XXIX Giornate Cardiologiche Torinesi
"ADVANCES IN CARDIAC ARRHYTHMIAS AND GREAT INNOVATIONS IN CARDIOLOGY"
Turin, October 27-28, 2017
Centro Congressi Unione Industriale

Cellular therapy: where do we stand?

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Questions I need to be answered

- *Which is the origin of the universe?*
- *Is Maradona better than Pelè?*
- *Cell therapy: where do we stand?*
- *Why cucumber in McD cheeseburger?*

A CLINICAL OVERVIEW

- ***Have we done a good job?***
- ***Is there (if any) a way to go?***
- ***Our experience in Milan in RA***

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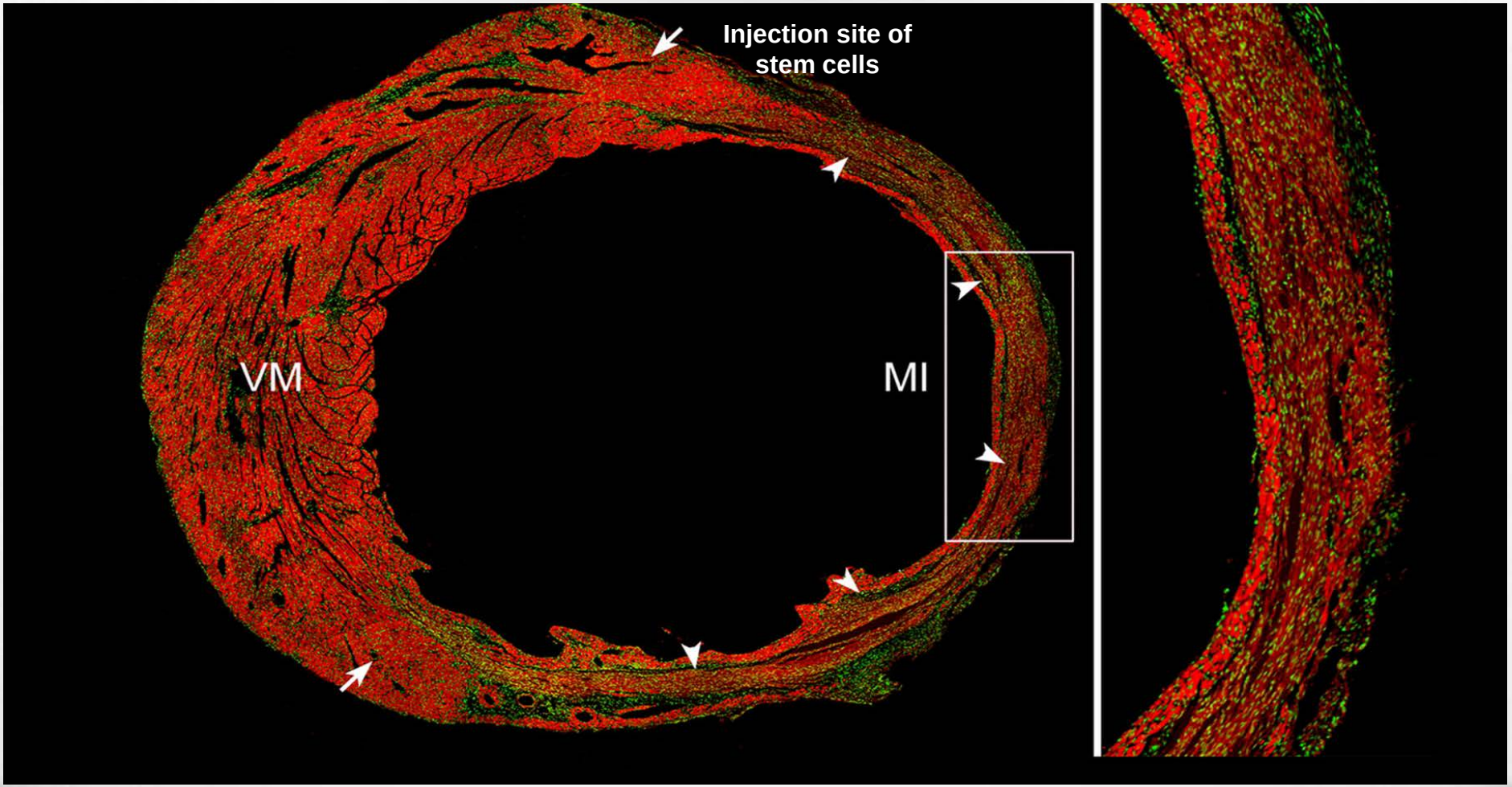
NEW CELLS IN OLD HEART



(Orlic D, Nature 2001)

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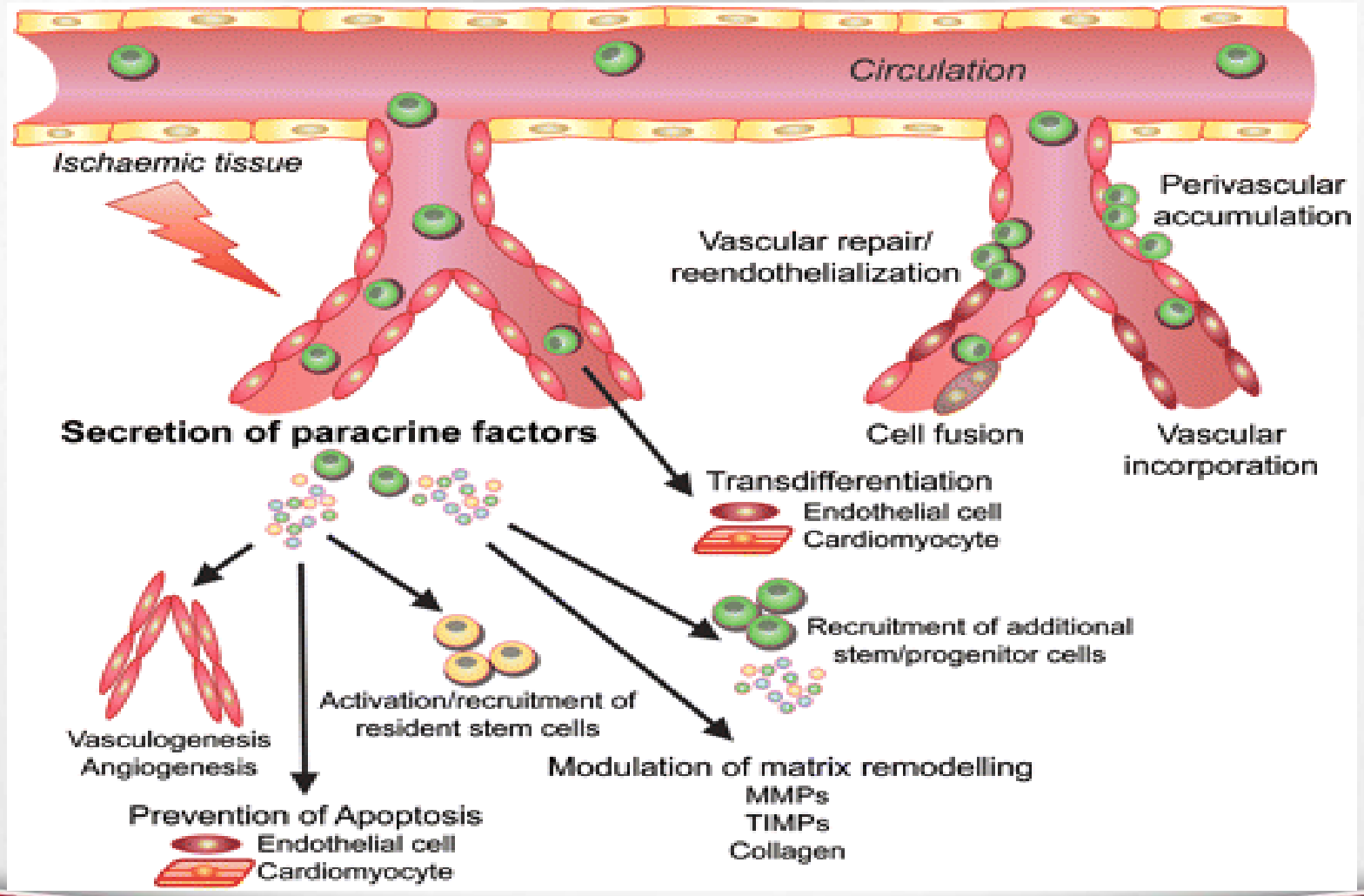
Proposed mechanisms of ischemic tissue repair via stem and progenitor cell-based therapies



Tongers J, EHJ 2012

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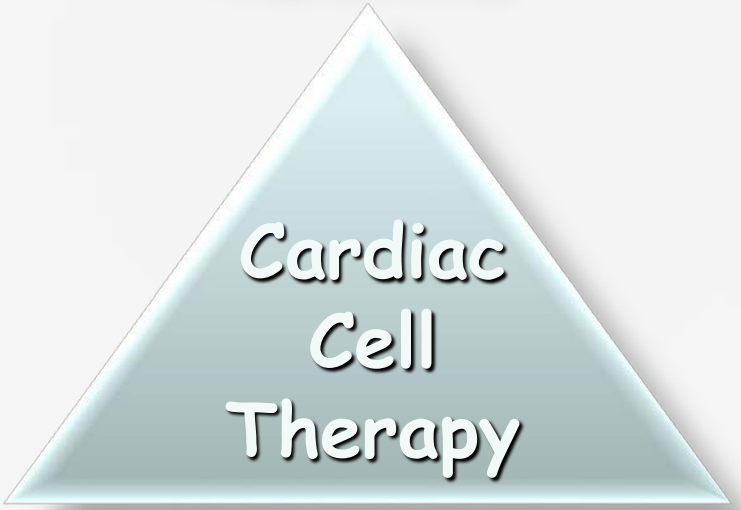
Cells are not molecules!

