EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical aspects for cell-based therapies for cardiac repair

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Presented by: Name Surname
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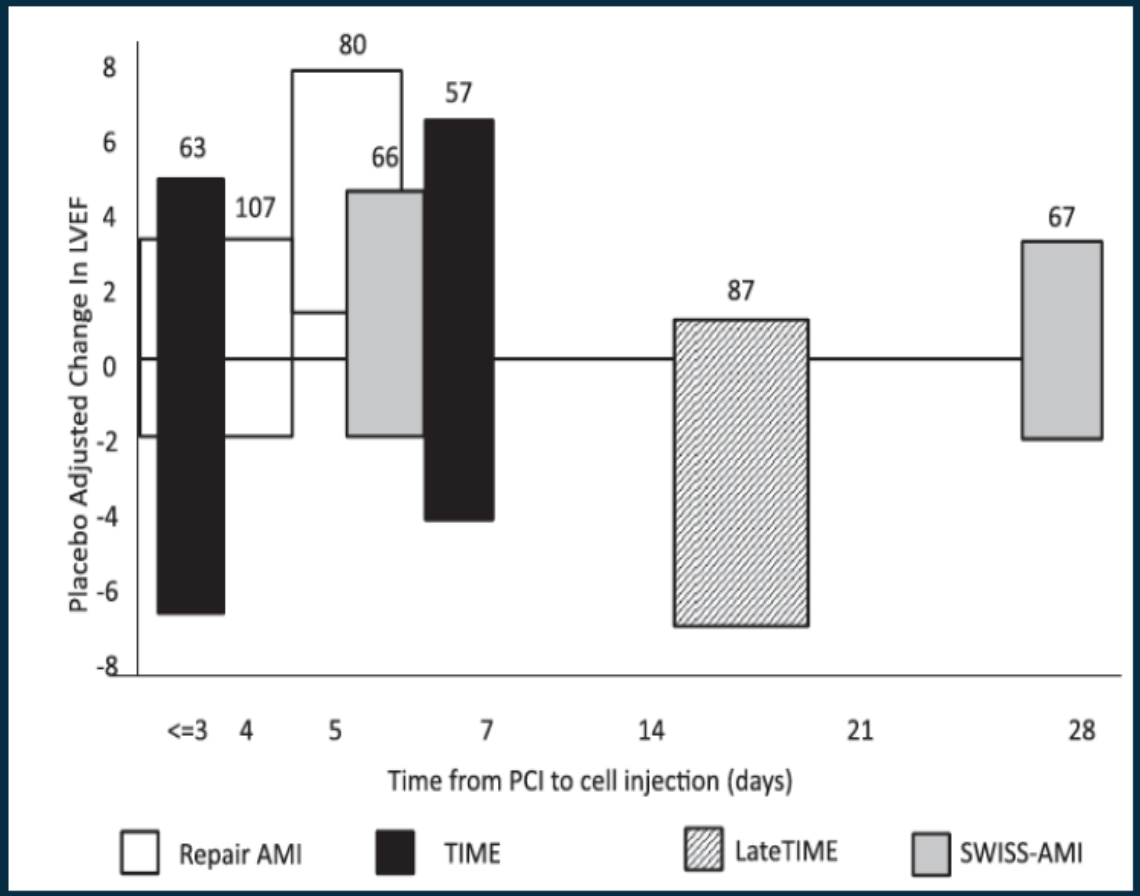
Efficacy of Stem cell applications? What we learned from clinical trials today!

