Stem cell treatment

Stem cell therapy for AMI will emerge as the standard care?

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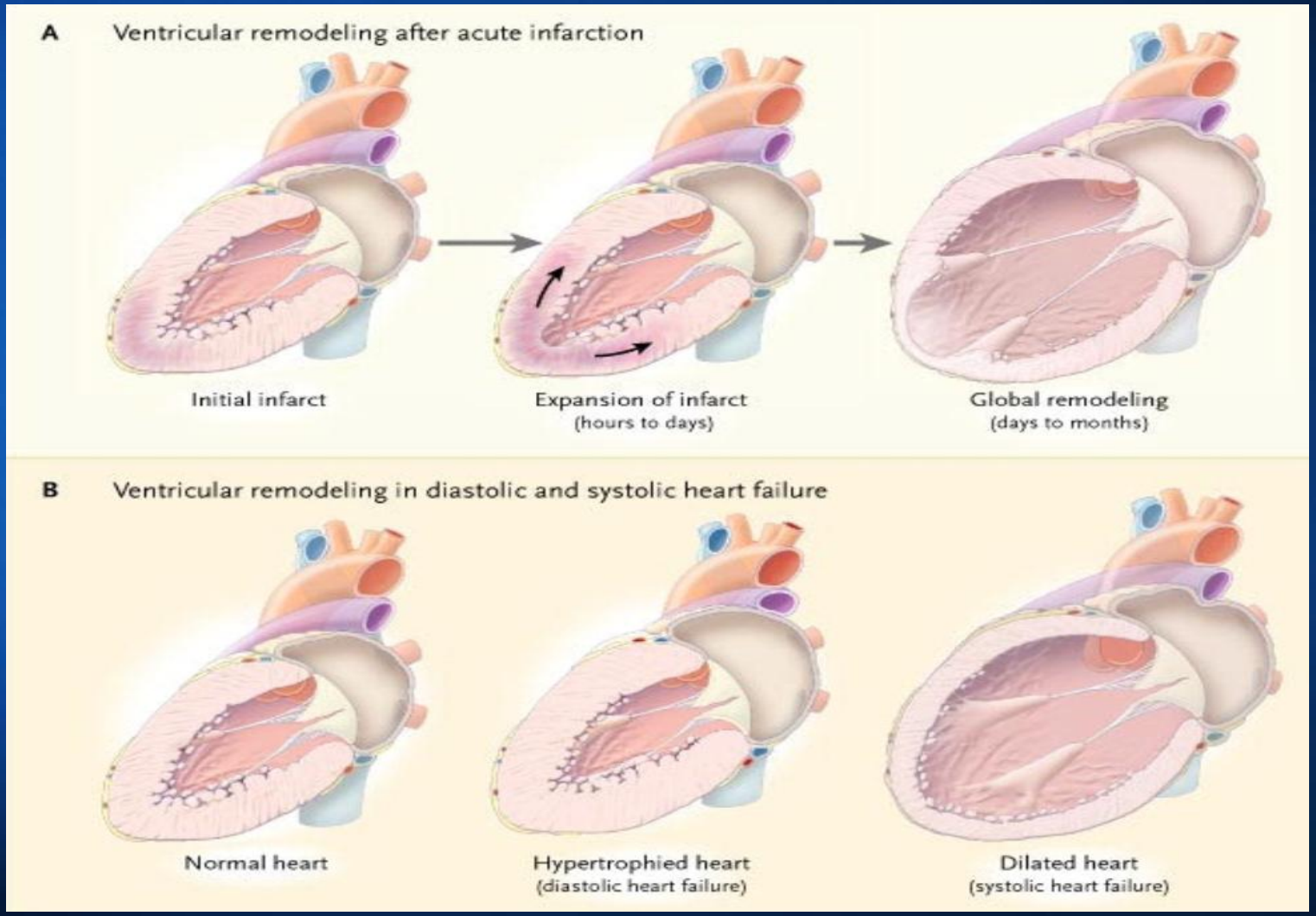
Key questions?

- Does BMC therapy work in the patient population at risk post-AMI ?
- Do potential beneficial effects persist over time ?
- Do beneficial effects translate into improved clinical outcome ?

Left Ventricular Remodelling



Jessup M, et al. N Engl J Med 2003; 348:2007-2018, 2003.

Does BMC therapy work in the patient population at risk post-AMI ?

Meta-analysis of randomized and cohort studies of progenitor cell therapy in ischemic heart disease

