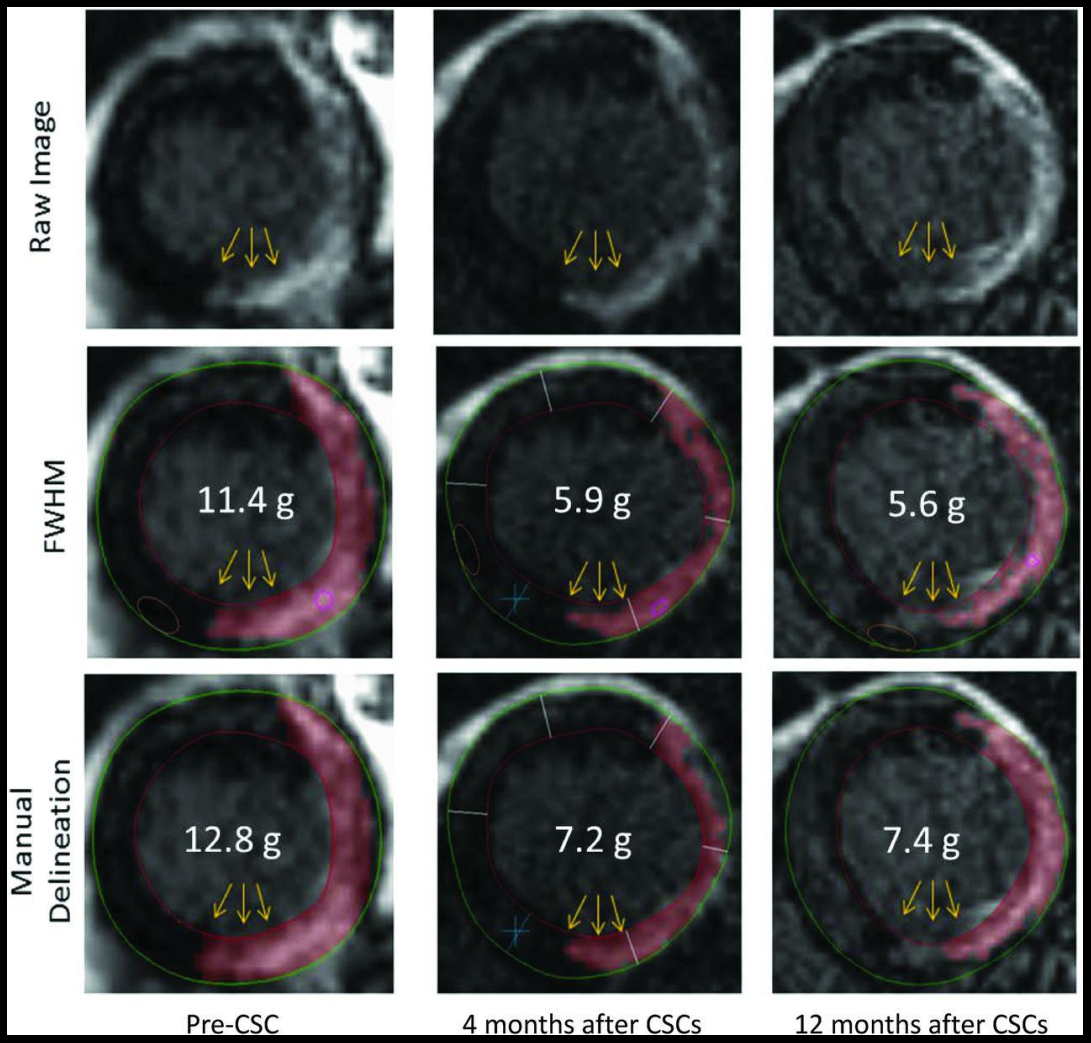
Bolli R, Chugh A, D'Amario D et al., Lancet, 2011

SCIPIO: Results

Infarct size



Bolli R, Chugh A, D'Amario D et al., Lancet, 2011

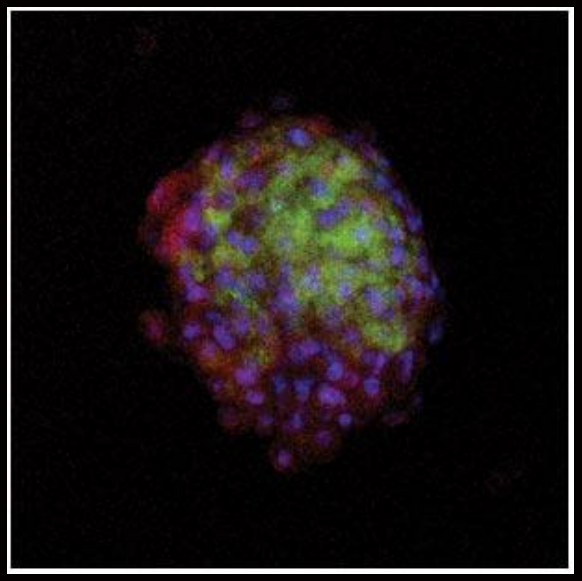


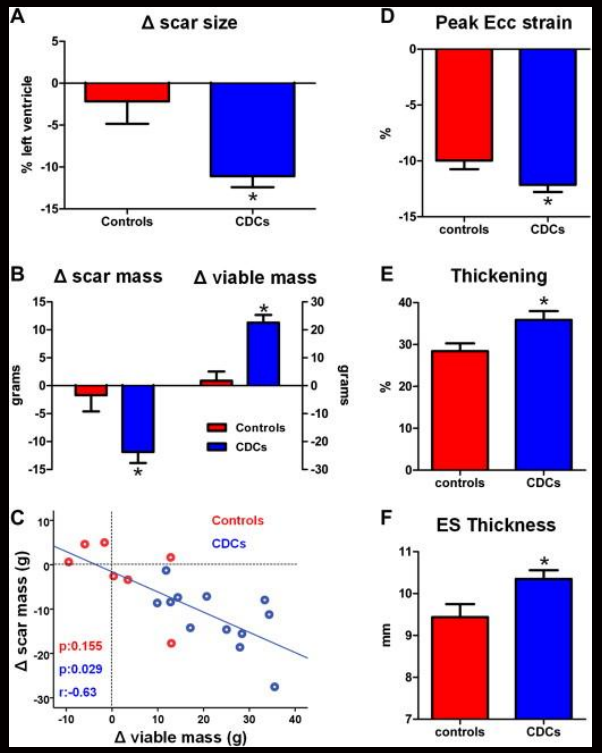
Summary

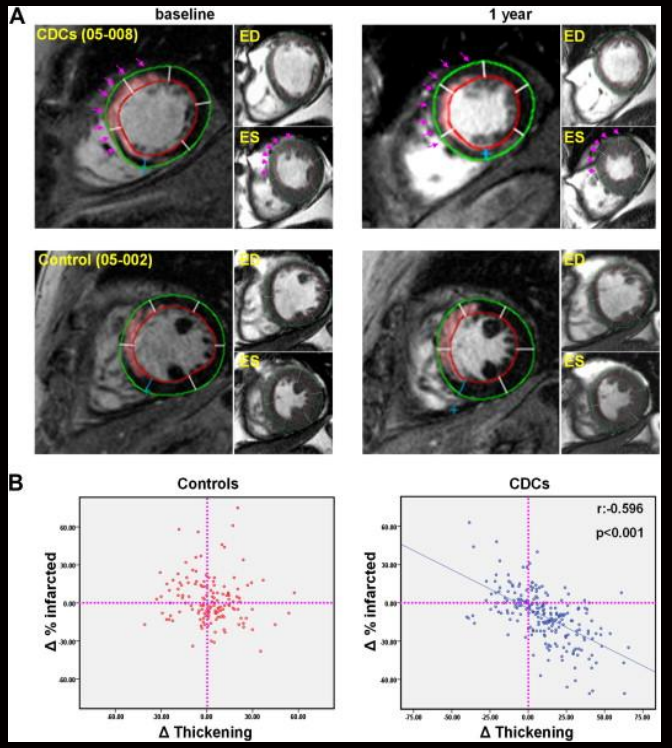
- Safety profile for intracoronary infusion of CSC is apparent
- Feasibility of the procedure has been demonstrated
- Preliminary results are more than encouraging and warrants investigation in a larger volume of patients
- Paucity of surgical candidates implies need for other methods of tissue procurement

Bolli R, Chugh A, D'Amario D et al., Lancet 2011

CADUCEUS Trial (CArdiosphere-Derived aUtologous stem CEIls to reverse ventricUlar dySfunction)

