MEDICAL COLLEGE OF WISCONSIN

Stem Cells for the Failing Heart

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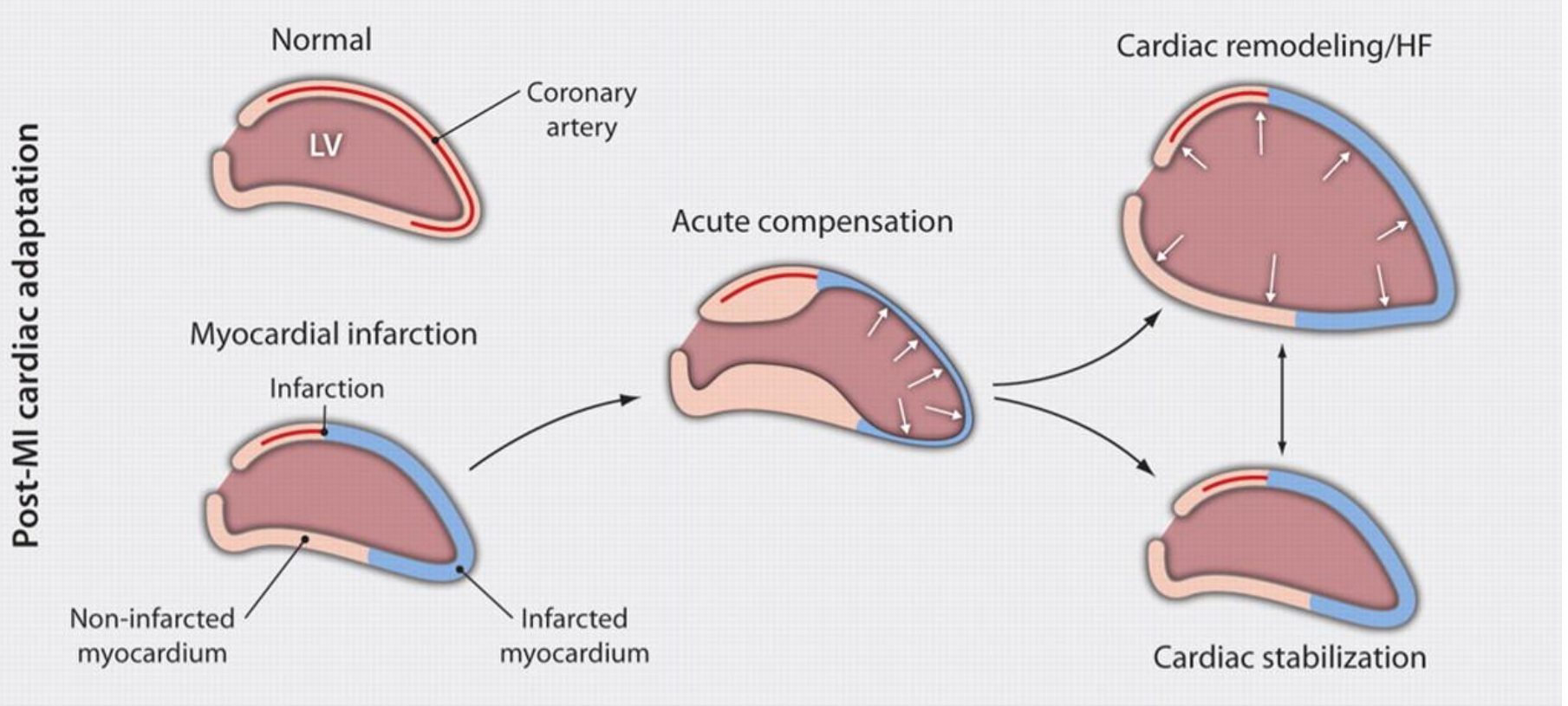
3rd DUBROVNIK CARDIOLOGY HIGHLIGHTS

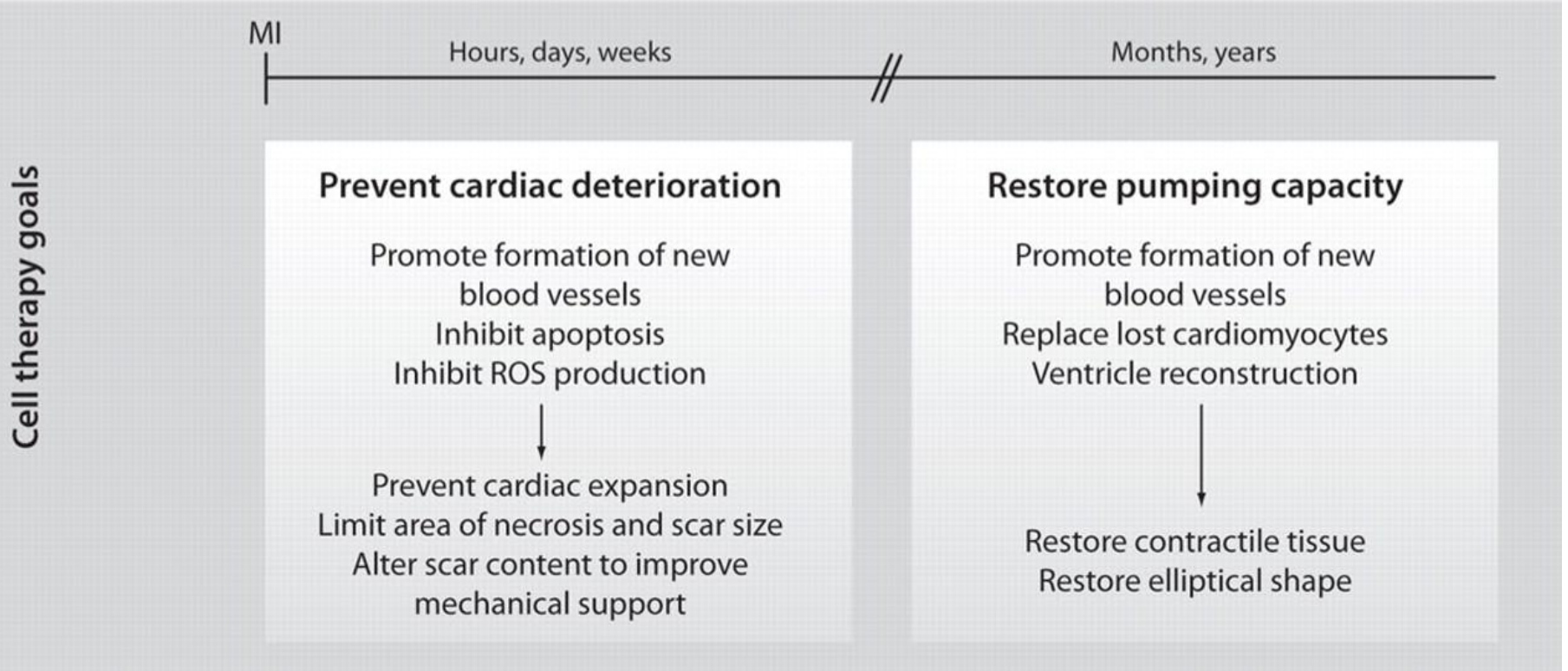
OVERVIEW

- ✓ New modalities for HF treatment
- ✓ Stem cell therapy - potentially disease modifying
- ✓ Individual clinical studies
- ✓ Meta-analyses
- ✓ Future directions and likely outcomes

New modalities for HF treatment

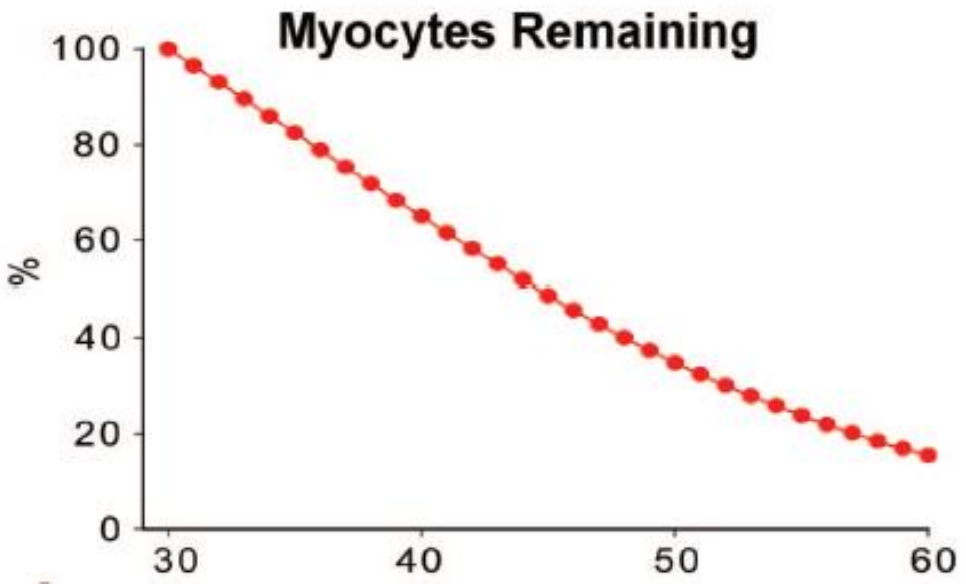
- ✓ The management of HF has extended the lifespan of this patient population; however, not able to reverse the disease
- ✓ Short of heart transplantation, there are currently limited options to overcome the poor prognosis of end-stage HF
- ✓ This urgent clinical need drives the exploration of cardiac repair with stem cells
- ✓ Many efforts aim to use the regenerative properties of stem cells for strategies to repair injured myocardium

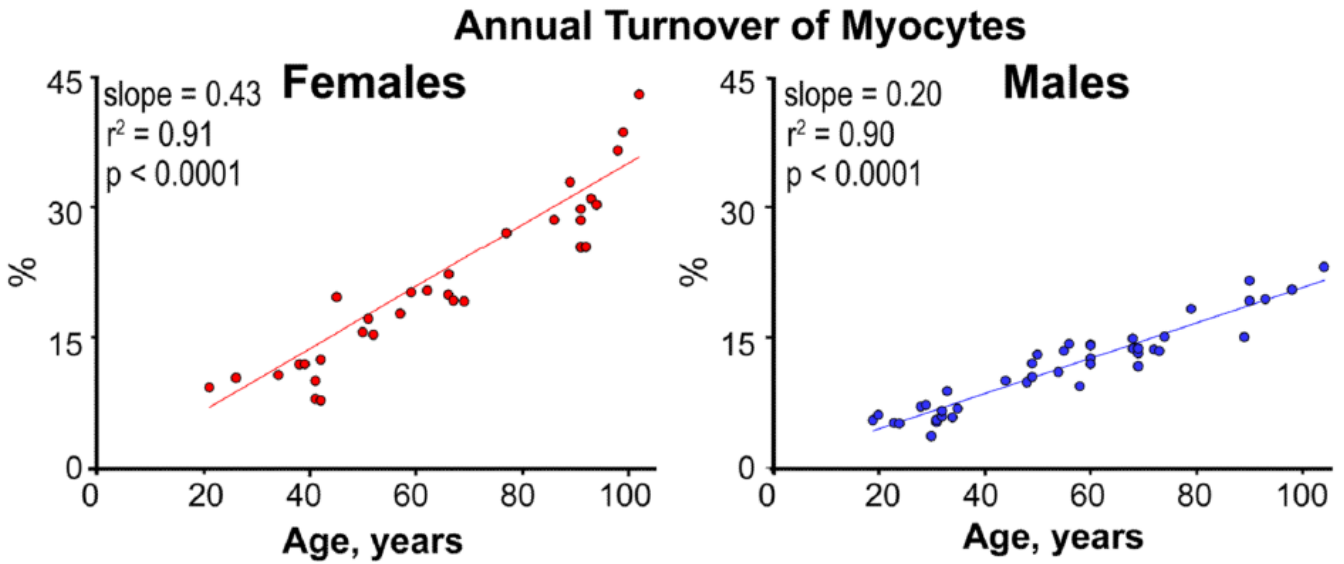

Post-MI cardiac adaptation
Normal
LV
Coronary artery
Myocardial infarction
Infarction
Non-infarcted myocardium
Infarcted myocardium
Acute compensation
Cardiac remodeling/HF
Cardiac stabilization


Cell therapy goals
MI
Hours, days, weeks
Months, years
Prevent cardiac deterioration
Promote formation of new blood vessels
Inhibit apoptosis
Inhibit ROS production
Prevent cardiac expansion
Limit area of necrosis and scar size
Alter scar content to improve mechanical support
Restore pumping capacity
Promote formation of new blood vessels
Replace lost cardiomyocytes
Ventricle reconstruction
Restore contractile tissue
Restore elliptical shape

New modalities for HF treatment

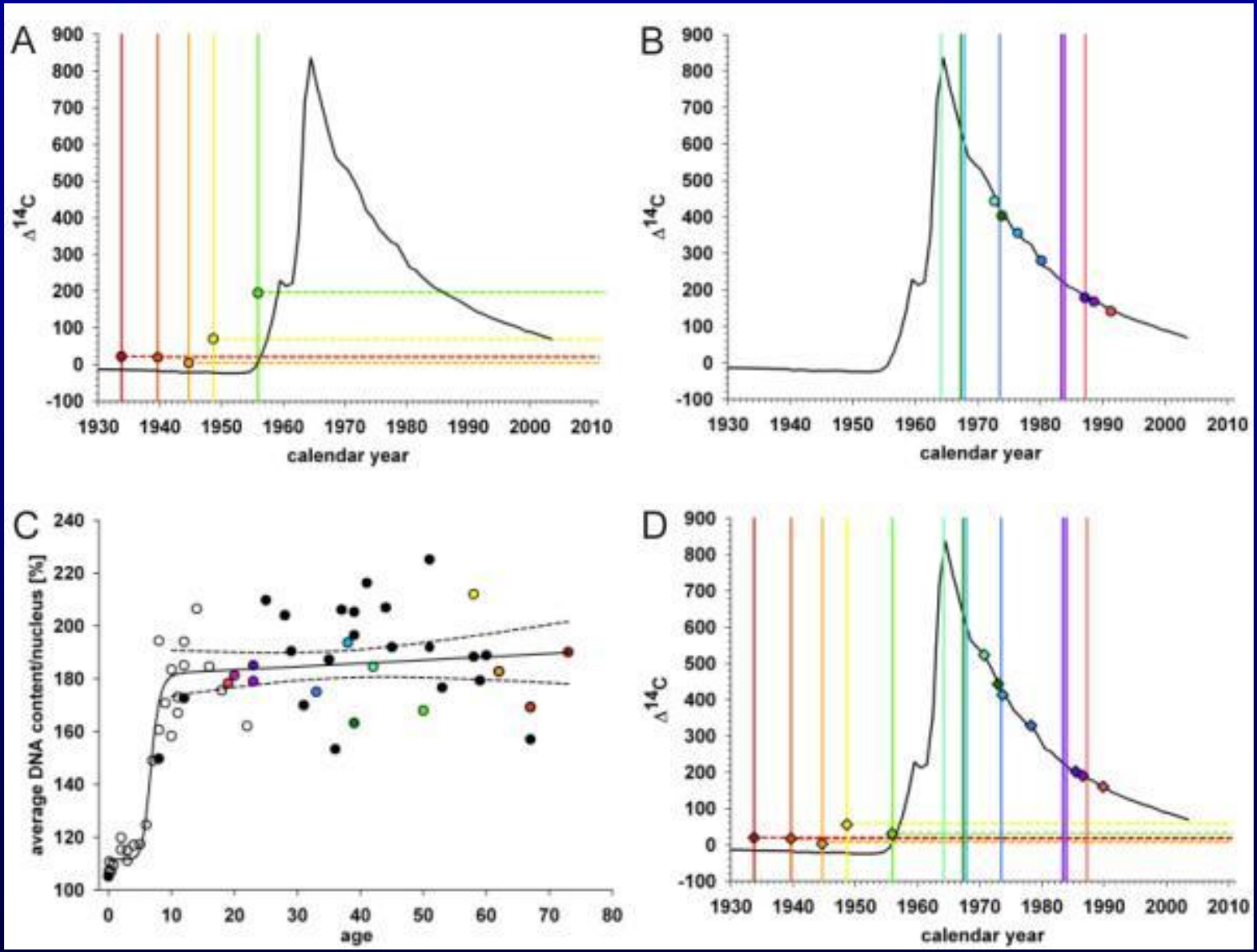
- ✓ For nearly a century, the heart has been considered a terminally-differentiated post-mitotic organ unable to replace dying cardiomyocytes
- ✓ This premise is no longer valid
- ✓ Pool of resident cardiac stem cells (CSCs) that can acquire the cardiomyocyte, vascular smooth muscle, and endothelial cell lineages has been identified in the human heart





