

Clinical aspects for cell-based therapies for cardiac repair

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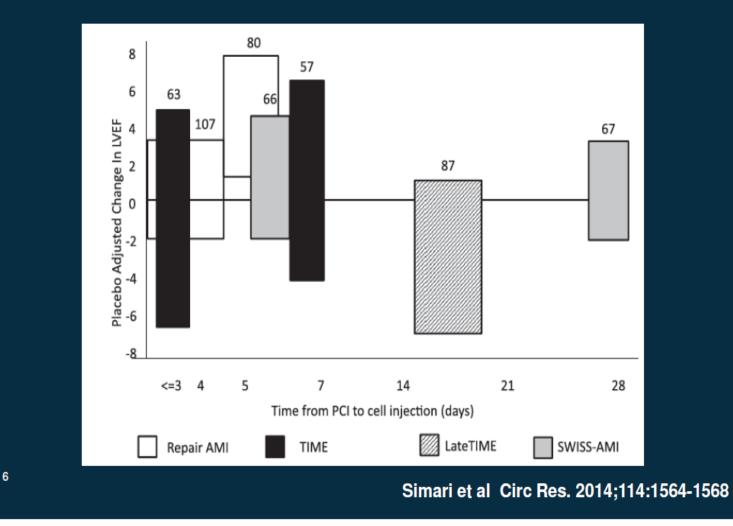
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Efficacy of Stem cell applications? What we learned from clinical trials today!

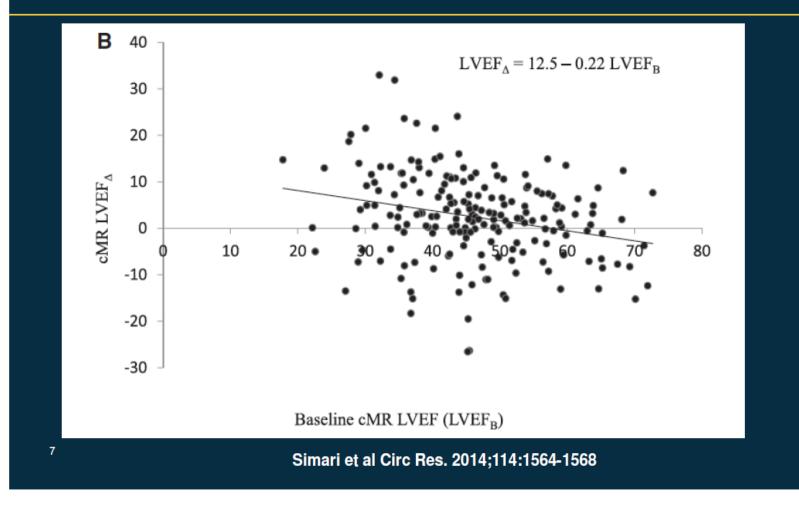
- Not clear when, what, how and how much.
- Much debate on efficacy and reliability of the data reported.
- No standardization of products and assessments in vitro and in vivo.



Timing of BMC transplantation



Δ LVEF vs Baseline LVEF



Recommendations on imaging modalities in cardiac repair:

Any method chosen to estimate LVEF must be used both for baseline as well as follow up

Any method chosen for a trial should be the one used on all patients enrolled

Change in infarct size should be evaluated by CT or MR.

256+ CT will probably be the modality of choice in the future but CMR is currently the gold standard