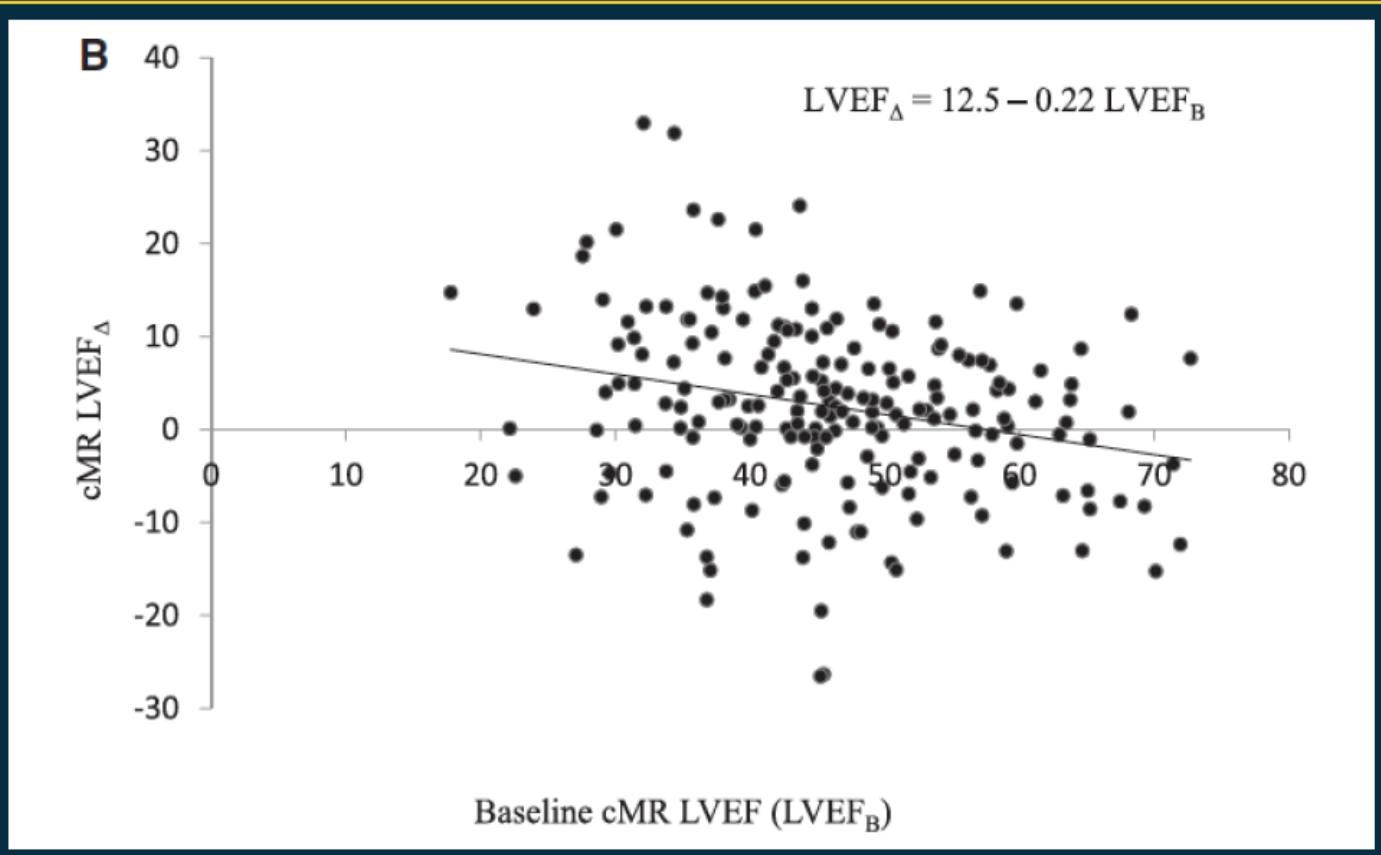
- Not clear when, what, how and how much.
- Much debate on efficacy and reliability of the data reported.
- No standardization of products and assessments *in vitro* and *in vivo*.