Study or Subcategory	N	Treatment, Mean (SD), %	N	Control Mean (SD), %	Weight, %	WMD (Random), % (95% CI)
RCTs						
Assmus et al,[14] 2006 (BMCs)	28	2.90 (3.60)	18	−1.20 (3.00)	8.09	4.10 (2.18 to 6.02)
Assmus et al,[14] 2006 (CPCs)	26	−0.40 (2.20)	18	−1.20 (3.00)	8.33	0.80 (−0.82 to 2.42)
Chen et al,[16] 2004	34	18.00 (6.71)	35	6.00 (7.91)	6.62	12.00 (8.54 to 15.46)
Erbs et al,[17] 2005	11	7.20 (11.47)	11	0.00 (8.97)	2.80	7.20 (−1.40 to 15.80)
Ge et al,[18] 2006	10	4.80 (9.56)	10	−1.90 (5.85)	3.68	6.70 (−0.25 to 13.65)
Hendrikx et al,[19] 2006	10	6.10 (8.60)	10	3.60 (9.10)	3.21	2.50 (−5.26 to 10.26)
Janssens et al,[20] 2006	33	3.40 (6.90)	34	2.20 (7.30)	6.68	1.20 (−2.20 to 4.60)
Kang et al,[21] 2006 (AMI)	25	5.10 (9.32)	25	−0.10 (12.43)	4.26	5.20 (−0.89 to 11.29)
Kang et al,[21] 2006 (OMI)	16	0.00 (12.80)	16	0.20 (10.61)	3.01	−0.20 (−8.35 to 7.95)
Lunde et al,[23] 2006	50	1.20 (7.50)	50	4.30 (7.10)	7.21	−3.10 (−5.96 to −0.24)
Meyer et al,[24] 2006	30	5.90 (8.90)	30	3.10 (9.60)	5.43	2.80 (−1.88 to 7.48)
Ruan et al,[27] 2005	9	5.96 (11.10)	11	−3.21 (7.18)	2.89	9.17 (0.77 to 17.57)
Schächinger et al,[28] 2006	95	5.50 (7.30)	92	3.00 (6.50)	8.04	2.50 (0.52 to 4.48)
Subtotal	87		82		23.21	3.83 (1.18 to 6.48)
Test for Heterogeneity: $\chi^2_5 = 4.32$ ($P = .51$), $I^2 = 0\%$						
Test for Overall Effect: $Z = 2.83$ ($P = .005$)						
Total	**499**		**477**		100	3.66 (1.93 to 5.40)
Test for Heterogeneity: $\chi^2_{19} = 64.73$ ($P < .001$), $I^2 = 70.6\%$						
Test for Overall Effect: $Z = 4.14$ ($P < .001$)						

Favors Control | Favors BMC Treatment

−10 −5 0 5 10

WMD Random (95% CI)