ATMP

Cell type/MoA
Source
Auto/Allo



Disease

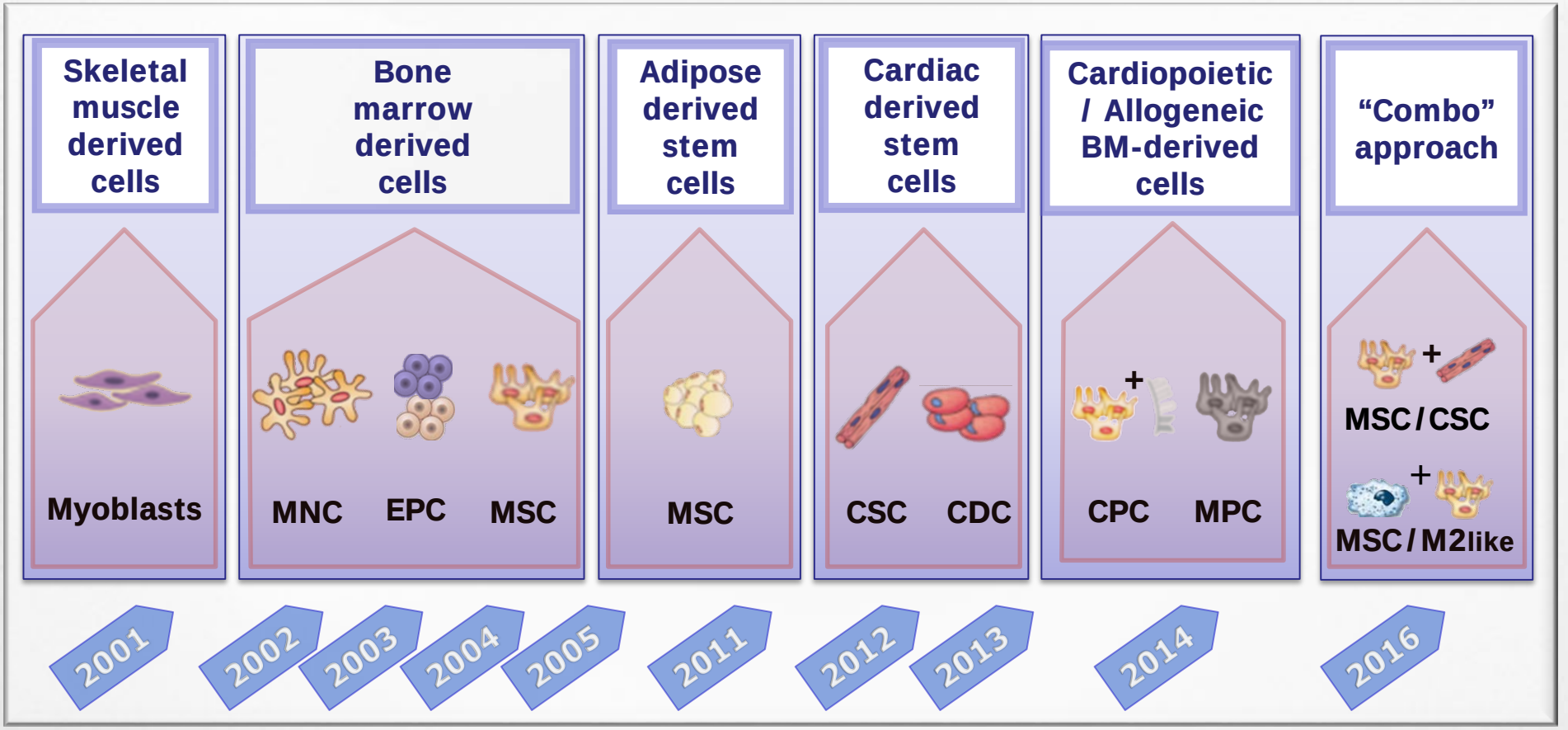
Acute/Chronic

STEMI/IHF/DCM

Patient

Age
Genetics
Comorbidities
Medications

CELLS IN THE SPOTLIGHT: THE SEARCH FOR POTENCY



FIRST GENERATION

SECOND GENERATION

THIRD GENERATION

Editorial

Bone Marrow Cell Therapy for Ischemic Heart Disease

The Never Ending Story

Giulio Pompilio, Patrizia Nigro, Beatrice Bassetti, Maurizio C. Capogrossi

- *24 meta-analyses of about 80 RCTs,*
- *Heterogeneity of target disease, including criteria, surrogate endpoints, methods.*
- Weak functional benefit (when present),
- No conclusive data about clinical impact.

Circ Res, 2015

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Where we stand…

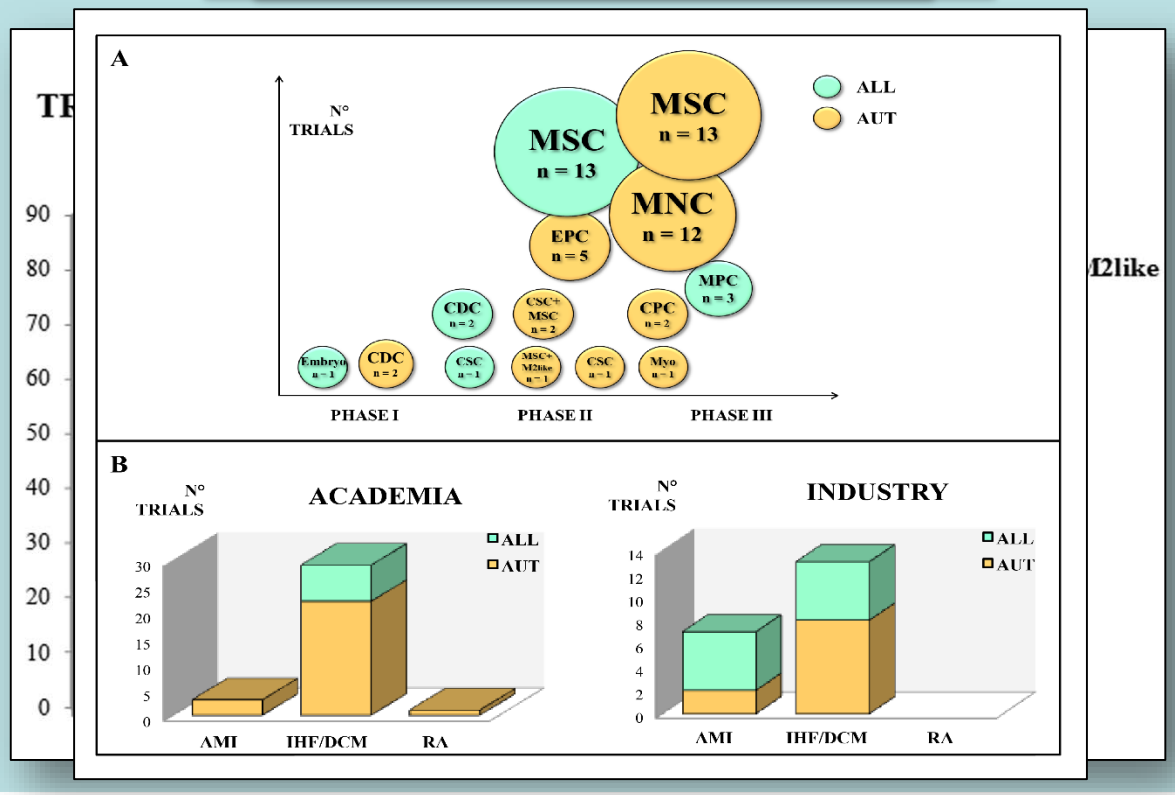
- *MoA: paracrine paradigm*
- *Few preclinical comparative studies*
- *Very few clinical comparative studies*
- *Mixed results very difficult to compare*

