Stem Cell Therapy for Ischemic Cardiomyopathy: Is the stem cell therapy useful?

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Treatment modalities for HF (I-CMP)

	Mechanism of Action	Effects on	
		Loss of myocardium	Inadequate blood supply
Medical Treatment	Inhibit Neurohumoral response	May prevent further loss	+
Cardiac resynchronization therapy	Resynchronize contraction	-	+/-
Surgical ventricular restoration	Restoring geometry	-	+/-
Ventricular assist device	Unloading cardiac load	-	+/-
Artificial heart	New mechanical contractile apparatus	+++	Not indicated
Heart Transplantation	New heart	+++	+++
Stem cell transplantation	Regeneration of myocardium and blood vessels	++	++

Stem cell therapy for I-CMP

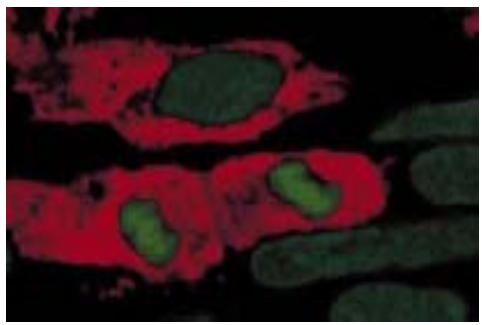
- Presence of Natural Repair Mechanism
  1. Proliferation of cardiomyocytes.
  2. Presence and sources of Stem cells
  3. Cardiomyogenic differentiation of Stem cells
  4. Evidences from In vivo experiments
  – Mechanisms of Improvements

- Considerations for Cellular Cardiomyoplasty
- Current Status of Clinical Trials for MI
- Comparison of Methods for Stem Cell Therapy
- Limitation of Stem Cell therapy
- Future to go

1. Proliferation of Cardiomyocytes.

- Evidence of proliferative potential.
  - Human cardiomyocyte divide after MI

Beltrami AP, et al. NEJM 2001



  - In end stage heart failure

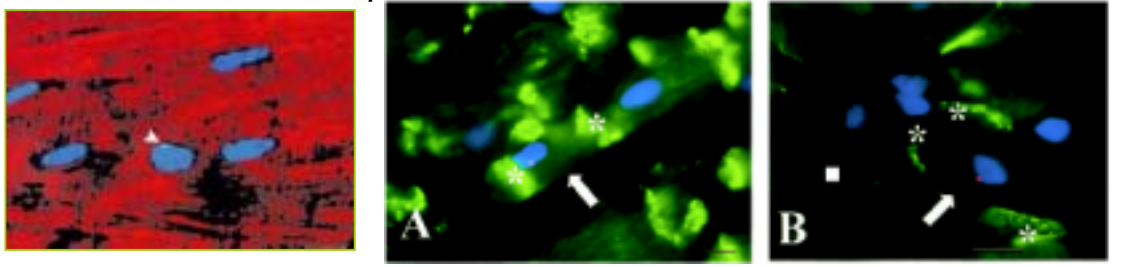
Kastura J, et al. PNAS USA 1998

  - In transplanted heart.

Muller P, et al. Circulation 2002

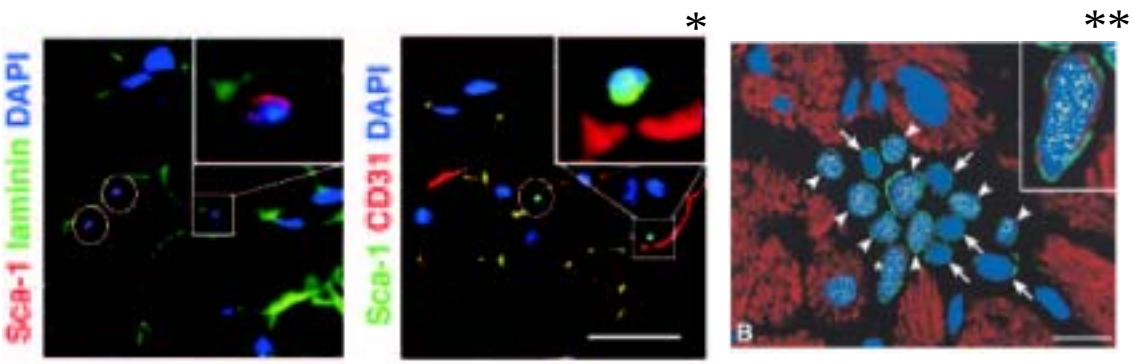
2. Presence and Sources of Stem Cells

- Chimerism of transplanted heart (Extracardiac stem cell)
  - Extracardiac cell can integrate into myocardium.



Quaini F, et al. NEJM 2002*
Laflamme MA, et al. Cir Res 2002
Deb A, et al. Circulation 2003
Muller P, et al. Circulation 2002**

- Presence of cardiac stem cells

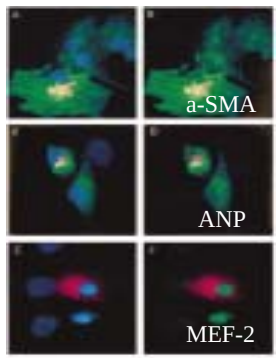


Hidemasa O, et al. PNAS USA 2003*
Beltrami AP, et al. Cell 2003**

3. Cardiomyogenic differentiation of Stem cells

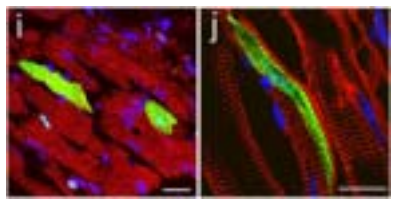
- Differentiation of extracardiac/cardiac stem cells.
  - EPC