Stem Cells vs no Stem cells – LVESV <12 mo

Study or subgroup	BMSC		No BMSC		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I measured by MRI)						
Kang 2006	25	-5.4 (14.79)	25	6.5 (24.49)	· · · ·	2.2 %	-11.90 [-23.11, -0.69]
Lunde 2006	45	-5 (29.73)	45	-9 (25.87)		21%	4.00 [-7.51, 15.51]
Quyyumi HD 2011	2	2.7 (13.3)	10	-1.84 (17.1)		0.7 %	4.54 [-16.72, 25.80]
Quyyumi LD 2011	5	14.4 (24.6)	10	-1.84 (17.1)		0.5 %	16.24 [-7.79, 40.27]
Quyyumi MD 2011	4	-9.9 (18.1)	10	-1.84 (17.1)		0.7 %	-8.06 [-28.72, 12.60]
Schachinger 2006	27	0.4 (23.4)	27	9.1 (22.9)		1.8 %	-8.70 [-21.05, 3.65]
Tendera S 2009	51	3 (27.07)	20	-1.6 (10.31)		3.2 %	4.60 [-4.10, 13.30]
Tendera U 2009	46	-2 (14.55)	20	-1.6 (10.31)	_	5.2 %	-0.40 [-6.57, 5.77]
Subtotal (95% CI)	205		167	<	-	16.4 %	-0.95 [-6.05, 4.15]
Heterogeneity: $Tau^2 = 15.6$	52; Chi ² =	10.15, df = 7 (P	= 0.18); l ² = 3	1%			
Test for overall effect: Z =	0.37 (P =	0.71)					
2 measured by left ventricu	lar angiog	raphy					
Huikuri 2008	36	-10 (30.3)	36	-1.2 (11.5)		2.4 %	-8.80 [-19.39, 1.79]
Schachinger 2006	95	-0.6 (19)	92	5.6 (22)		5.5 %	-6.20 [-12.10, -0.30]
Yao DD 2009	15	-4.9 (1.53)	12	-2.5 (2.41)	-	12.4 %	-2.40 [-3.97, -0.83]
Yao SD 2009	12	-3.5 (2.17)	12	-2.5 (2.41)	+	11.9 %	-1.00 [-2.83, 0.83]
Subtotal (95% CI)	158		152		•	32.2 %	-2.33 [-4.17, -0.49]
Heterogeneity: $Tau^2 = 1.25$	$hi^2 = 4$	4.91. df = 3 (P =	0.18): I ² =39%				
Test for overall effect: Z =	2.48 (P =	0.013)					
3 measured by SPECT							
Cao 2009	41	-13.47 (4.47)	45	-9.85 (4.16)	-	11.9 %	-3.62 [-5.45, -1.79]
Meluzin HD 2008	20	-5 (13.42)	20	9 (15.65)		3.1 %	-14.00 [-23.04, -4.96]
Meluzin LD 2008	20	I (13.42)	20	9 (15.65)		3.1 %	-8.00 [-17.04, 1.04]
Piepoli 2010	17	-2.4 (12.58)	15	1.8 (15.49)		27%	-4.20 [-14.06, 5.66]
Plewka 2009	26	5 (34.3)	10	3.4 (28)		0.6 %	1.60 [-20.19, 23.39]
btotal (95% CI) 12							