Leri A et al. Circulation Research 2011;109:941-961

Birth date of cardiac cells

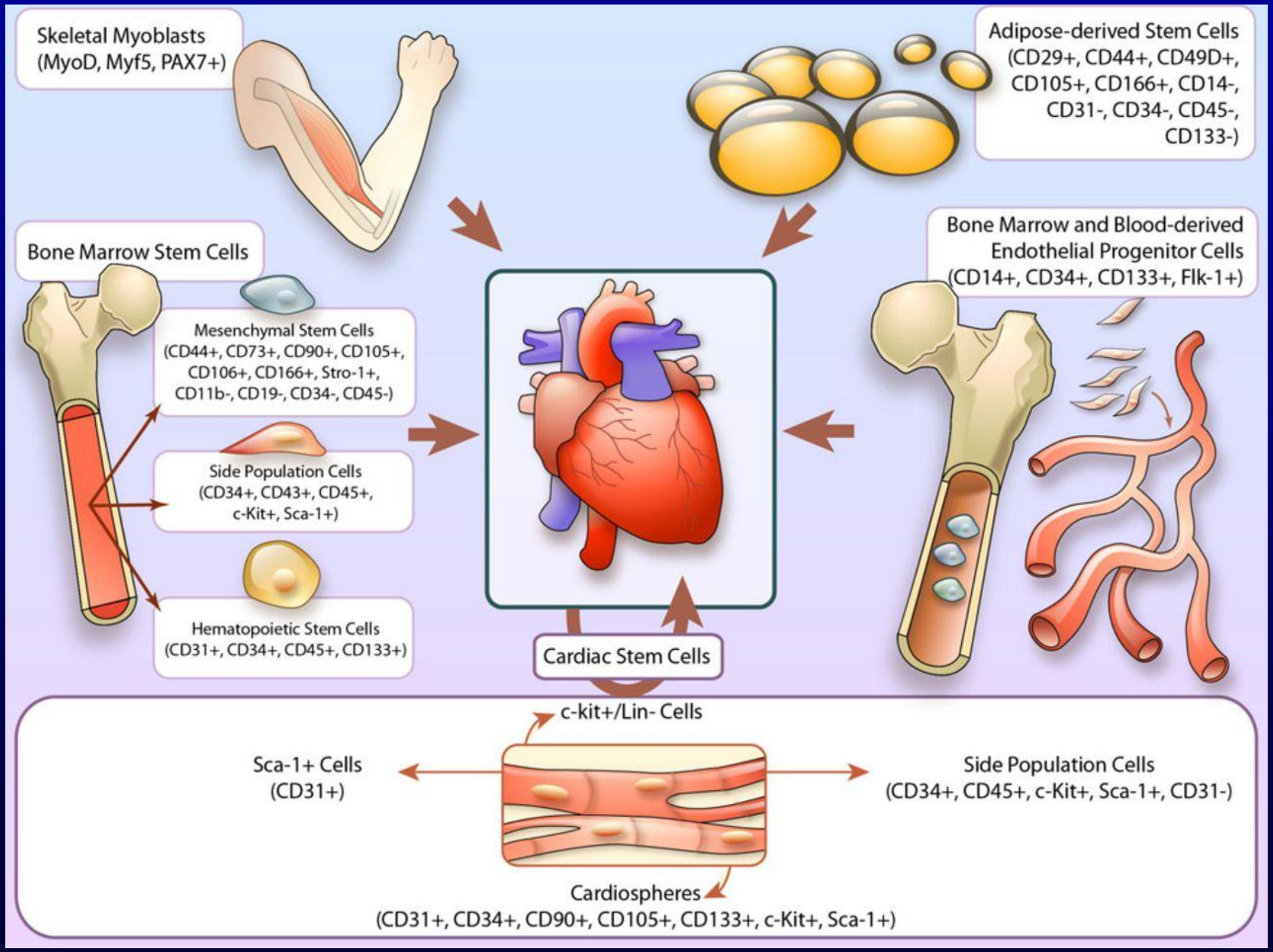


Science. 2009 April 3; 324(5923): 98–102

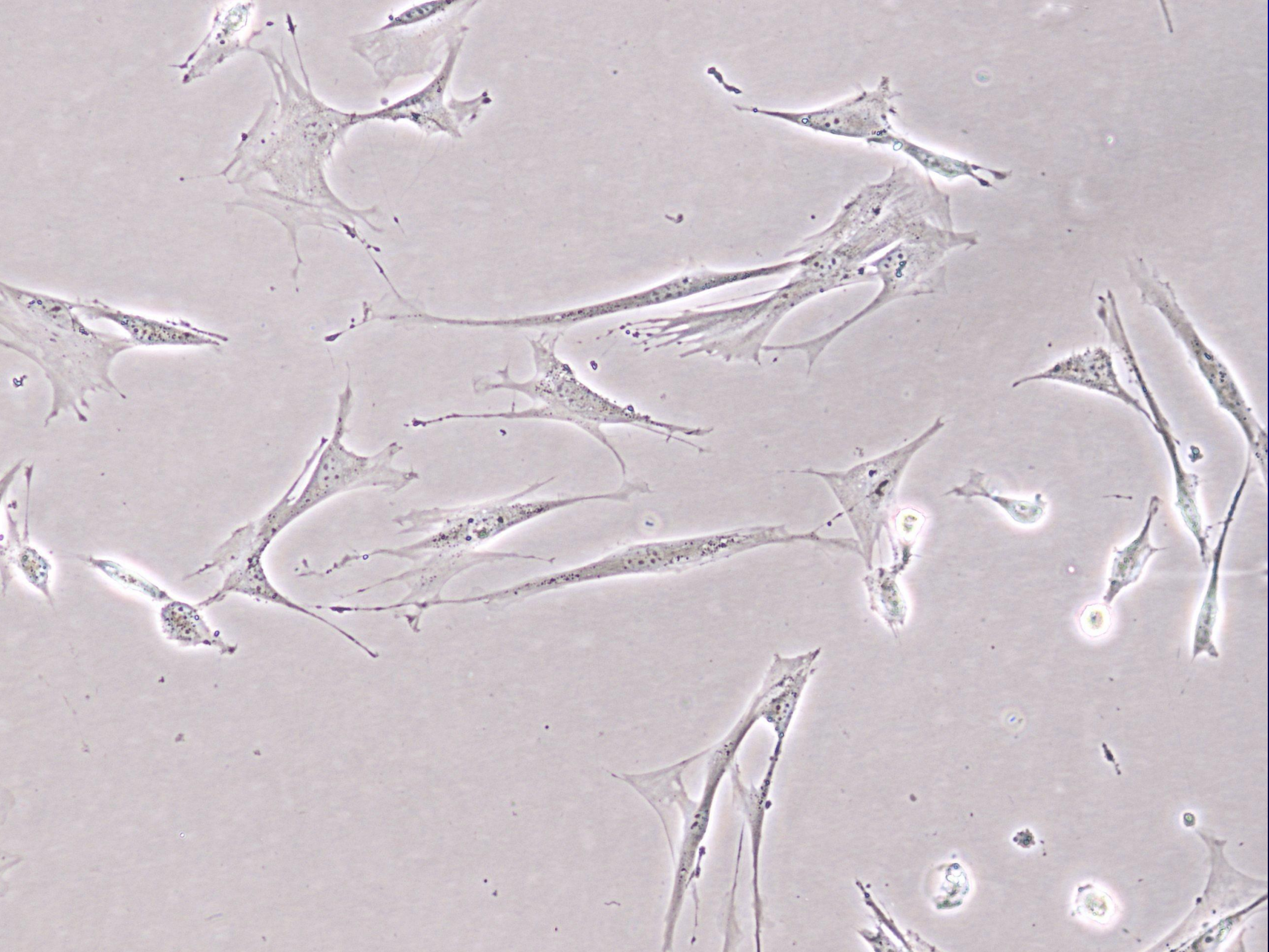
The role of hCSCs in restoring damaged myocardium

- ✓ Spontaneous cardiac repair is minimal; regenerative response to the non-infarcted tissue
- ✓ Spontaneous myocyte regeneration does not compensate for the loss of myocytes in the chronically pressure-overloaded heart
- ✓ Spontaneous cardiac repair may delay, but does not avoid or reverse the progression of HF

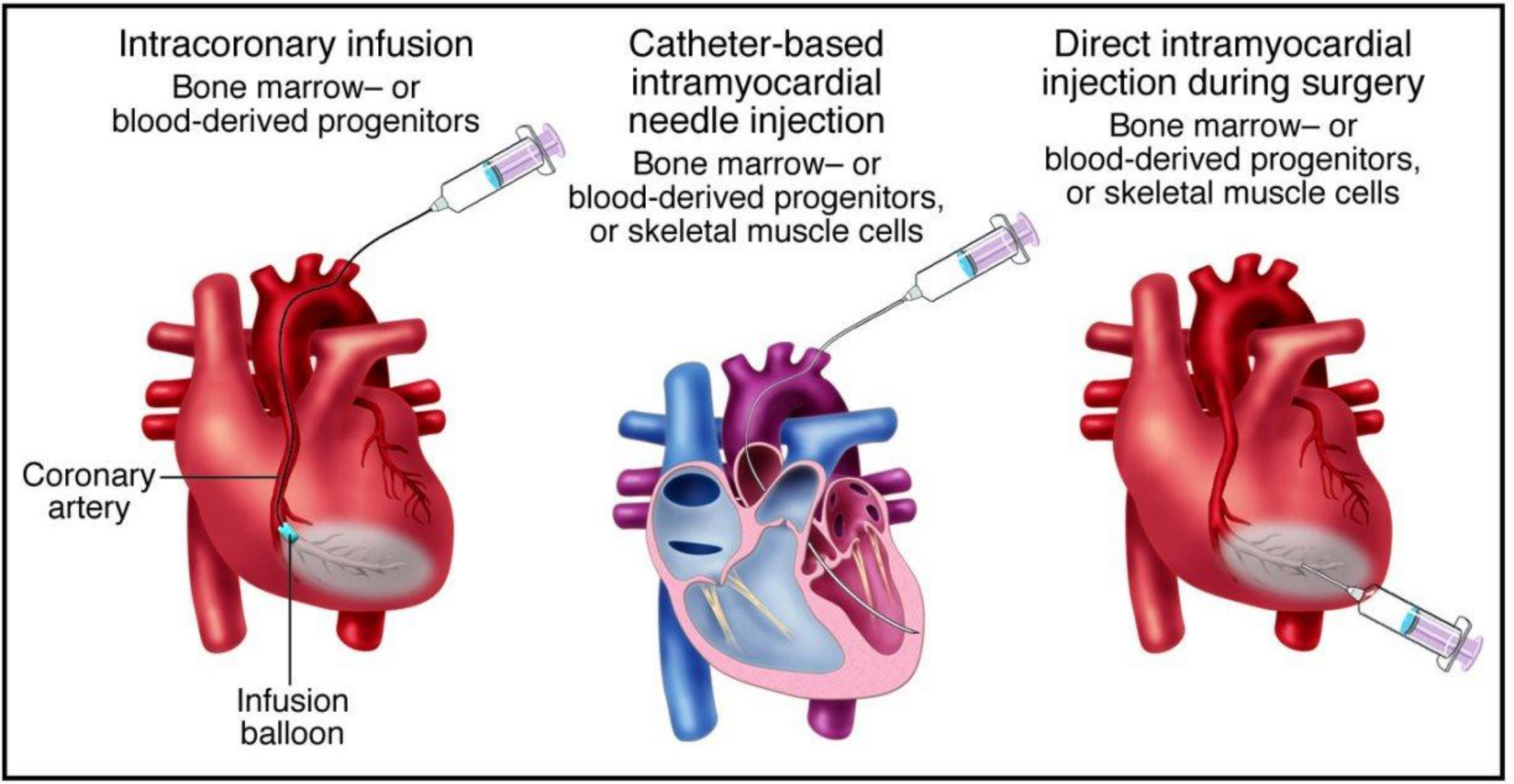
Sources of stem cells for cardiac regeneration and potential reparative mechanisms