Timing of BMC transplantation



Simari et al Circ Res. 2014;114:1564-1568

ΔLVEF vs Baseline LVEF



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Simari et al Circ Res. 2014;114:1564-1568

Recommendations on imaging modalities in cardiac repair:

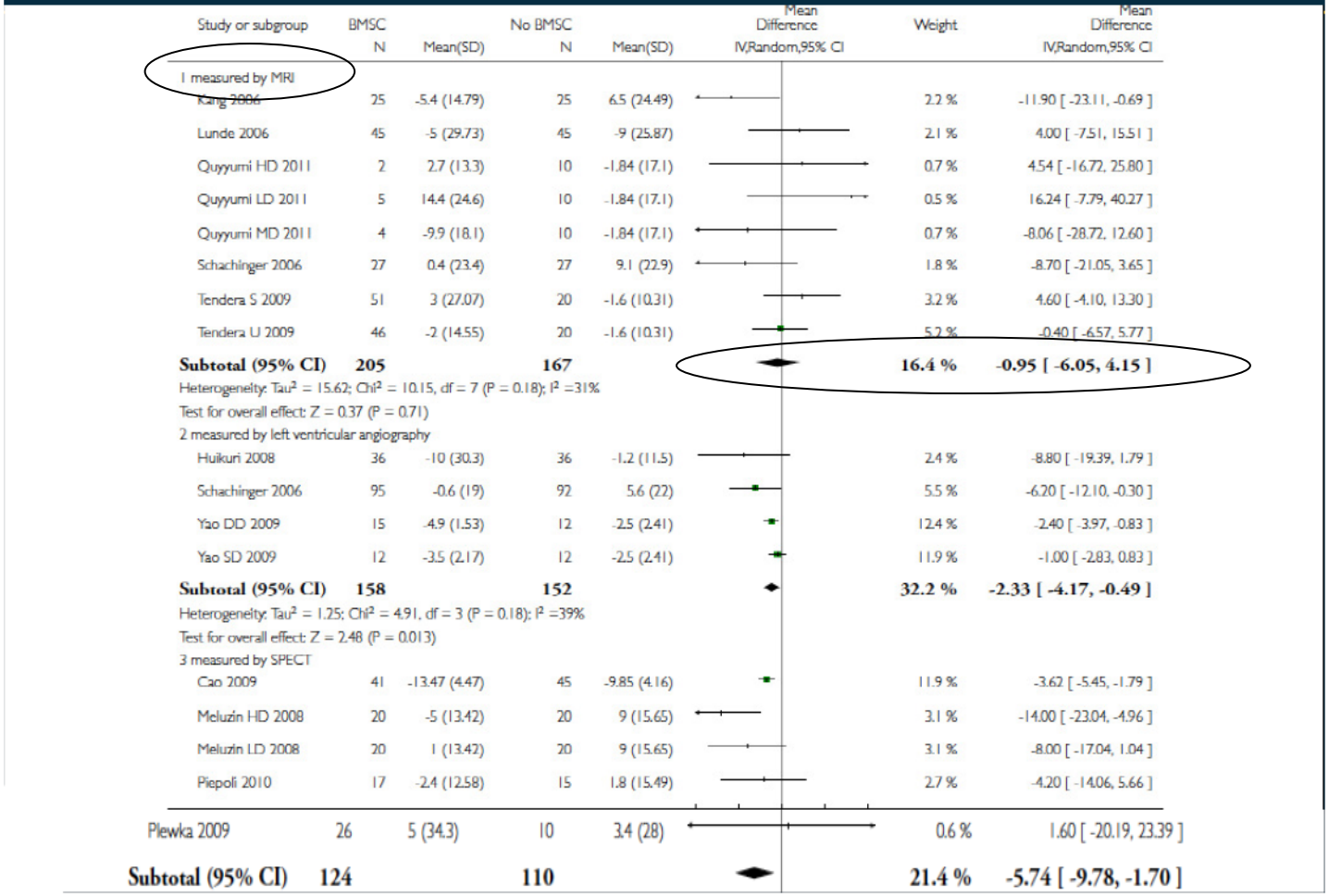
Any method chosen to estimate LVEF must be used both for baseline as well as follow up

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.