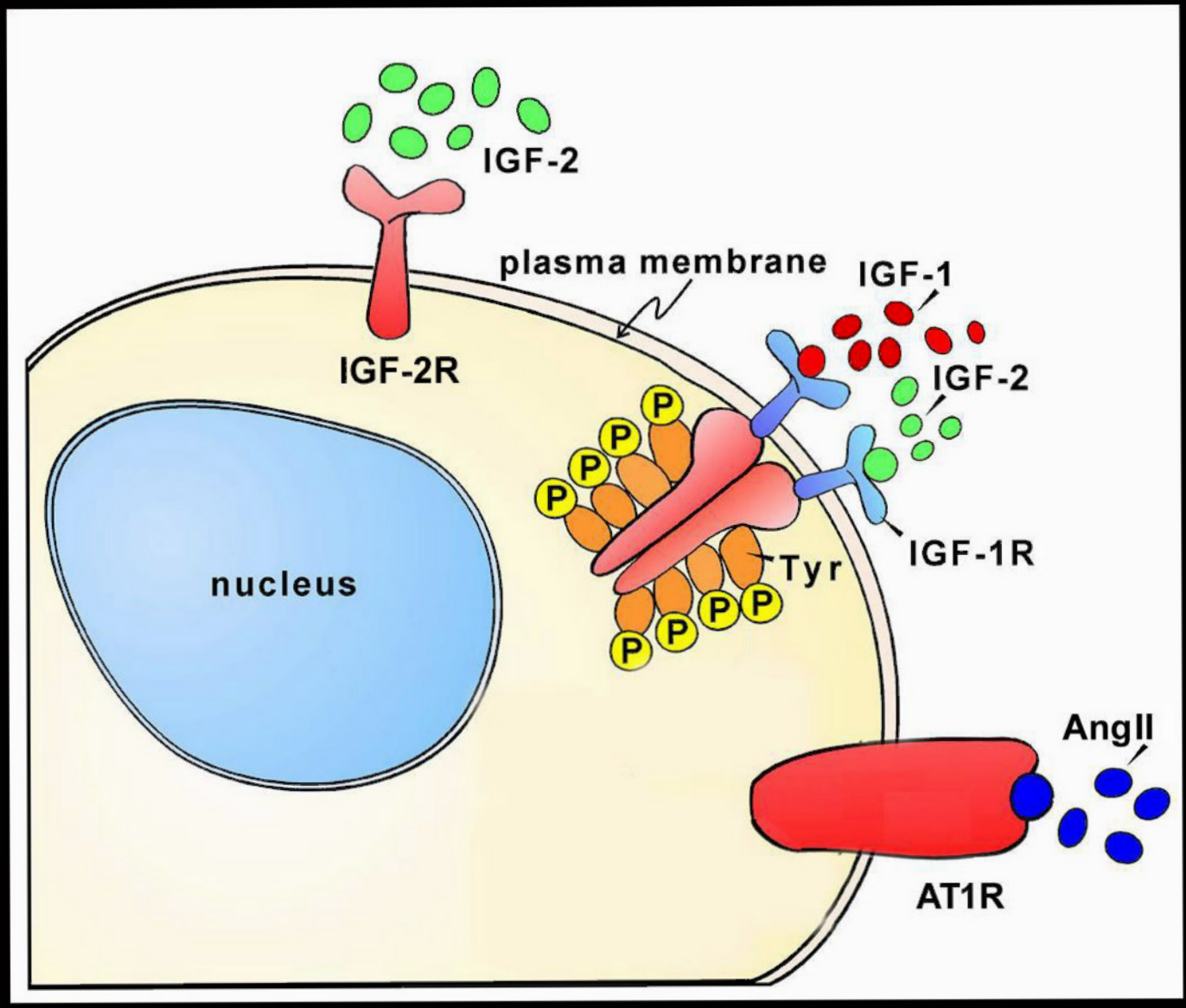


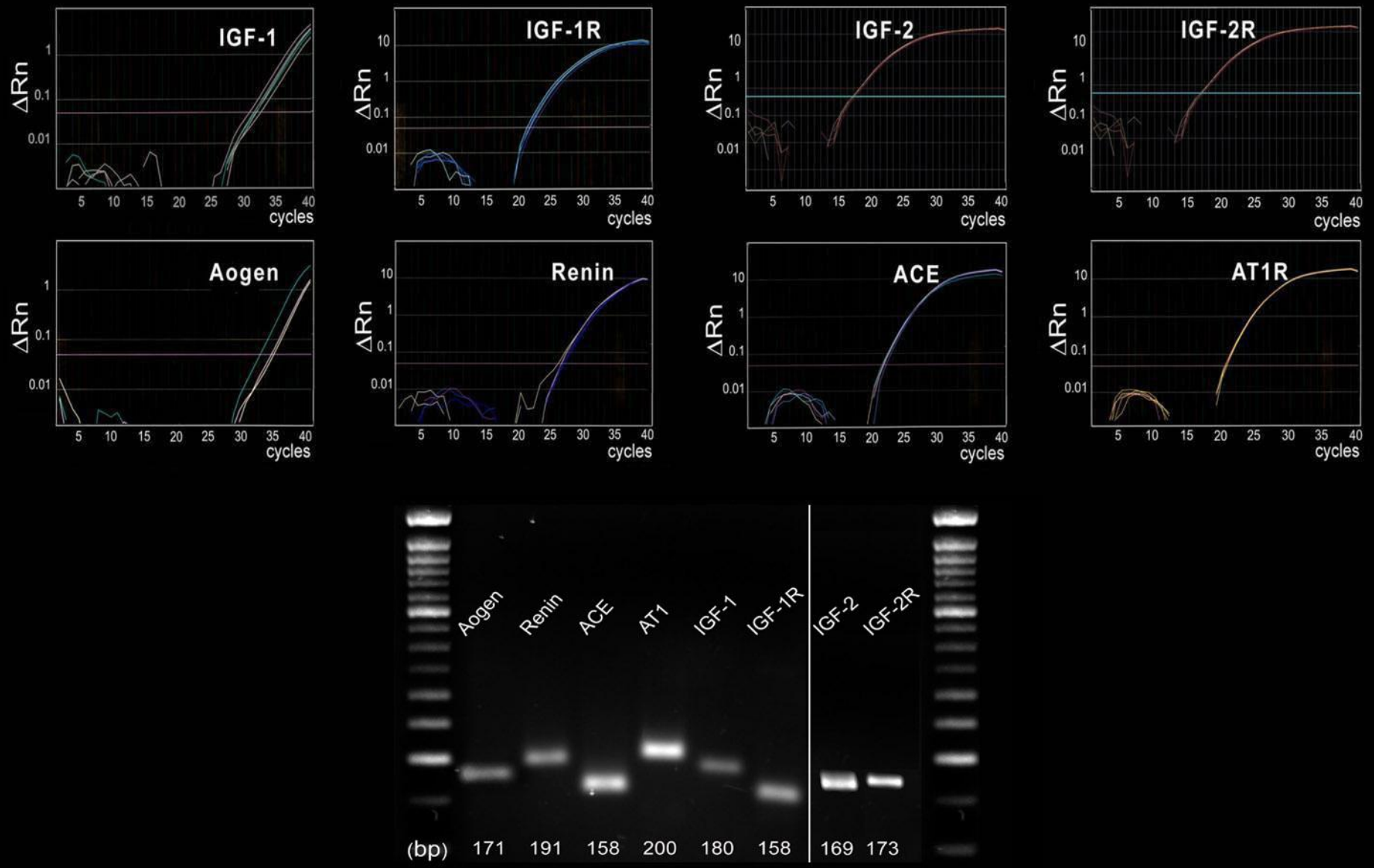




Malliaras et al, JACC 2014

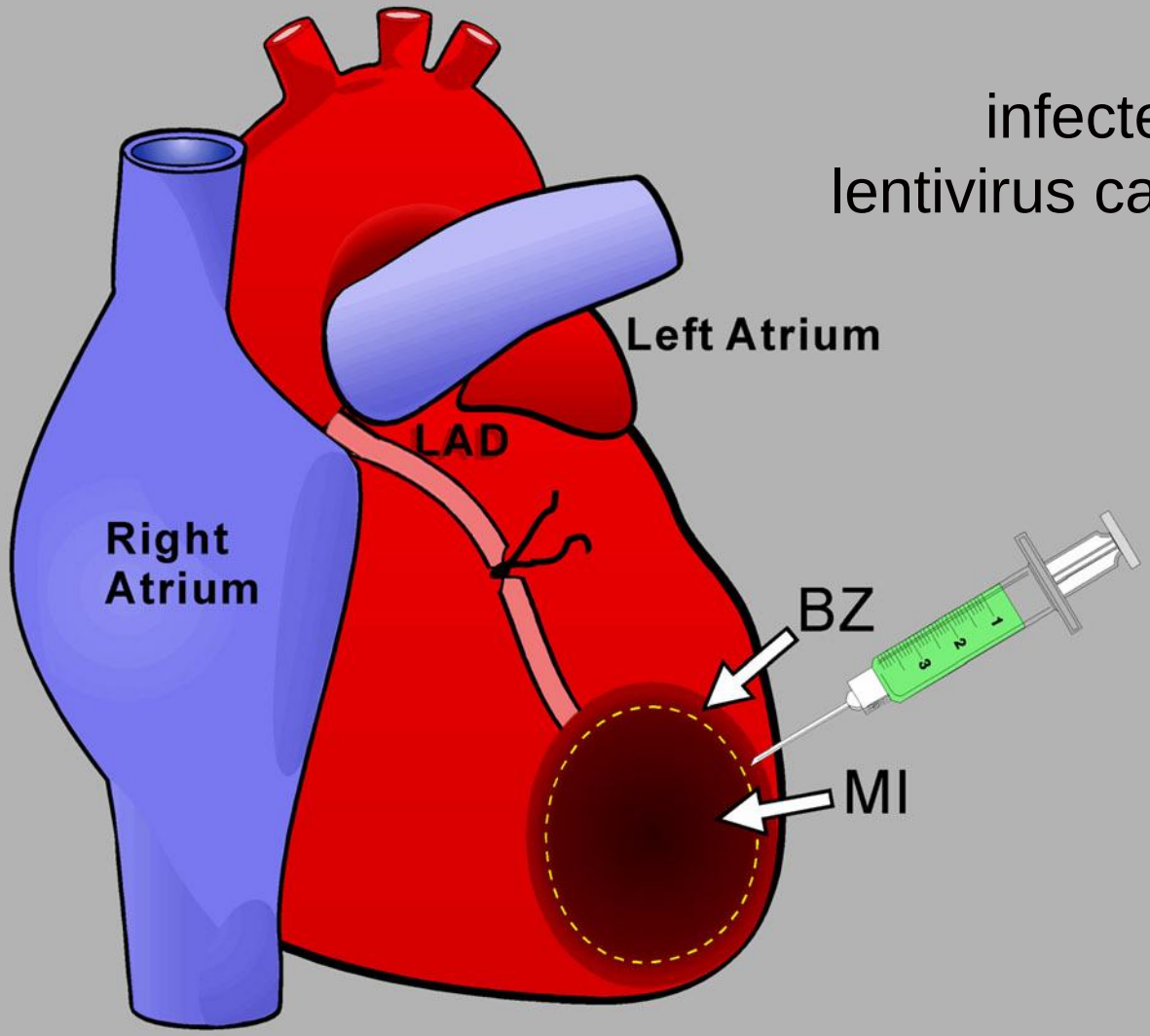
- **Second Generation of cells**
- **Selection of patients**
- **New tecnique for isolation**