Stem Cells vs no Stem cells – LVESV >12 mo

Study or subgroup	BMSC		Control		Difference	Weight	Difference	
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI	
I measured by MRI								
Lunde 2006	45	2 (32.41)	45	-3 (29.4)		3.6 %	5.00 [-7.78, 17.78]	
Schachinger 2006	26	23.9 (32.6)	33	32.3 (28.66)	· · · · · ·	2.5 %	-8.40 [-24.29, 7.49]	
Zhukova 2009	8	-18 (25.89)	2	3.3 (15.69)	+	0.9 %	-21.30 [-49.49, 4.89]	_
Subtotal (95% CI)	79		80	<		7.0 %	-4.61 [-18.12, 8.90]	>
Heterogeneity: $Tau^2 = 63$	2.35; Chi ² =	3.56, df = 2 (P =	= 0.17); 1 ² = 4	4%		10 T		
Test for overall effect: Z	= 0.67 (P =	0.50)						
2 measured by left ventri	cular angiog	raphy						
Yao DD 2009	15	-8.8 (1.65)	12	-4.5 (2.3)	-	15.8 %	-4.30 [-5.85, -2.75]	
Yao SD 2009	12	-6.1 (2.04)	12	-4.5 (2.3)	-	15.6 %	-1.60 [-3.34, 0.14]	
Subtotal (95% CI)			24		+	31.5 %	-2.98 [-5.63, -0.34]	
Heterogeneity: $Tau^2 = 2$.			0.02); 12 =81	%				
Test for overall effect: Z	= 2.21 (P =	0.027)						
3 measured by SPECT		14.04 (4.70)	45	0.05 (5.00)	-	15.0.00	0.015 1012 5001	
Cao 2009	41	-16.06 (4.72)	45	-8.05 (5.28)	-	15.2 %	-8.01 [-10.12, -5.90]	
Meluzin HD 2008	20	-3 (11.18)	20	17 (15.65)	•	6.5 %	-20.00 [-28.43, -11.57]	
Meluzin LD 2008	20	2 (15.65)	20	17 (15.65)	· • •	5.4 %	-15.00 [-24.70, -5.30]	
Piepoli 2010	17	-12.5 (20.82)	15	-0.5 (8.52)	<u> </u>	4.6 %	-12.00 [-22.80, -1.20]	
Subtotal (95% CI)	98		100		-	31.7 %	-12.96 [-19.29, -6.64]	
Heterogeneity: Tau ² = 26	6.32; Chi ² =	9.14, df = 3 (P =	= 0.03); l ² =6	7%				
Test for overall effect Z	= 4.02 (P =	0.000059)						
4 measured by echocard	ography							
Cao 2009	41	-13.1 (5.49)	45	-4.6 (6.18)	-	14.7 %	-8.50 [-10.97, -6.03]	
Grajek 2010	27	10.2 (14.34)	12	19.1 (19.17)	· · · · ·	3.9 %	-8.90 [-21.02, 3.22]	
Lunde 2006	50	0 (21.63)	50	6 (23.02)		6.2 %	-6.00 [-14.76, 2.76]	
Piepoli 2010	17	-7.2 (17.34)	15	-1.8 (11.66)		5.1 %	-5.40 [-15.54, 4.74]	
Subtotal (95% CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z :	0; Chi ² = 0.6		122 .90); I ² =0.05	6	•	29.8 %	-8.19 [-10.46, -5.92]	
otal (95% CI)	339		326		•	100.0 %	-7.27 [-10.00, -4.53]	
eterogeneity: $Tau^2 = 11.69$		95 df - 12 /Pz/		-77%		100.0 70	-/.2/[-10:00,-1:55]	
eterogeneny: 1aur = 11.65; est for overall effect: Z = 5.2			0.00001); F	-1176				
		· ·						
est for subgroup differences	: Chi ² = 13.	01, df = 3 (P =	0.00), 14 =7	1%				