Power Is Nothing Without Control

The Enduring Search for the Best Cell in Cardiac Cell Therapy at a Crossroads

Beatrice Bassetti, Maurizio C. Capogrossi, Giulio Pompilio

Cell types in actively enrolling trials



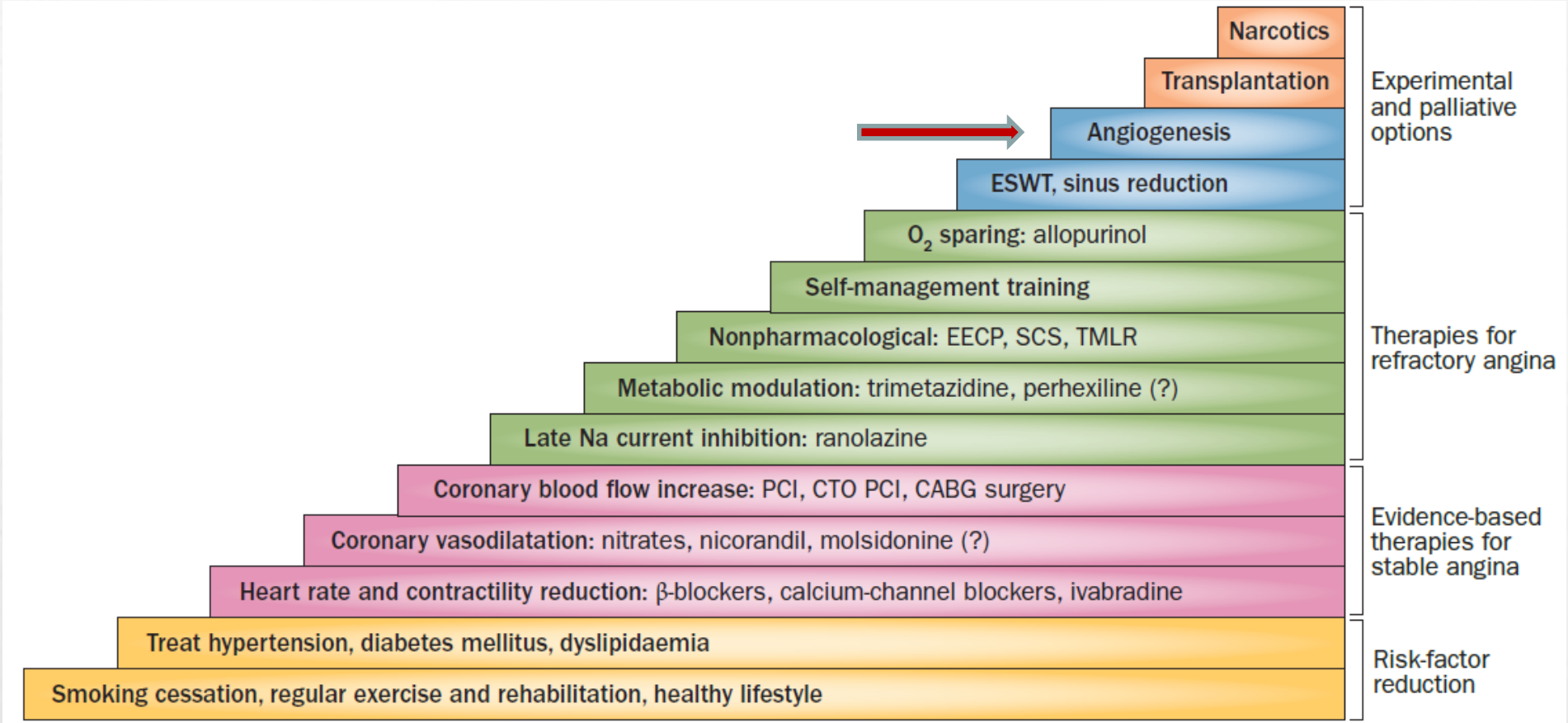
Who may benefit?

- *ADVANCED ISCHEMIC HEART FAILURE*
- *REFRACTORY ANGINA*

Refractory ischemic cardiomyopathy

- More patients with refractory angina.
  - US: 100.000 – 200.000 new cases/year (Am J Cardiol 1999;84:598)
  - EU: 120.000 – 180.000 new cases/year
- Factors: aging, statins, better treatments
- Significant morbidity
- Frequent ER/hospital visits

When the going get tough..



Impact of Cell Therapy on Myocardial Perfusion and Cardiovascular Outcomes in Patients With Angina Refractory to Medical Therapy

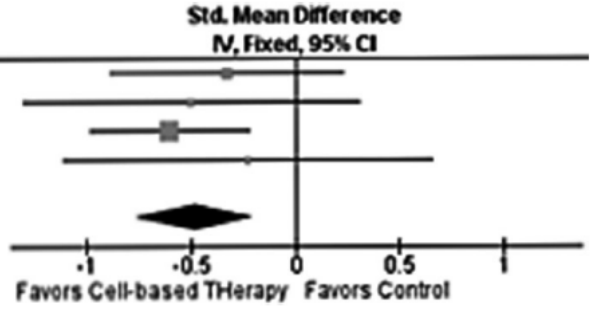
A Systematic Review and Meta-Analysis

6 Studies with 353 participants included

SPECT

Study or Subgroup	Cell-based Therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
van Ramshorst et al, 2009	-3.4	6	25	-1.1	7.7	25	24.8%	-0.33 [-0.89, 0.23]
Tse et al, 2007	-0.5	5	19	2.4	6.9	9	11.9%	-0.50 [-1.30, 0.31]
Losordo et al (LD), 2011	-117.4	221.2	55	0.1	161.1	56	53.4%	-0.60 [-0.98, -0.22]
Jimenez-Quevedo et al, 2014	-0.5	2.2	17	0	1.9	7	9.9%	-0.23 [-1.11, 0.66]
Total (95% CI)			**116**			**97**	**100.0%**	**-0.49 [-0.76, -0.21]**

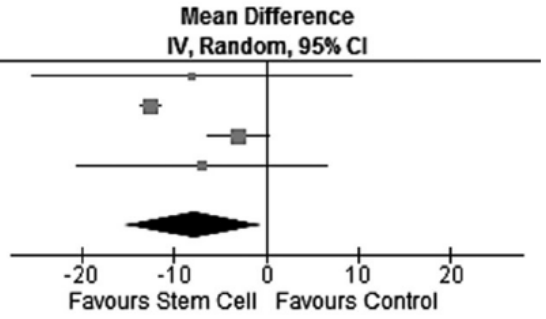
Heterogeneity: Chi² = 1.01, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)



A Frequency of Anginal Episodes

Study or Subgroup	Stem Cell Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Losordo et al, 2007	-12.6	18.2	6	-4.5	20.1	18	12.3%	-8.10 [-25.37, 9.17]	2007
Wang et al, 2010	-15.6	4	56	-3	1.2	56	36.8%	-12.60 [-13.69, -11.51]	2010
Losordo et al (LD), 2011	-16.6	8.9	55	-13.6	9	56	34.5%	-3.00 [-6.33, 0.33]	2011
Jimenez-Quevedo et al, 2014	-8.5	8.1	17	-1.5	17.6	7	16.5%	-7.00 [-20.59, 6.59]	2014
Total (95% CI)			**134**			**137**	**100.0%**	**-7.81 [-15.22, -0.41]**	

Heterogeneity: Tau² = 38.50; Chi² = 29.43, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.07 (P = 0.04)

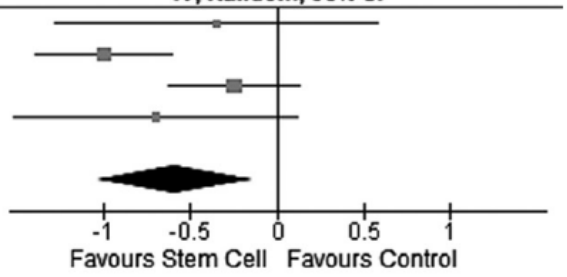


Kahn AR, Circ Res 2016

B Use of Anti-anginal Medications

Study or Subgroup	Stem Cell Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Losordo et al, 2007	-8.1	14.7	6	4.1	37.9	18	15.1%	-0.35 [-1.28, 0.58]	2007
Wang et al, 2010	-11	5.2	56	-4.1	8.3	56	33.1%	-0.99 [-1.38, -0.60]	2010
Losordo et al (LD), 2011	-6.3	8.1	55	-4.2	8.8	56	34.0%	-0.25 [-0.62, 0.13]	2011
Jimenez-Quevedo et al, 2014	-3.5	3.9	19	-0.5	4.8	9	17.8%	-0.69 [-1.51, 0.12]	2014
Total (95% CI)			**136**			**139**	**100.0%**	**-0.59 [-1.03, -0.14]**	

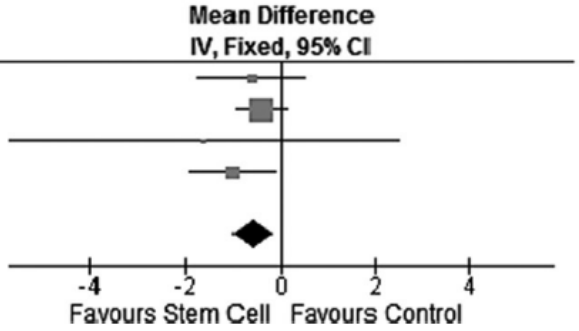
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 7.54$, df = 3 (P = 0.06); $I^2 = 60\%$
Test for overall effect: Z = 2.60 (P = 0.009)



C Change in CCS Class

Study or Subgroup	Stem Cell Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Losordo et al, 2007	-1.4	1	6	-0.8	1.7	18	14.1%	-0.60 [-1.72, 0.52]	2007
van Ramshorst et al, 2009	-0.8	0.8	25	-0.4	1.1	25	62.2%	-0.40 [-0.93, 0.13]	2009
Wang et al, 2010	-2.4	8.4	56	-0.8	13.2	56	1.1%	-1.60 [-5.70, 2.50]	2010
Jimenez-Quevedo et al, 2014	-1	1.5	17	0	0.7	7	22.7%	-1.00 [-1.88, -0.12]	2014
Total (95% CI)			**104**			**106**	**100.0%**	**-0.58 [-1.00, -0.16]**	