    Bardoff C, et al. Circulation 2003



  - BM MSC

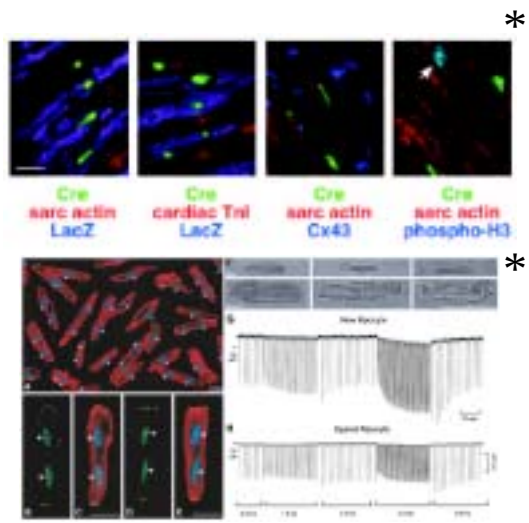
    Kawata et al.Blood 2004



  - Cardiac stem cells

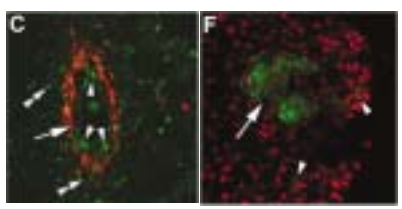
    Hidemasa O, et al. PNAS USA 2003*

    Beltrami AP, et al. Cell 2003**



  - Epicardially derived cells

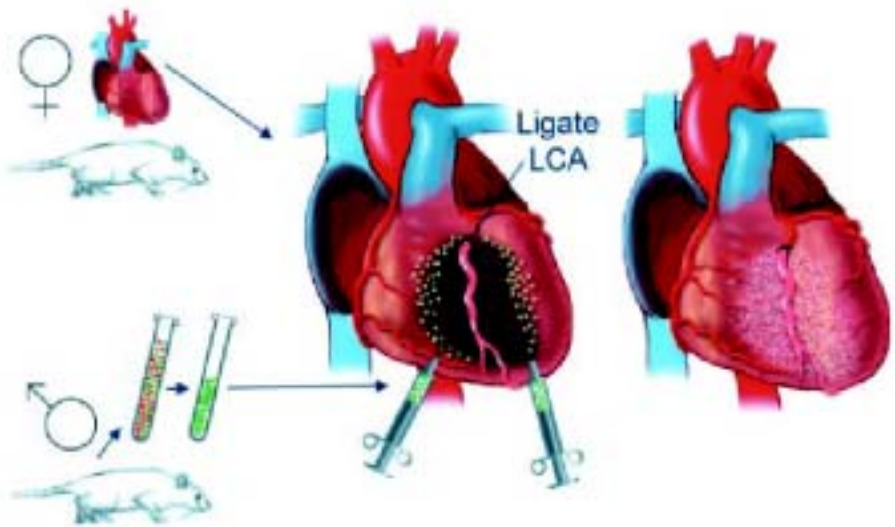
    Wessels A, et al Anat Res 2004

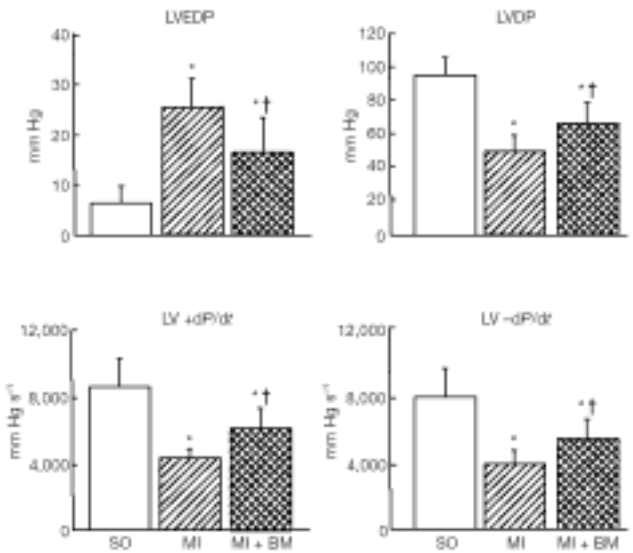


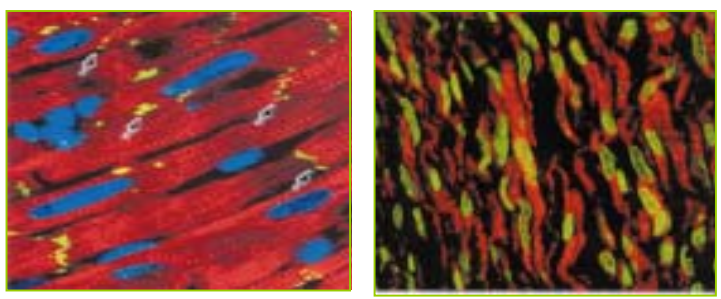
4. Evidences from In vivo experiments

- Stem cell can regenerate myocardium.

Orlic et al. Nature med 2001



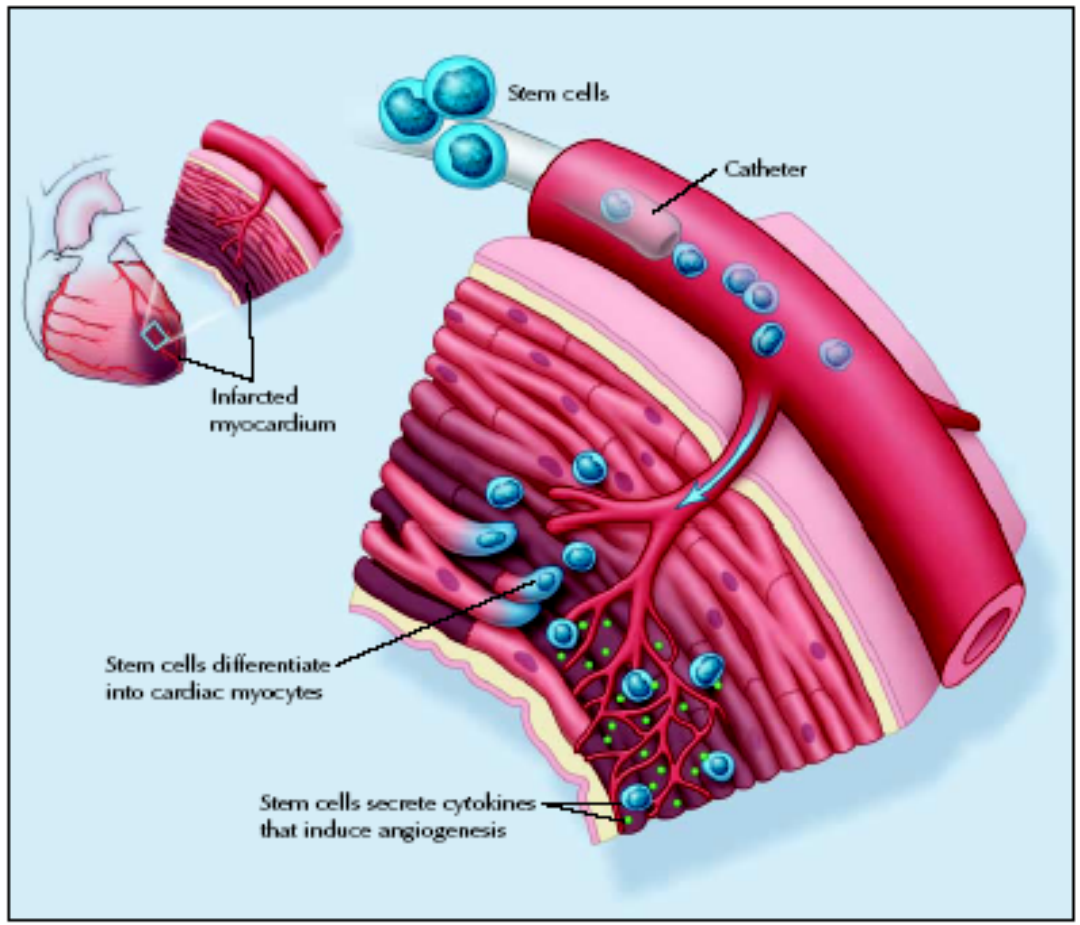




•Mechanisms of Improvements

- Myogenesis
- Angiogenesis
- Paracrine effect

- Myocardial regeneration
- New vessel formation
- Prevent remodeling
- Inhibit cell loss



Kang et al. CMAJ 2004

Stem cell therapy for I-CMP

- Presence of Natural Repair Mechanism
- Considerations for Cellular Cardiomyoplasty
  1. Sources of Stem Cells
  2. Methods of Delivery
  3. Other Considerations
- Current Status of Clinical Trials for MI
- Comparison of Methods for Stem Cell Therapy
- Limitation of Stem Cell therapy
- Future to go