LVEF in relation to dosage - MRI

Study or	subgroup	Experimental		Control		Difference	Waght	Difference
1.0		N	Mean(SD)	N	Mean(SD)	IN/Poind,95% CI		N/Fboad,95% C
	SC ≤1 x 10	(B) cells				100007		
Lunde 20	006	44	1.2 (7.5)	44	43 (7.1)	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	7.5 %	-3.10 [-6.15, -0.05]
Roncall	2010	47	1.9 (6.89)	44	22 (6.87)	-	8.7 %	-0.30 [-3.13, 2.53]
Traverse	2010	30	6.2 (9.8)	10	9.4 (10)		1.4 %	-320 [-1032, 392]
Subtotal	(95% CI)	121		98		-	17.5 %	-1.72 [-3.71, 0.27]
Heterogene	atty: Chi ² = 1.5	2, df = 2 (P = 0.3)	B); 1 ² =0.0%					20
Test for over	ral effect Z =	L69 (P = 0.091)						
2 Dose BM	SC ≤1 x 10	(9) calls						
Hirsch 2	010	67	3.8 (7.4)	60	4 (5.8)	-	13.2.%	-0.20 [-2.50, 2.10]
Huang 2	006	20	7 (6.7)	20	45 (1.99)		6.7 %	2.50 [-0.73, 5.73]
Janssens	2006	30	3.4 (6.9)	30	2.2 (7.3)		5.4 %	1.20 [-2.39, 4.79
Schachin	ger 2006	27	3.2 (6.8)	27	0.8 (6.8)		5.3 %	2.40 [-1.23, 603]
Tendera	U 2009	46	44 (10.92)	20	0.5 (9.08)	+++	2.7 %	390 [-1.18, 898]
Wohrle	2010	28	1.8 (5.3)	12	5.7 (8.4)	<u> </u>	2.6 %	-390 [-9.04, L24]
Yao DD	2009	15	7.3 (3.43)	12	2.1 (1.71)	-	17.6 %	5.20 [321, 7.19
Yao SD 3	2009	12	5.2 (2.72)	12	2.1 (1.71)	-	21.1 %	3.10 [1.28, 492]
Subtotal	(95% CI)	245		193		•	74.5 %	2.56 [1.59, 3.52]
Heterogene	atty: Chi ² = 19	54, df = 7 (P = Q	D1); 1 ² =6496					
Test for over	ral effect Z =	5.18 (P < 0.0000	0					
3 Dose BM	SC ≤1 x 10	(10) calls						
Kang 200	06	25	5.1 (9.1)	25	-0.2 (8.6)		2.9 %	530 [0.39, 10.21
Mayer 2	006	30	6.7 (6.5)	30	0.7 (8.1)		5.0 %	600 [2.28, 9.72]
Subtotal	(95% CI)	55		55		-	7.9 %	5.74 [2.78, 8.71]
Heterogene	alty: $CH^2 = DI$	15, df = 1 (P = 0.8)	2); 12 =0.0%					
		3.80 (P = 0.0001	1)					
Total (95 Heterogene		421 .29, df = 12 (P = 0	100003); (2 =72	346 x		•	100.0 %	2.06 [1.22, 2.89]
	-	4.83 (P < 0.0000						
Test for sub	group differen	ces Chi ² = 20.79,	df = 2 (P = 0.00	0), 1 ² =90%				
						1.1.1		



Infarct size

Stem Cells vs no Stem cells – size >12 mo

Study or subgroup	BMSC		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV/Random,95% CI	_	N,Random,95% CI
I Measured by MRI							
Lunde 2006	45	-4.3 (8.53)	43	-5.9 (9.2)	- +	12.2 %	1.60 [-211, 531]
Schachinger 2006	22	10.5 (5.7)	26	135 (8.2)	+	11.6 %	-300 [-695, 095]
Yao DD 2009	15	-11.3 (372)	12	-2.7 (2.69)	-	15.4 %	-8.60 [-1 1.02, -6.18]
Yao SD 2009	12	-62 (2.58)	12	-2.7 (2.69)		162.%	-350 [-5.61, -1.39]
Subtotal (95% CI)	94		93			55.3 %	-3.54 [-7.54, 0.45]
Heterogeneity: Tau ² = 14.1	$12; Chl^2 = 3$	12.79, df = 3 (P = 0	100004); I ² :	=87%			
Test for overall effect: Z =	1.74 (P = 0	1082)					
2 Measured by SPECT							
Cao 2009	41	-7.83 (3.44)	-15	-58 (354)		17.6 %	-203 [-351, -055]
Meluzin HD 2008	20	-10 (447)	20	-6 (4.47)		145 %	-4.00 [-6.77, -1.23]
Meluzin LD 2008	20	-9 (671)	20	-6 (4.47)		12.6 %	-300 [-653, 053]
Subtotal (95% CI)	81		85		•	44.7 %	-2.53 [-3.75, -1.31]
Heterogeneity: Tau ² = 0.0;	$Ch^2 = 1.9$	9, df = 2 (P = 0.45)	; I ² =0.0%				
Total (95% CI)	175		178		+	100.0 %	-3.36 [-5.50, -1.22]
Heterogeneity: Tau ² = 6.22	2; Chi ² = 26	127, df = 6 (P = 0.0	0000B); 1 ² =	79%			
Test for overall effect Z =	108 (P = 0	10021)	-				
Test for subgroup difference	es Chi ² = (123, df = 1 (P = 0/	63), 1 ² =0.09	κ.			
_		-					
					-10 -5 0 5	10	
					Ferours BMSC Ferours rs		