IGF-2
plasma membrane
IGF-1
IGF-2R
IGF-2
nucleus
P
P
P
P
P
P
P
P
P
Tyr
IGF-1R
AngII
AT1R

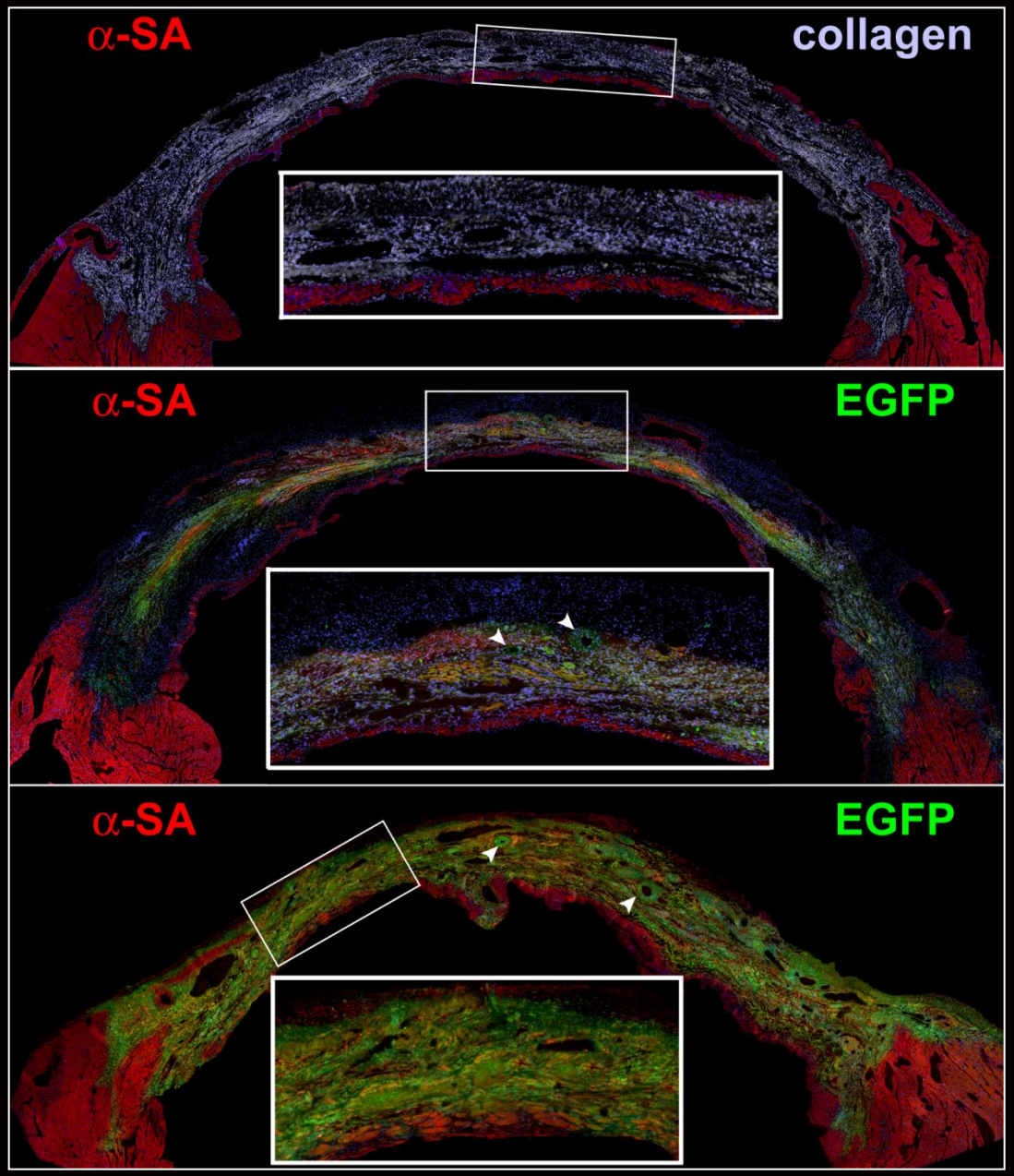


D'Amario et al, Circulation Research 2011

IGF-1R^{POS}hCSCs vs unselected hCSCs



infected with
lentivirus carrying EGFP

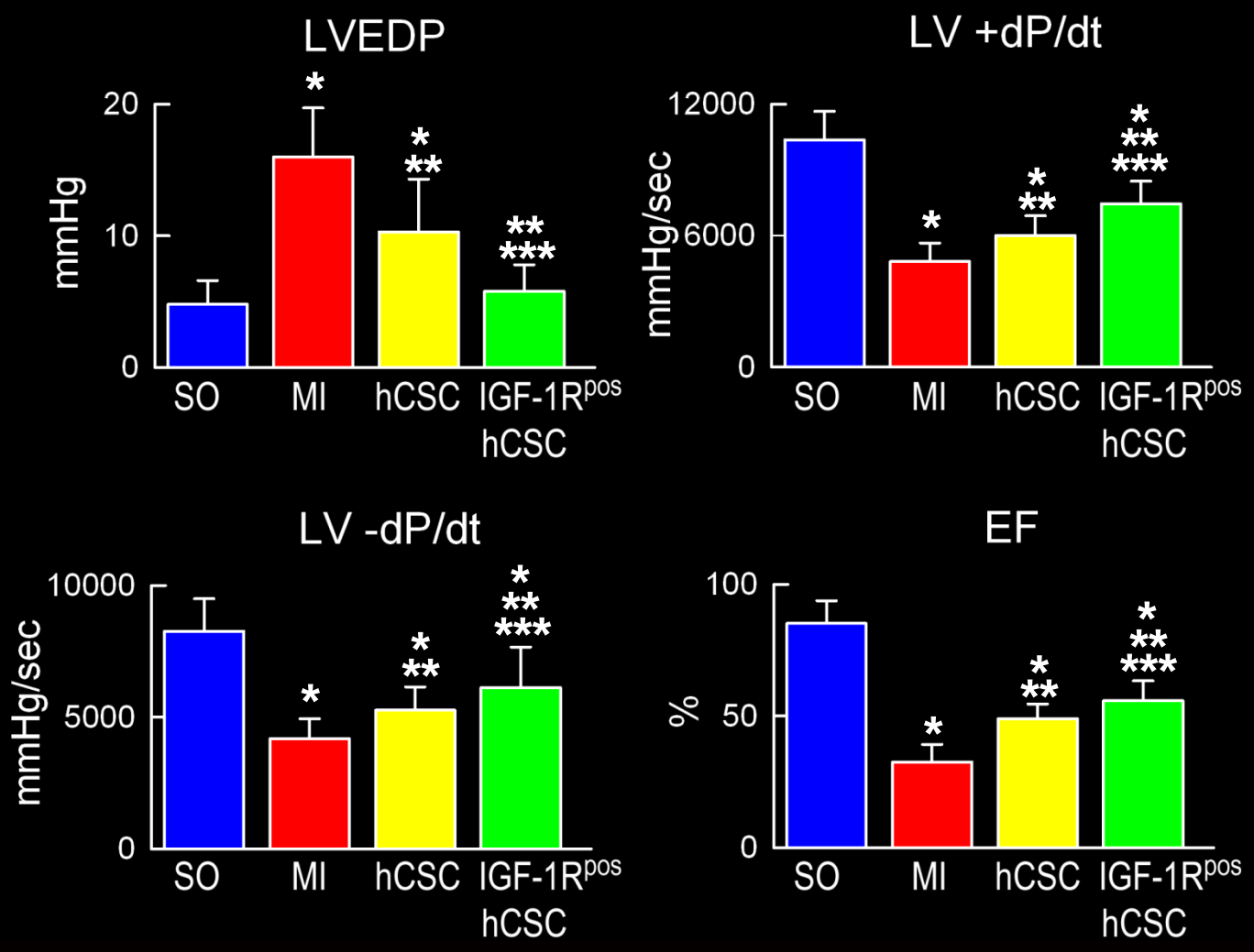


MI only

Unselected hCSCs

IGF-1R^{pos} hCSCs

D'Amario et al, Circulation Research



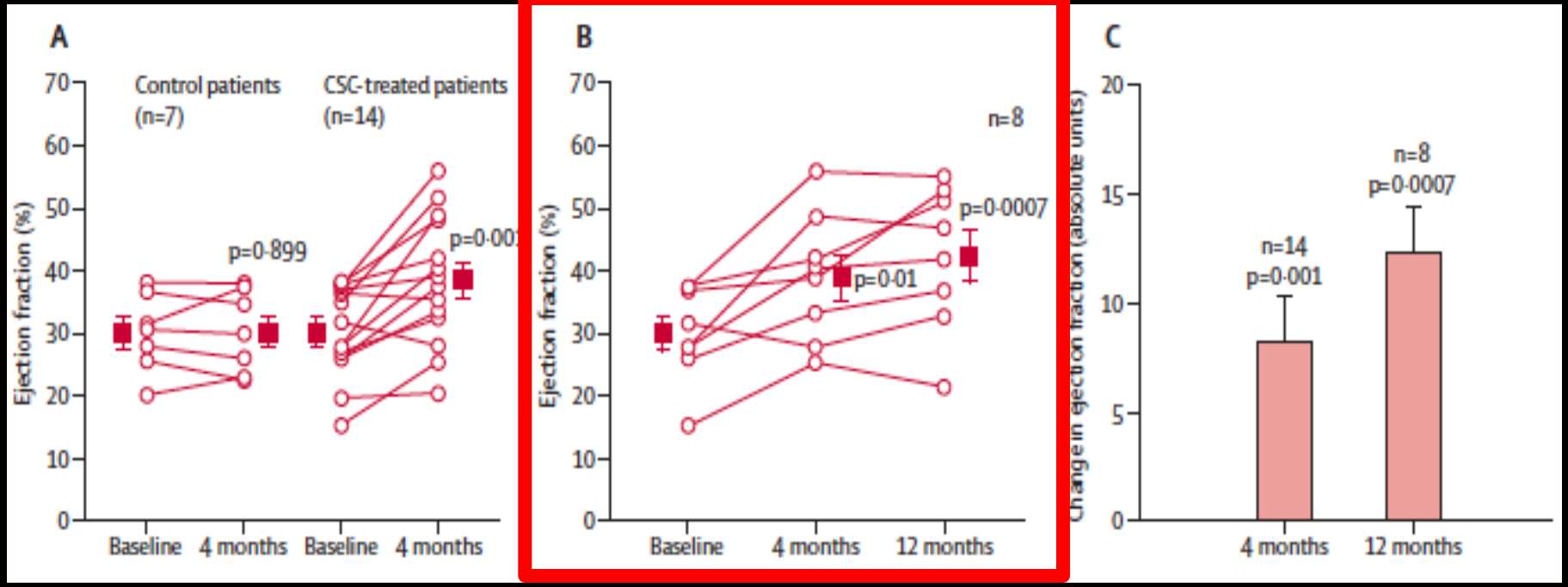
D'Amario et al, Circulation Research

The expression of IGF-1R identifies a pool of younger hCSCs with enhanced growth reserve in vitro and in vivo pointing to this hCSC subset as the ideal candidate cell for the management of human heart failure.

- Second Generation of cells
- Selection of patients
- New tecnique for isolation

SCIPIO: Results

Ejection Fraction



Bolli R., Chugh A., D'Amario D. et al., Lancet, 2011

To define whether a pool of functionally competent hCSCs can be harvested from patients with ischemic cardiomyopathy, independently from age, sex and comorbidities.