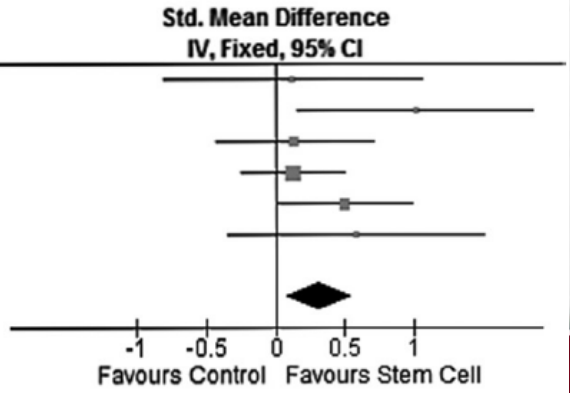
Heterogeneity: $Chi^2 = 1.55$, df = 3 (P = 0.67); $I^2 = 0\%$
Test for overall effect: Z = 2.69 (P = 0.007)



A Exercise Tolerance

Study or Subgroup	Stem Cell Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Losordo et al, 2007	0.5	1.3	18	0.3	2.1	6	6.3%	0.13 [-0.80, 1.05]	2007
Tse et al, 2007	0.14	0.33	19	-0.25	0.46	9	7.6%	1.01 [0.17, 1.85]	2007
van Ramshorst et al, 2009	9	43.2	24	2	53.9	25	17.2%	0.14 [-0.42, 0.70]	2009
Wang et al, 2010	4.5	12.27	56	2.5	17.7	56	39.3%	0.13 [-0.24, 0.50]	2010
Losordo et al (LD), 2011	140	171	53	58	146	25	23.2%	0.50 [0.01, 0.98]	2011
Jimenez-Quevedo et al, 2014	137	163.7	15	4.2	316.4	7	6.4%	0.58 [-0.34, 1.50]	2014
Total (95% CI)			**185**			**128**	**100.0%**	**0.31 [0.08, 0.55]**	

Heterogeneity: $Chi^2 = 4.96$, df = 5 (P = 0.42); $I^2 = 0\%$
Test for overall effect: Z = 2.64 (P = 0.008)



Kahn AR, Circ Res 2016

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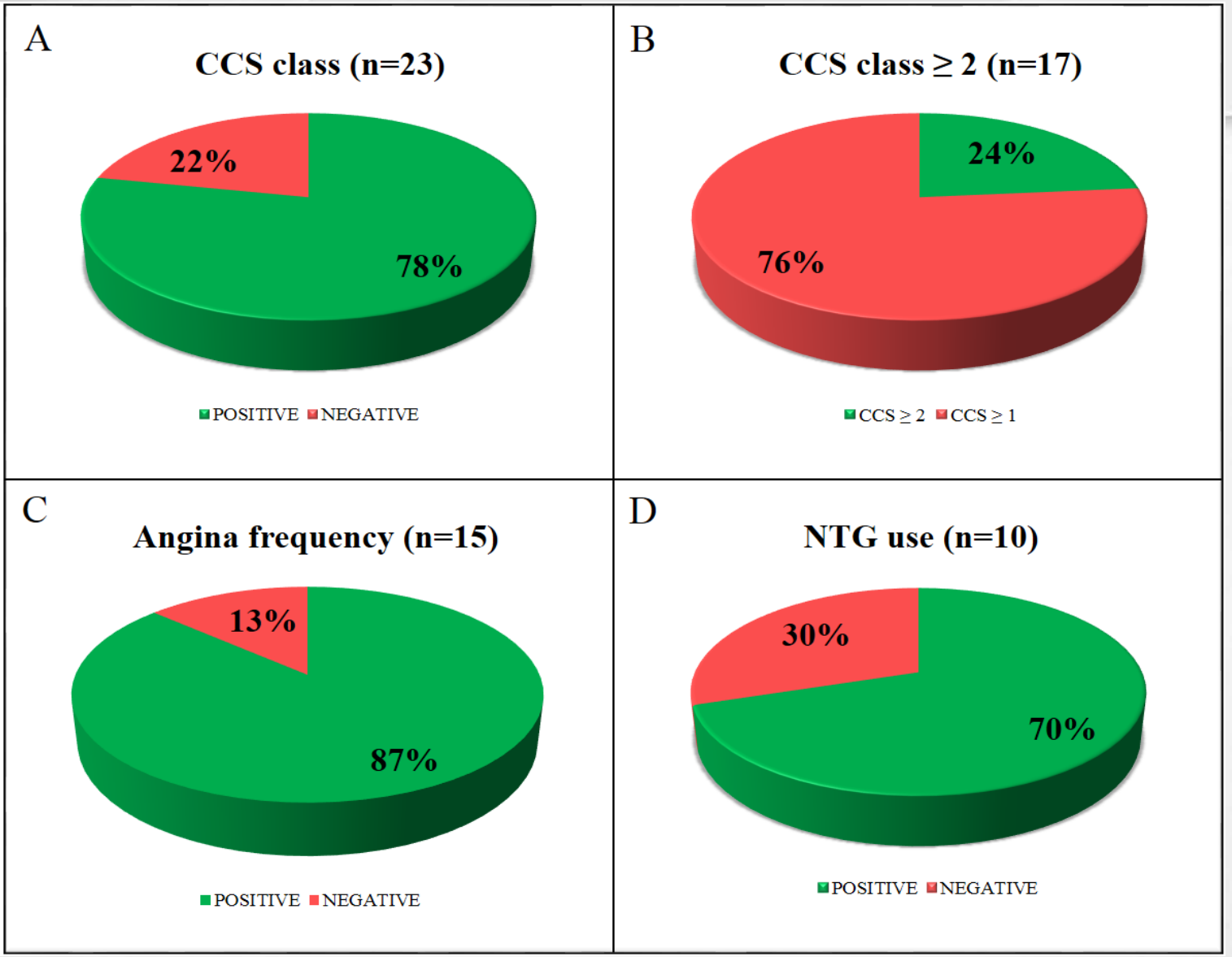

Bassetti B and Pompilio G, Stem Cell Int 2017 (in press)

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The RENEW Trial

Efficacy and Safety of Intramyocardial Autologous CD34$^+$ Cell Administration in Patients With Refractory Angina

- Randomized, double-blind, multicenter trial **comparing IM cell administration with no intervention (standard of care) or IM placebo injections (active control) in patients with refractory angina.**
- CD34$^+$ cells using an ISOLEX 300i system after G-CSF mobilization (Baxter Healthcare Corporation).
- NOGA XP-guided endocardial injections using MyoStar catheter (Biosense Webster)
- **Primary efficacy endpoint: TET at 12 months**
- **Treated set: 112 patients** randomized (28 SOC, **27 active control, 57 CD34$^+$**)
- **Premature termination by the Sponsor (Baxter HC) due to "strategic considerations" (at less of one quarter of planned enrollment).**