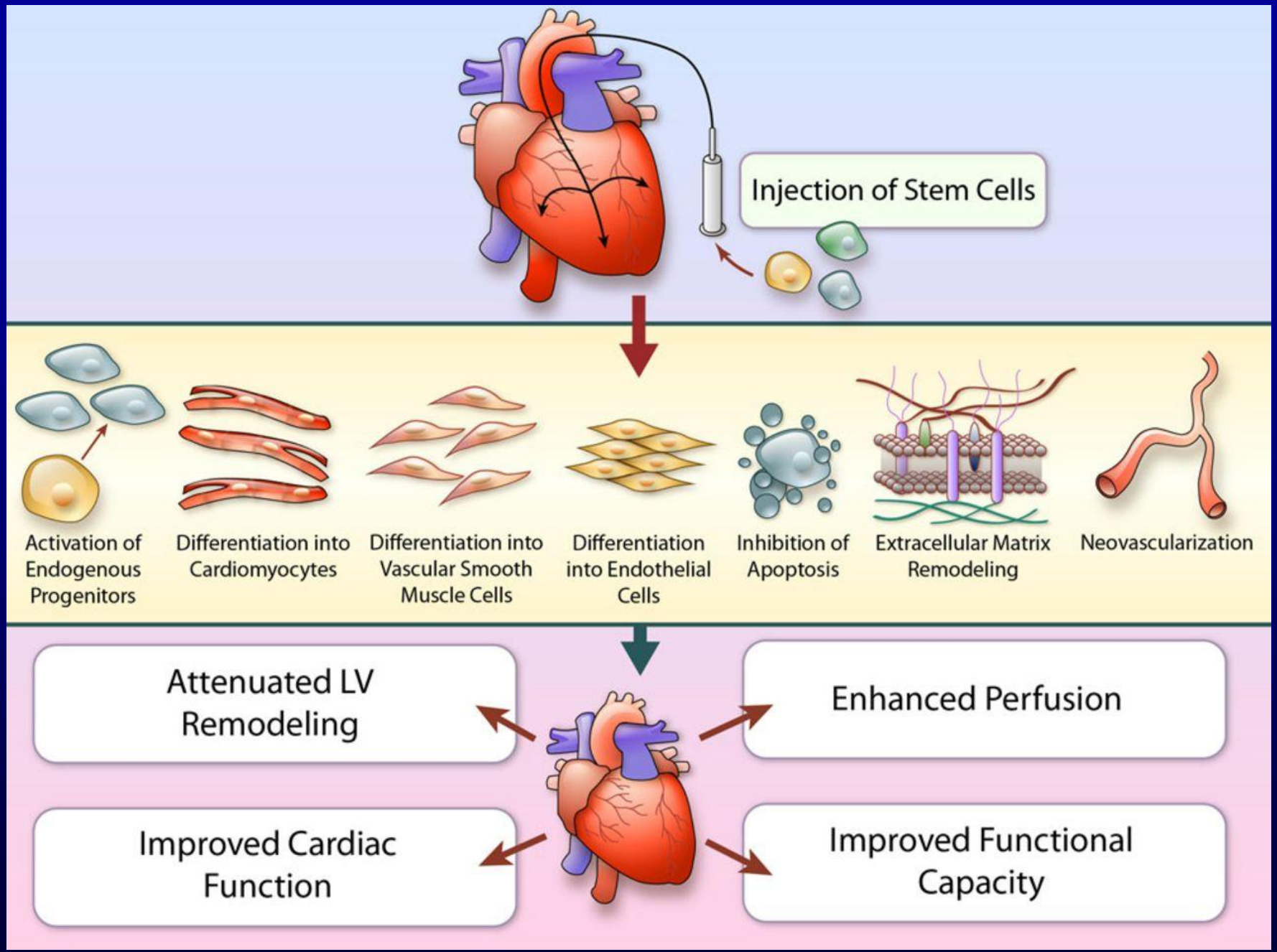
Sanganalmath S, Bolli R. Circulation Research 2013;113:810-834



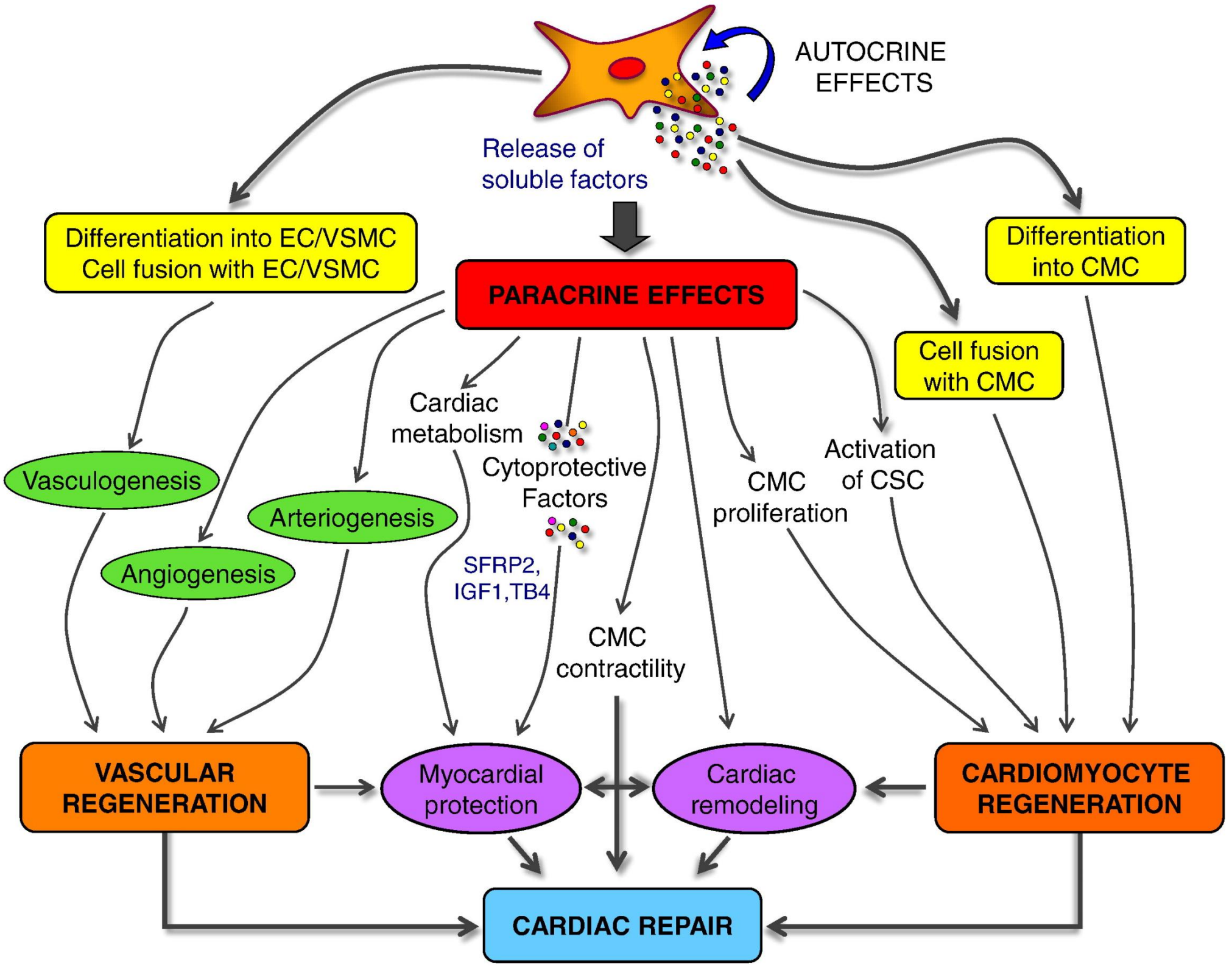
Implantation of stem cells



Potential mechanisms of action of stem cells



Sanganalmath S, Bolli R. Circulation Research 2013;113:810-834


AUTOCRINE
EFFECTS
Release of
soluble factors
Differentiation into EC/VSMC
Cell fusion with EC/VSMC
PARACRINE EFFECTS
Differentiation
into CMC
Cell fusion
with CMC
Cardiac
metabolism
Cytoprotective
Factors
SFRP2,
IGF1,TB4
Vasculogenesis
Arteriogenesis
Angiogenesis
CMC
proliferation
Activation
of CSC
CMC
contractility
VASCULAR
REGENERATION
Myocardial
protection
Cardiac
remodeling
CARDIOMYOCYTE
REGENERATION
CARDIAC REPAIR

Implantation of stem cells

- ✓ Most transferred cells are dead within a week
- ✓ Difficult for cells to engraft, survive, proliferate, and differentiate
- ✓ Clinical trials demonstrate that autologous cell based therapies for cardiovascular repair are feasible and safe
- ✓ Although efficacy of cell-based therapy has been limited, it holds enormous promise at preventing or reversing myocardial remodeling and promoting tissue regeneration

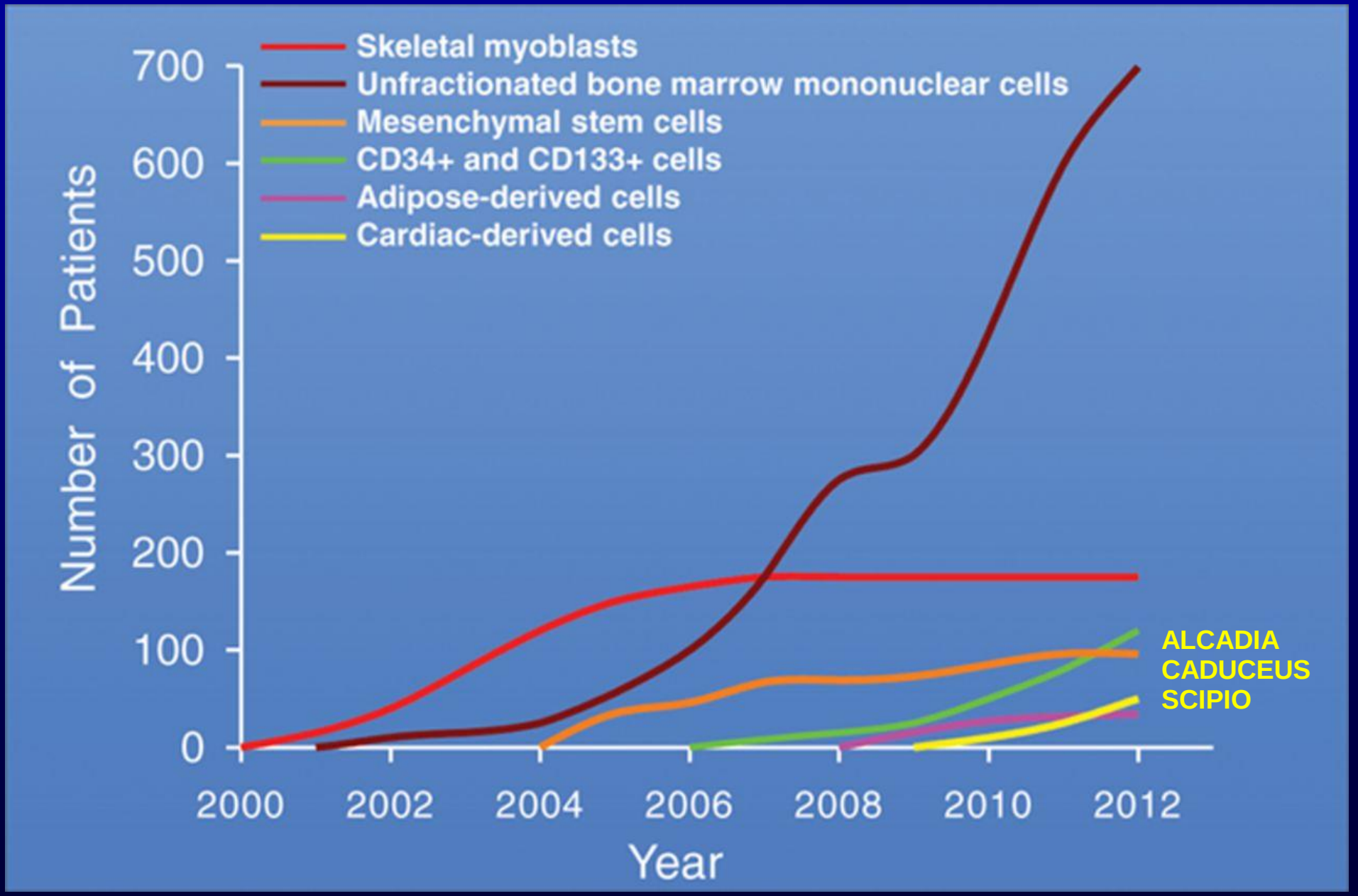
Clinical studies using MSCs

342 studies examining the effects of MSCs

160 studies examining the effects of MSCs in heart failure

http://clinicaltrials.gov (September 2013)

Use of various types of stem cell therapies in patients with cardiovascular disease



Sanganalmath S, Bolli R. Circulation Research 2013;113:810-834

Trials with Negative results:

- ✓Late-TIME, Transplantation in Myocardial Infarction Evaluation
- ✓Cardiovascular Cell Therapy Research Network [CCTRN]
- ✓TIME

Trials with Positive results:

- ✓Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON)
- ✓Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy (SCIPIO)
- ✓Cardiosphere-derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS)

EUROPEAN SOCIETY OF CARDIOLOGY®

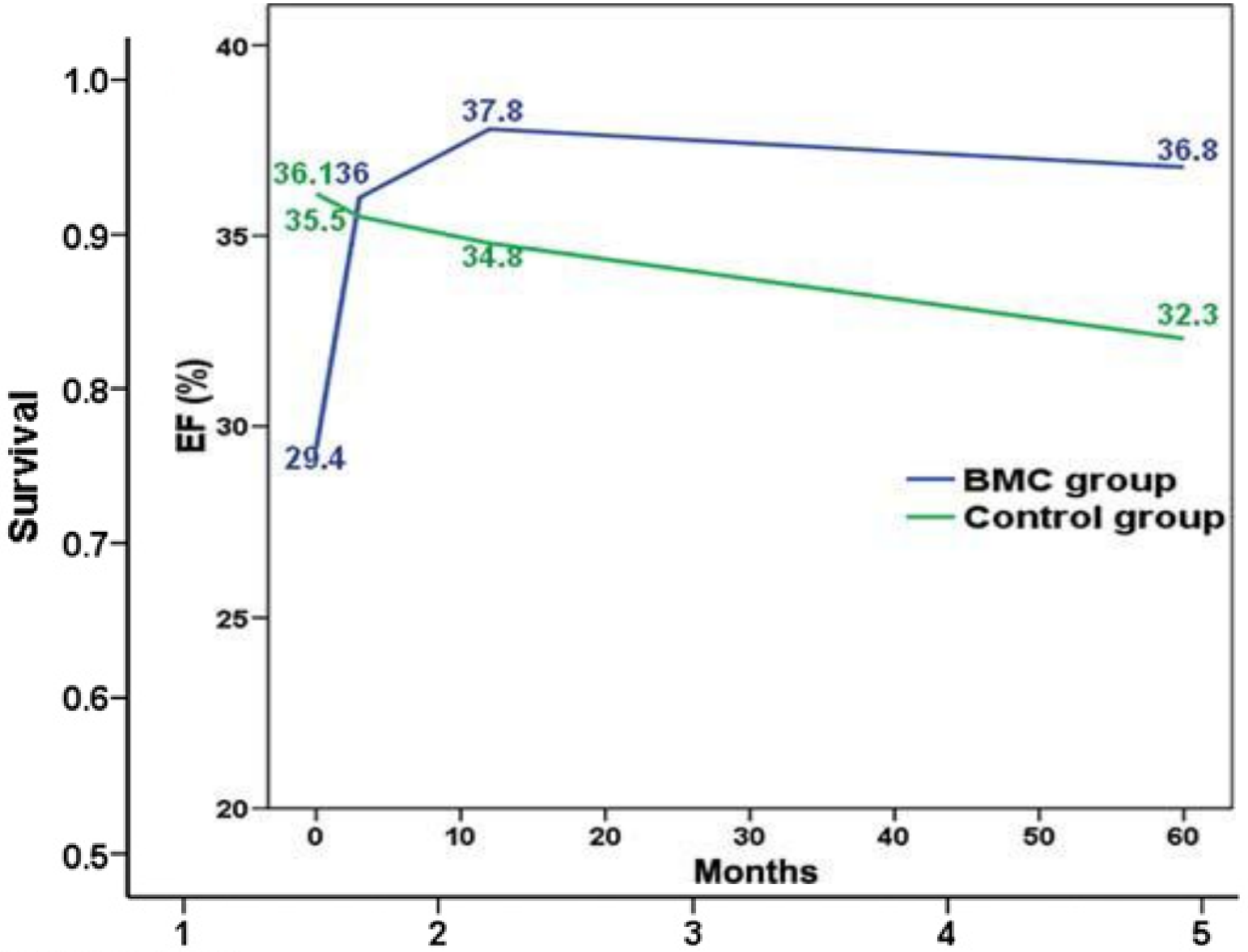
European Journal of Heart Failure (2010) **12**, 721–729
doi:10.1093/eurjhf/hfq095