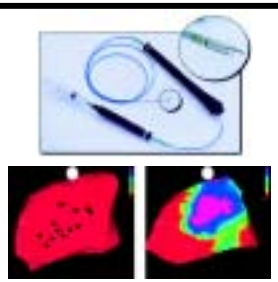
1. Sources of Stem Cells

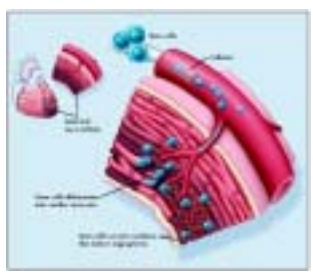
	Embryonic stem cell	Bone marrow stem cell*	Skeletal myoblast
Accessibility	Poor	Good	Excellent
Prolonged survival and proliferation	Possible	Possible (> 1year)	Probable (> 1year)
Controlled proliferation	Poor (risk of tumor)	Fair	Good
Differentiation and Integration	Promising	Promising	Relatively Poor
Ethical problem	Yes	No	No
Rejection	Yes	No	No
Route of administration	IM	IM, IC, IV	IM >> IC

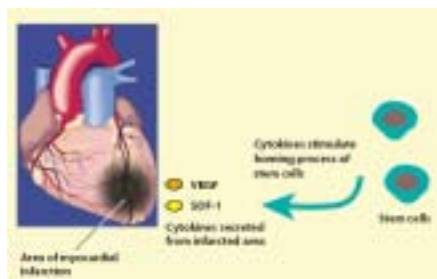
* Peripheral blood stem cell, cord blood stem cell, EPC

2. Methods of Delivery

Route of delivery	Advantages	Disadvantages
Intramyocardial	Highly efficient	Isolated cell nest Most invasive (surgical approach) Complex (catheter based approach)
Intracoronary	High dose and maximal concentration Homogenous homing and engraftment to border zone	Single pass effect (low efficiency)
Intravenous	Simple and least invasive	Very low efficiency (boost homing)
Mobilization	Simplest and noninvasive	Very low efficiency, systemic adverse reaction (inflammation)



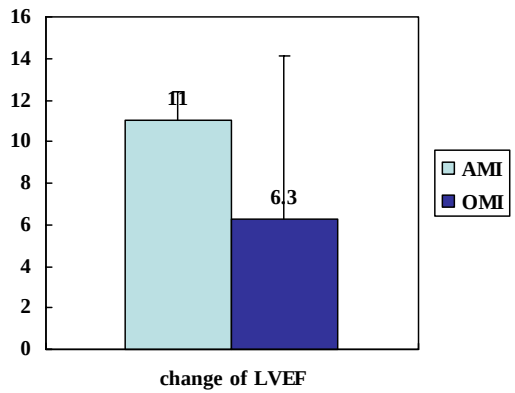




3. Other Considerations

- Timing of delivery
  - In case of AMI: post-AMI 7-14 day (?)
  - In case of OMI:
    1. Inadequate stimuli for cardiac repair
    2. dysfunction of progenitor cell

Li et al. Ann Thorac Surg 2001



- Underlying disease
  - Ischemic vs. nonischemic

- Cell dose / composition

Stem cell therapy for I-CMP

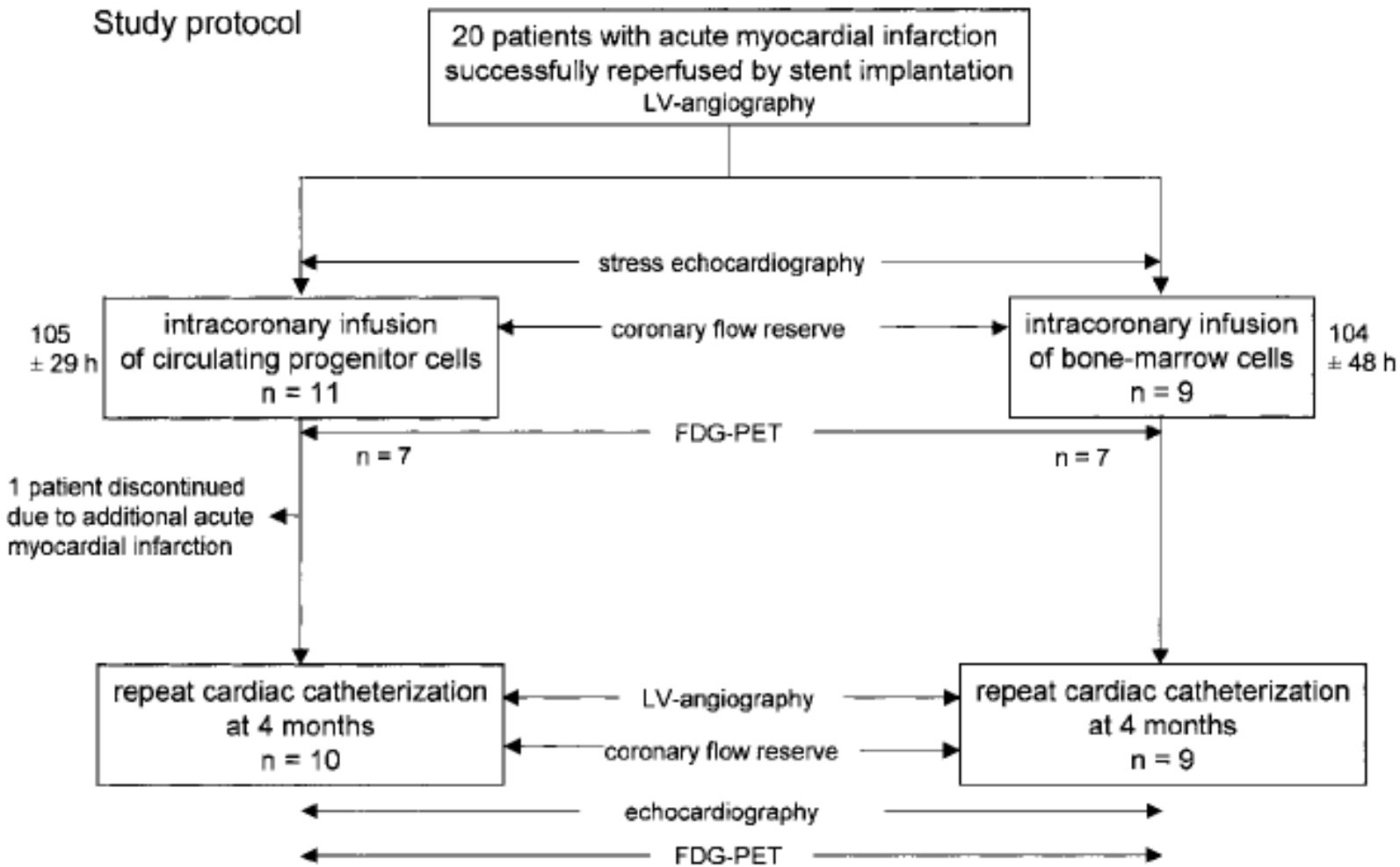
- Presence of Natural Repair Mechanism
- Considerations for Cellular Cardiomyoplasty
- Current Status of Clinical Trials for MI
  - ✓ Overview
  - ✓ TOPCARE-AMI
  - ✓ BOOST Trial
  - ✓ Trials of Chen et al.
  - ✓ MAGIC Cell Trial
- Comparison of Methods for Stem Cell Therapy
- Limitation of Stem Cell therapy
- Future to go