To test whether CSC characteristics are critical determinants of LVR following complete revascularization at 1 year follow up.

STUDY DESIGN

Enrollment

55 Consecutive Patients

< 1 Week

Tissue Harvesting

55 Patients underwent CABG

2D Ecocardiography, laboratory tests, physical examination
NYHA class assesment
Growth Fatcors Serum Level

17 Patients were lost at the FU:
10 = foreign residents
5 = not available for follow-up
2 = malignancies

12 ± 1 Months

38 Patients

Follow-Up

2D Ecocardiography, laboratory tests, physical examination
NYHA class assesment
Growth Fatcors Serum Level

D'Amario et al, Circulation 2014

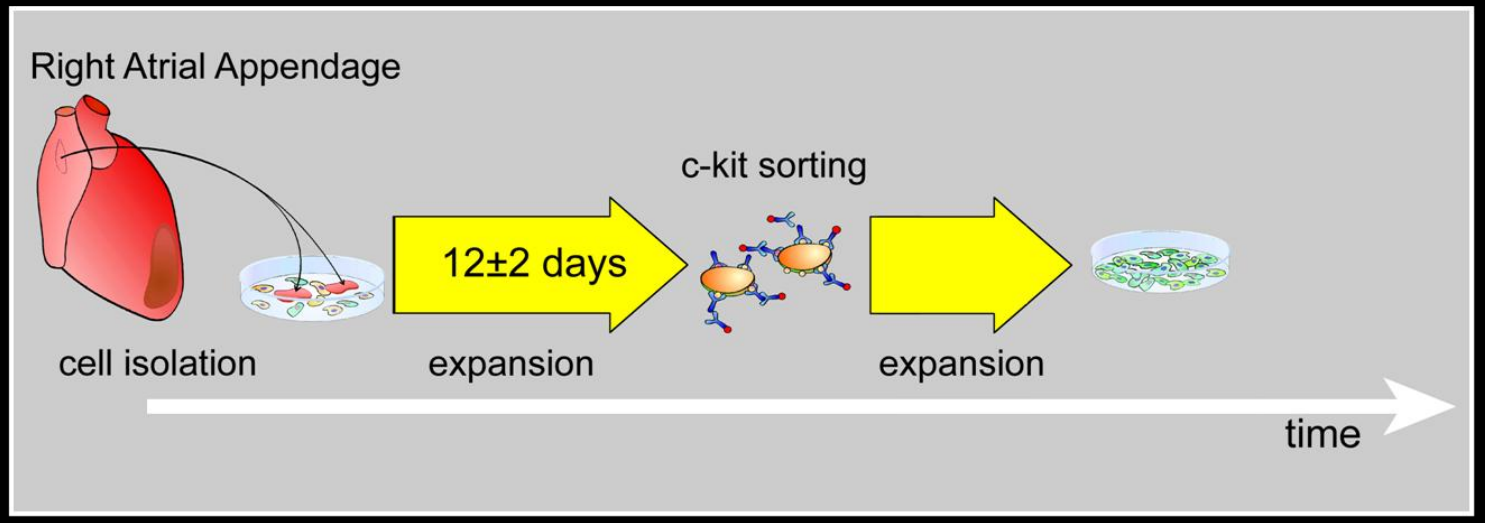
Study Population

Patients (n)	**38**
Age-yr (mean±SD)	**69±9**
Gender	
Female (n;%)	**5 (13%)**
Male (n;%)	**33 (87%)**
Body mass index kg/m2	**28±4**
CV risk factors	
Family history (n;%)	**28 (74%)**
Smoke (n;%)	**23 (61%)**
Hypertension (n;%**)**	**37 (97%)**
Hypercholesterolemia (n;%)	**30 (79%)**
Diabetes mellitus (n;%)	**24 (63%)**
BUN ≥ 24 mg/dl (n;%)	**5 (13%)**
Uric Acid ≥ 8 mg/dl (n;%)	**3 (8%)**