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

- ✓ Open label, non-randomized, prospective study
- ✓ Intracoronary BMC therapy improves ventricular performance, quality of life, and survival in patients with heart failure
- ✓ These effects were present when BMC were administered in addition to standard therapeutic regimes
- ✓ No side effects were observed

STAR-heart study



Number of survivors:				
BMC group, n=191	191	190	187	184
Control group n=199	197	190	181	168

Eur J Fail. 2010 Jul;12(7):721-9.

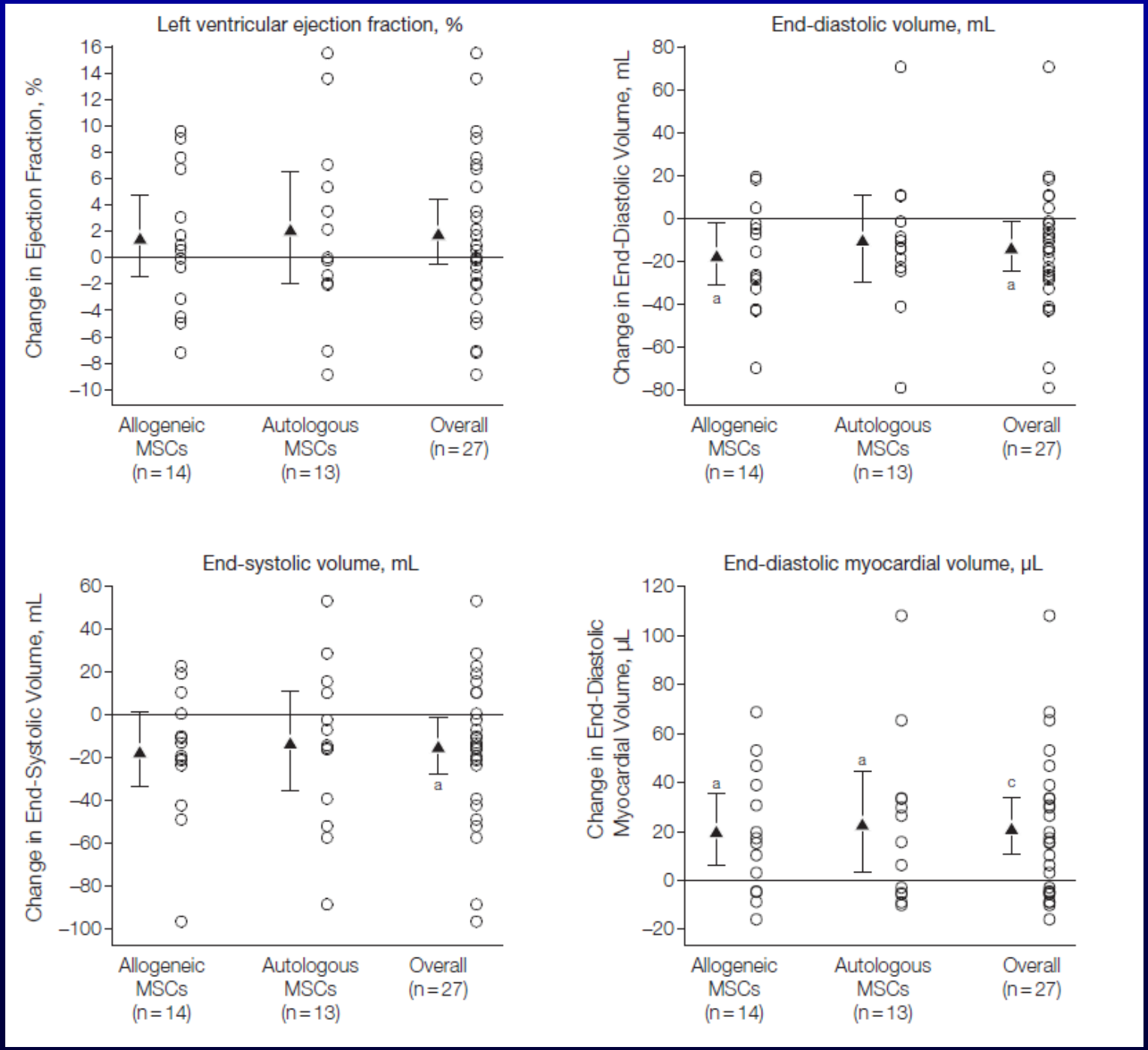
ONLINE FIRST

Comparison of Allogeneic vs Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy

The POSEIDON Randomized Trial

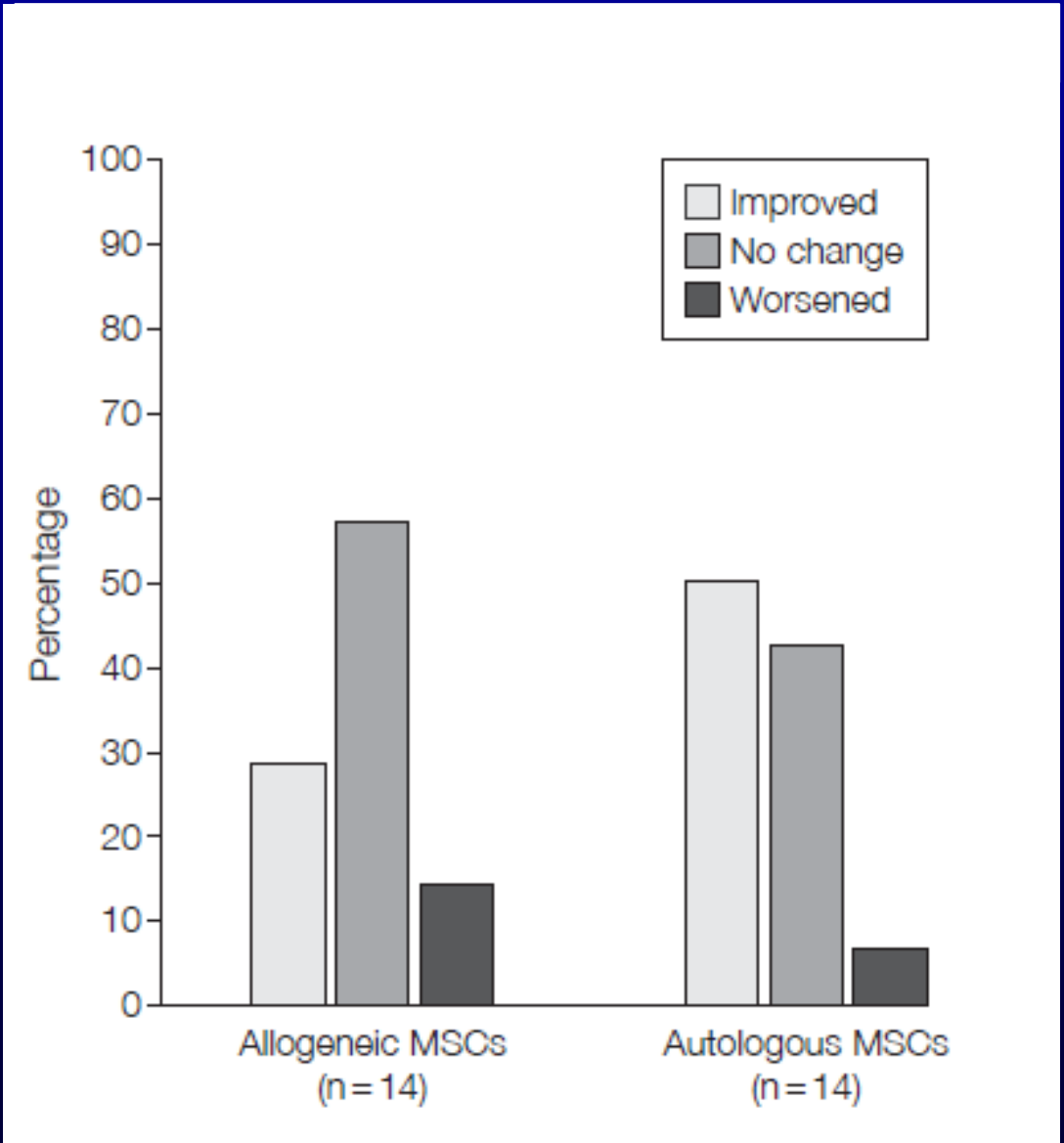
- ✓ Phase 1/2 randomized comparison with 13-month follow-up (n=30)
- ✓ Absence of significant ***alloimmune*** reactions in patients receiving allogeneic MSCs
- ✓ Cell therapy may not only improve left ventricular structure but may also improve quality of life and functional capacity

JAMA. 2013 Aug 21;310(7):750



JAMA. 2013 Aug 21;310(7):750

Change in New York Heart Association Classification Quality of Life



JAMA. 2013 Aug 21;310(7):750

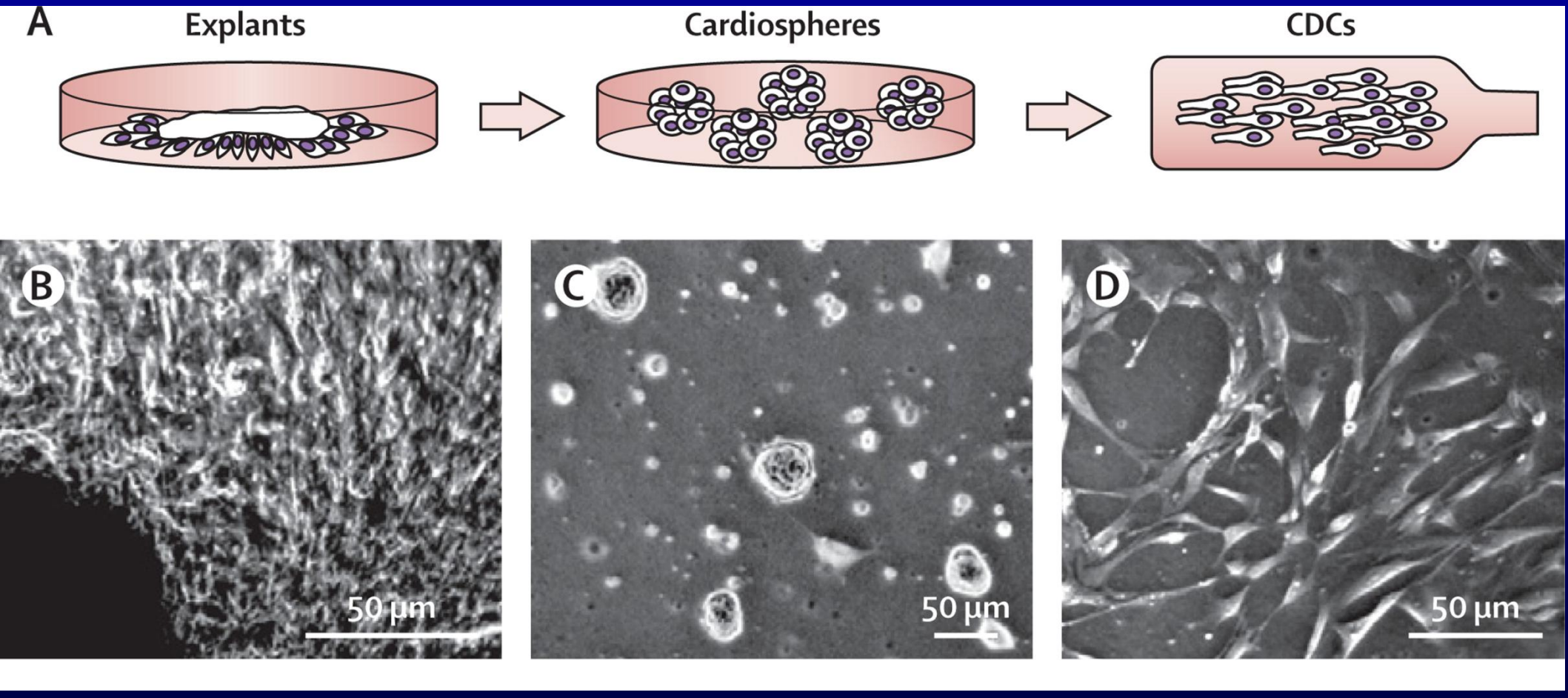
Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial

Lancet 2012; 379: 895–904

Raj R Makkar, Rachel R Smith, Ke Cheng, Konstantinos Malliaras, Louise E J Thomson, Daniel Berman, Lawrence S C Czer, Linda Marbán, Adam Mendizabal, Peter V Johnston, Stuart D Russell, Karl H Schuleri, Albert C Lardo, Gary Gerstenblith, Eduardo Marbán