Stem Cells vs no stem cells - mortality

Study or subgroup	BMSC	no BMSC	Risk Ratio	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I Short term follow-up (<12 r	months)				
Huikuri 2008	0/40	1/40		3.0 %	0.33 [0.01, 7.95]
Janssens 2006	1/33	0/34		3.0 %	3.09 [0.13, 73.20]
Kang 2006	0/25	1/25		3.0 %	0.33 [0.01, 7.81]
Meyer 2006	0/30	1/30	· · · · ·	3.0 %	0.33 [0.01, 7.87]
Nogueira VG 2009	1/10	0/6	· · · · · · · · · · · · · · · · · · ·	3.2 %	1.91 [0.09, 40.60]
Penicka 2007	3/17	0/10		3.6 %	4.28 [0.24, 75.20]
Piepoli 2010	2/19	4/19		12.1 %	0.50 [0.10, 2.41]
Plewka 2009	2/40	2/20		8.4 %	0.50 [0.08, 3.29]
Quyyumi HD 2011	1/6	0/15		3.2 %	6.86 [0.32, 148.44]
Roncalli 2010	1/48	0/44		3.0 %	2.76 [0.12, 65.92]
Schachinger 2006	2/101	2/103	_	7.9 %	1.02 [0.15, 7.10
Tendera S 2009	1/80	1/40		4.0 %	0.50 [0.03, 7.79]
Tendera U 2009	1/80	1/40		4.0 %	0.50 [0.03, 7.79]
Wohrle 2010	1/29	1/13		4.1 %	0.45 [0.03, 6.63
Zhukova 2009	0/8	1/3		3.4 %	0.15 [0.01, 2.91
Subtotal (95% CI)	566	442	+	68.9 %	0.75 [0.39, 1.46]
otal events: 16 (BMSC), 15 (n	no BMSC)				

Stem Cells vs no stem cells – mortality > 12 mo

BMSC	no BMSC	Risk Ratio	Weight	Risk Ratio
n/N	n/N	H,Random,95%	, regit	H,Random,95%
0/41	1/45		3.0 %	0.37 [0.02, 8.72]
1/27	0/12	<u> </u>	3.1 %	1.39 [0.06, 31.93]
1/50	1/50		4.0 %	1.00 [0.06, 15.55]
2/30	1/29		5.4 %	1.93 [0.19, 20.18]
1/99	6/101		6.8 %	0.17 [0.02, 1.39]
2/8	۱ <mark>۵</mark>		8.9 %	0.50 [0.08, 3.13]
255	239	•	31.1 %	0.59 [0.22, 1.56]
BMSC)				
	0/41 1/27 1/50 2/30 1/99 2/8 2/8 255	n/N n/N 0/41 1/45 1/27 0/12 1/50 1/50 2/30 1/29 1/99 6/101 2/8 1/2 255 239	n/N n/N H,Random,95% 0/41 1/45 1/27 0/12 1/50 1/50 2/30 1/29 1/99 6/101 2/8 1/2 255 239	M- H,Random,95% CI 30 % CI 0/41 1/45 3.0 % 1/27 0/12 3.1 % 1/50 1/50 4.0 % 2/30 1/29 5.4 % 1/99 6/101 6.8 % 2/8 1/2 8.9 % 255 239 31.1 %



The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all- cause mortality in acute myocardial infarction