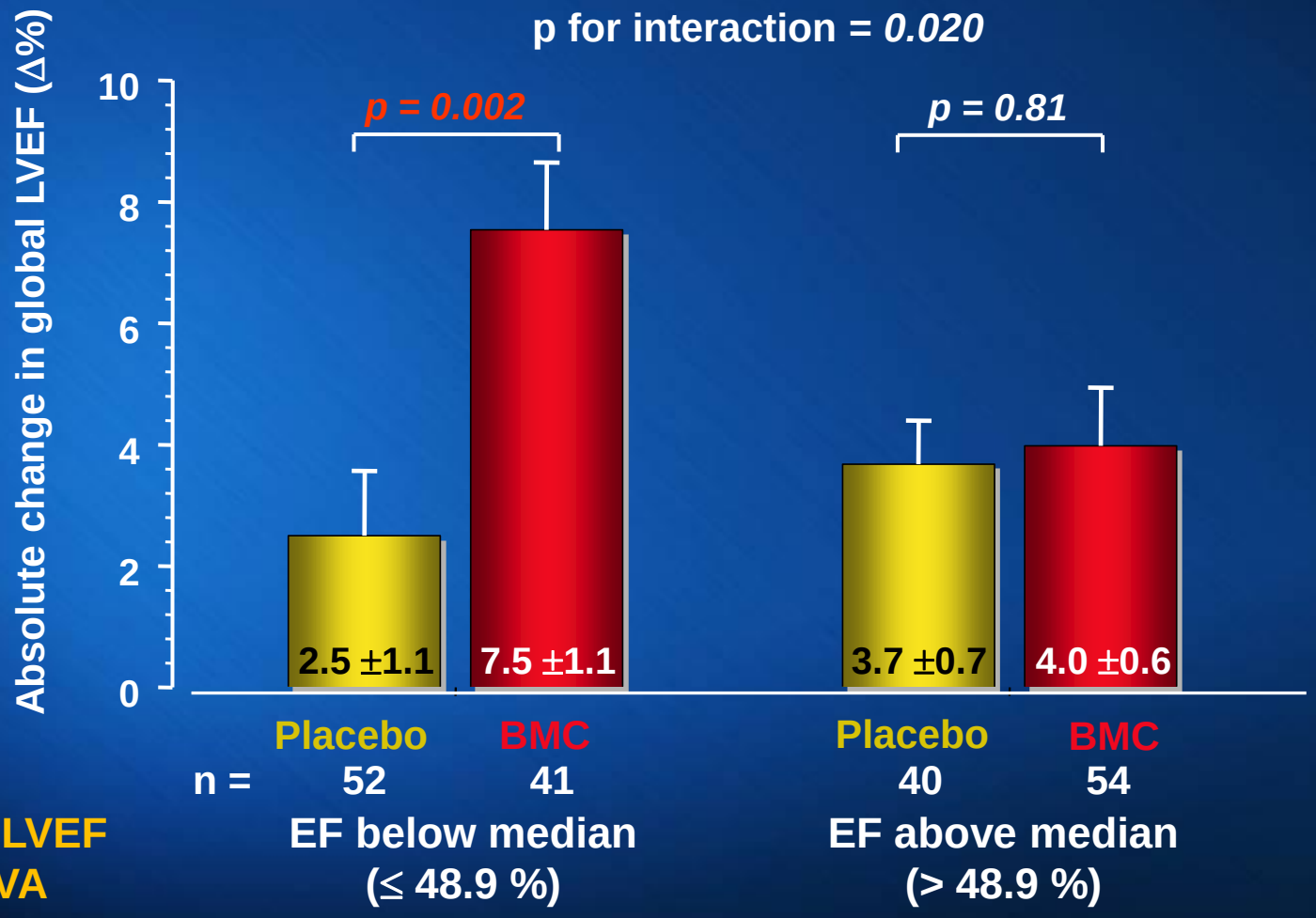
N = 976

overall treatment effect: + 3.7 percentage points increase in EF

p < 0.001

Abdel-Latif, Arch Intern Med 2007; 167:989-997

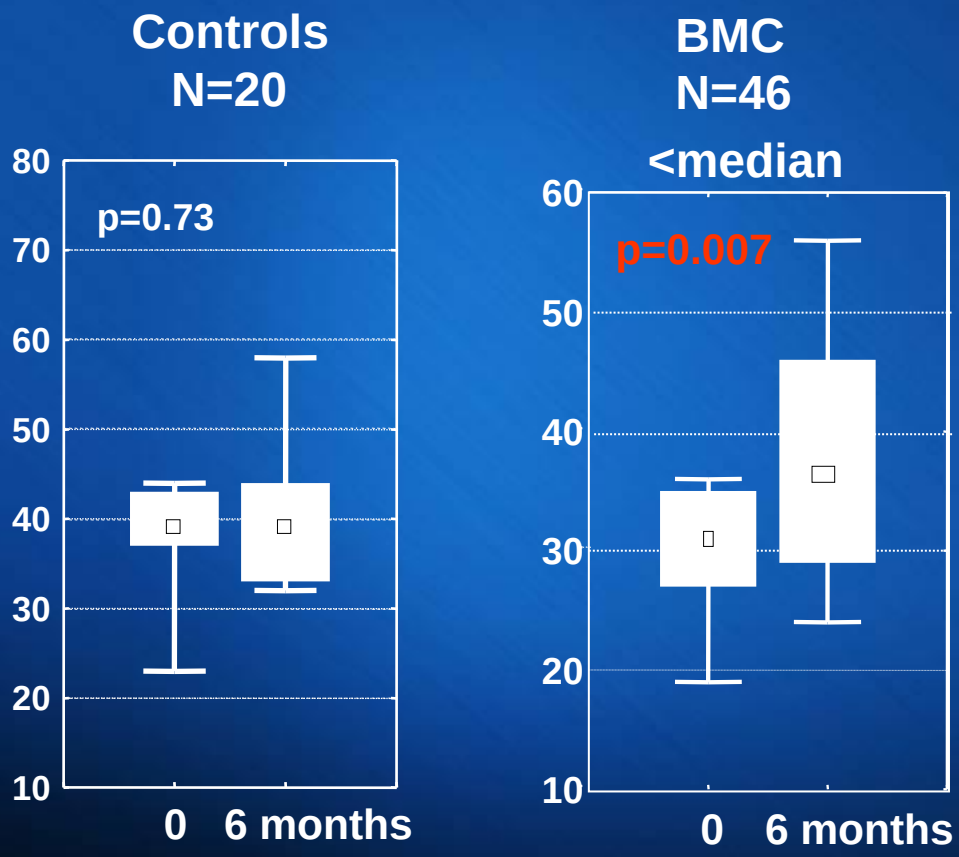
Enhanced contractile recovery by BMC is confined to patients with failed initial recovery



Schächinger et al. N Engl J Med 2006

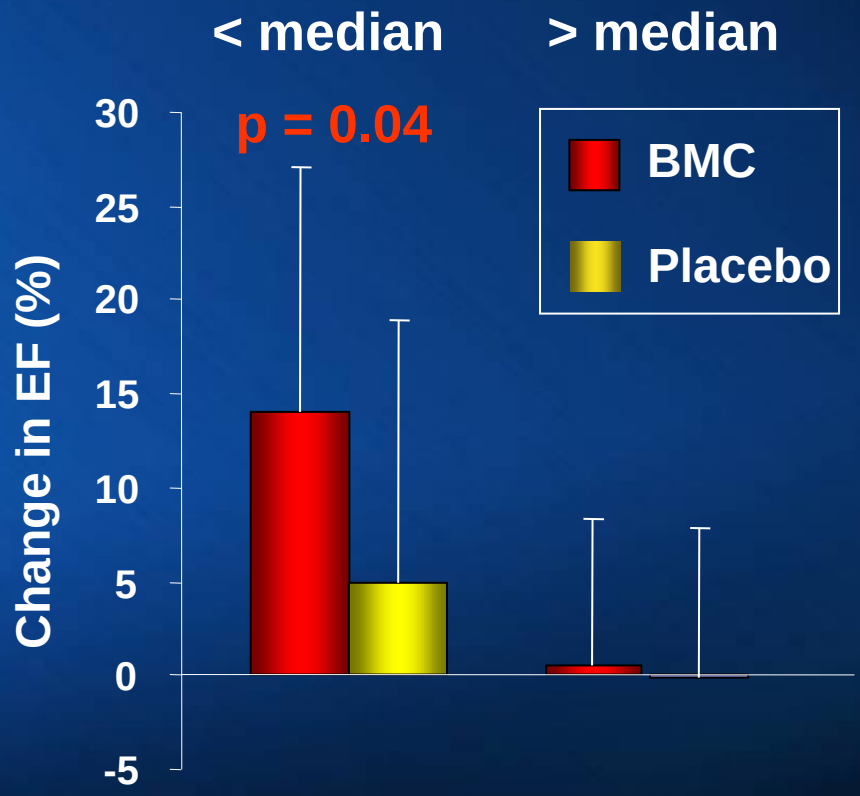
Enhanced contractile recovery by BMC in patients with failed initial recovery – results of recent controlled trials