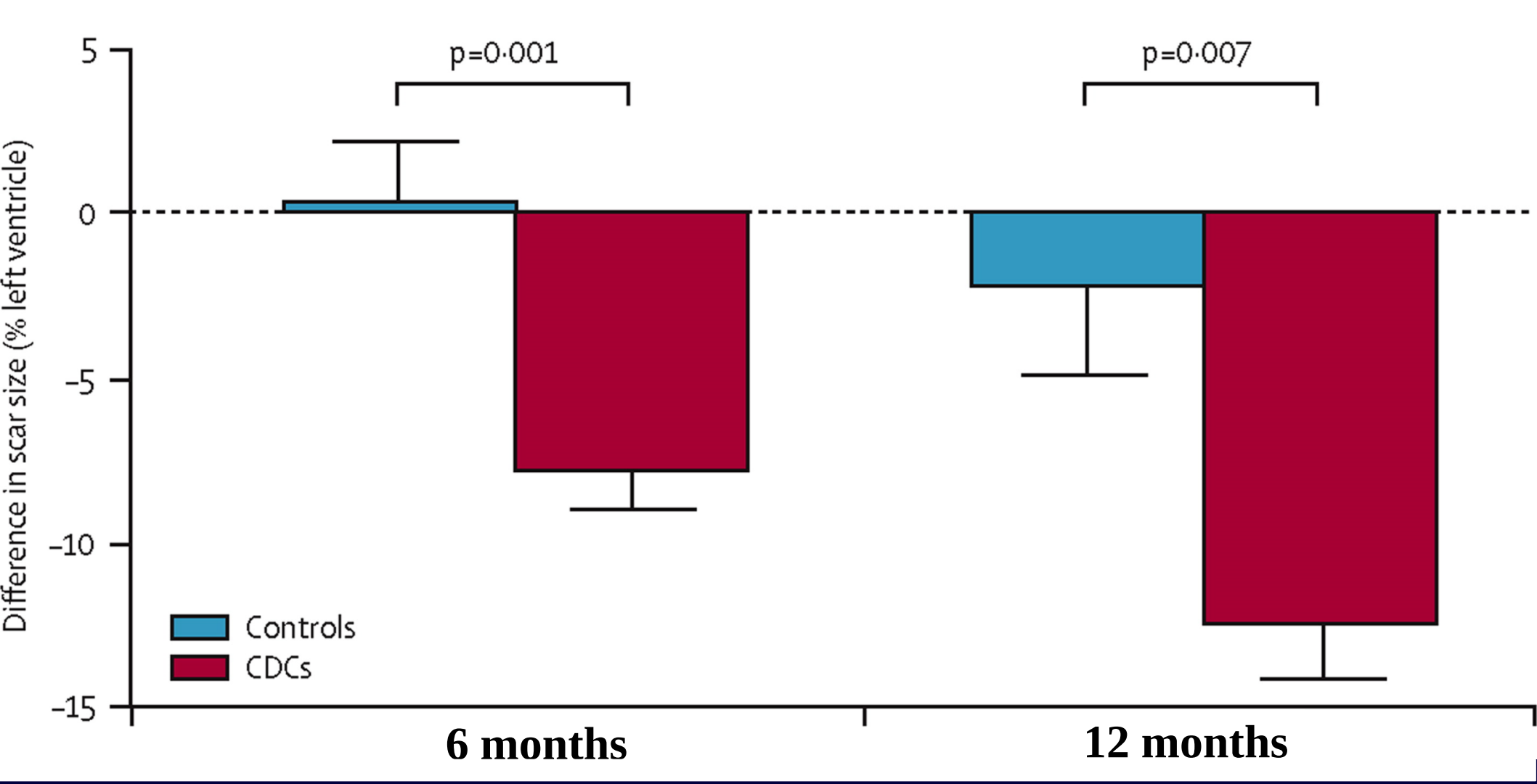
- ✓ Infusion of autologous CDCs after myocardial infarction is safe
- ✓ Significant increases in viable myocardium is consistent with therapeutic regeneration
- ✓ No differences in EF or volumes

Manufacture of cardiosphere-derived cells



Lancet 2012; 379: 895–904

CADUCEUS trial changes in scar size



Lancet 2012; 379: 895–904

Administration of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy: The SCIPIO Trial

Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance

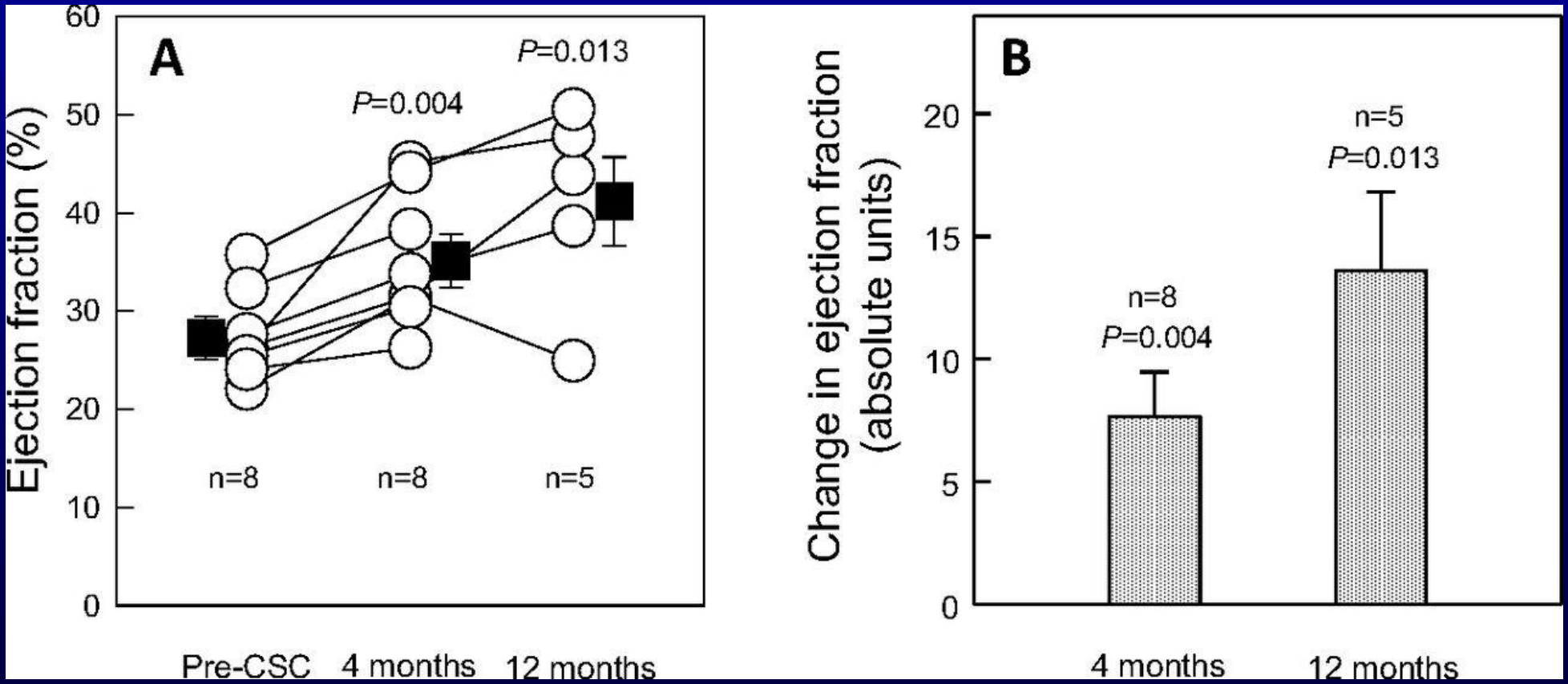
Atul R. Chugh, MD; Garth M. Beache, MD; John H. Loughran, MD; Nathan Mewton, MD, PhD; Julius B. Elmore, MD; Jan Kajstura, PhD; Patroklos Pappas, MD; Antone Tatooles, MD; Marcus F. Stoddard, MD; Joao A.C. Lima, MD; Mark S. Slaughter, MD; Piero Anversa, MD; Roberto Bolli, MD

Circulation. 2012;126:S54–S64

- ✓ CSC infusion produces a striking improvement in both global and regional LV function
- ✓ Reduction in infarct size
- ✓ Increase in viable tissue that persist at least 1 year and are consistent with cardiac regeneration

SCIPIO trial – LVEF

Baseline (27.5 ± 1.6%)
4 months after CSC infusion (35.1 ± 2.4%),
12 months after CSC infusion (41.2 ± 4.5%).



Circulation. 2012;126:S54–S64

European Journal of Heart Failure (2012) **14**, 91–105
doi:10.1093/eurjhf/hfr148

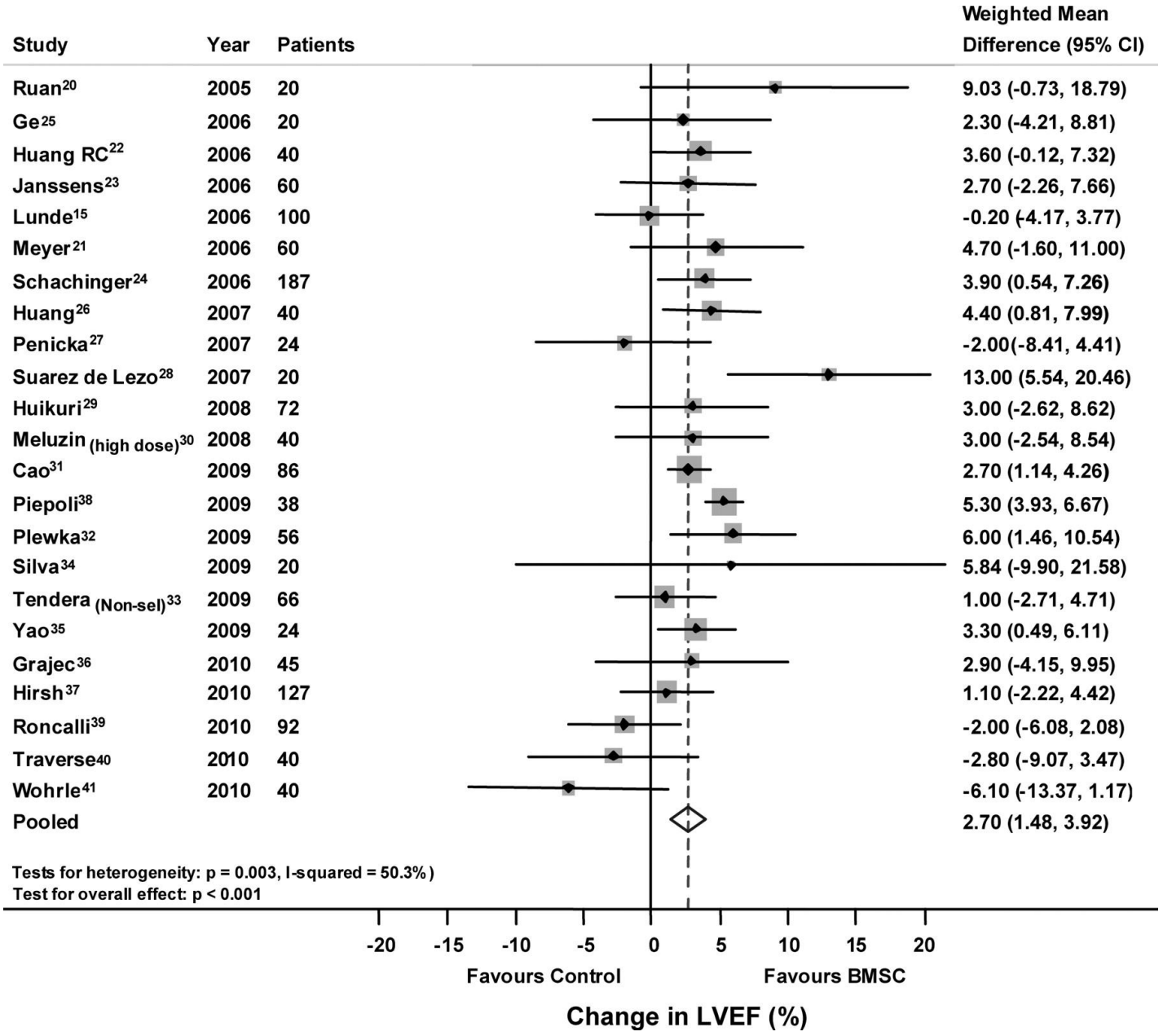
Short- and long-term outcomes of intracoronary and endogenously mobilized bone marrow stem cells in the treatment of ST-segment elevation myocardial infarction: a meta-analysis of randomized control trials

Hendrik Zimmet[1], Pramote Porapakkham[2], Pornwalee Porapakkham[3], Yusuke Sata[4], Steven Joseph Haas[1], Silviu Itescu[5], Andrew Forbes[1], and Henry Krum[1]*

Meta-analysis of 29 studies (1830 patients)

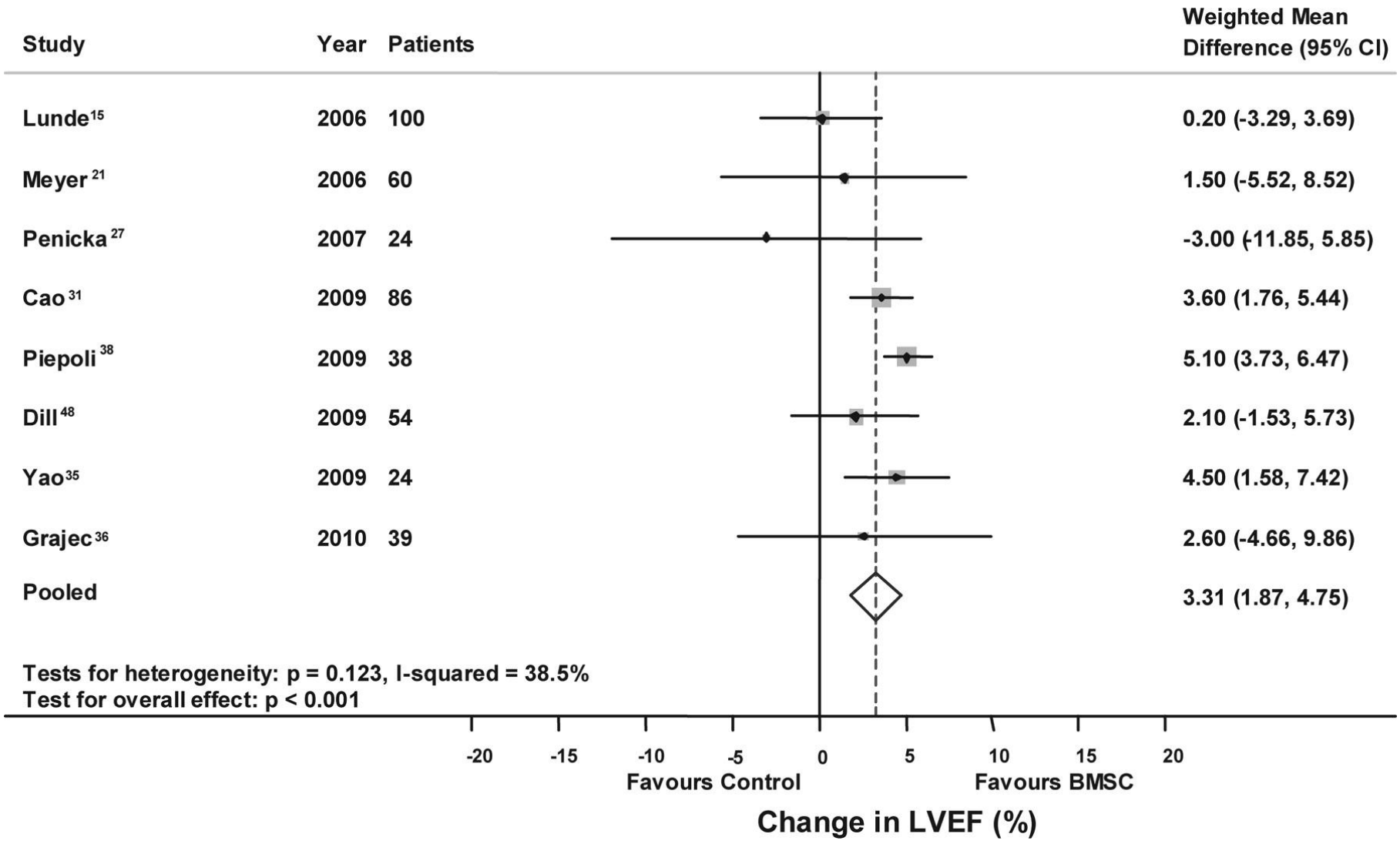
- ✓ Intracoronary BMSC therapy post-STEMI improves LVEF beyond standard medical treatment, in both the short and longer term