Current Status of Clinical Trials for MI

	N	Method of delivery (Underling disease)	LVEF	Outcome*	Follow-up Period	Donor cell	Complications
Hamano et al	5	Myocardial injection during CABG (OMI)	NA	P	Up to 1 y	Bone marrow cells	None
Strauer et al	10	Intracoronary infusion after PCI (AMI)	57%	P/L	3 mo	Bone marrow cells	None
Assmus et al	20	Intracoronary infusion after PCI (AMI)	51%	P/L(9%)/S/E	4 mo	Bone marrow cells/ Progenitor cells	None
Menasché et al	10	Myocardial injection during CABG (OMI)	24%	L(8%)	10.9 mo	Skeletal myoblasts	Death, VT
Stamm et al	12	Myocardial injection during CABG (OMI)	36%	L(9%)	3-9 mo	Bone marrow cells	SVT
Pagani et al	5	Myocardial injection during LVAD (OM)	NA	NA	68-191 d	Skeletal myoblasts	Arrhythmia, LVAD death
Tse et al	8	Myocardial injection during catheterization (angina)	58%	P/L(5%)	3 mo	Bone marrow cells	None
Perin et al	14	Myocardial injection during catheterization (OMI)	30%	P/L(6%)/S/E	4 mo	Bone marrow cells	Death
Galinaes et al	21	Myocardial injection during CABG (OMI)	NA	L	10 mo	Bone marrow cells	None
Wollert et al	30	Intracoronary infusion after PCI (AMI)	50%	L(6%)/P	6 mo	Bone marrow cells	None
Smits et al	5	Myocardial injection during catheterization	36%	L(9%)	6 mo	Skeletal myoblasts	VT
Kang et al	24	Intracoronary infusion after PCI (AMI+OMI)	49%	P/L(8%)/S/E	1 y	Peripheral blood cells	Restenosis
Aviles et al	5	Intracoronary infusion after PCI (AMI)	53%	L(5%)	6 mo	Bone marrow cells	Heart attack
Chen et al	34	Intracoronary infusion after PCI (AMI)	49%	P/L(13%)	6 mo	Bone marrow cells	None

* P: perfusion, L: LV systolic function, S:symptom, E: exercise capacity

Profile of TOPCARE-AMI

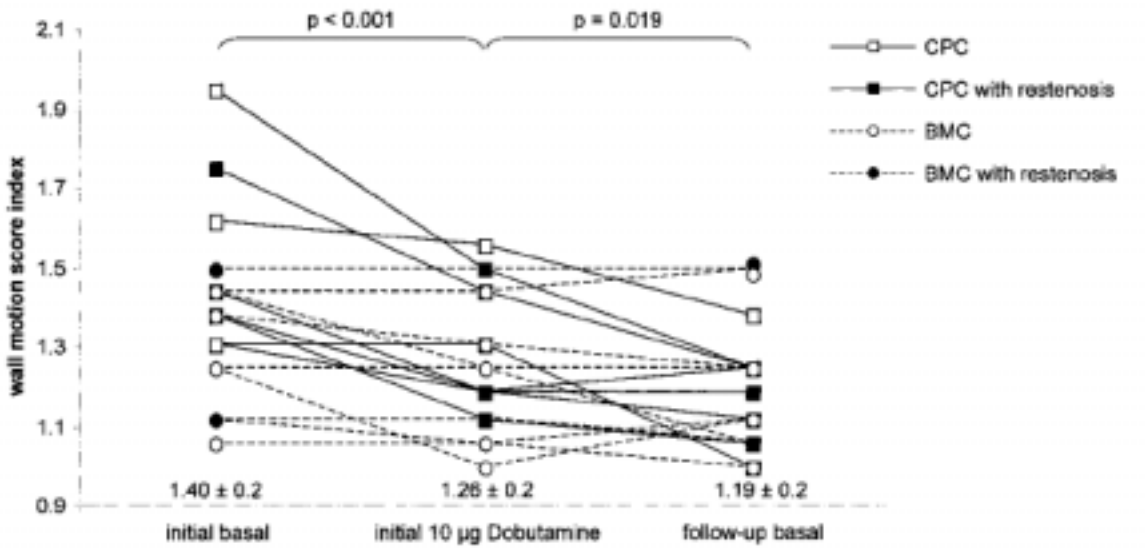


4 months F/U results of TOPCARE-AMI

- Change of LVEF (%)

	Baseline	Follow up
Cell therapy (n=19)	51.6 ± 9.6	60.1 ± 8.6
Historical control (n=11)	51.0 ± 10.0	53.5 ± 7.9