D'Amario et al, Circulation 2014

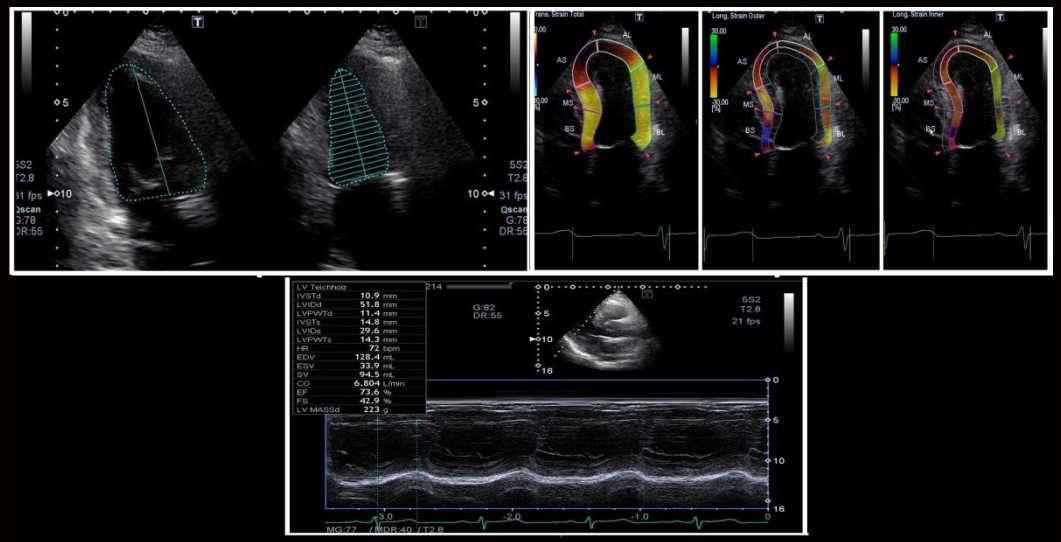
Clinical Presentation

Acute coronary syndrome (n;%)	**16 (42%)**
Stable angina (n;%)	**22 (58%)**
NYHA functional class	
I	**2 (5%)**
II	**21 (55%)**
III	**15 (40%)**
IV	**0 (0%)**
Previous CV events (n;%)	**4 (11%)**
Previous coronary revascularization (n;%)	**1 (3%)**
Ejection fraction (EF) - mean ± SD	**54±11**
Patients with EF< 45% (n;%)	**8 (21%)**

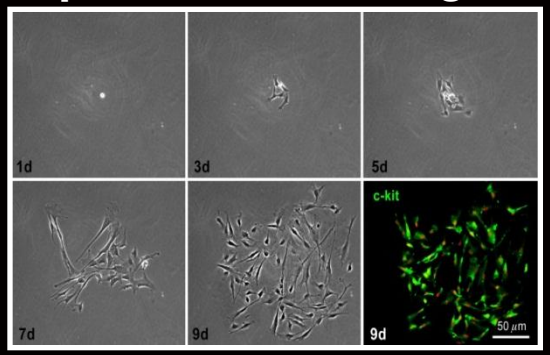


D'Amario et al, Circulation Research, 2011

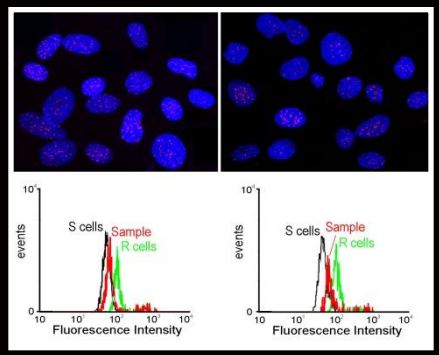
Left Ventricular Remodeling and Cardiac Stem Cell