Effect of intracoronary BMSC on LVEF at 3–6 months



Zimmet H et al. Eur J Heart Fail 2012;14:91-105

Effect of intracoronary BMSC on LVEF at 12–18 months



Zimmet H et al. Eur J Heart Fail 2012;14:91-105

Heart Failure

Adult Bone Marrow Cell Therapy Improves Survival and Induces Long-Term Improvement in Cardiac Parameters

A Systematic Review and Meta-Analysis

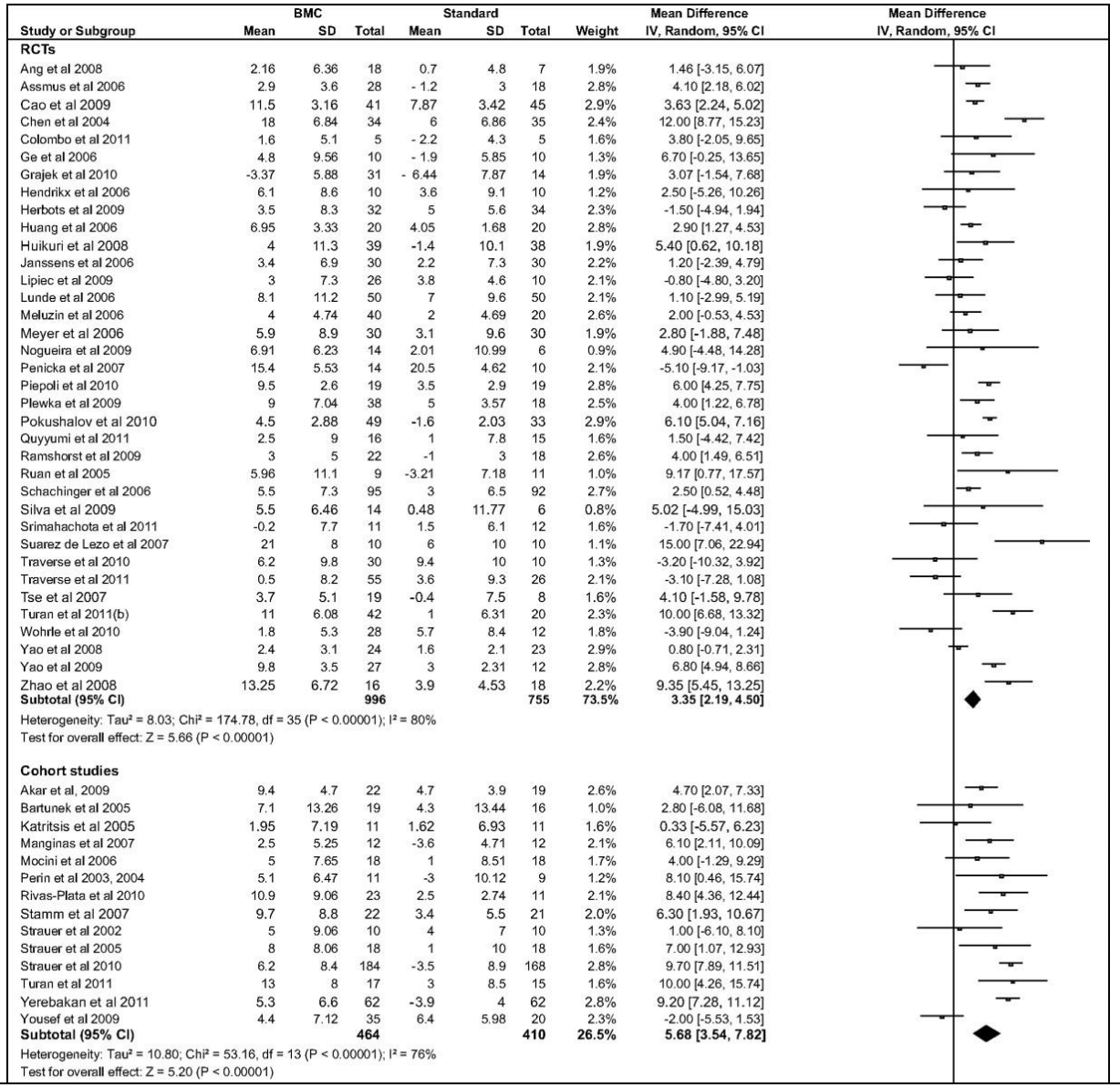
Vinodh Jeevanantham, MD; Matthew Butler, MD; Andre Saad, MD; Ahmed Abdel-Latif, MD; Ewa K. Zuba-Surma, PhD; Buddhadeb Dawn, MD

Meta-analysis of 50 studies (2625 patients)

- ✓ Improvement of LV function, infarct size, and remodeling in patients with ischemic heart disease compared with standard therapy
- ✓ Benefits persist during long-term follow-up
- ✓ Reduction in deaths, recurrent myocardial infarction, and stent thrombosis

Circulation, 126(5):551-568, 2012

Forest plot of unadjusted difference in mean change in LVEF in patients treated with BMCs compared with control subjects

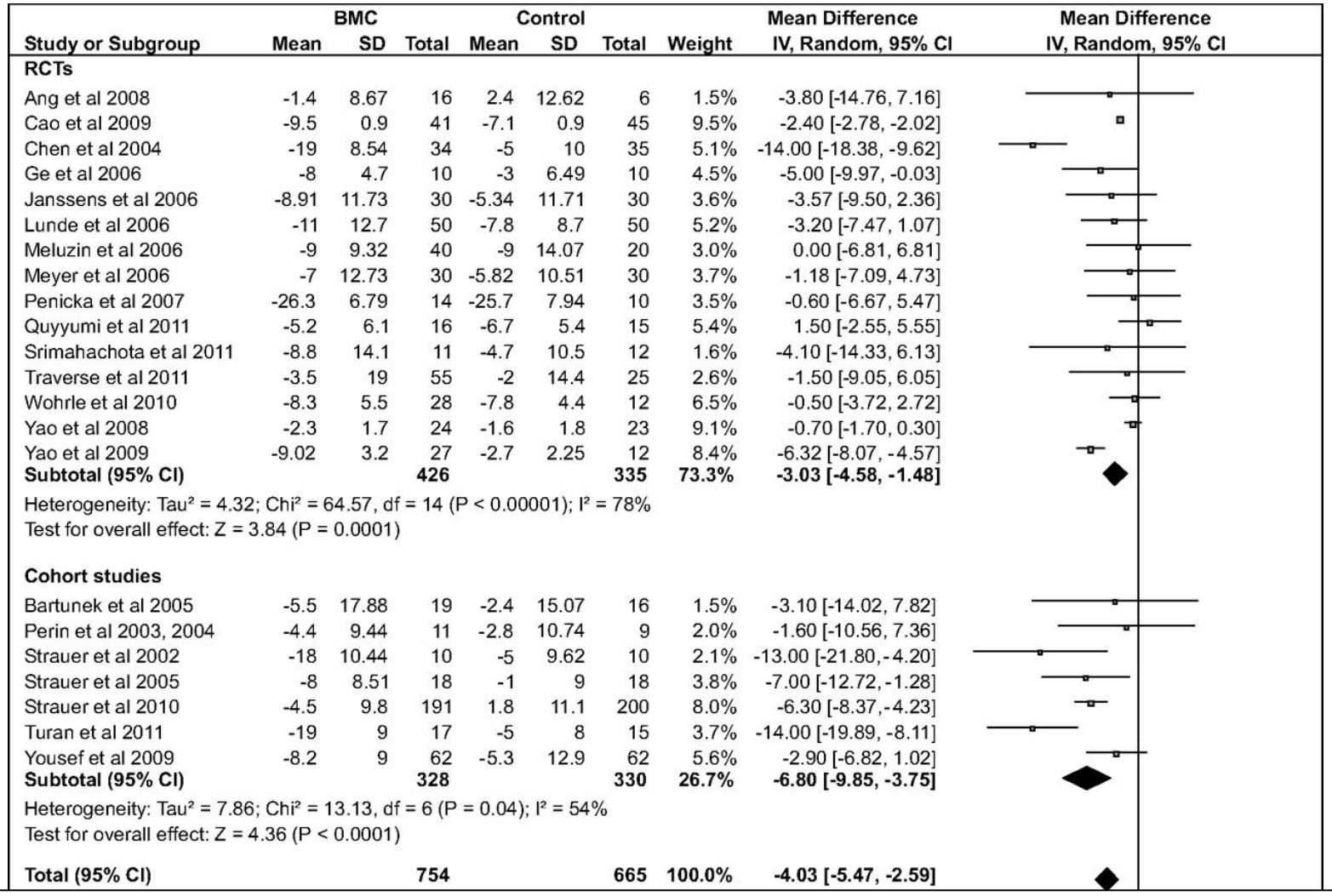


Study or Subgroup	BMC Mean	BMC SD	BMC Total	Standard Mean	Standard SD	Standard Total	Weight	Mean Difference IV, Random, 95% CI
RCTs								
Ang et al 2008	2.16	6.36	18	0.7	4.8	7	1.9%	1.46 [-3.15, 6.07]
Assmus et al 2006	2.9	3.6	28	- 1.2	3	18	2.8%	4.10 [2.18, 6.02]
Cao et al 2009	11.5	3.16	41	7.87	3.42	45	2.9%	3.63 [2.24, 5.02]
Chen et al 2004	18	6.84	34	6	6.86	35	2.4%	12.00 [8.77, 15.23]
Colombo et al 2011	1.6	5.1	5	- 2.2	4.3	5	1.6%	3.80 [-2.05, 9.65]
Ge et al 2006	4.8	9.56	10	- 1.9	5.85	10	1.3%	6.70 [-0.25, 13.65]
Grajek et al 2010	-3.37	5.88	31	- 6.44	7.87	14	1.9%	3.07 [-1.54, 7.68]
Hendrikx et al 2006	6.1	8.6	10	3.6	9.1	10	1.2%	2.50 [-5.26, 10.26]
Herbots et al 2009	3.5	8.3	32	5	5.6	34	2.3%	-1.50 [-4.94, 1.94]
Huang et al 2006	6.95	3.33	20	4.05	1.68	20	2.8%	2.90 [1.27, 4.53]
Huikuri et al 2008	4	11.3	39	-1.4	10.1	38	1.9%	5.40 [0.62, 10.18]
Janssens et al 2006	3.4	6.9	30	2.2	7.3	30	2.2%	1.20 [-2.39, 4.79]
Lipiec et al 2009	3	7.3	26	3.8	4.6	10	2.1%	-0.80 [-4.80, 3.20]
Lunde et al 2006	8.1	11.2	50	7	9.6	50	2.1%	1.10 [-2.99, 5.19]
Meluzin et al 2006	4	4.74	40	2	4.69	20	2.6%	2.00 [-0.53, 4.53]
Meyer et al 2006	5.9	8.9	30	3.1	9.6	30	1.9%	2.80 [-1.88, 7.48]
Nogueira et al 2009	6.91	6.23	14	2.01	10.99	6	0.9%	4.90 [-4.48, 14.28]
Penicka et al 2007	15.4	5.53	14	20.5	4.62	10	2.1%	-5.10 [-9.17, -1.03]
Piepoli et al 2010	9.5	2.6	19	3.5	2.9	19	2.8%	6.00 [4.25, 7.75]
Plewka et al 2009	9	7.04	38	5	3.57	18	2.5%	4.00 [1.22, 6.78]
Pokushalov et al 2010	4.5	2.88	49	-1.6	2.03	33	2.9%	6.10 [5.04, 7.16]
Quyyumi et al 2011	2.5	9	16	1	7.8	15	1.6%	1.50 [-4.42, 7.42]
Ramshorst et al 2009	3	5	22	-1	3	18	2.6%	4.00 [1.49, 6.51]
Ruan et al 2005	5.96	11.1	9	-3.21	7.18	11	1.0%	9.17 [0.77, 17.57]
Schachinger et al 2006	5.5	7.3	95	3	6.5	92	2.7%	2.50 [0.52, 4.48]
Silva et al 2009	5.5	6.46	14	0.48	11.77	6	0.8%	5.02 [-4.99, 15.03]
Srimahachota et al 2011	-0.2	7.7	11	1.5	6.1	12	1.6%	-1.70 [-7.41, 4.01]
Suarez de Lezo et al 2007	21	8	10	6	10	10	1.1%	15.00 [7.06, 22.94]
Traverse et al 2010	6.2	9.8	30	9.4	10	10	1.3%	-3.20 [-10.32, 3.92]
Traverse et al 2011	0.5	8.2	55	3.6	9.3	26	2.1%	-3.10 [-7.28, 1.08]
Tse et al 2007	3.7	5.1	19	-0.4	7.5	8	1.6%	4.10 [-1.58, 9.78]
Turan et al 2011(b)	11	6.08	42	1	6.31	20	2.3%	10.00 [6.68, 13.32]
Wohrle et al 2010	1.8	5.3	28	5.7	8.4	12	1.8%	-3.90 [-9.04, 1.24]
Yao et al 2008	2.4	3.1	24	1.6	2.1	23	2.9%	0.80 [-0.71, 2.31]
Yao et al 2009	9.8	3.5	27	3	2.31	12	2.8%	6.80 [4.94, 8.66]
Zhao et al 2008	13.25	6.72	16	3.9	4.53	18	2.2%	9.35 [5.45, 13.25]
Subtotal (95% CI)			**996**			**755**	**73.5%**	**3.35 [2.19, 4.50]**
Heterogeneity: Tau² = 8.03; Chi² = 174.78, df = 35 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 5.66 (P < 0.00001)								
Cohort studies								
Akar et al, 2009	9.4	4.7	22	4.7	3.9	19	2.6%	4.70 [2.07, 7.33]
Bartunek et al 2005	7.1	13.26	19	4.3	13.44	16	1.0%	2.80 [-6.08, 11.68]
Katritsis et al 2005	1.95	7.19	11	1.62	6.93	11	1.6%	0.33 [-5.57, 6.23]
Manginas et al 2007	2.5	5.25	12	-3.6	4.71	12	2.1%	6.10 [2.11, 10.09]
Mocini et al 2006	5	7.65	18	1	8.51	18	1.7%	4.00 [-1.29, 9.29]
Perin et al 2003, 2004	5.1	6.47	11	-3	10.12	9	1.2%	8.10 [0.46, 15.74]
Rivas-Plata et al 2010	10.9	9.06	23	2.5	2.74	11	2.1%	8.40 [4.36, 12.44]
Stamm et al 2007	9.7	8.8	22	3.4	5.5	21	2.0%	6.30 [1.93, 10.67]
Strauer et al 2002	5	9.06	10	4	7	10	1.3%	1.00 [-6.10, 8.10]
Strauer et al 2005	8	8.06	18	1	10	18	1.6%	7.00 [1.07, 12.93]
Strauer et al 2010	6.2	8.4	184	-3.5	8.9	168	2.8%	9.70 [7.89, 11.51]
Turan et al 2011	13	8	17	3	8.5	15	1.6%	10.00 [4.26, 15.74]
Yerebakan et al 2011	5.3	6.6	62	-3.9	4	62	2.8%	9.20 [7.28, 11.12]
Yousef et al 2009	4.4	7.12	35	6.4	5.98	20	2.3%	-2.00 [-5.53, 1.53]
Subtotal (95% CI)			**464**			**410**	**26.5%**	**5.68 [3.54, 7.82]**
Heterogeneity: Tau² = 10.80; Chi² = 53.16, df = 13 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 5.20 (P < 0.00001)								