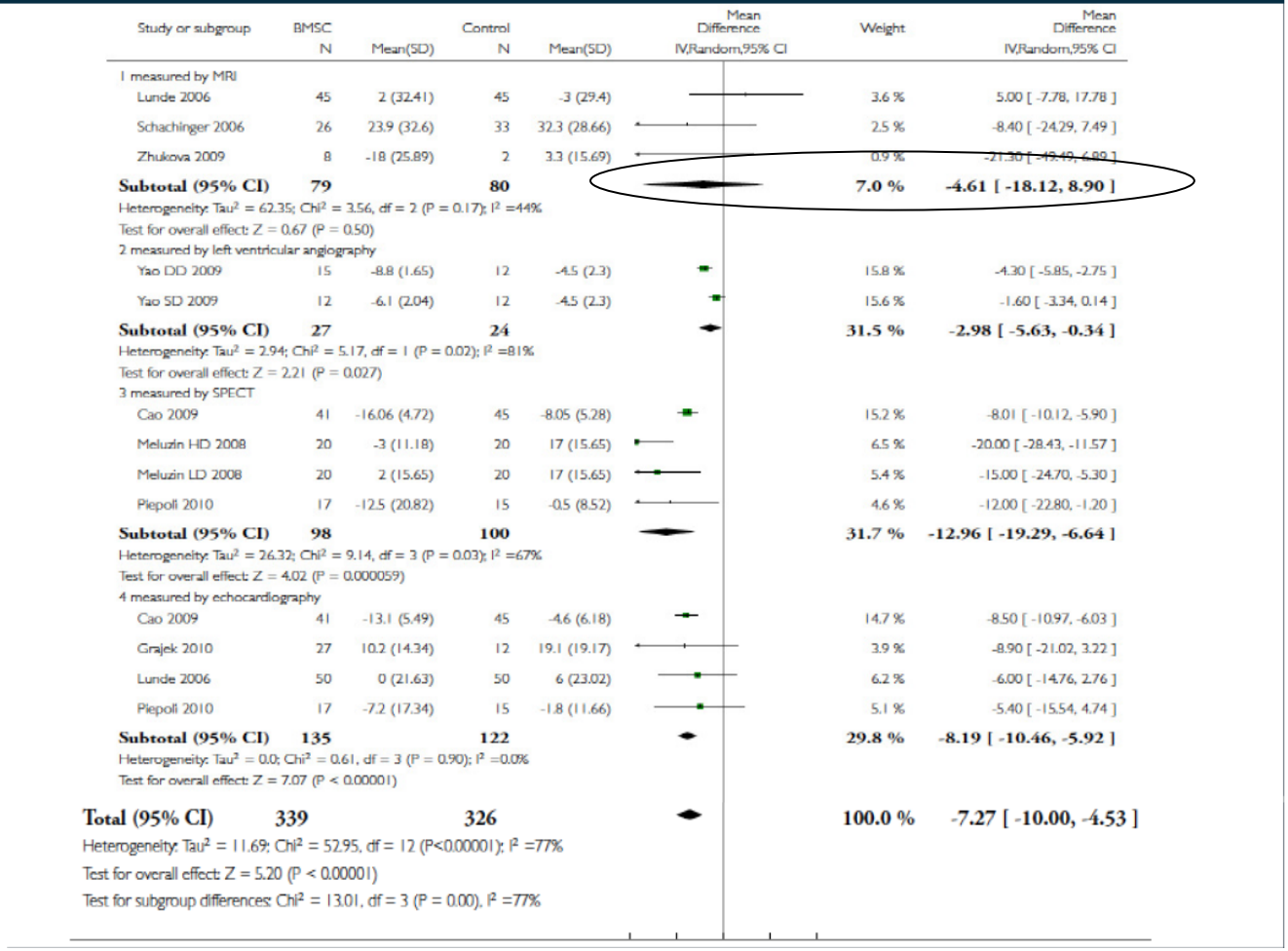
256+ CT will probably be the modality of choice in the future but **CMR is currently the gold standard**