Povsic TJ et al., *JACC Cardiovasc Int* 2016

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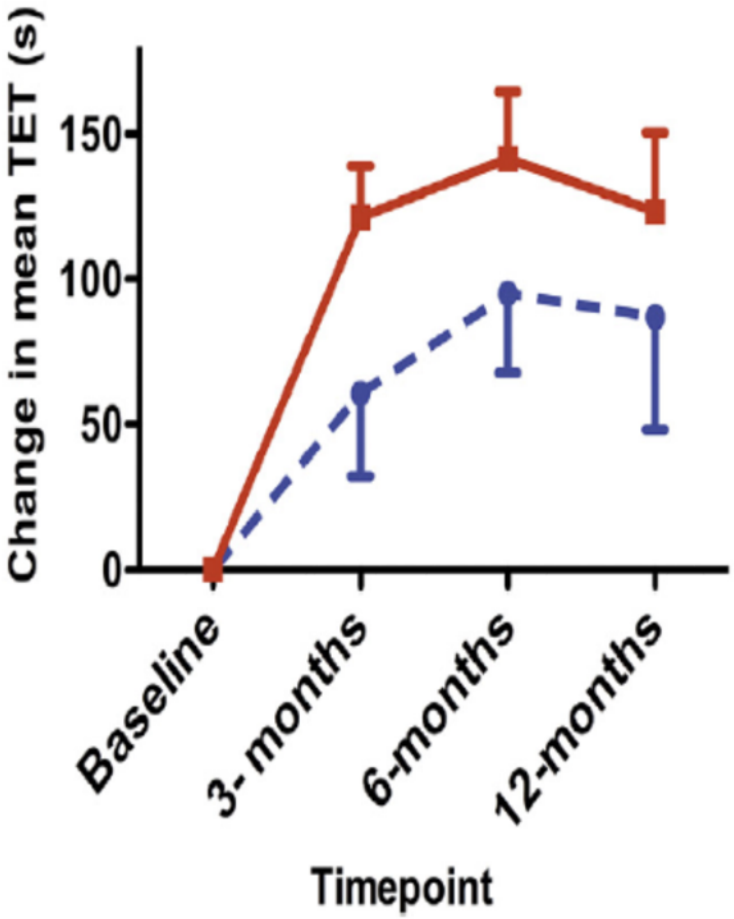
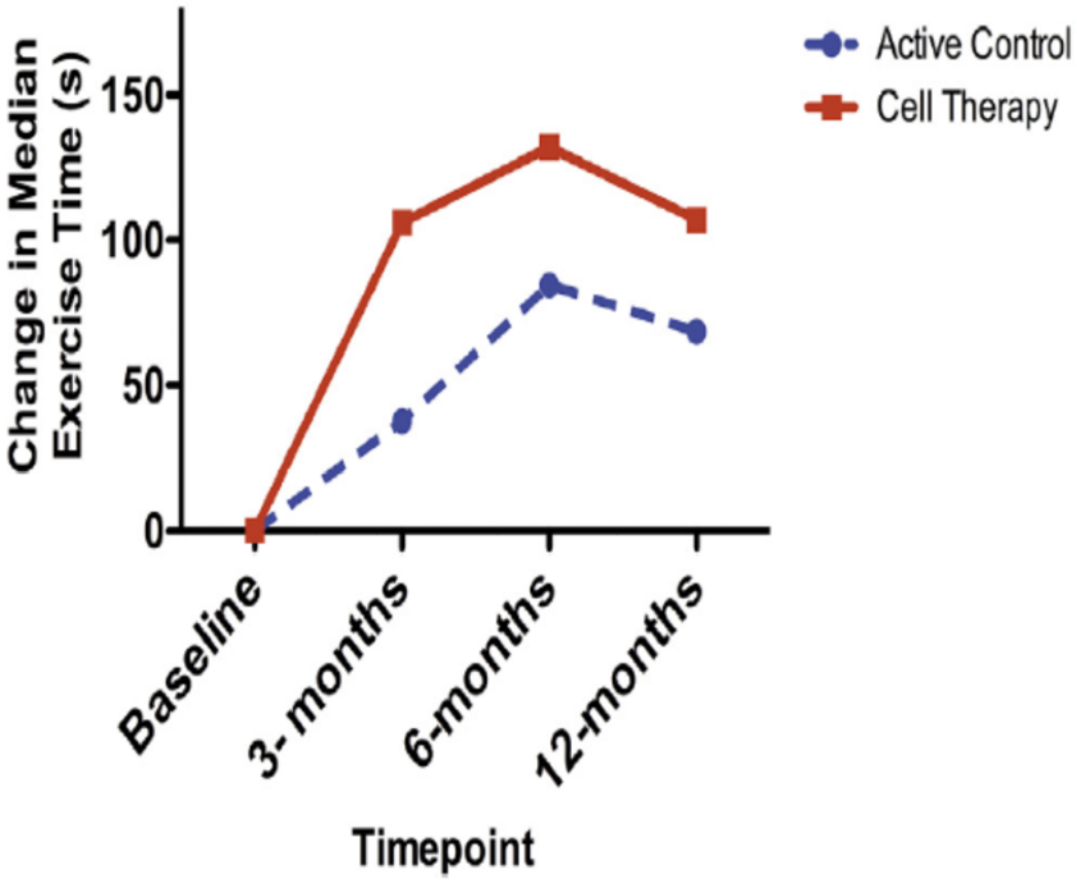
CHANGE IN TOTAL EXERCISE TIME





Povsic TJ et al., *JACC Cardiovasc Int 2016*

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The cell product PTC-CD133

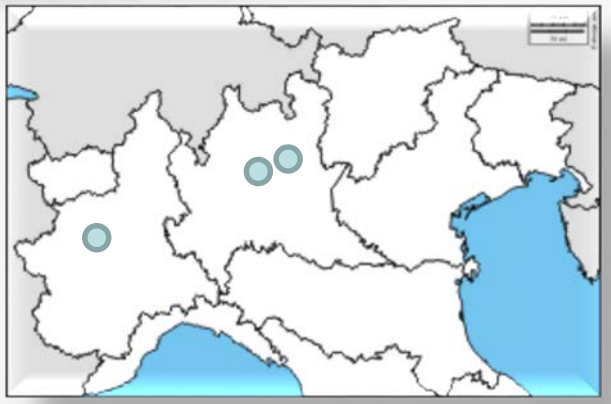
Parameter	Analytical Procedure	Specification	SOP
Purity (%CD133+ cells on CD45+ viable cells)	Flow Cytometry	≥80%	LABTCG-SV-POS 141005-090.2
Viability (% negative cells to Propidium Iodide)	Flow Cytometry	≥80%	LABTCG-SV-POS 141005-090.2
Cellularity (number of total viable nucleated cells)	Trypan blue exclusion method	1-12 x 10^6	LABTCG-SV-POS 061204-014.4
Sterility	Sterility test (Eu Farmacopeia)	Negative	Validation report by Eurofins Biolab n° CC130.07
Endotoxin	LAL test	<0.5 EU/mL	LABTCG-SV-POS 171204-027.3

" Phase I trial of endocavitary injection of bone-marrow derived CD133+ cells in ischemic refractory cardiomyopathy (RECARDIO Trial)

- Phase I, prospective, multicentric to assess safety and preliminary efficacy of endocavitary injection of autologous BM-derived CD133+
- **10 patients with refractory cardiomyopathy (CCS III-IV; EF >45%)**
- **Efficacy follow-up** 6 months; safety follow-up 12 months
- Sponsored by Ministry of Health (RF2010)

STUDY POPULATION

- **Milano – CCM**
- **Monza – H San Gerardo (GMP)**
- **Torino - Molinette**



INCLUSION CRITERIA

- **Ischemic heart failure not amenable to any type of revascularization procedure,**
- **CCS and/or NYHA class III/IV under state-of-the-art maximal therapy,**
- **LVEF between 20% and 45%,**
- **Peak $V0_2 \leq 21$ mL/Kg/min,**
- Presence of a reversible perfusion defect ≥ 10% of the LV myocardium as determined by gated-SPECT,
- 18 years ≤ Age ≤ 80 years.

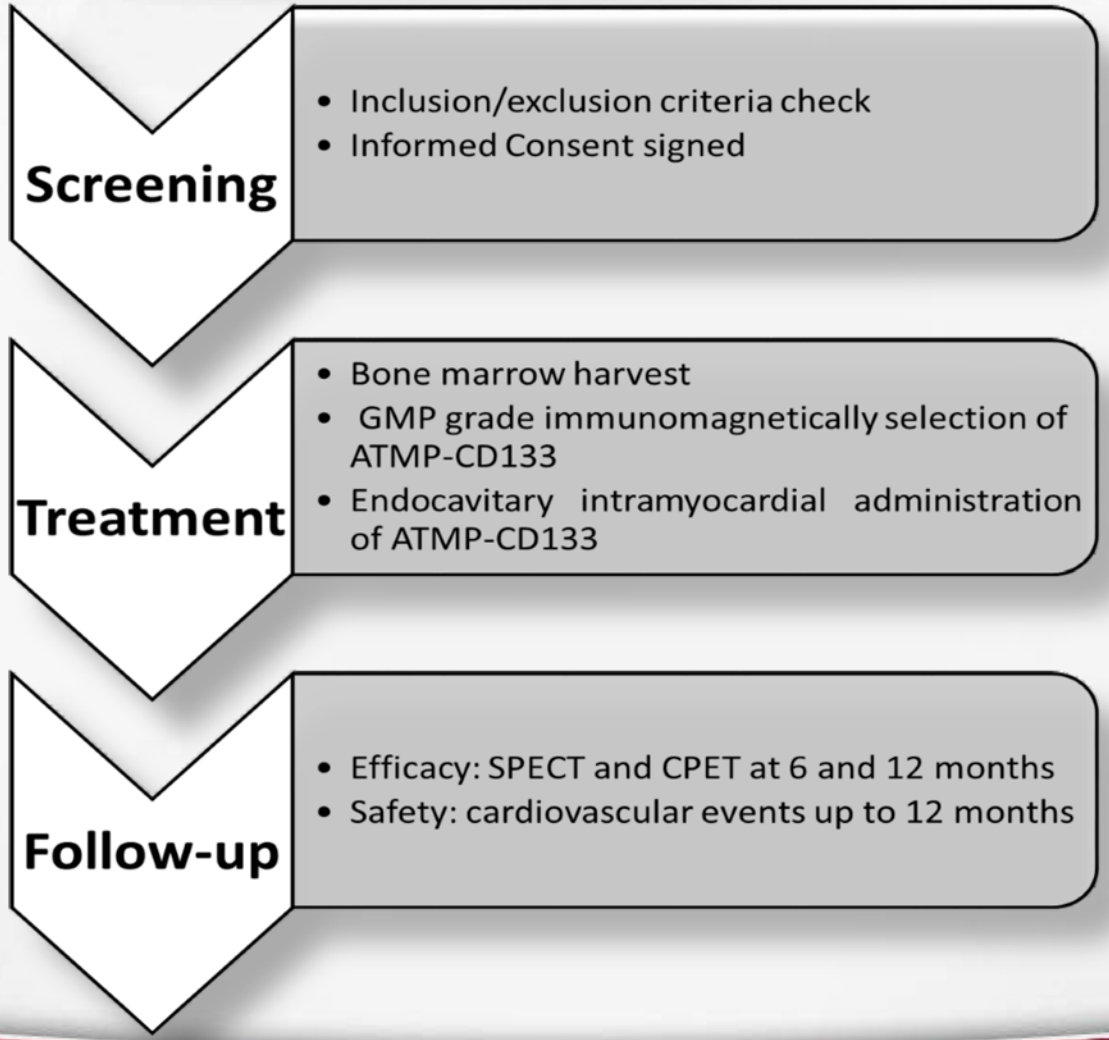
PRIMARY ENDPOINTS

- **MACE up to 12 months:**
  - Death
  - Non fatal MI
  - Hospitalization due to IHF
- **SAEs up to 6 months:**
  - Cardiac perforation
  - Pericardial tamponade
  - Sustained VT
  - Ectopic tissue formation
  - Malignant arrhythmias