REGENT trial



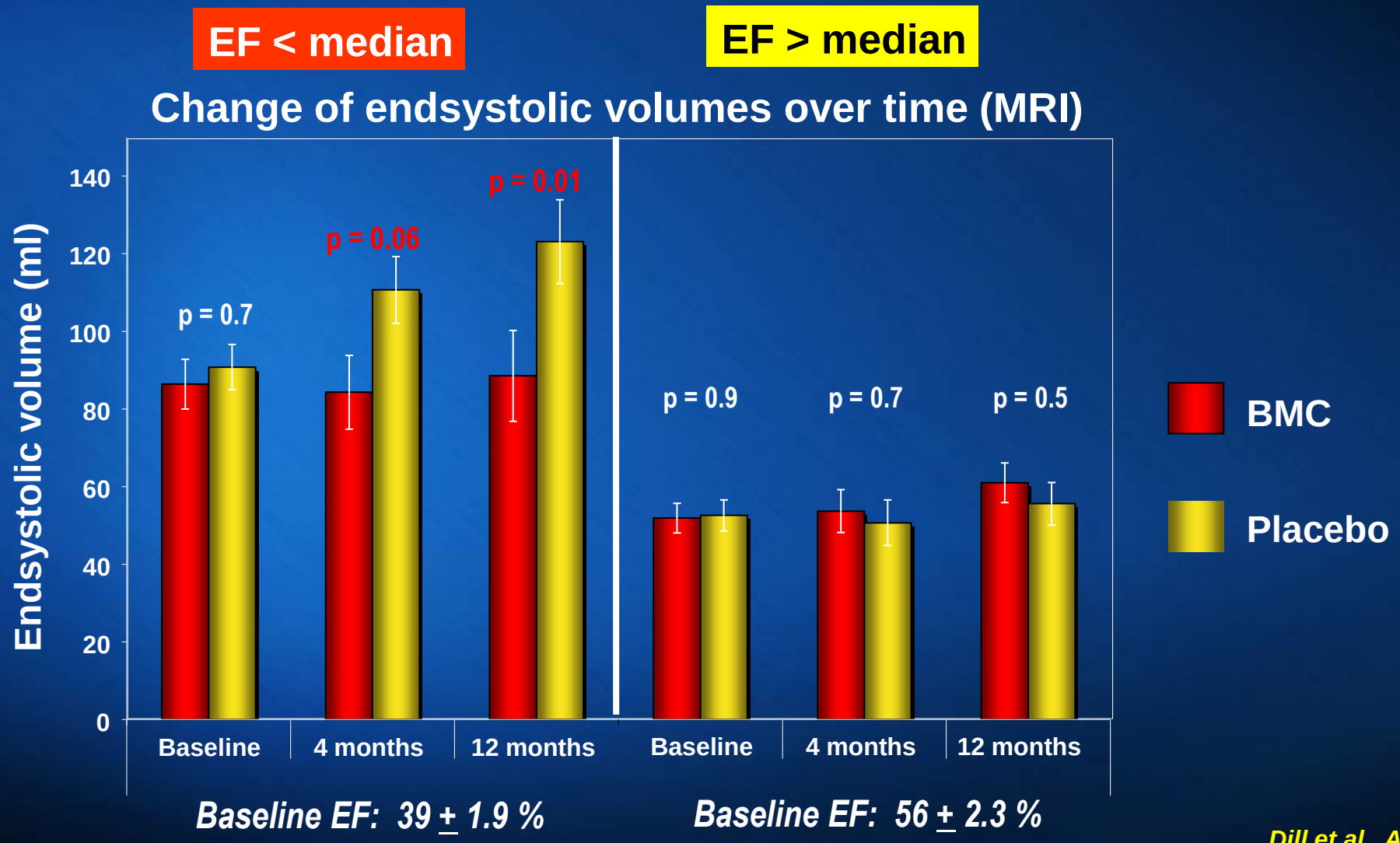
Courtesy of M Tendera, European Heart Journal, 2009

FINNCELL trial



Courtesy of H. Huikuri, European Heart Journal, 2008

Adverse remodeling is confined to patients with failed initial recovery of EF and abrogated by BMC therapy



Dill et al., AHJ 2009

Isolated CABG Combined with Bone Marrow Mononuclear Cells Delivered Through a Graft Vessel for Pts with Previous MI and Chronic Heart Failure

Single-center, placebo-controlled, randomized trial.

6-Month Follow-up	Stem Cell Group (n = 31)	Placebo Group (n = 29)	*P* Value
Change in LVEF	10.62%	5.69%	0.029
6-Min Walking Test, m	500	470	0.009

There were no deaths or MIs in either group during follow-up, and no arrhythmias occurred in the postoperative period.

Conclusion: Patients with a previous MI and chronic heart failure could poten tially benefit from isolated CABG combined with bone marrow stem cells deli vered through a graft vessel.

Hu S, et al. *J Am Coll Cardiol*. 2011;57:2409-2415.

Do potential effects persist ?

European Heart Journal (2009) **30**, 1986–1994
doi:10.1093/eurheartj/ehp220

CLINICAL RESEARCH
Coronary heart disease

Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up‡

Feng Cao[1†*], Dongdong Sun[1†], Chengxiang Li[1†], Kazim Narsinh[2], Li Zhao[1], Xue Li[1], Xuyang Feng[1], Jun Zhang[3], Yunyan Duan[3], Jing Wang[4], Dingjing Liu[4], and Haichang Wang[1*]

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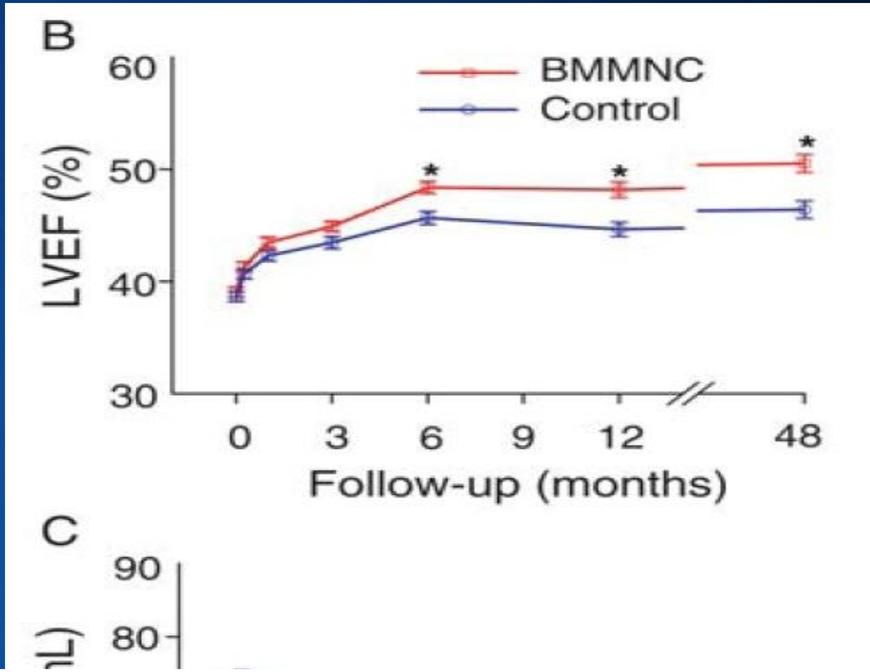
Aims To evaluate the safety profile and efficacy of bone marrow mononuclear cells (BMMNC) transplantation for ST-segment elevation myocardial infarction (STEMI) by assessing patients and their left ventricular function at up to 4 years follow-up.