Stem Cells vs no Stem cells – LVESV <12 mo

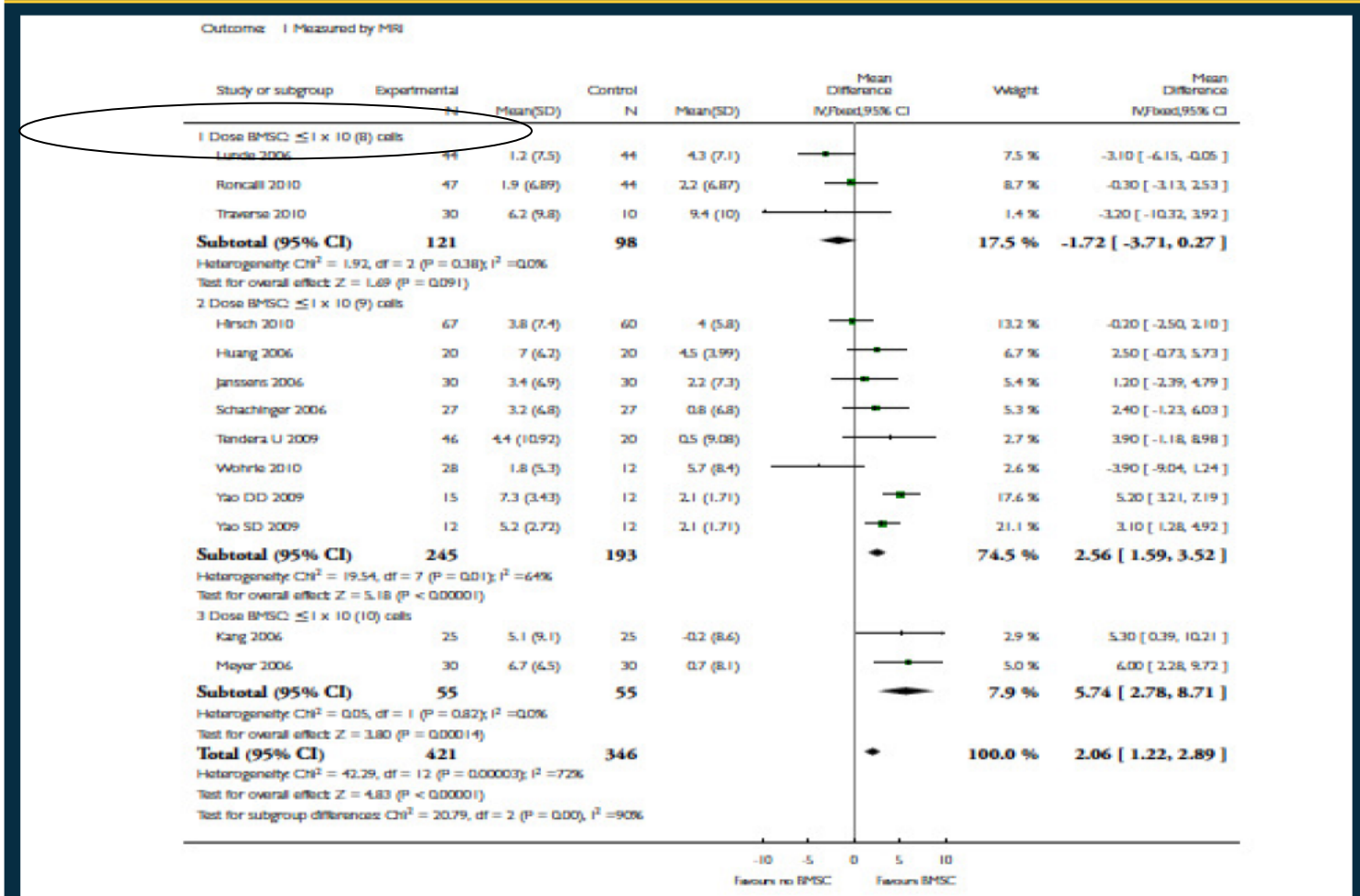


Study or subgroup	BMSC N	Mean(SD)	No BMSC N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 measured by MRI							
Kang 2006	25	-5.4 (14.79)	25	6.5 (24.49)		2.2 %	-11.90 [-23.11, -0.69]
Lunde 2006	45	-5 (29.73)	45	-9 (25.87)		2.1 %	4.00 [-7.51, 15.51]
Quyyumi HD 2011	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: $Tau^2 = 15.62$; $Chi^2 = 10.15$, df = 7 (P = 0.18); $I^2 = 31\%$							
Test for overall effect: Z = 0.37 (P = 0.71)							