Transplantation of BMCs resulted in a 4% increase in mean LVEF

Jeevanantham V et al. Circulation 2012;126:551-568

Forest plot of mean change in infarct scar size in patients treated BMCs compared with control subjects



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Ang et al 2008	-1.4	8.67	16	2.4	12.62	6	1.5%	-3.80 [-14.76, 7.16]
Cao et al 2009	-9.5	0.9	41	-7.1	0.9	45	9.5%	-2.40 [-2.78, -2.02]
Chen et al 2004	-19	8.54	34	-5	10	35	5.1%	-14.00 [-18.38, -9.62]
Ge et al 2006	-8	4.7	10	-3	6.49	10	4.5%	-5.00 [-9.97, -0.03]
Janssens et al 2006	-8.91	11.73	30	-5.34	11.71	30	3.6%	-3.57 [-9.50, 2.36]
Lunde et al 2006	-11	12.7	50	-7.8	8.7	50	5.2%	-3.20 [-7.47, 1.07]
Meluzin et al 2006	-9	9.32	40	-9	14.07	20	3.0%	0.00 [-6.81, 6.81]
Meyer et al 2006	-7	12.73	30	-5.82	10.51	30	3.7%	-1.18 [-7.09, 4.73]
Penicka et al 2007	-26.3	6.79	14	-25.7	7.94	10	3.5%	-0.60 [-6.67, 5.47]
Quyyumi et al 2011	-5.2	6.1	16	-6.7	5.4	15	5.4%	1.50 [-2.55, 5.55]
Srimahachota et al 2011	-8.8	14.1	11	-4.7	10.5	12	1.6%	-4.10 [-14.33, 6.13]
Traverse et al 2011	-3.5	19	55	-2	14.4	25	2.6%	-1.50 [-9.05, 6.05]
Wohrle et al 2010	-8.3	5.5	28	-7.8	4.4	12	6.5%	-0.50 [-3.72, 2.72]
Yao et al 2008	-2.3	1.7	24	-1.6	1.8	23	9.1%	-0.70 [-1.70, 0.30]
Yao et al 2009	-9.02	3.2	27	-2.7	2.25	12	8.4%	-6.32 [-8.07, -4.57]
Subtotal (95% CI)			**426**			**335**	**73.3%**	**-3.03 [-4.58, -1.48]**
Heterogeneity: Tau² = 4.32; Chi² = 64.57, df = 14 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 3.84 (P = 0.0001)								
Cohort studies								
Bartunek et al 2005	-5.5	17.88	19	-2.4	15.07	16	1.5%	-3.10 [-14.02, 7.82]
Perin et al 2003, 2004	-4.4	9.44	11	-2.8	10.74	9	2.0%	-1.60 [-10.56, 7.36]
Strauer et al 2002	-18	10.44	10	-5	9.62	10	2.1%	-13.00 [-21.80, -4.20]
Strauer et al 2005	-8	8.51	18	-1	9	18	3.8%	-7.00 [-12.72, -1.28]
Strauer et al 2010	-4.5	9.8	191	1.8	11.1	200	8.0%	-6.30 [-8.37, -4.23]
Turan et al 2011	-19	9	17	-5	8	15	3.7%	-14.00 [-19.89, -8.11]
Yousef et al 2009	-8.2	9	62	-5.3	12.9	62	5.6%	-2.90 [-6.82, 1.02]
Subtotal (95% CI)			**328**			**330**	**26.7%**	**-6.80 [-9.85, -3.75]**
Heterogeneity: Tau² = 7.86; Chi² = 13.13, df = 6 (P = 0.04); I² = 54%								
Test for overall effect: Z = 4.36 (P < 0.0001)								
Total (95% CI)			**754**			**665**	**100.0%**	**-4.03 [-5.47, -2.59]**

Transplantation of BMCs resulted in a 4% decrease in infarct scar size

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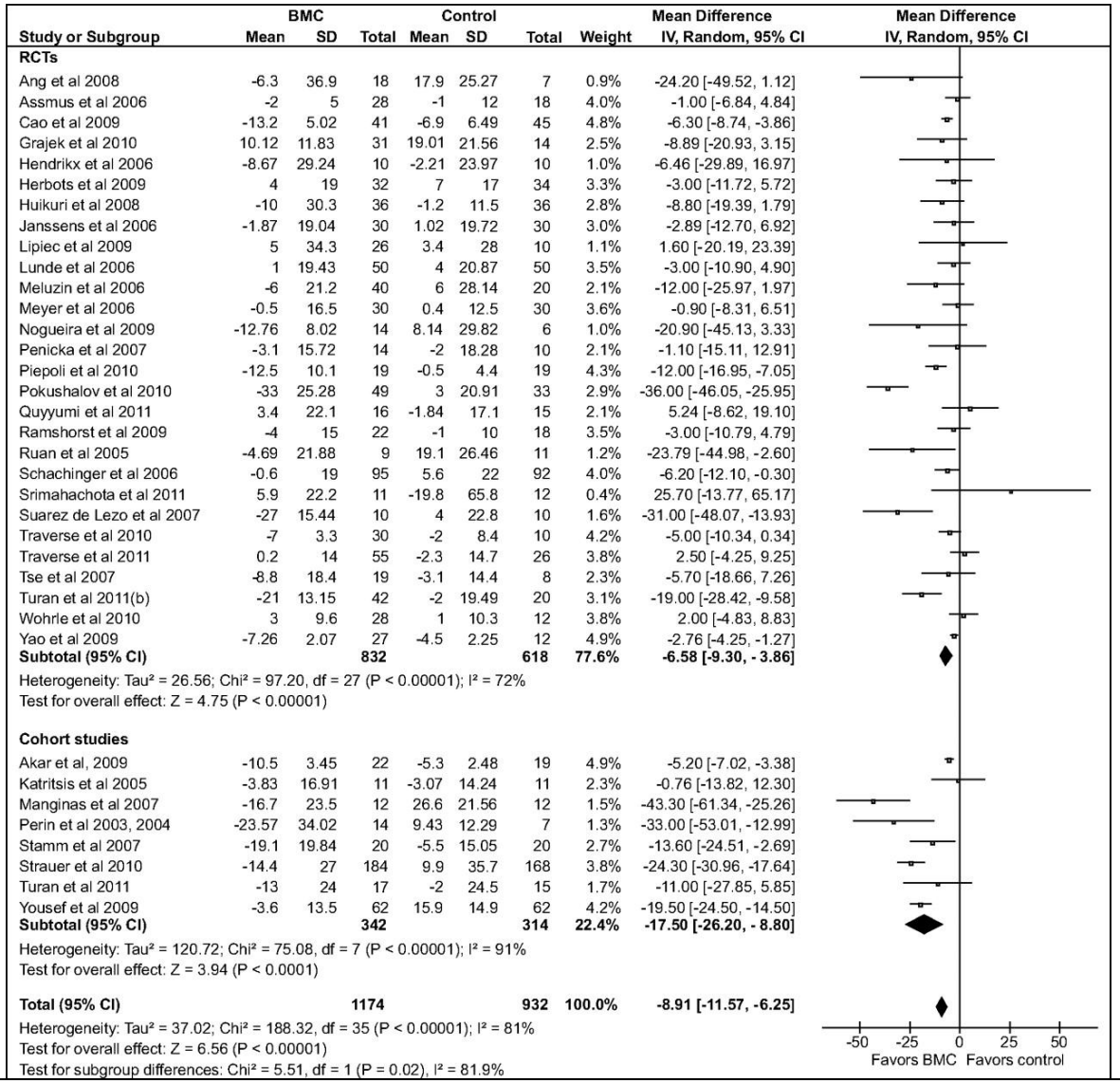
Forest plot of mean change in LVESV in patients treated with BMCs compared with control subjects



Transplantation of BMCs resulted in a 9% decrease in mean LVESV

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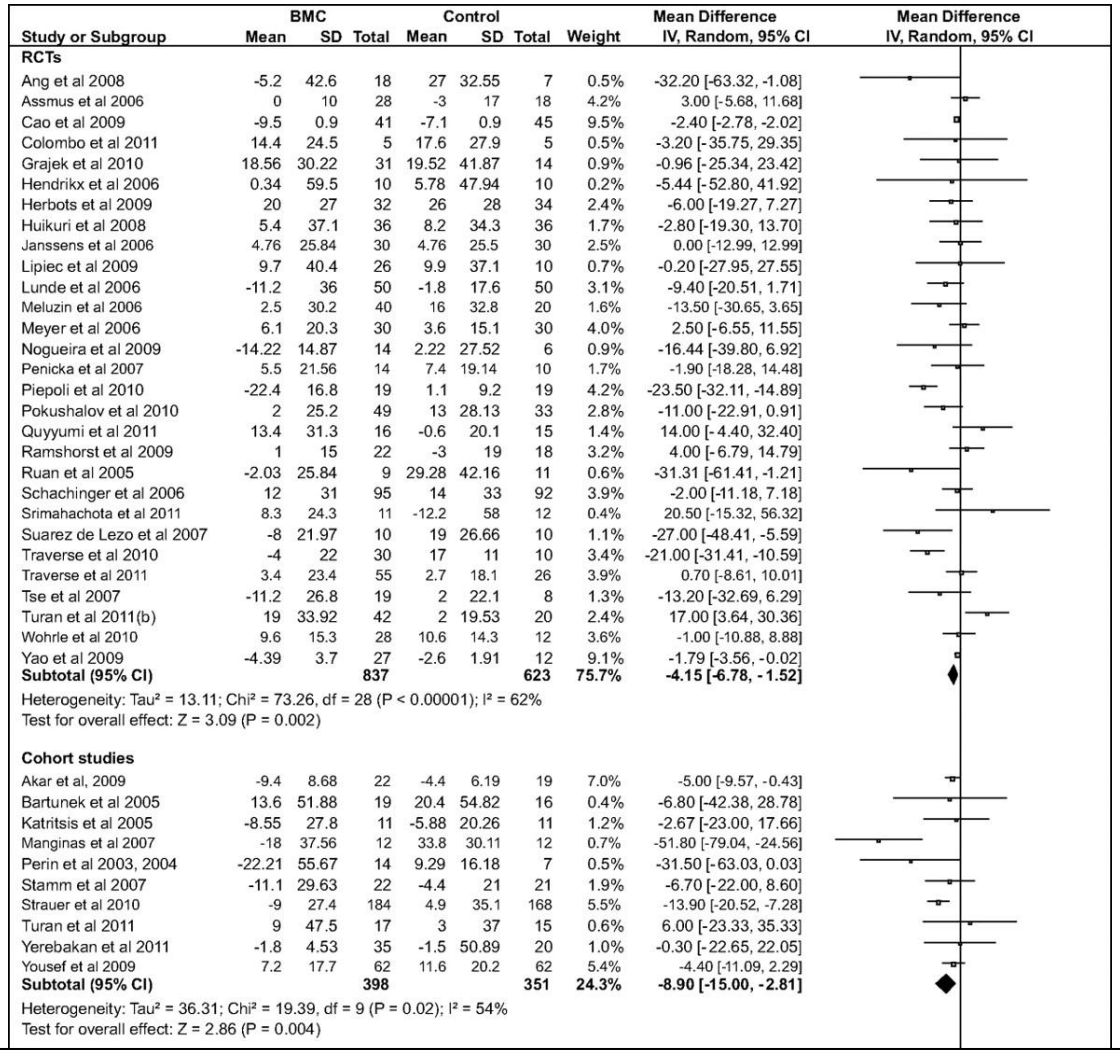
Forest plot of mean change in LVEDV in patients treated with BMCs compared with control subjects