Methods and results Eighty-six patients with STEMI who had successfully undergone percutaneous coronary intervention (PCI) were randomized to receive intracoronary injection of BMMNC ($n = 41$) or saline ($n = 45$). Left ventricular ejection fraction, as evaluated by UCG, was markedly improved at 6 months (0.484 ± 0.5 vs. 0.457 ± 0.6, $P = 0.001$), 1 year (0.482 ± 0.7 vs. 0.446 ± 0.6, $P < 0.001$), and 4 years …



Conclusion:

- Intracoronary delivery of autologous BMMNC is safe and feasible for STEMI patients whohave undergone PCI
- It can lead to long-term improvement in myocardial function.

‡This work was performed in Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, 710032, China

Feng Cao, et al. Eur Heart J (2009) 30, 1986–1994

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

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See page 642 for the editorial comment on this article (doi:10.1093/eurheartj/hfq105)

Aims Despite accumulated evidence that intracoronary bone marrow cell (BMC) therapy may be beneficial in acute myocardial infarction, there are only limited data available on the effectiveness of BMC's in chronic heart failure. The aim of this study was to quantitatively investigate ventricular haemodynamics, geometry, and contractility as well as the long-term clinical outcome of BMC treated patients with reduced left ventricular ejection fraction (LVEF) due to chronic ischaemic cardiomyopathy.

Methods and results Patients with chronic heart failure ($n = 391$ LVEF ≤35%) due to ischaemic cardiomyopathy were enrolled in the present study. Of these, 191 patients (mean NYHA class 3.22) underwent intracoronary BMC therapy. The control group (mean NYHA class 3.06) consisted of 200 patients with comparable LVEF. Assessments of haemodynamics at rest and exercise, quantitative ventriculography, spiroergometry, 24 h Holter ECG, late potentials, and heart rate variability were analysed. Over 3 months to 5 years of follow-up [illegible]

ventricular geometry, and contractility. (ii) the long-term effects [illegible]

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STAR-heart Study:

391 patients with chronic HF (EF ≤35%) due to ischemic cardiomyopathy.

Stem cell group:191 patients
Control group: 200 patients

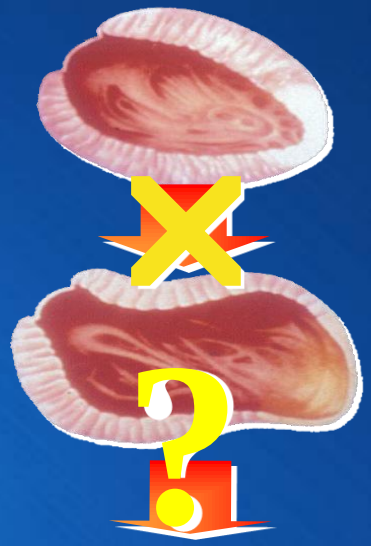
Conclusion:

- **Intracoronary BMC therapy improves ventricular performance, QOL 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.**

Feng Cao, et al. Eur Heart J (2010) 12, 721–729

Do beneficial effects of BMC therapy on adverse remodeling translate into clinical benefit ?