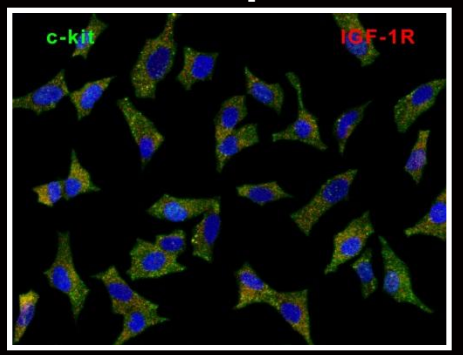
Population Doubling Time



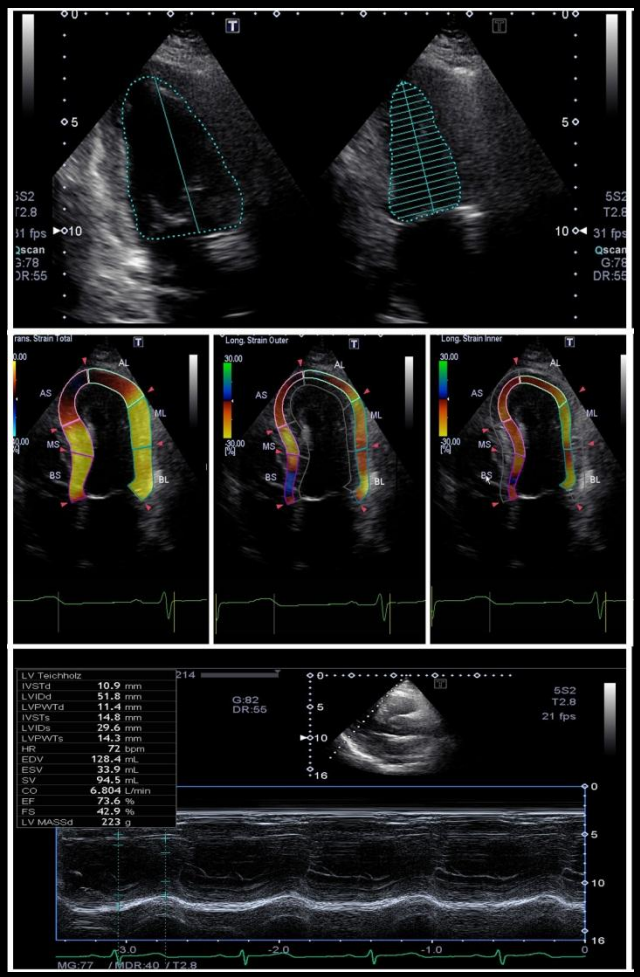
Telomere/Telomerase



IGF-1R expression

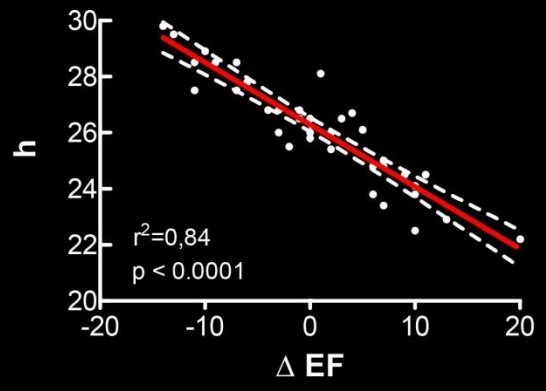


Left Ventricular Remodeling and Cardiac Stem Cell

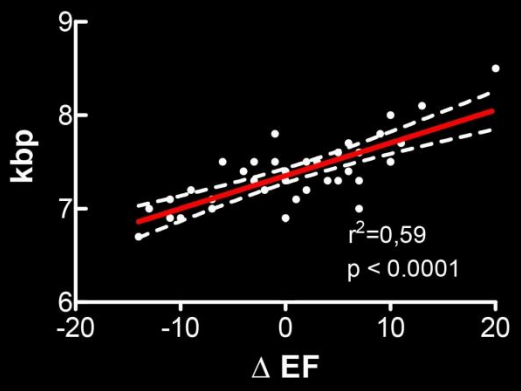


Δ Ejection Fraction

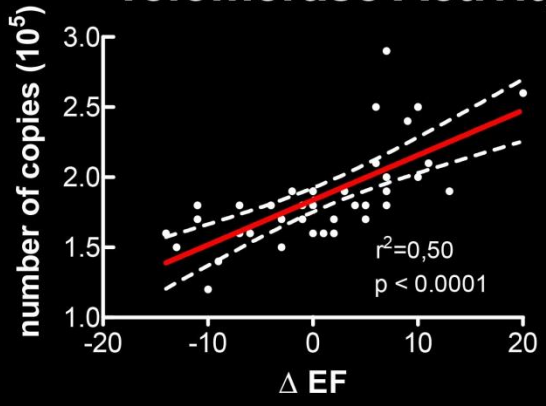
Population Doubling Time



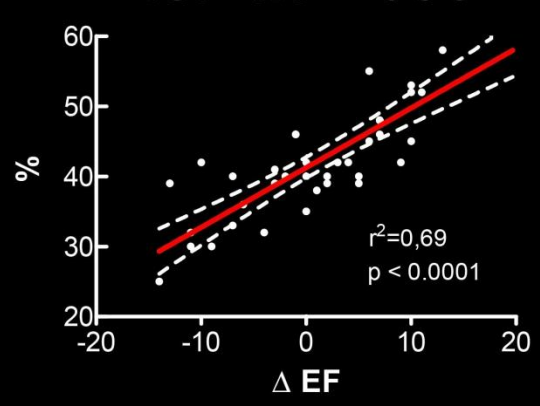
Telomere Length



Telomerase Activity



IGF-1R^{pos} CSC



D'Amario et al, Circulation 2014

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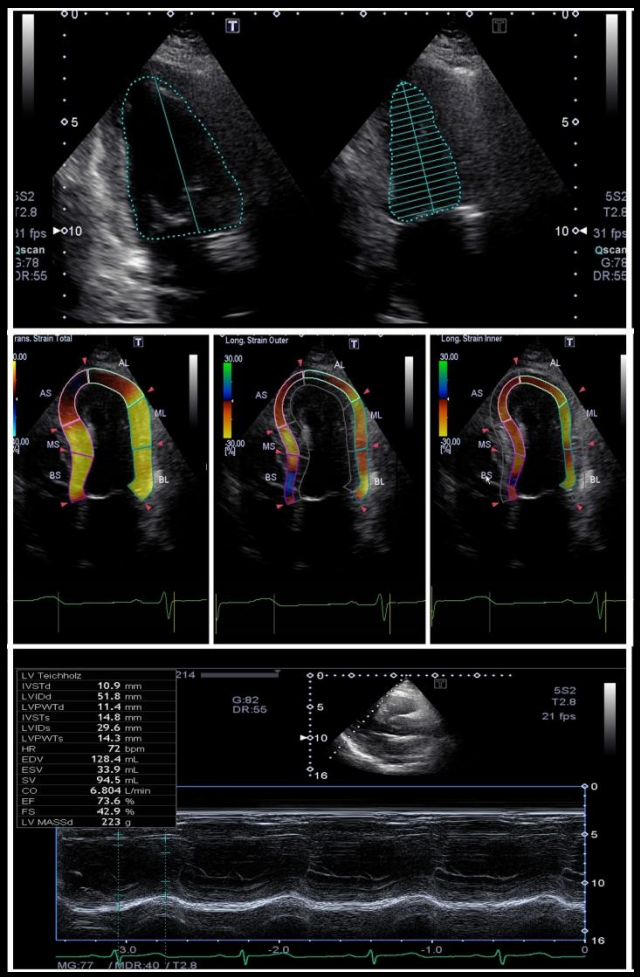
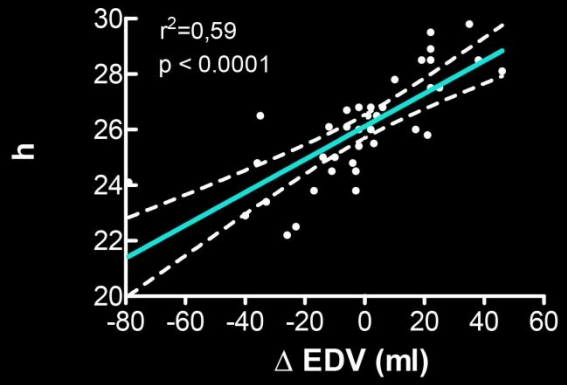
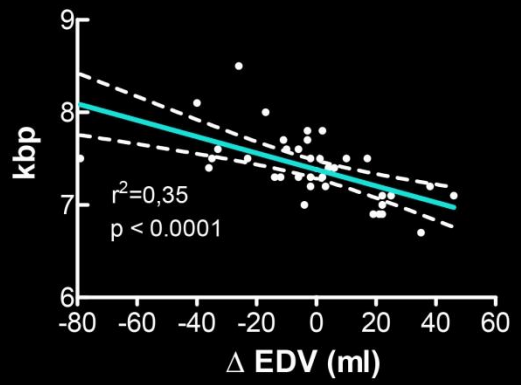


Δ End Diastolic Volume

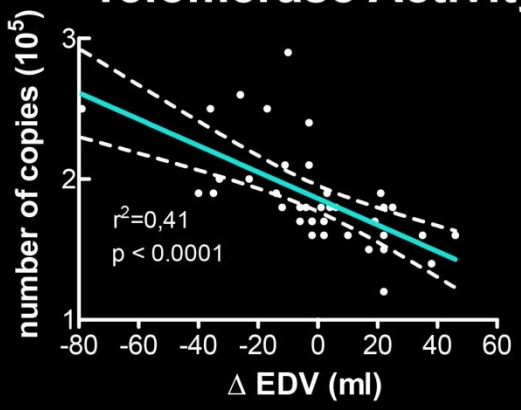
Population Doubling Time



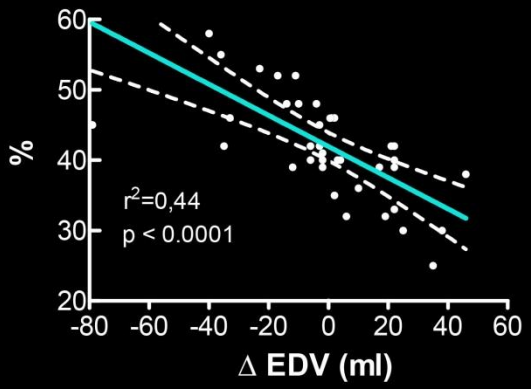
Telomere Length



Telomerase Activity



IGF-1R^{pos} CSC



D'Amario et al, Circulation 2014

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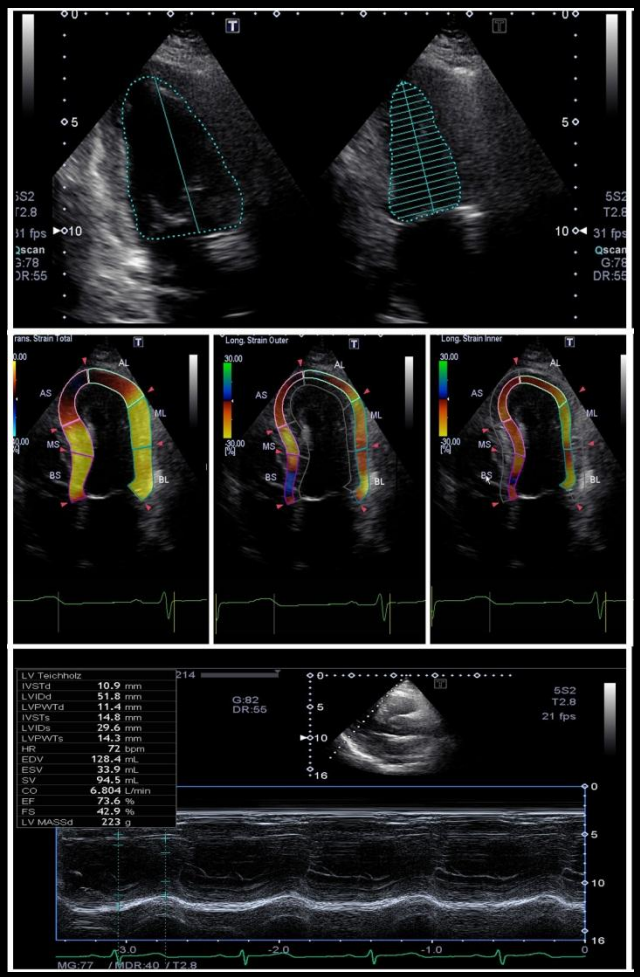
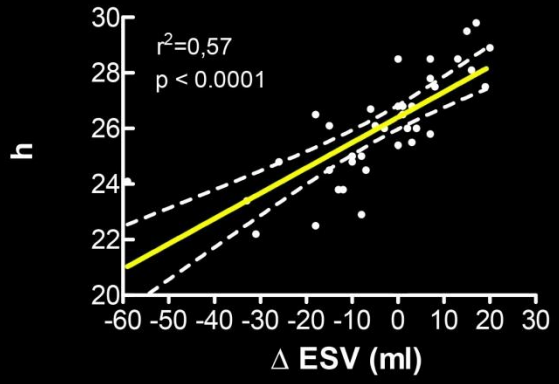
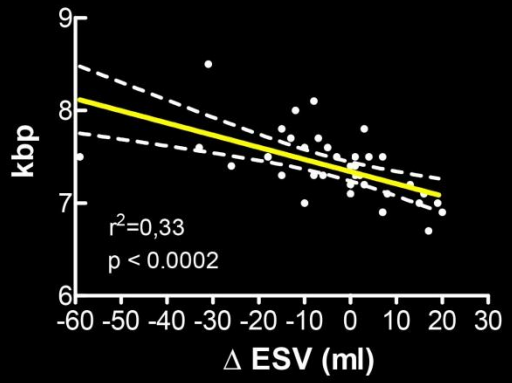