Study or Subgroup	BMC Mean	BMC SD	BMC Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
RCTs								
Ang et al 2008	-5.2	42.6	18	27	32.55	7	0.5%	-32.20 [-63.32, -1.08]
Assmus et al 2006	0	10	28	-3	17	18	4.2%	3.00 [-5.68, 11.68]
Cao et al 2009	-9.5	0.9	41	-7.1	0.9	45	9.5%	-2.40 [-2.78, -2.02]
Colombo et al 2011	14.4	24.5	5	17.6	27.9	5	0.5%	-3.20 [-35.75, 29.35]
Grajek et al 2010	18.56	30.22	31	19.52	41.87	14	0.9%	-0.96 [-25.34, 23.42]
Hendrikx et al 2006	0.34	59.5	10	5.78	47.94	10	0.2%	-5.44 [-52.80, 41.92]
Herbots et al 2009	20	27	32	26	28	34	2.4%	-6.00 [-19.27, 7.27]
Huikuri et al 2008	5.4	37.1	36	8.2	34.3	36	1.7%	-2.80 [-19.30, 13.70]
Janssens et al 2006	4.76	25.84	30	4.76	25.5	30	2.5%	0.00 [-12.99, 12.99]
Lipiec et al 2009	9.7	40.4	26	9.9	37.1	10	0.7%	-0.20 [-27.95, 27.55]
Lunde et al 2006	-11.2	36	50	-1.8	17.6	50	3.1%	-9.40 [-20.51, 1.71]
Meluzin et al 2006	2.5	30.2	40	16	32.8	20	1.6%	-13.50 [-30.65, 3.65]
Meyer et al 2006	6.1	20.3	30	3.6	15.1	30	4.0%	2.50 [-6.55, 11.55]
Nogueira et al 2009	-14.22	14.87	14	2.22	27.52	6	0.9%	-16.44 [-39.80, 6.92]
Penicka et al 2007	5.5	21.56	14	7.4	19.14	10	1.7%	-1.90 [-18.28, 14.48]
Piepoli et al 2010	-22.4	16.8	19	1.1	9.2	19	4.2%	-23.50 [-32.11, -14.89]
Pokushalov et al 2010	2	25.2	49	13	28.13	33	2.8%	-11.00 [-22.91, 0.91]
Quyyumi et al 2011	13.4	31.3	16	-0.6	20.1	15	1.4%	14.00 [-4.40, 32.40]
Ramshorst et al 2009	1	15	22	-3	19	18	3.2%	4.00 [-6.79, 14.79]
Ruan et al 2005	-2.03	25.84	9	29.28	42.16	11	0.6%	-31.31 [-61.41, -1.21]
Schachinger et al 2006	12	31	95	14	33	92	3.9%	-2.00 [-11.18, 7.18]
Srimahachota et al 2011	8.3	24.3	11	-12.2	58	12	0.4%	20.50 [-15.32, 56.32]
Suarez de Lezo et al 2007	-8	21.97	10	19	26.66	10	1.1%	-27.00 [-48.41, -5.59]
Traverse et al 2010	-4	22	30	17	11	10	3.4%	-21.00 [-31.41, -10.59]
Traverse et al 2011	3.4	23.4	55	2.7	18.1	26	3.9%	0.70 [-8.61, 10.01]
Tse et al 2007	-11.2	26.8	19	2	22.1	8	1.3%	-13.20 [-32.69, 6.29]
Turan et al 2011(b)	19	33.92	42	2	19.53	20	2.4%	17.00 [3.64, 30.36]
Wohrle et al 2010	9.6	15.3	28	10.6	14.3	12	3.6%	-1.00 [-10.88, 8.88]
Yao et al 2009	-4.39	3.7	27	-2.6	1.91	12	9.1%	-1.79 [-3.56, -0.02]
Subtotal (95% CI)			**837**			**623**	**75.7%**	**-4.15 [-6.78, -1.52]**
Heterogeneity: $Tau^2 = 13.11$; $Chi^2 = 73.26$, df = 28 ($P < 0.00001$); $I^2 = 62\%$								
Test for overall effect: Z = 3.09 (P = 0.002)								
Cohort studies								
Akar et al, 2009	-9.4	8.68	22	-4.4	6.19	19	7.0%	-5.00 [-9.57, -0.43]
Bartunek et al 2005	13.6	51.88	19	20.4	54.82	16	0.4%	-6.80 [-42.38, 28.78]
Katritsis et al 2005	-8.55	27.8	11	-5.88	20.26	11	1.2%	-2.67 [-23.00, 17.66]
Manginas et al 2007	-18	37.56	12	33.8	30.11	12	0.7%	-51.80 [-79.04, -24.56]
Perin et al 2003, 2004	-22.21	55.67	14	9.29	16.18	7	0.5%	-31.50 [-63.03, 0.03]
Stamm et al 2007	-11.1	29.63	22	-4.4	21	21	1.9%	-6.70 [-22.00, 8.60]
Strauer et al 2010	-9	27.4	184	4.9	35.1	168	5.5%	-13.90 [-20.52, -7.28]
Turan et al 2011	9	47.5	17	3	37	15	0.6%	6.00 [-23.33, 35.33]
Yerebakan et al 2011	-1.8	4.53	35	-1.5	50.89	20	1.0%	-0.30 [-22.65, 22.05]
Yousef et al 2009	7.2	17.7	62	11.6	20.2	62	5.4%	-4.40 [-11.09, 2.29]
Subtotal (95% CI)			**398**			**351**	**24.3%**	**-8.90 [-15.00, -2.81]**
Heterogeneity: $Tau^2 = 36.31$; $Chi^2 = 19.39$, df = 9 (P = 0.02); $I^2 = 54\%$								
Test for overall effect: Z = 2.86 (P = 0.004)								

Transplantation of BMCs resulted in a 5% decrease in mean LVEDV

Jeevanantham V et al. Circulation 2012;126:551-568

Cell types used for cardiac repair

Cell type	Source	Advantages	Disadvantages
Bone marrow	BM Blood	Autologous Paracrine effects	Pluripotency uncertain
Adult cardiac progenitor cells	Cardiac biopsy	Autologous Differentiate into all cardiac lineages Paracrine effects	Invasive cardiac biopsy Xenogenic anti-bodies used for isolation

To improve the outcome of current cell therapy for cardiac regeneration in the future:

- ✓ Resolve the issues concerning optimal cell type, factors, dosage, patient population, and route and timing of administration
- ✓ Proceed with rigorous, large-scale, rationally designed, and randomized clinical trials

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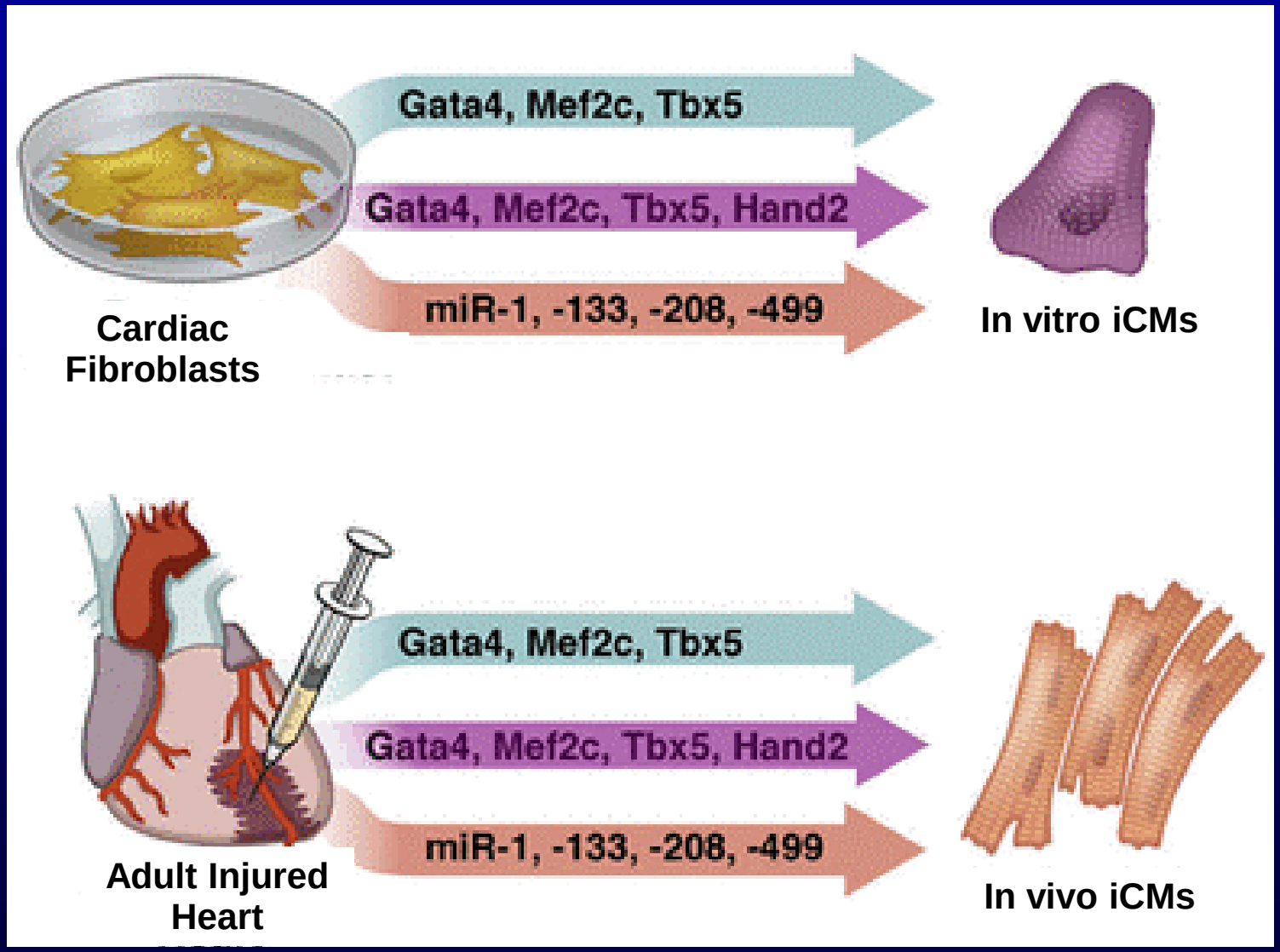
- ✓ Tissue engineering
- ✓ MicroRNA regulation of cardiac regeneration
- ✓ Reprogramming the fibroblasts

Approaches to direct cardiac reprogramming



Qian L, Srivastava D. Circulation Research 2013;113:915-921

Likely outcomes in the future

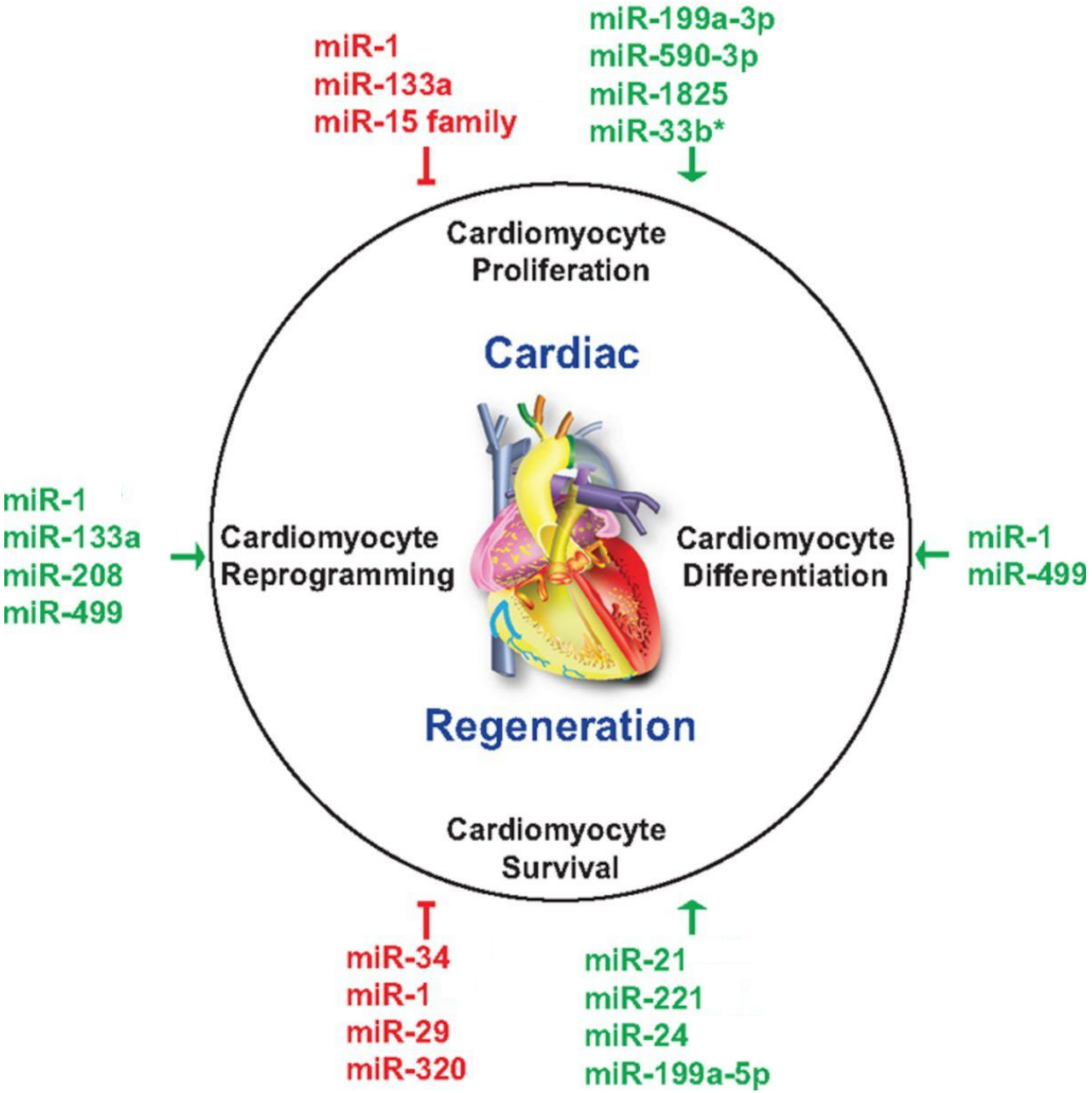
- ✓ Off-the-shelf products likely in decade or so
- ✓ Different mixture of cells for patients with recent MI and those with chronic HF
- ✓ Infused into the coronary arteries for patients with dilated nonischemic cardiomyopathy
- ✓ Transendocardial injection to patients with major coronary blockages
- ✓ Cell therapy unlikely a sole treatment for HF, but an important adjunct to other therapeutic approaches, (prolonged LVA, microRNA, and gene therapy)

Thomas E. Starzl MD, PhD
("The father of modern transplantation")

"The history of medicine is that what was inconceivable yesterday and barely achievable today often becomes routine tomorrow"


Thank you
MEDICAL
COLLEGE
OF WISCONSIN

MicroRNA regulation of cardiac regeneration



Circ Res 2013;112:1412-1414

Remuscularising the Failing Heart

- ✓ Myocardial infarction - one billion myocytes dead
- ✓ Intramyocardial cell injection - over 95% of the cells are lost
- ✓ Calculated therapeutic cell dose - 20 billion myocytes
- ✓ Total myocytes number of the heart is 4 billion