EFFICACY ASSESSMENT

- An increase of Summed Stress Score (SSS) or Summed Difference Score (SDS) on regional perfusion at stress gated-SPECT

TRIAL FLOW CHART



TREATMENT

A) Bone marrow aspiration from the iliac posterior crest

B) CD133+ cells immunomagnetically selected at GMP facility

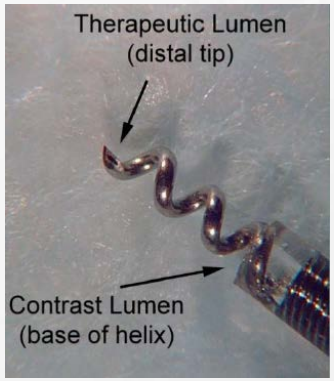
C) Patient referred to the CathLAb the day after

D) Percutaneous inoculation of $CD133^{+}$ cells into ischemic regions of the LV through an endocavitary flouroscopy-based approach

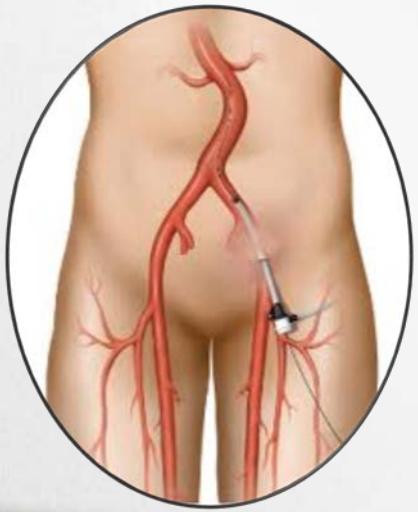
DELIVERY SYSTEM

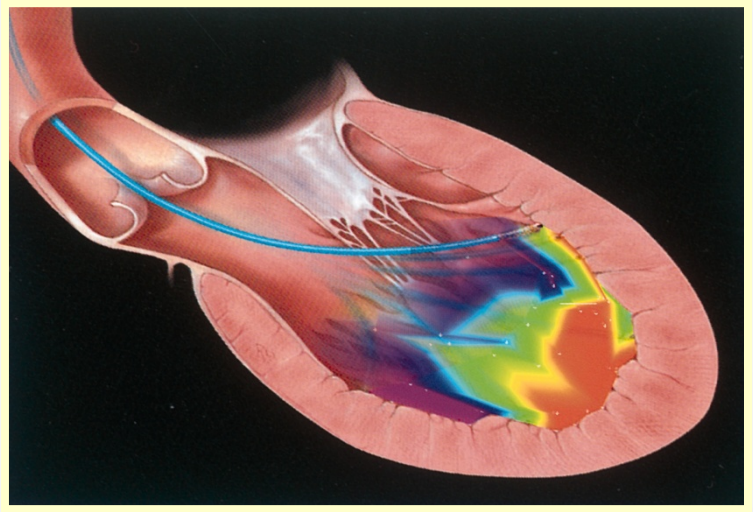
BIOCARDIA HELIX INFUSION CATHTER SYSTEM

- Intended for the infusion of agents into myocardium
- Endovascular route
- Fluoroscopy-based navigation

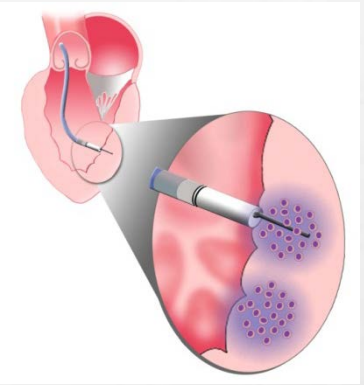


Retrograde



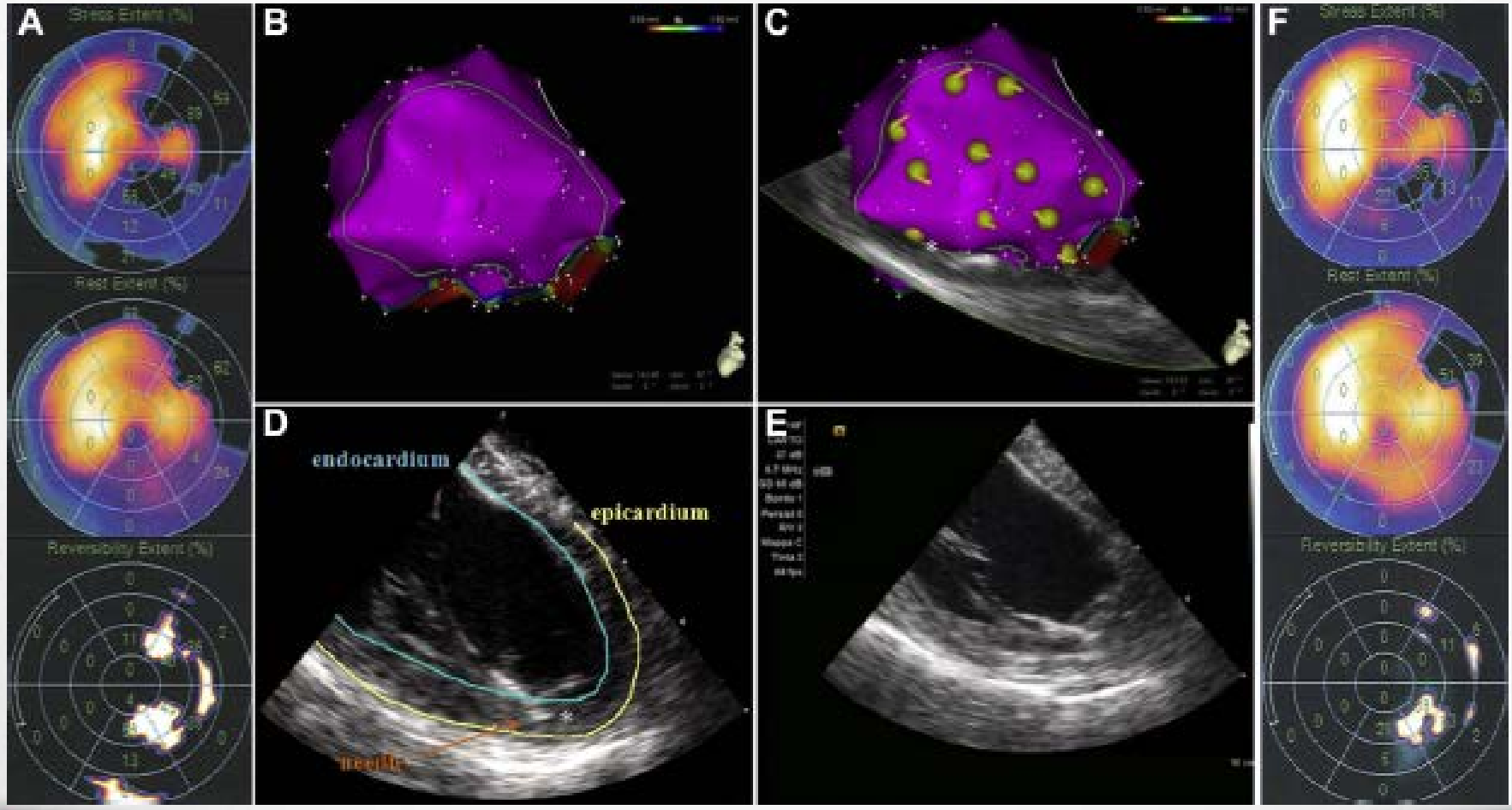


Target zone



Novel Application of 3-Dimensional Real-Time Cardiac Imaging to Guide Stem Cell-Based Therapy

Corrado Carbucicchio, MD,[a] Michela Casella, MD,[a] Valentina Catto, BE,[a] Beatrice Bassetti, MSc,[b] Alberto Bestetti, MD,[c] and Giulio Pompilio, MD[b,d]



Can J Cardiol, 2015

Centro Cardiologico Monzino

TREATED PATIENTS

Patients	BM volumes	CD133 x 10^6	Purity	Vitality	N° of injections
1-001	328	7,62	93,76	99,95	11
1-002	309	3,38	75,36	99,86	12
1-003	398	3,96	88,45	99,95	11
1-004	328	4,56	90,01	99,91	12
1-005	334	8,13	83,2	99,86	12
1-006	410	4,21	89,54	99,81	12
1-007	438	12,67	92,95	99,97	11
1-008	390	11,47	87,34	99,91	12
1-009	400	7,01	87,48	98,63	13
3-001	280	2,66	89,1	99,89	12
Mean ± SD	**362 ± 49**	**6,57 ± 3,27**	**87,71 ± 4,98**	**99,77 ± 0,38**	**12 ± 1**