Δ End Sistolic Volume

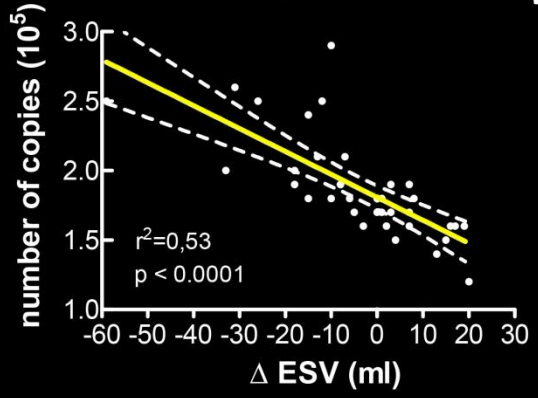
Population Doubling Time



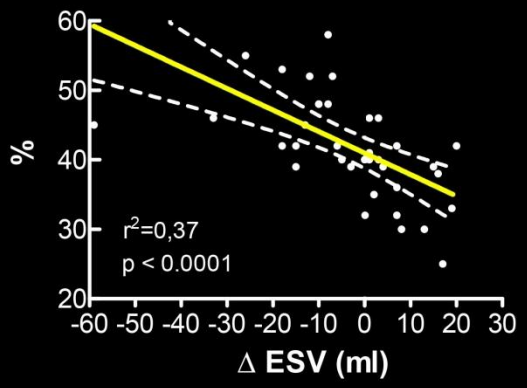
Telomere Length



Telomerase Activity

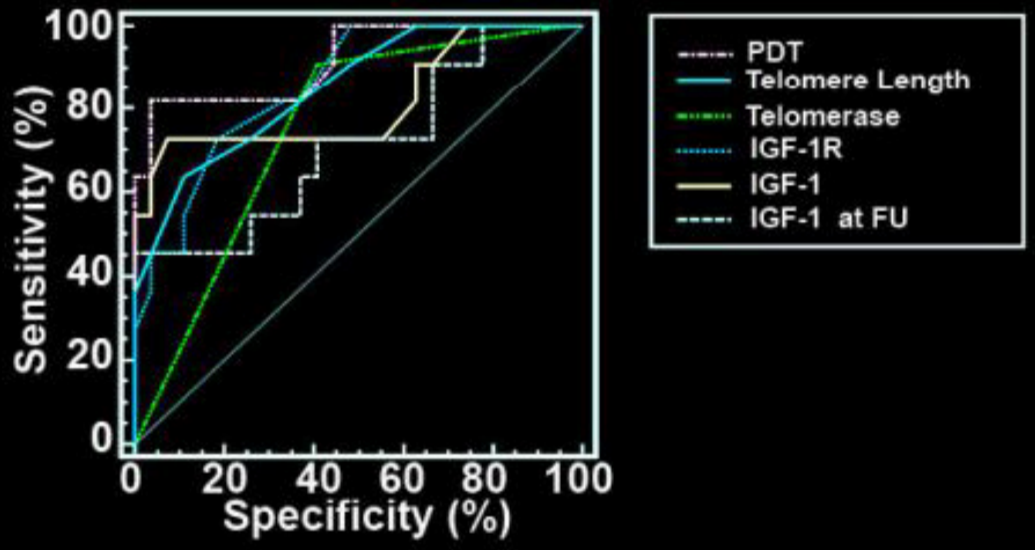


IGF-1R^{pos} CSC



D'Amario et al, Circulation 2014

	AUC	p	CI 95%	Cut Off	Sensitivity	Specificity
PDT	0.92	< 0.001	0.78 – 0.98	> 26.8	81.8	96.3
Telomere length	0.85	< 0.001	0.70 – 0.94	≤ 7	90.9	59.3
Telomerase	0.75	0.002	0.59 – 0.88	≤ 1.6	63.6	88.9
IGF1-R	0.86	< 0.001	0.71 - 0.95	≤ 39.0	72.7	81.5
IGF1	0.81	< 0.001	0.66 - 0.92	≤ 52.7	72.7	96.3
IGF1 at follow-up	0.71	0.01	0.54 - 0.85	≤ 81.8	45.4	100



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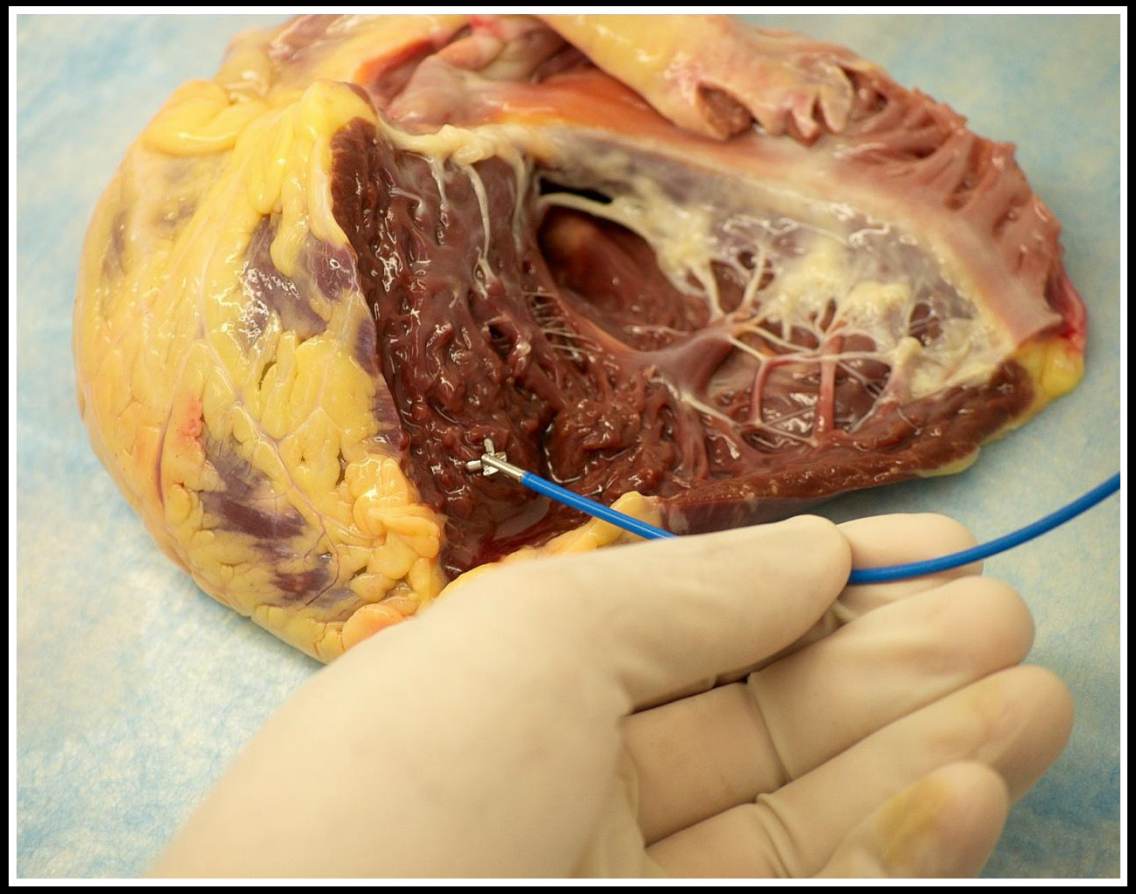
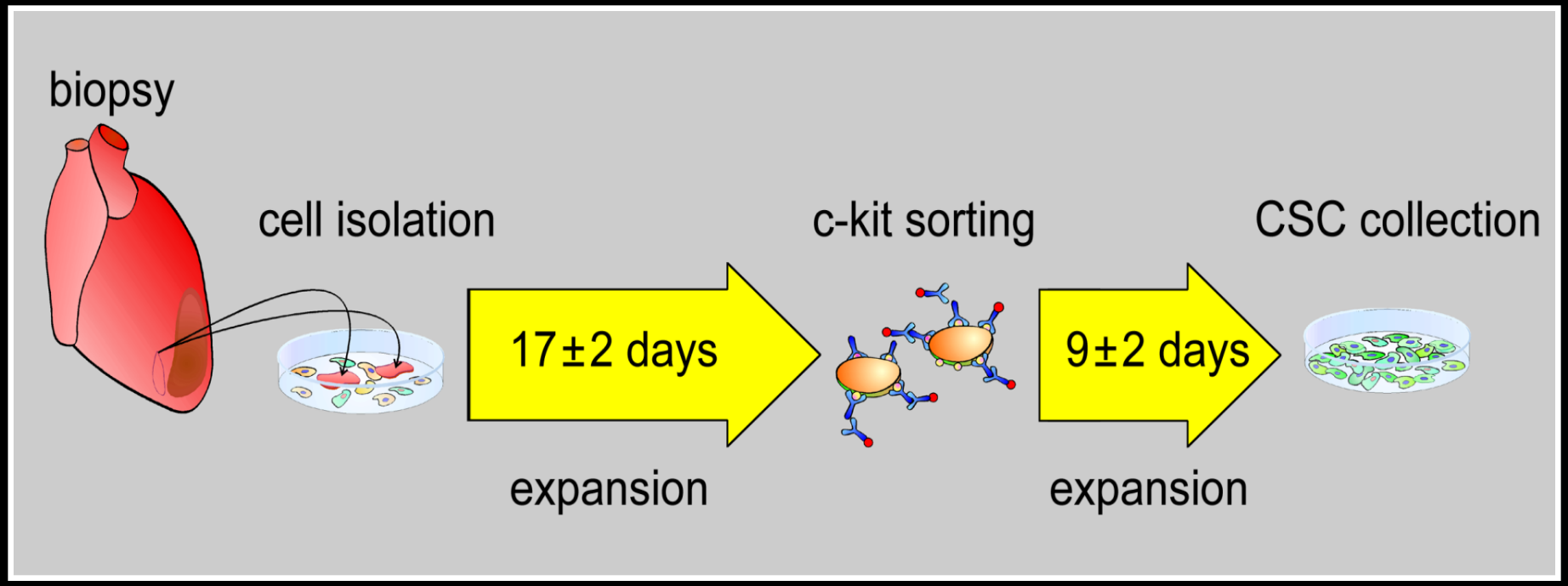
- Selection of patients
- New tecnique for isolation