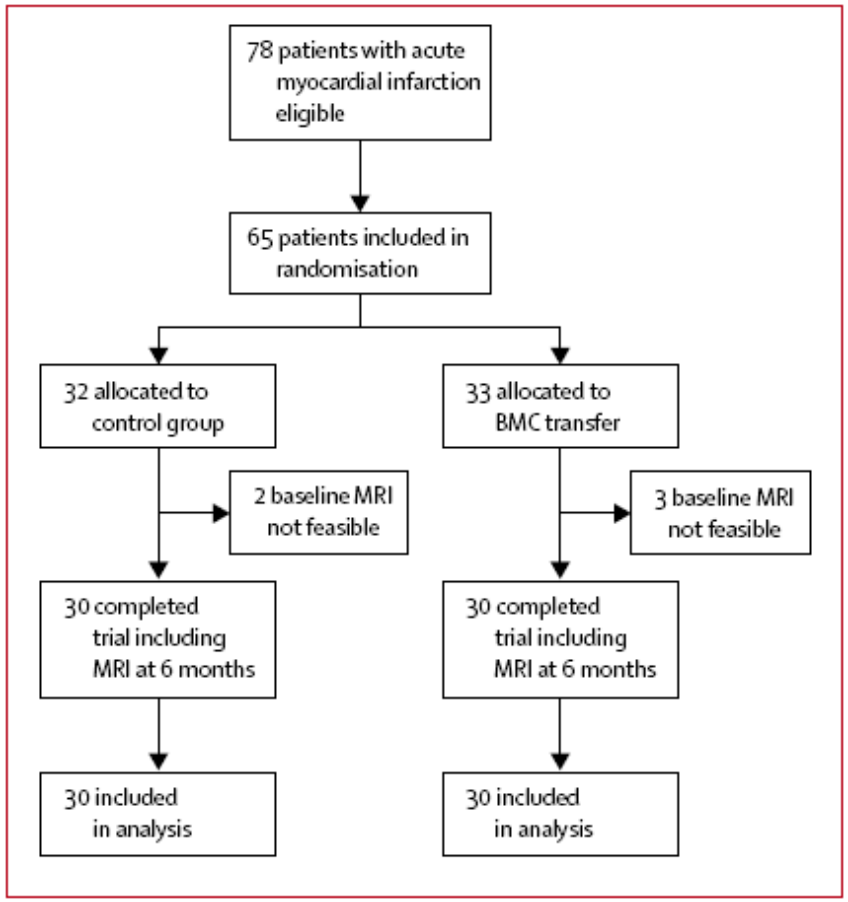
- Change of WMSI



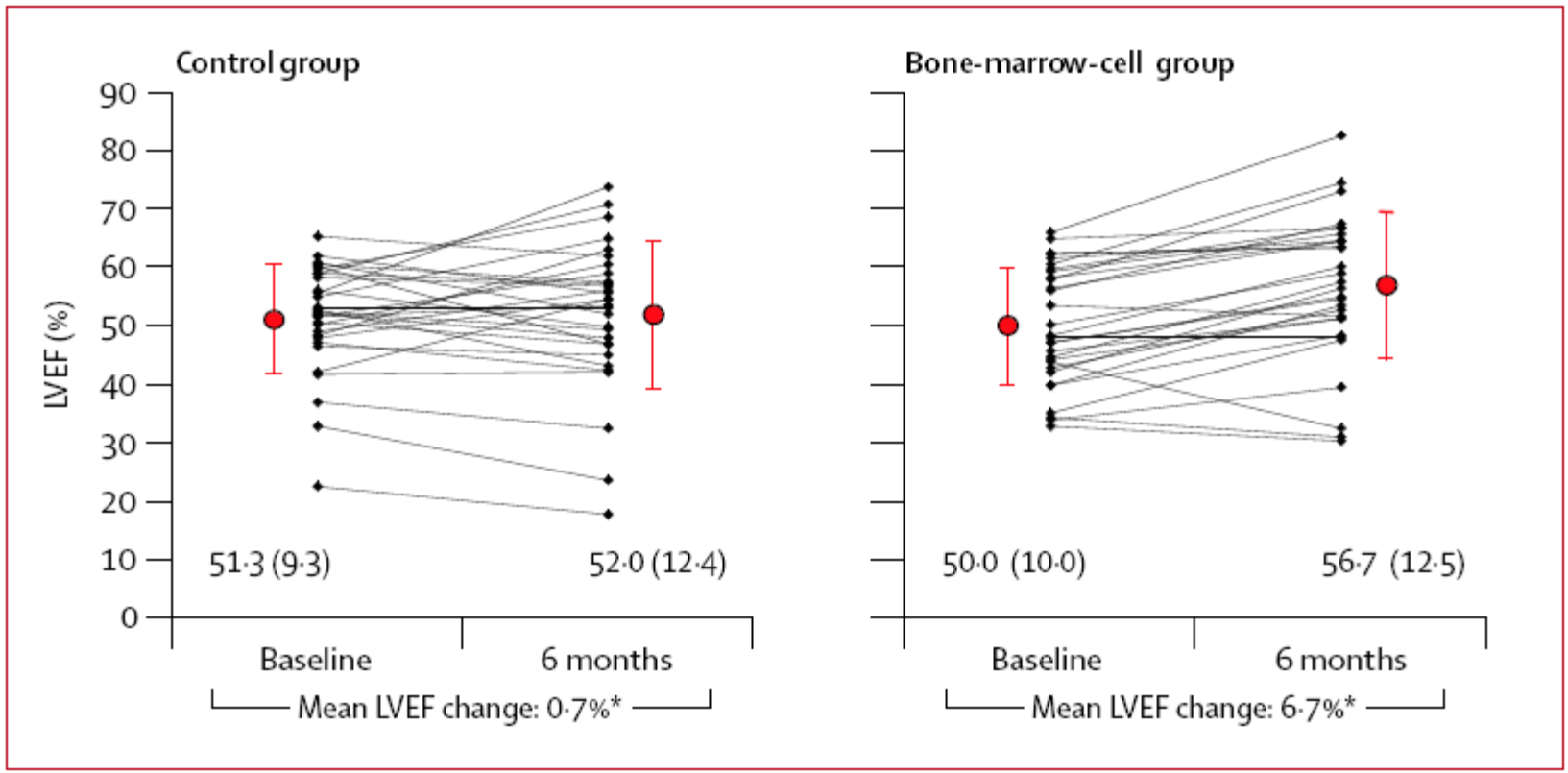
Profile of BOOST trial

Eligible patients

- Within 5 days of the onset of symptoms of a first STEMI
- Successful PCI with stent implantation in the infarct related artery
- Hypokinesia or akinesia involving more than two thirds of the left-ventricular anteroseptal, lateral, and/or inferior wall



6months F/U results of BOOST trial



Intracoronary infusion of BM cell after primary angioplasty improves LV function

TABLE 2 Comparison of Left Ventricular Hemodynamics in the Two Groups of Patients

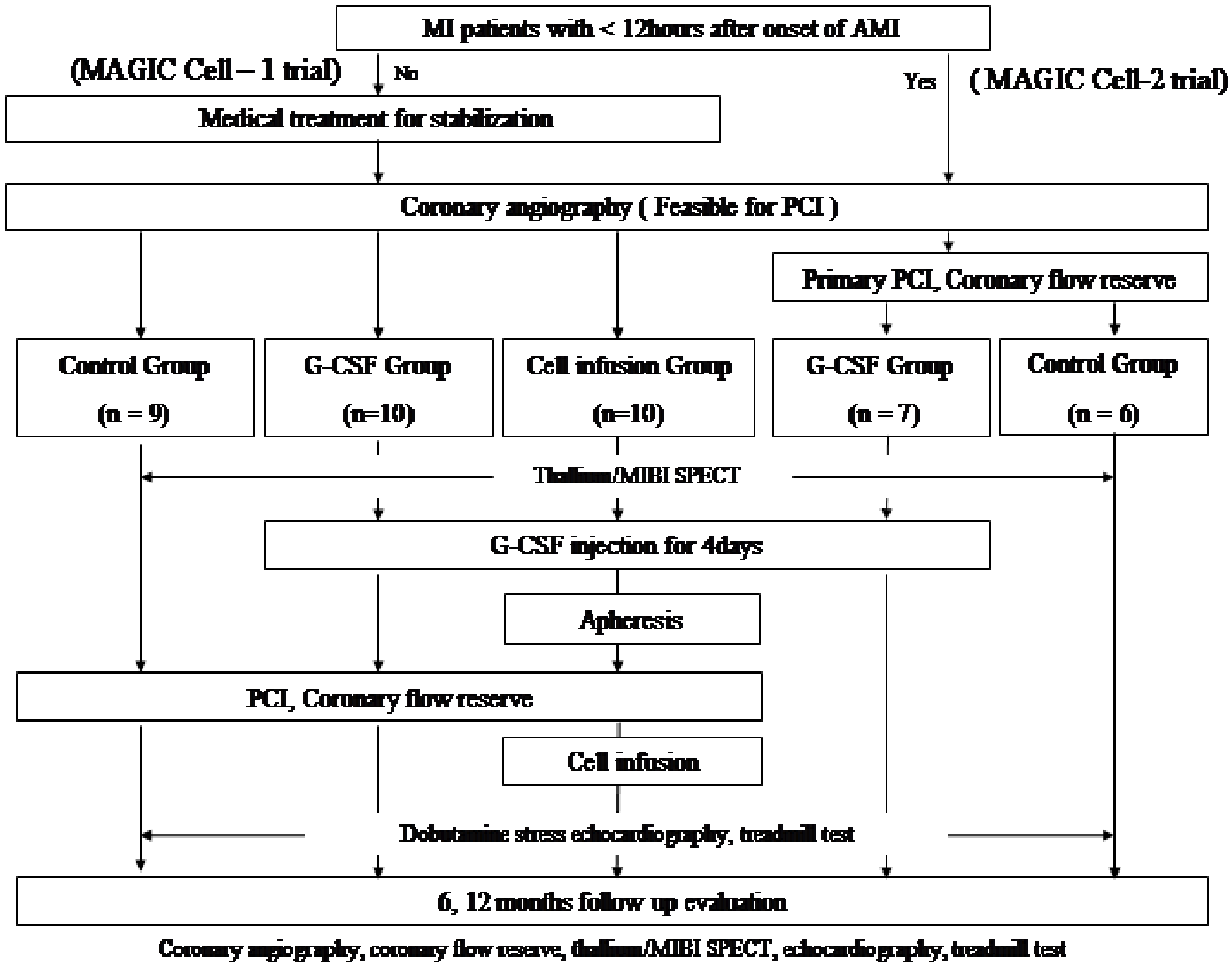
Variables	BMSC Group	Control Group	p Value
Patients (n)	34	35	0.20
Functional defect (%)			
Just before BMSC implantation	32 ± 11	33 ± 10	0.20
At 3-mo follow-up	13 ± 5	28 ± 10	0.001
Infarcted area movement velocity (cm/s)			
Just before BMSC implantation	2.17 ± 1.3	2.19 ± 1.5	0.20
At 3-mo follow-up	4.2 ± 2.5	2.7 ± 1.7	0.01
Left ventricular ejection fraction (%)			
Just before BMSC implantation	49 ± 9	48 ± 10	0.20
At 3-mo follow-up	67 ± 11	53 ± 18	0.01
At 6-mo follow-up	67 ± 3	54 ± 5	0.01