acute
myocardial infarction



Left Ventricular Remodeling

- Ejection fraction ⇩
- End-systolic volume ⇧

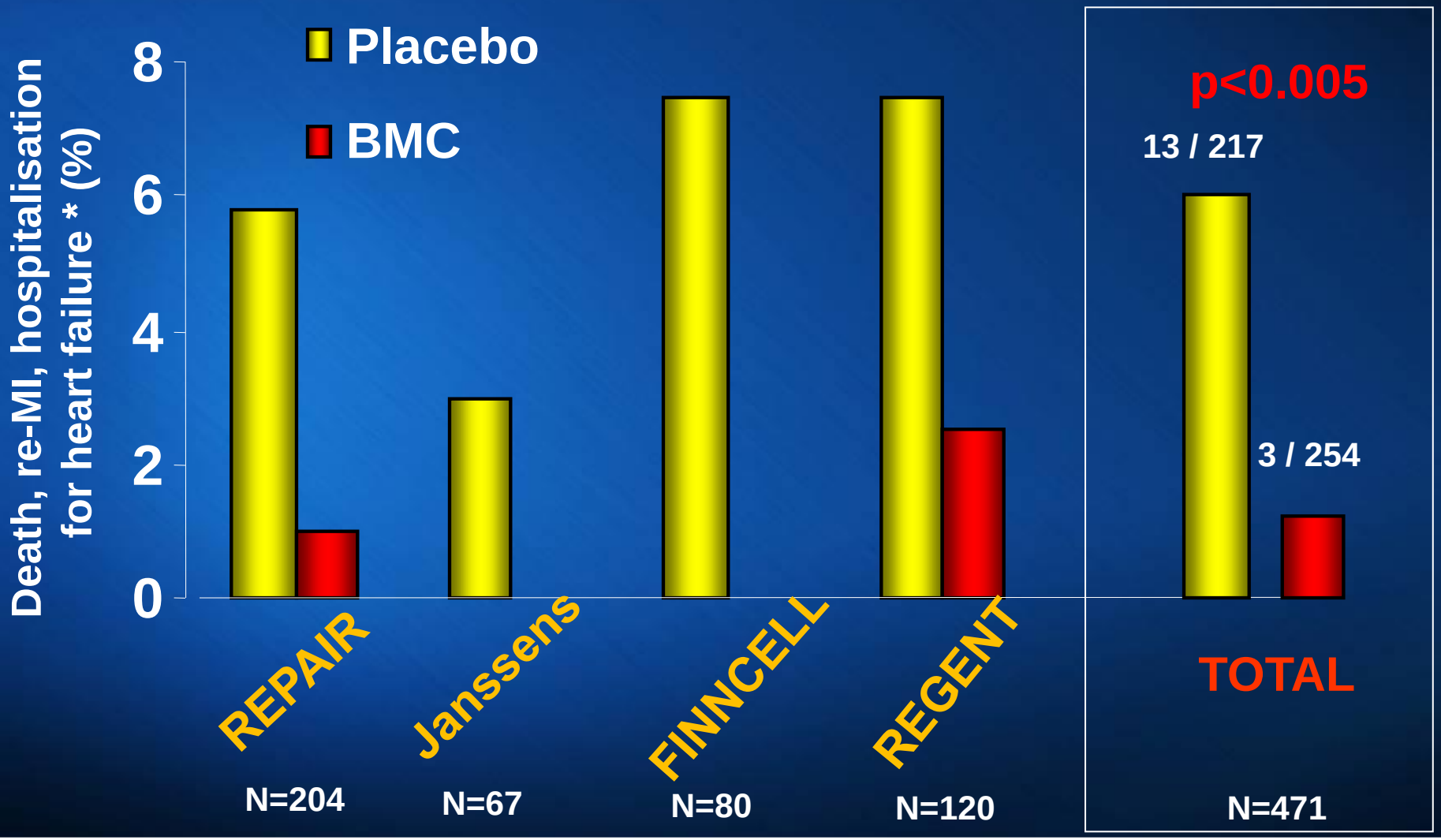
Cardiovascular Events

- **Mortality ⇧**
- **Ischemic events ⇧**
- **Rehospitalization for heart failure ⇧**

Therapies preventing adverse remodelling… → ***… reduce adverse cardio vascular events***

ACEI , ARB, ß-Blocker, Aldosteron-Ant.

Death, Re-MI, Heart Failure at 4-6 Months in randomized, (placebo)-controlled BMC trials



BMC therapy is associated with improved clinical outcome at 2 years

# exposed to risk							
	Placebo	103	93	90	86	86	
	BMC	101	99	98	97	95	

Assmus B, et al. Cir Heart Fail.2010;3;89-96.

Intramyocardial, Autologous CD34+ Cell Therapy for Refractory Angina

Multicenter, randomized trial of 167 pts assigned to placebo or low- or high-dose intramyocardial injections.

1-Year Follow-up	Low-Dose	Placebo	*P* Value
Angina Frequency, episodes per week	6.3 ± 1.2	11.0 ± 1.2	0.035
Exercise Tolerance Test Improvement, seconds	140 ± 171	58 ± 146	0.017

Differences between the high-dose and placebo groups were not significant. Safety endpoints were equivalent between all groups.

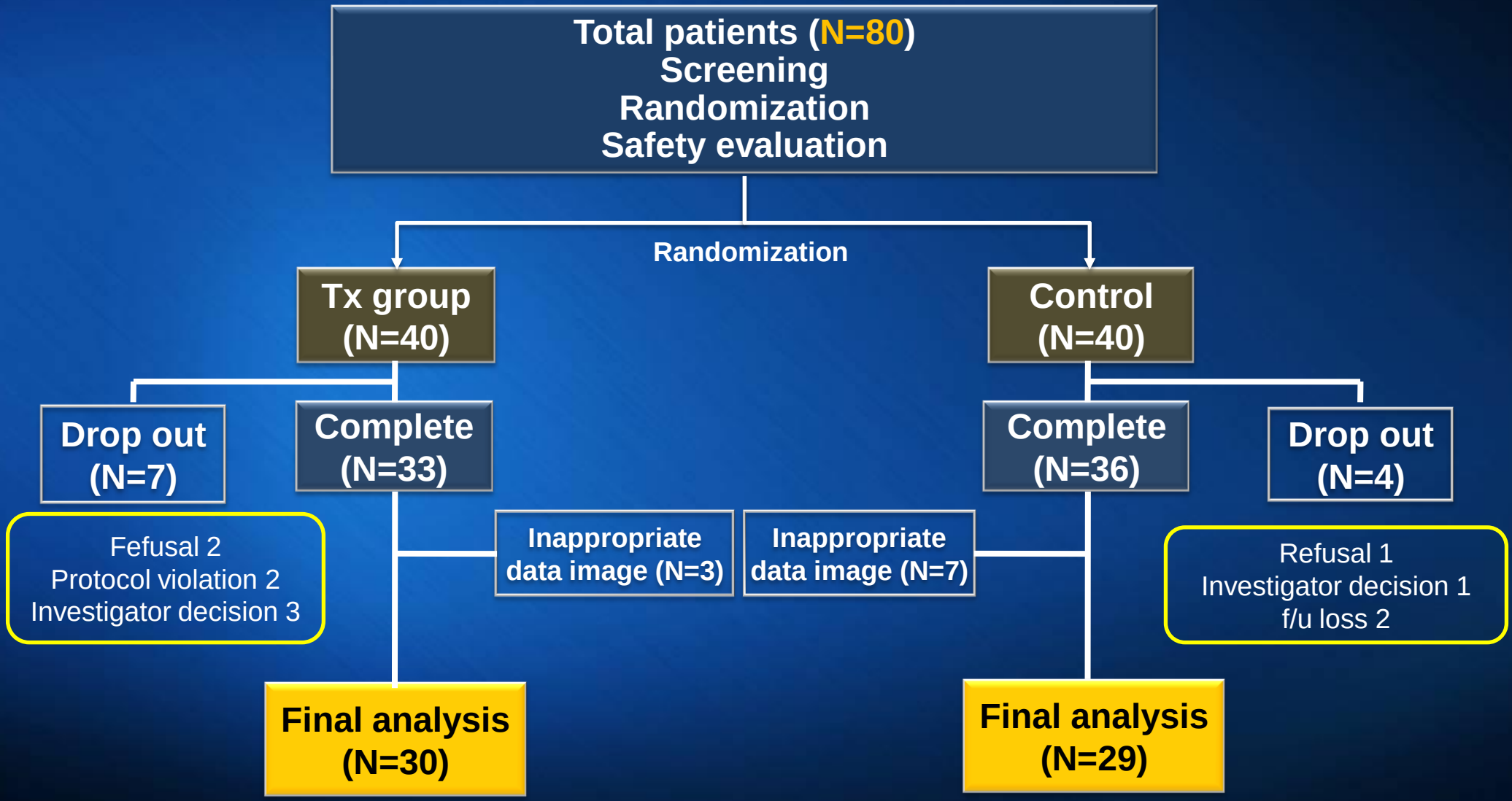
Conclusion: Patients with refractory angina who received intramyocardial injections of autologous CD34+ cells experienced significant improvements in angina frequency and exercise tolerance.