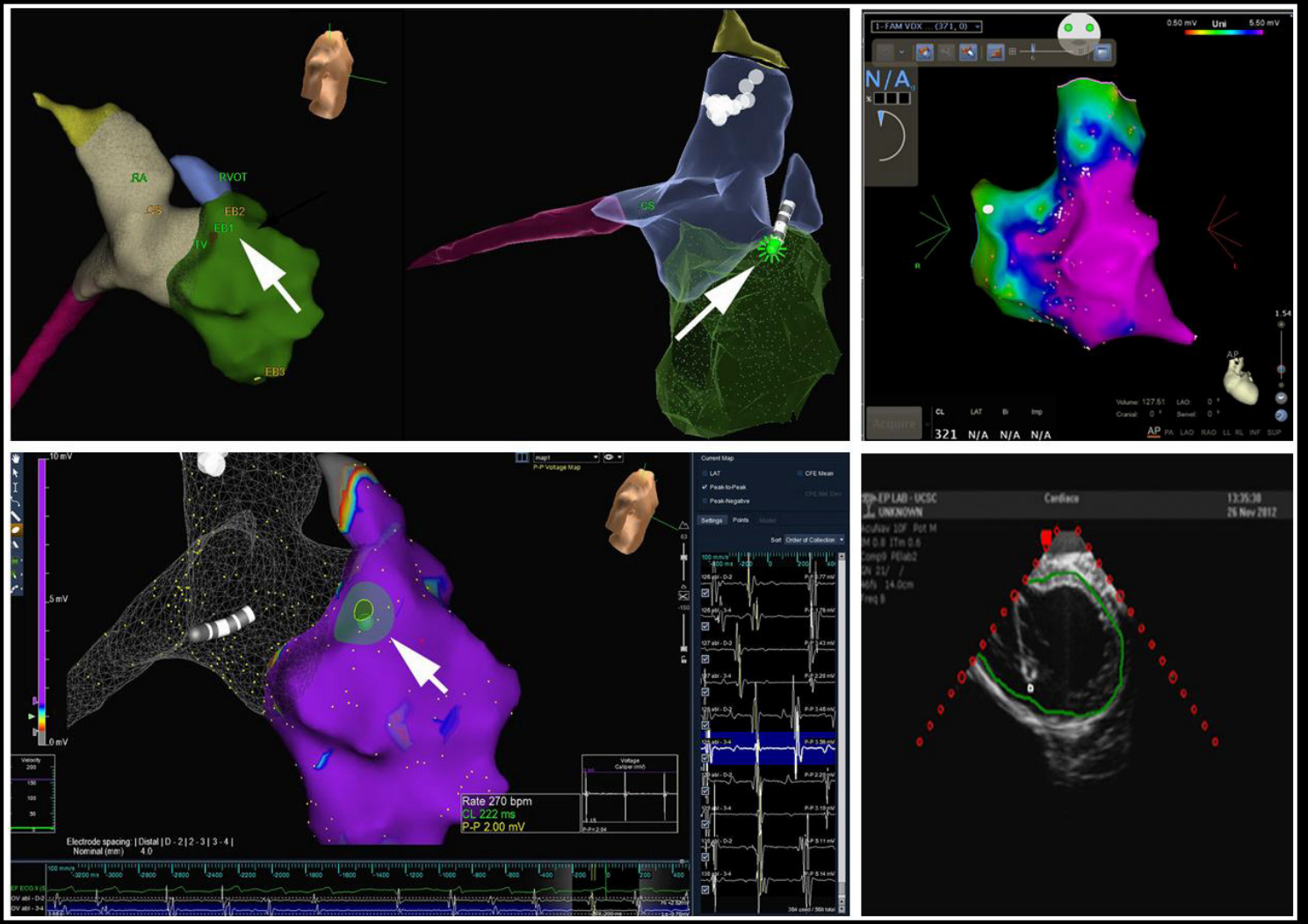


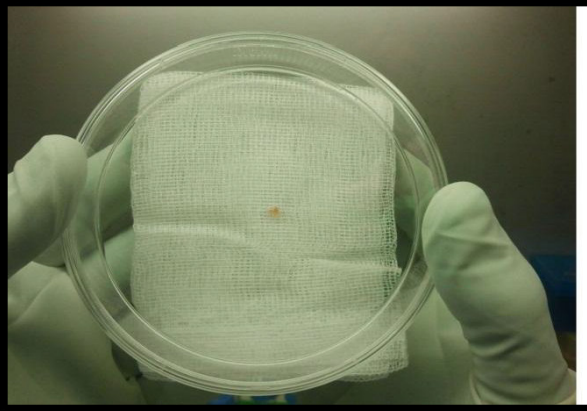
75 mg

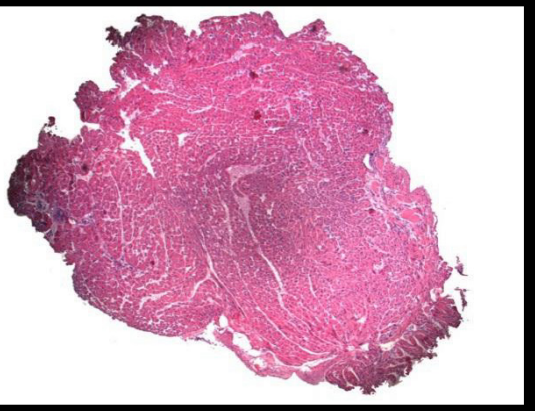
1.3 mg
x 3-5



D'Amario et al, Circulation Research 2011


RA
RVOT
CS
EB2
EB1
TV
EB3
CS
1-FAM VDX ... (371, 0)
0.50 mV
Uni
5.50 mV
N/A
1.54
AP
CL
LAT
Bi
Imp
321 N/A N/A N/A
AP PA LAO RAO LL RL INF SUP
.10 mV
.5 mV
.0 mV
map1
P-P Voltage Map
Current Map
LAT
CFE Mean
Peak-to-Peak
Peak-Negative
Settings
Points
Sort
Order of Collection
Rate 270 bpm
CL 222 ms
P-P 2.00 mV
Electrode spacing: | Distal | D - 2 | 2 - 3 | 3 - 4 |
Nominal (mm) 4.0
EP LAB - UCSC
UNKNOWN
Cardiac
13:35:30
26 Nov 2012

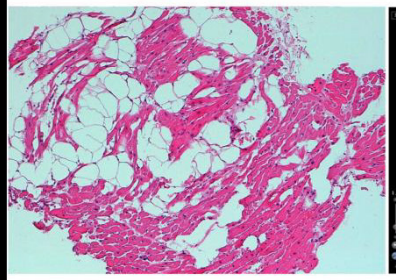


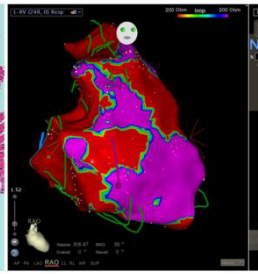


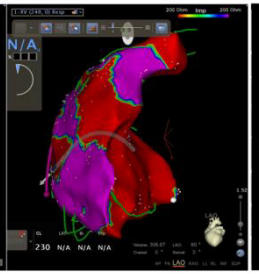
Histopathological Diagnosis	33
Amyloidosis	2
Antiphospholipid syndrome	1
ARVC	4
Myocarditis	12
Virus Genome Positivity	3
Idiopathic Dilated Cardiomyopathy	14

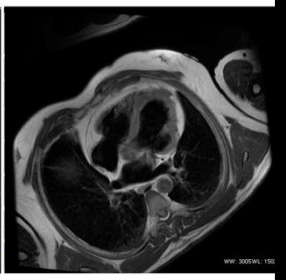
Major Complications	0
Hemopericardium/Tamponade	0
Stroke	0
Minor Complications	3
Transient Chest Pain	0
Non Sustained VT	3
Transient Hypotension	0

ARVC

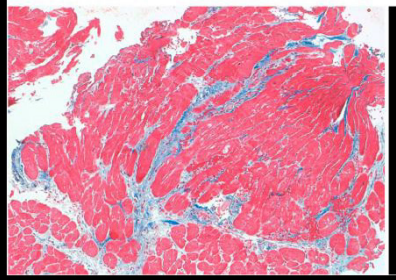


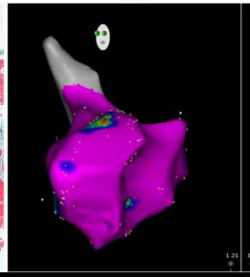


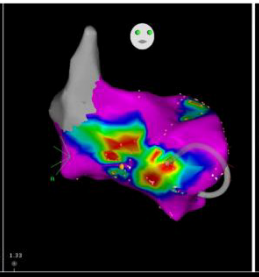


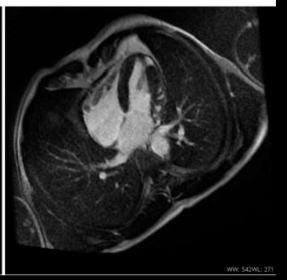


Myocarditis









- **Heart Failure is an international public health problem of pandemic proportions. The epidemics of HF represents a challenge for the National Health System.**

- **Currently there are no effective intervention to regenerate lost myocardial tissue and reverse the resultant dysfunction and heart remodeling.**

- **hCSCs and CDCs entered in the clinical scenario resulting in significant improvement in LV systolic function, quality of life ponting to this class of cell as the ideal candidate cell to treat HF in humans.**