SAFETY PROFILE

Patients	In-hosp Mortality	In-hosp Morbidity	3 months Mortality	3 months Morbidity	6 months Mortality	6 months Morbidity	12 months Mortality	12 months Morbidity
1-001	no	no	no	no	no	no	no	no
1-002	no	Pericardial effusion	no	no	no	no	no	no
1-003	no	no	no	Gastric ulcer	no	no	Subdural hematoma	no
1-004	no	no	no	no	no	CRT-D implant	no	no
1-005	no	no	no	no	no	no	no	CRT-D implant **NSTEMI**
1-006	no	no	no	no	no	no	no	No
1-007	no	no	no	no	no	no	-	-
1-008	no	no	no	no	no	no	-	-
1-009	no	no	-	-	-	-	-	-
3-001	no	no	no	no	no	Right sup fem PCI	no	no

No SAEs up to 6 months / 1 MACE at 12 months

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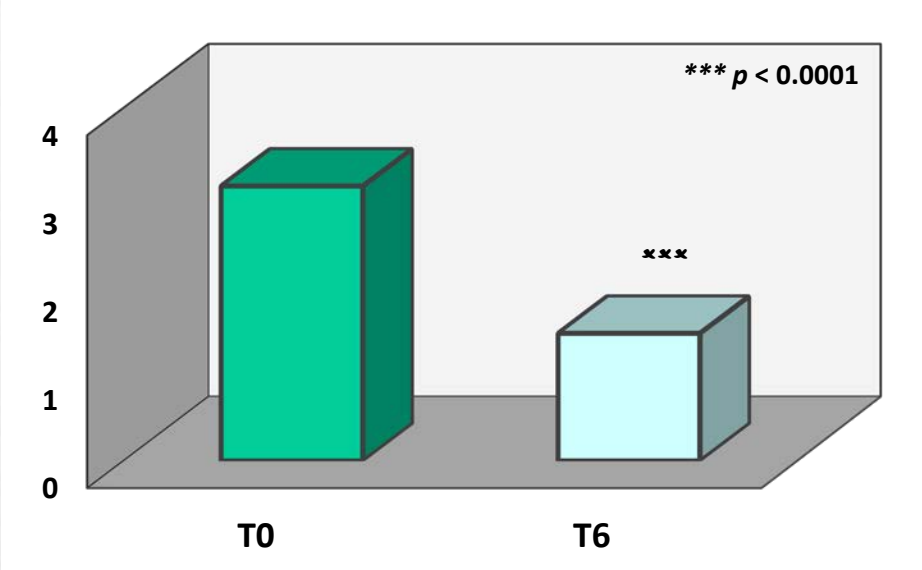
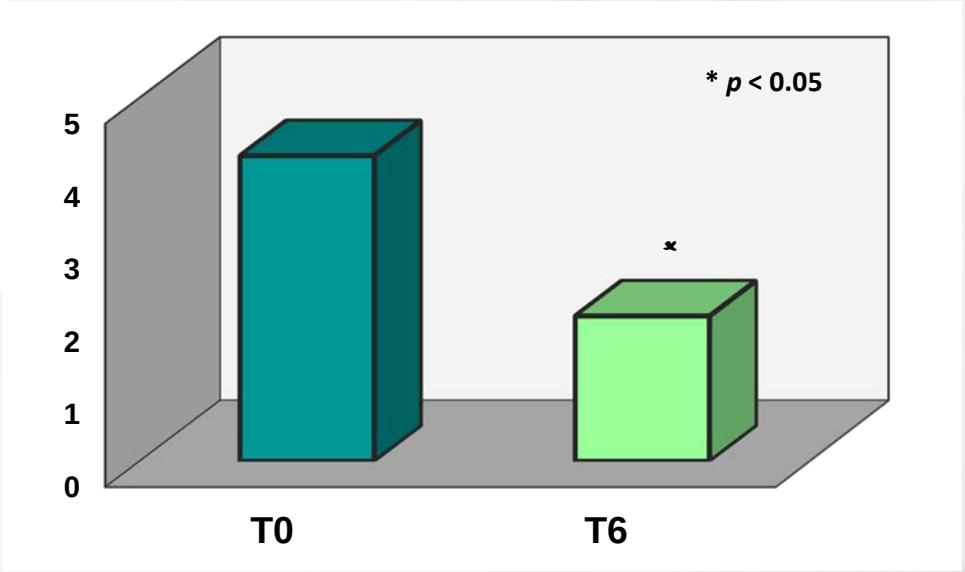
CLINICAL BENEFIT