* Total 4.8-6 x 10^{10} Bone marrow cells were infused without selection/modification.

Chen S et al. AJC 2004

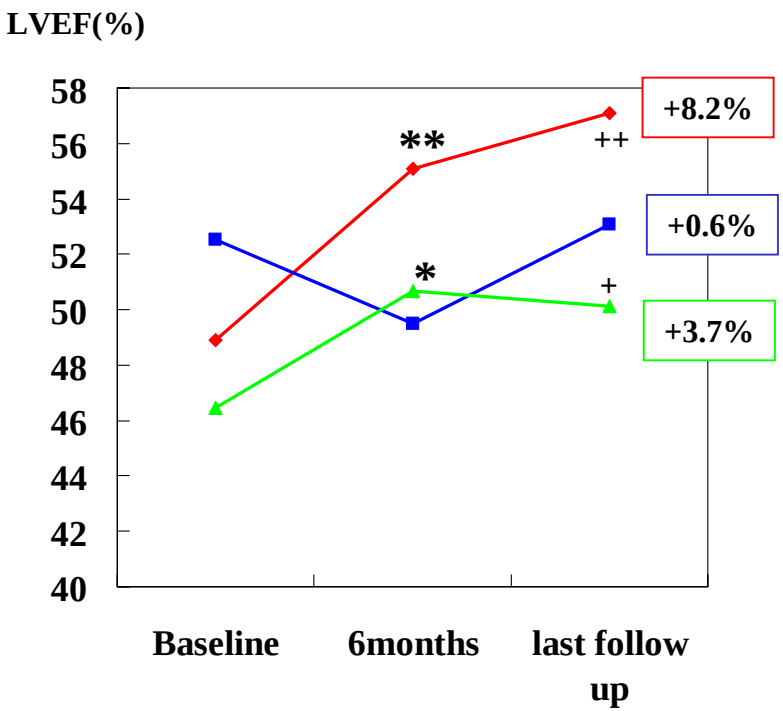
Profile of MAGIC Cell trial

This study was a randomized, controlled phase II clinical trial.

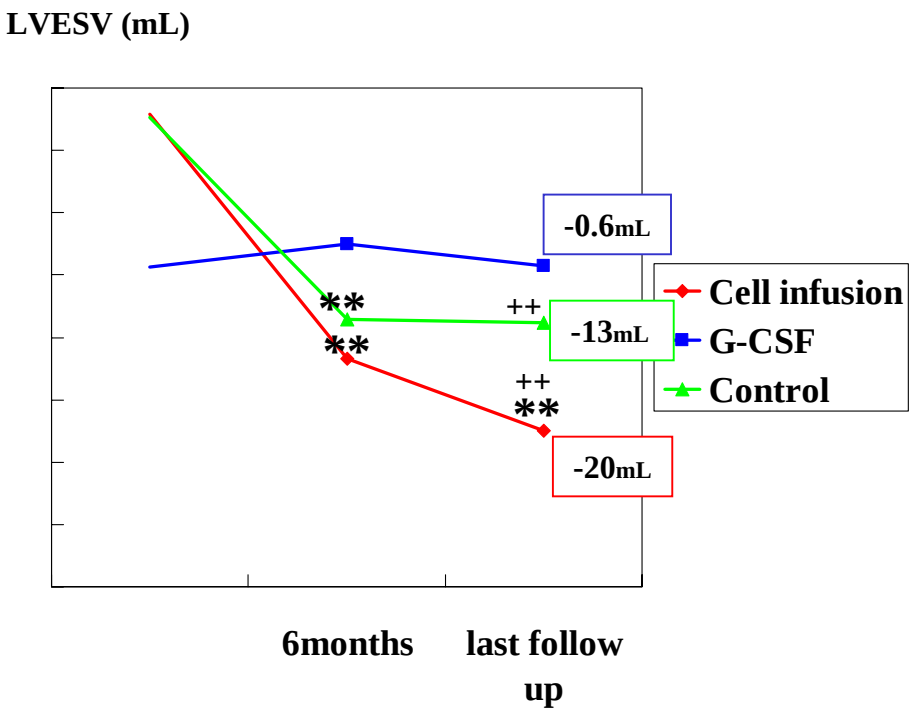


1 Year F/U Results of MAGIC Cell trial

Change of LVEF



Change of LVESV



Compared with previous exam: * : p <0.05, **: p <0.01
Compared with baseline exam: + : p <0.05, ++: p <0.01