Losordo DW, et al. Circ Res. 2011;109:428-436.

A Randomized, Open labeled, multicenter trial for Safety and Efficacy of intracoronary adult human mesenchymal STEM cells after AMI (ROSE-STEMMI)

- Clinical trials in korea
- Approved by KFDA and IRB submission
- Collaborate with FCB-Phamicell Co., Ltd.
- Randomized, open-labeled, multicenter trials (4 different university hospital)
- First human trial using MSC for AMI in Korea
- Started in March, 2007
- Ended in September, 2010

Total enrolled status



Endpoints

Primary endpoint:

→Access safety profile between therapy and the control group

→Change in global LVEF by cardiac SPECT at 6 mo. vs. BL between therapy groups and the control group

Secondary endpoints:

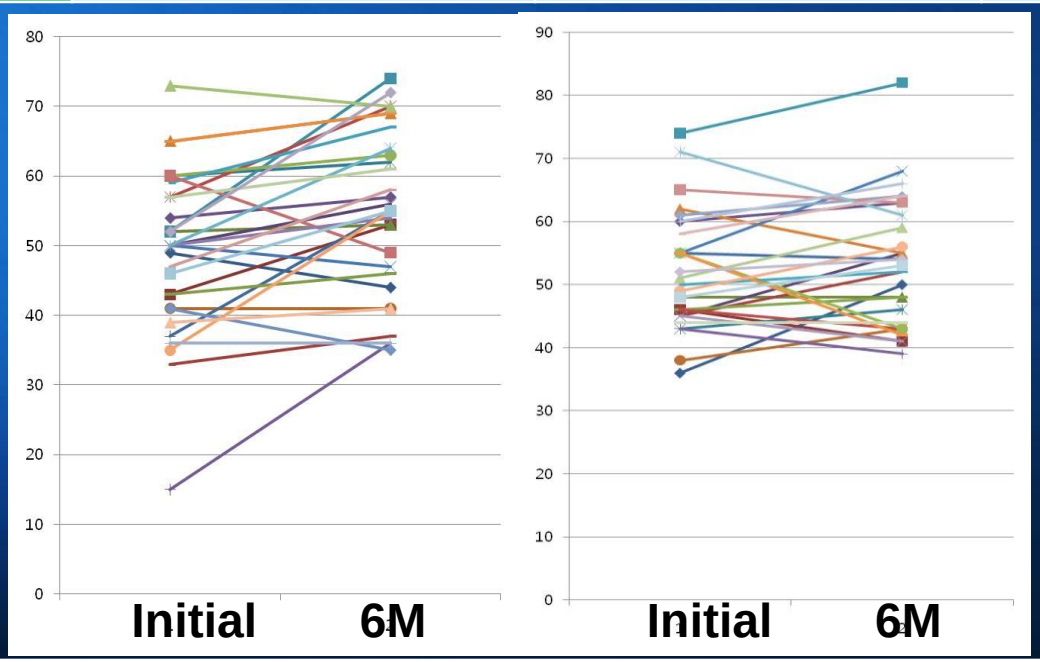
→ Change in global LVEF by Echo (3D, Simpson's)

→ Change in global LVEF by cardiac MRI (sub group)

→ MACE (death, MI, coronary revascularization, stroke)

Primary endpoint

	Treatment N=30	Control N=29	P value
EF (SPECT)			
initial	49.0 ± 11.7	52.2 ± 9.1	0.256
6 M	55.0 ± 11.8	53.9 ± 10.0	0.718
EF difference	5.9 ± 8.5	1.8 ± 6.9	0.043



Secondary endpoint (EF)