Diagnosis of myocardial infarction $\nabla \overline{}$ Days 3-5 Primary Angioplasty <12 hours \downarrow Echocardiogram EF<45% **BM** Aspiration 100mls Days 5-8 77 Repeat Standard care Angiography BMMNC infusion 2 years Study end-point - mortality

 3000 patient outcome study
End-point = 25 % reduction in death (all cause at 2 years)
STANDARDISATION of cell processing technique

BAMIEUROPEAN MEDICINES AGENCY

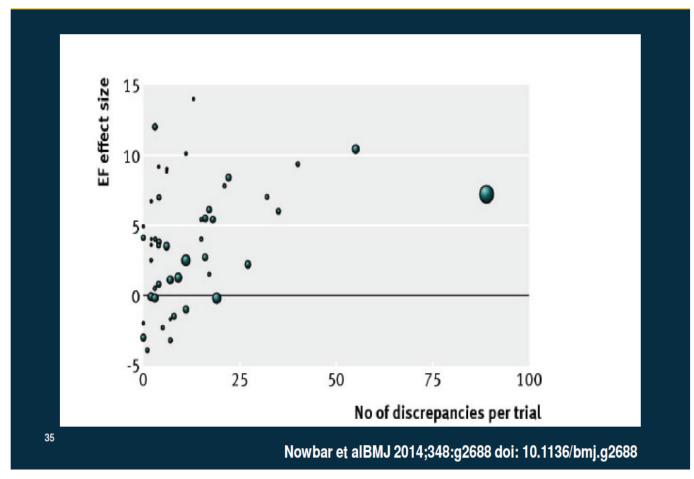


Over 1700 pts in 33 trials



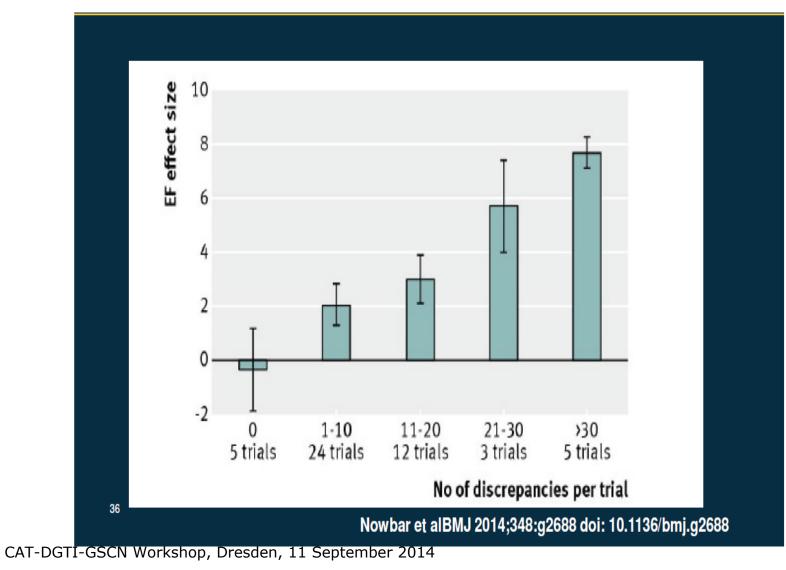
"Overall, bone marrow stem cell therapy improved left ventricular ejection fraction (LVEF) by 2.87%" Sustained after 12 months and dependant on the dose

Discrepancies vs functional outcome





Effect vs discrepancies



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Conclusions

With unselected and selected BMMNC: significant but very limited effect on Left Ventricular volumes and infarct size.

Very limited effect on mortality reduction; Outcome BAMI trial?

Not enough data on other cell sources yet to make firm statements.

Lack of standardization: product, dosage; application mode; assessment of efficacy clinical and preclinical



Publication bias ?

Solution: registration of ongoing studies

www.preclinicaltrials.eu



Morphology: Infarct size MRI LGE

Caduceus: cardiospheres

Scipio: cardiac stem cells

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