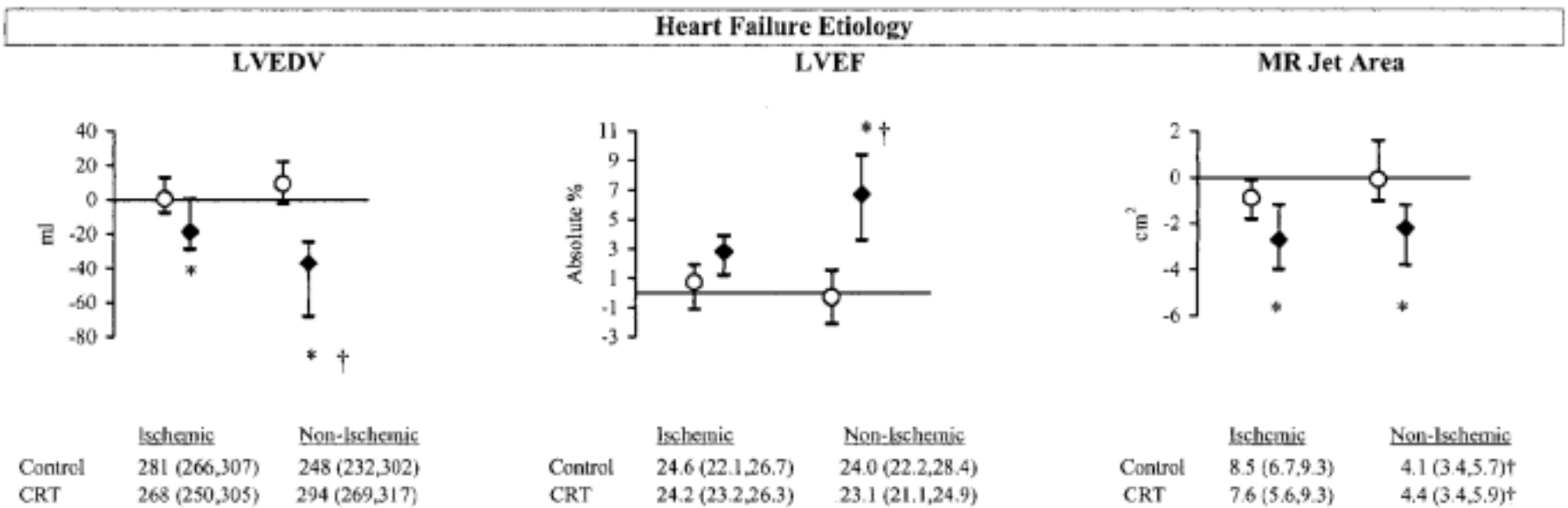
Stem cell therapy for I-CMP

- Presence of Natural Repair Mechanism
- Considerations for Cellular Cardiomyoplasty
- Current Status of Clinical Trials for MI
- Comparison of Methods for Stem Cell Therapy
  - ✓ Significance of benefits from stem cell therapy
  - ✓ Comparisons with other therapeutic modalities
    - o CRT, SVR
  - ✓ Comparisons of various stem cell therapies
- Limitation of Stem Cell therapy
- Future to go

Cardiac Resynchronization Therapy

Results from MIRACLE trial

	Control Group (n=151)			CRT Group (n=172)		
Parameter	Baseline	3 Months	6 Months	Baseline	3 Months	6 Months
LVEDV, cm^3	293.9±105.1	2.8 (−3.8, 12.3)	4.7 (−3.8, 11.1)	295.6±102.6	−22.6 (−33.3, −5.8)*	−27.2 (−37.1, −16.9)*
LVESV, cm^3	227.5 ±98.6	0.6 (−8.7, 8.7)	0.3 (−6.4, 13.3)	227.7±93.7	−21.8 (−29.7, −13.9)*	−25.6 (−37.4, −17.7)*
LVEF, %	24.3±6.8	0.6 (−0.4, 1.8)	0.4 (−0.8, 1.5)	24.5±6.8	2.3 (1.5, 3.2)*	3.6 (2.5, 5.8)*



	Ischemic	Non-Ischemic
Control	281 (266,307)	248 (232,302)
CRT	268 (250,305)	294 (269,317)

	Ischemic	Non-Ischemic
Control	24.6 (22.1,26.7)	24.0 (22.2,28.4)
CRT	24.2 (23.2,26.3)	23.1 (21.1,24.9)

	Ischemic	Non-Ischemic
Control	8.5 (6.7,9.3)	4.1 (3.4,5.7)†
CRT	7.6 (5.6,9.3)	4.4 (3.4,5.9)†

Circulation.2003

Surgical Ventricular Restoration

- The SVR with CABG/MV repair was performed in 1,198 patients between 1998 and 2003.
- Inclusion criteria:
  1. previous anterior myocardial infarction
  2. significant ventricular dilation (left ventricular end-systolic volume index [LVESVI] 60 ml/m2)
  3. a regional asynergy (non-contractile) > LV circumference of 35%.
- Thirty-day mortality after SVR was 5.3%

Table 1. LVESVI (ml/m^2) and Mitral Valve Repair

	No Mitral Repair	Mitral Repair	p Value
Preoperative	76.3	89.4	< 0.006
Postoperative	56.0	55.8	NS
Change	20.3	33.6	< 0.002

LVESVI = left ventricular end-systolic volume index.

Table 2. EF (%) and Mitral Valve Repair

	No Mitral Repair	Mitral Repair	p Value
Preoperative	31.0	25.4	< 0.0001
Postoperative	41.3	34.0	< 0.0001
Change	10.3	9.3	NS

EF = ejection fraction.

RESTORE Group . JACC 2004

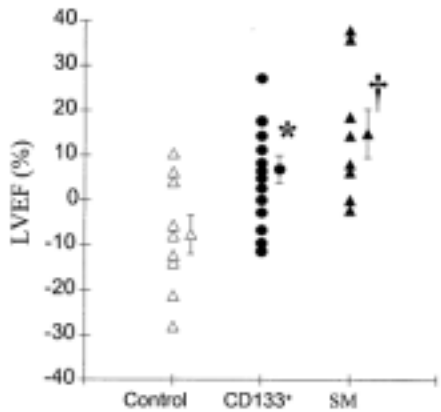
Significance of Benefits from Stem Cell Therapy

- Improvement of LVEF after stem cell therapy
  - in AMI: 6-18%
    - Mostly with intracoronary infusion and BMSC/ PBSC/ EPC
    - With preserved LV systolic function (mean LVEF: 49-57%)
    - Effects of revascularization: net gain: 5-13%
  - in OMI: 6-9% (no case control study)
    - Mostly with intramyocardial injection and SMB/ BMSC
    - With poor LV systolic function (mean LVEF: 24-36%)
    - Effects of revascularization (?): 6% (without) vs. 8-9% (with revascularization)

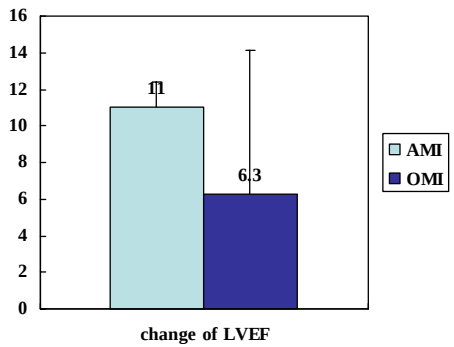
Different cell for different etiology?

- CD133+ BMSC vs. SMB in rat (post MI 10day)
  - No difference in angiogenesis
  - No CMC originated from CD133+cells

Agbulut O, et al. JACC 2004



- PBSC therapy is less effective in OMI



- Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts.