Changes of Canadian Class

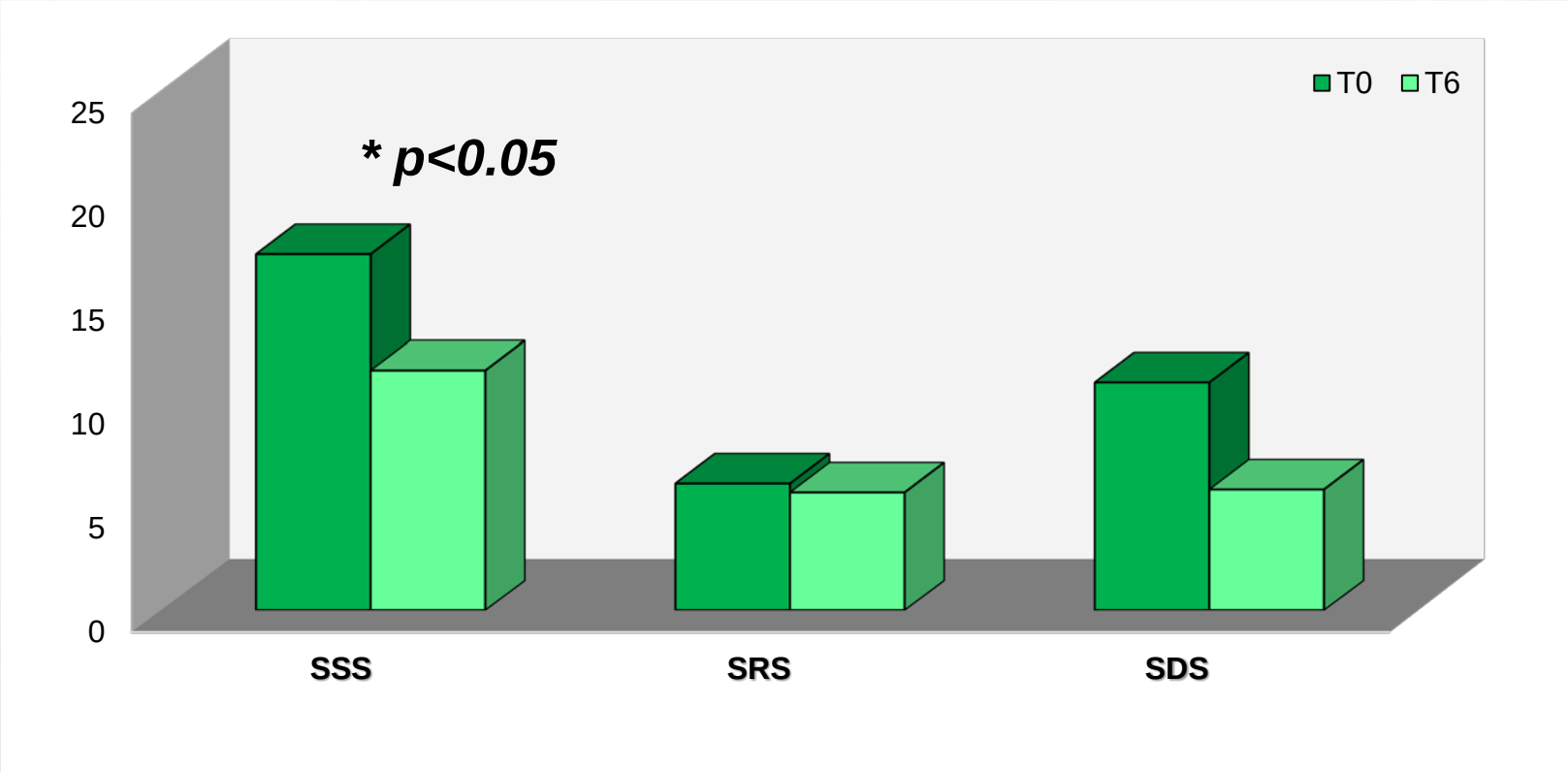


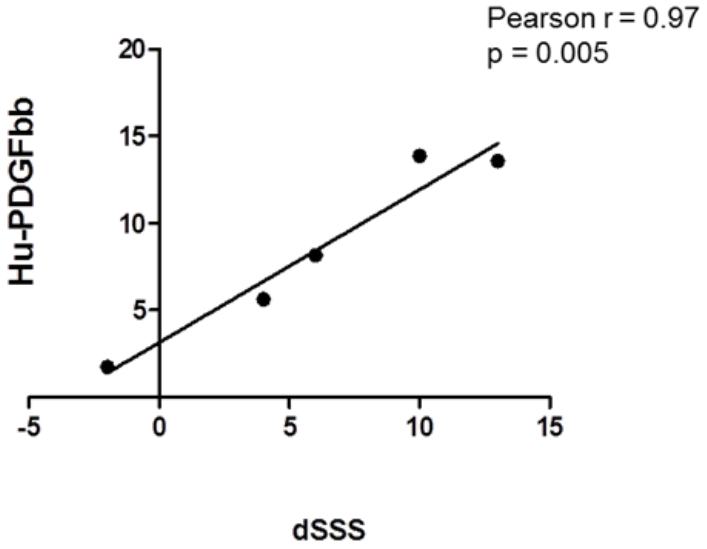
Nitrates assumption per week

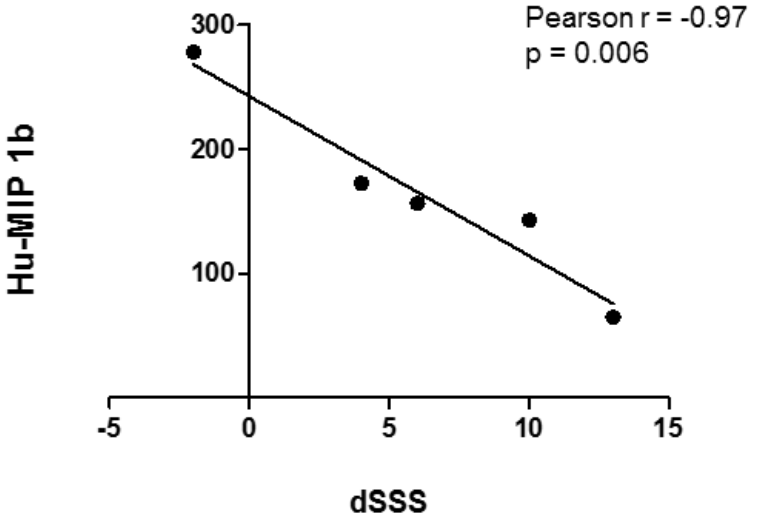


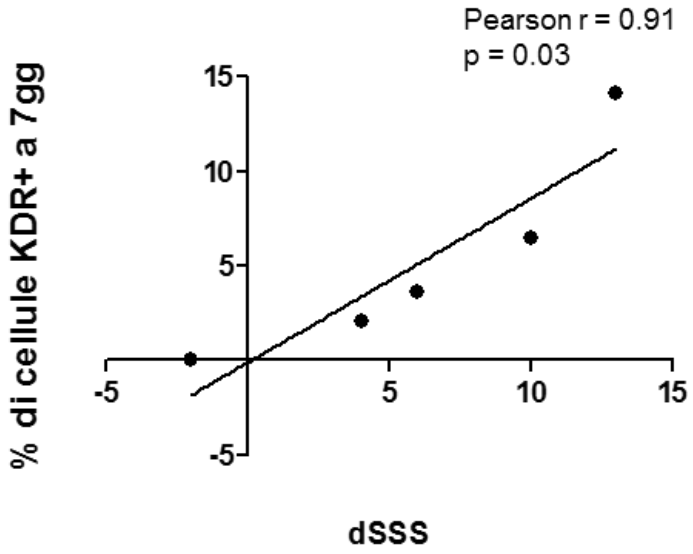
SPECT perfusion imaging

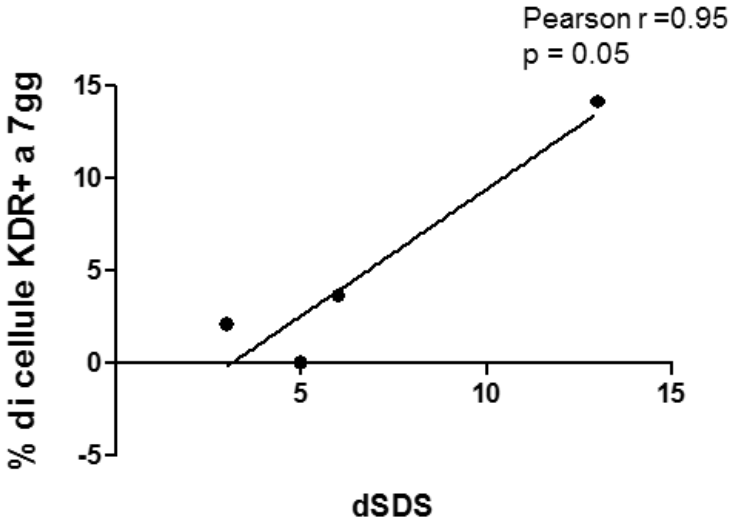
Summed stress (SSS) rest (SRS) and difference (SDS) scores at gated-SPECT




Pearson r = 0.97
p = 0.005
Hu-PDGFbb
20
15
10
5
-5
0
5
10
15
dSSS


Pearson r = -0.97
p = 0.006
Hu-MIP 1b
300
200
100
-5
0
5
10
15
dSSS


Pearson r = 0.91
p = 0.03
% di cellule KDR+ a 7gg
15
10
5
-5
-5
5
10
15
dSSS


Pearson r =0.95
p = 0.05
% di cellule KDR+ a 7gg
15
10
5
0
-5
5
10
15
dSDS

CONCLUSIONS

- ***Refractory ischemic cardiomyopathy/refractory angina appear to be a good target for cardiac cell therapy (cCT);***
- ***Patients to be entered in future pivotal trials need to be carefully selected for high likelihood to benefit;***
- ***In the Nederlands cCT is reimbursed on a hospital-based exception (Leiden) for the treatment of refractory angina.***

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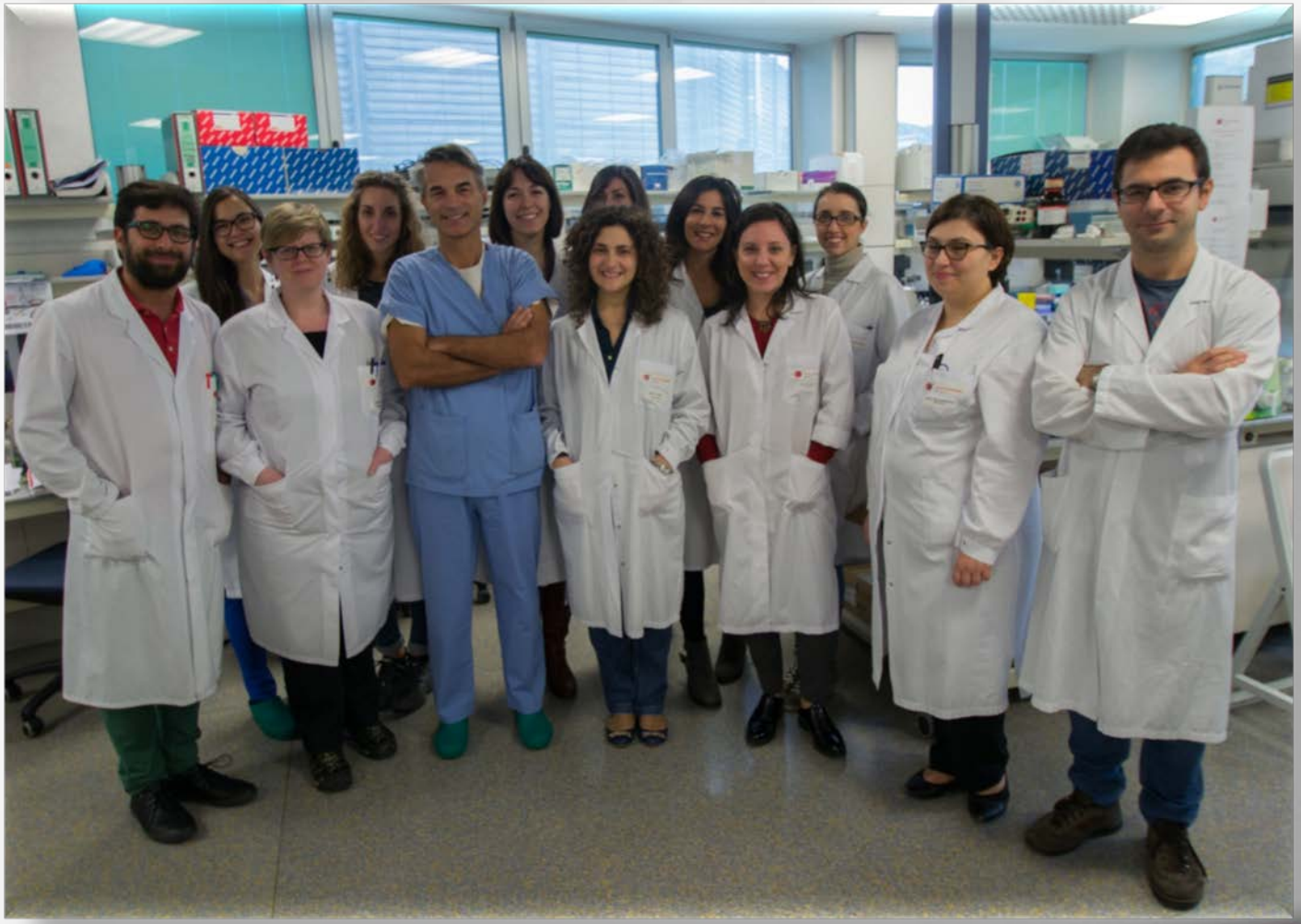

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