	Treatment N=30	Control N=29	P value
EF (SPECT)			
initial	49.0 ± 11.7	52.2 ± 9.1	0.256
6 M	55.0 ± 11.8	53.9 ± 10.0	0.718
EF (Simpson)			
initial	48.1 ± 8.0	51.0 ± 9.0	0.200
6 M	50.0 ± 8.4	50.5 ± 9.2	0.830
EF (MRI)	**N=10**	**N=7**	
initial	46.1 ± 15.2	54.9 ± 9.6	0.197
6 M	51.3 ± 13.6	54.6 ± 10.3	0.591
EF difference			
SPECT	5.9 ± 8.5	1.8 ± 6.8	**0.043**
Simpson	1.9 ± 2.7	-0.5 ± 1.8	**<0.001**
MRI	5.2 ± 7.6	-0.3 ± 0.9	**0.049**

6 months clinical follow up

Per patient analysis	MSC n = 23	Control n = 20
Death (n)	0	0
- Cardiac (n) (AMI, myocard. rupture, sudden death, heart failure)	0	0
- Cardiovascular (n) (stroke)	0	0
- Non-cardiovascular (n) (cancer, suicide)	0	0
Myocardial reinfarction (n)	0	0
Rehospitalization for heart failure (n)	0	0
Revascularization (n)	0	0
- Target vessel revascularization (n)	0	0
- Stent thrombosis (n)	0	0
- Non-target revascularization (n)	0	0
Ventricular arrhythmia or syncope (n)	0	0
Stroke (n)	0	0
other (n) 0	0	0
Combined		
Death, MI	0	0
Death, MI, Rehosp. for heart failure (n)	0	0
Death, MI, Revascularization (n)	0	0

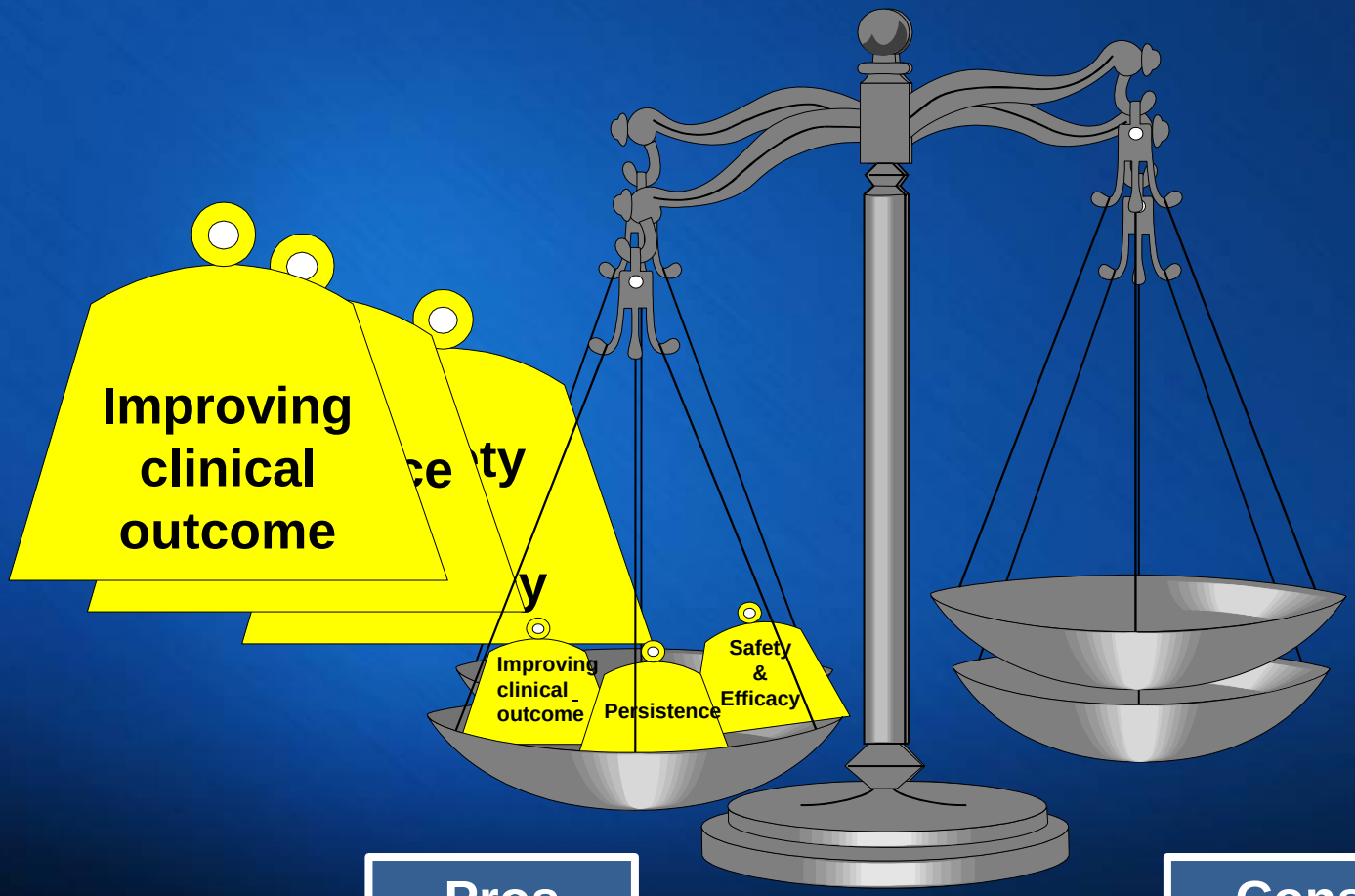
A Randomized, Open labeled, multicenter trial for Safety and Efficacy of intracoronary adult human mesenchymal STEM cells after AMI (ROSE-STEMMI)

Conclusion:

1. Intracoronary injection of autologous BM-derived hMSCs is safe and feasible in patients with STEMI.
2. In this trial, autologous BM-derived hMSCs provides temporal efficacy in post-infaction patients.

Conclusion

Stem cell therapy for AMI can be considered as the standard care



Thank you for your attention