Murry et al. Nature 2004, Leora et al. Nature 2004

- SMB transplantation showed benefit in sarcoglycan deficiency (D-CMP)

Pouly et al. Circulation 2004

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- Presence of Natural Repair Mechanism
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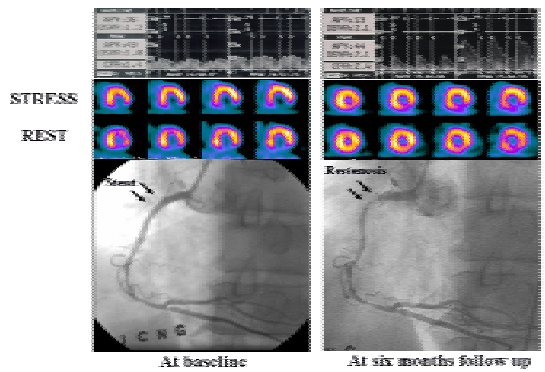
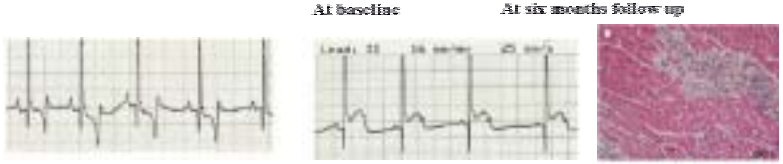
Potential Adverse Reactions

- Arrhythmia: especially SMB — Menasche, Lee et al. 2004
  - Electrical heterogeneity
  - Intrinsic arrhythmogenic potential
  - Increased nerve sprouting and sympathetic activation
  - Local tissue injury
- Restenosis



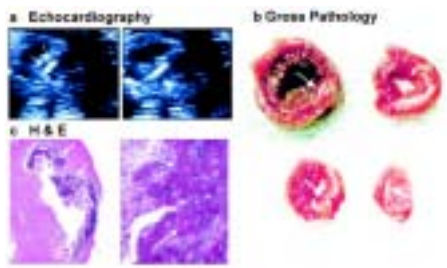
Kang et al. Lancet 2004

- Embolism



Vulliet et al. Lancet 2004

- Calcification



Yoon et al. Circulation 2004

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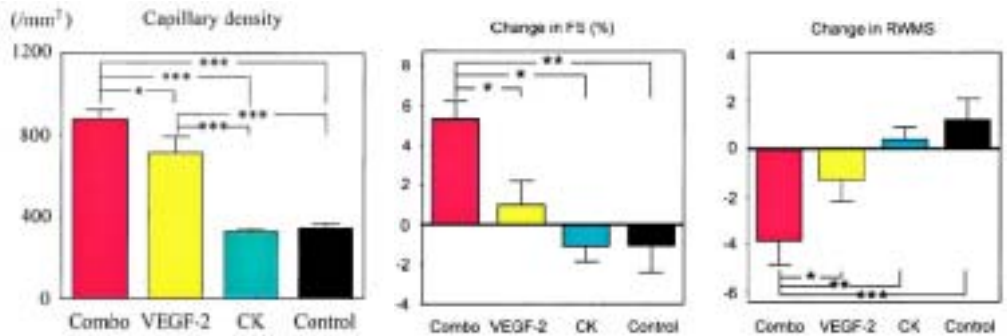
Future to go

- Combination therapy will enhance outcomes.
  - Cytokine + gene: G-CSF & SCF + VEGF-2 in MI (rat)

Kawamoto et al. Circulation 2004



  - Cell + gene:
    - MSC + Akt — Mangi et al. Nat med 2003
    - CSC + IGF-1 — Torella D, et al. Circ Res 2004
    - MSC + HGF — Duan et al. Mol Ther 2003
    - SMB + Connexin 43 — Suzuki et al.
    - SMB + VEGF …

Current standpoint

- Stem cell Therapy can be an one of established therapy for I-CMP in near future.
- Further modification of method and clarification of stem cell biology are essential.
- Combination therapy with cell and gene therapy will improve outcomes.

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- 서울대학교병원 순환기내과 전임의
- 서울대학교병원 심혈관센터, 분당서울대학교병원 심장센터
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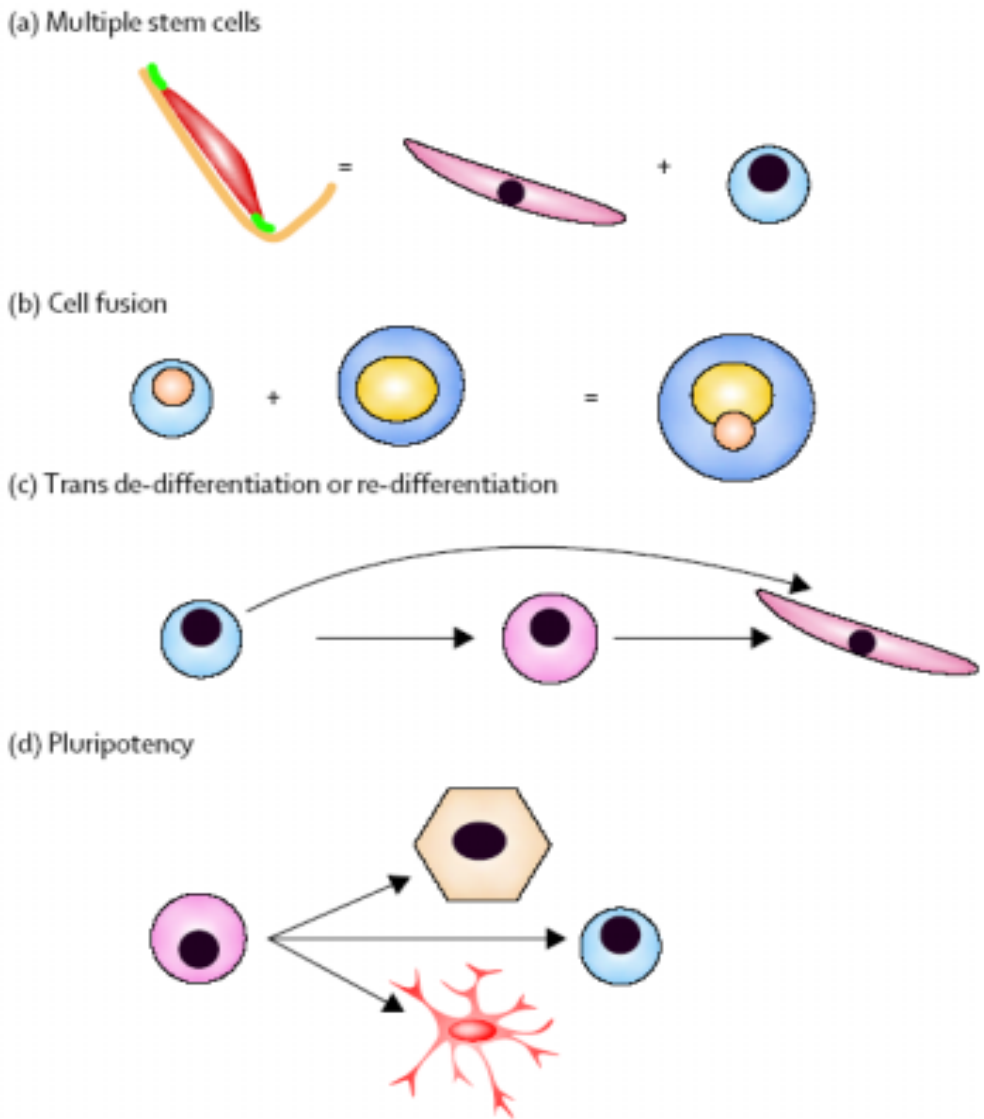
Complementary slides

- Possible explanation for plasticity



Lee M, et al. Lancet 2004