2 measured by left ventricular angiography							
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: $Tau^2 = 1.25$; $Chi^2 = 4.91$, 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	1 (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)		2.7 %	-4.20 [-14.06, 5.66]
Plewka 2009	26	5 (34.3)	10	3.4 (28)		0.6 %	1.60 [-20.19, 23.39]
Subtotal (95% CI)	**124**		**110**			**21.4 %**	**-5.74 [-9.78, -1.70]**

Stem Cells vs no Stem cells – LVESV >12 mo

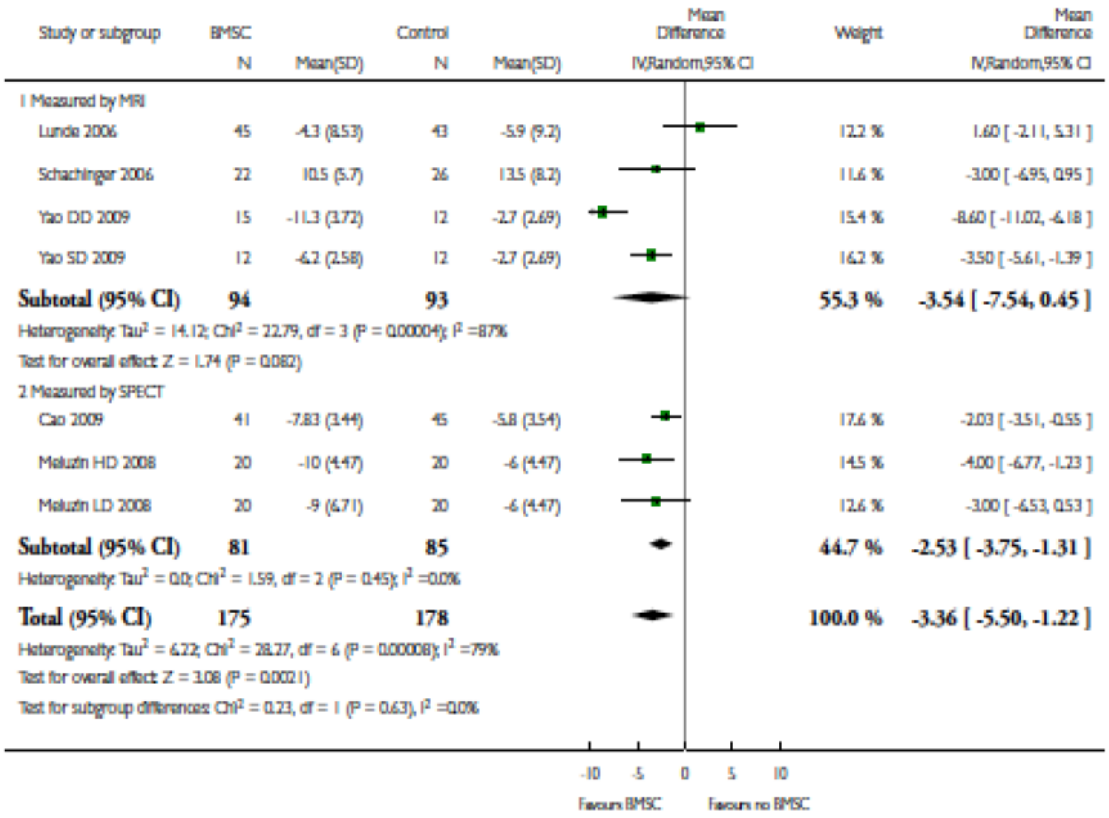


LVEF in relation to dosage - MRI



Infarct size

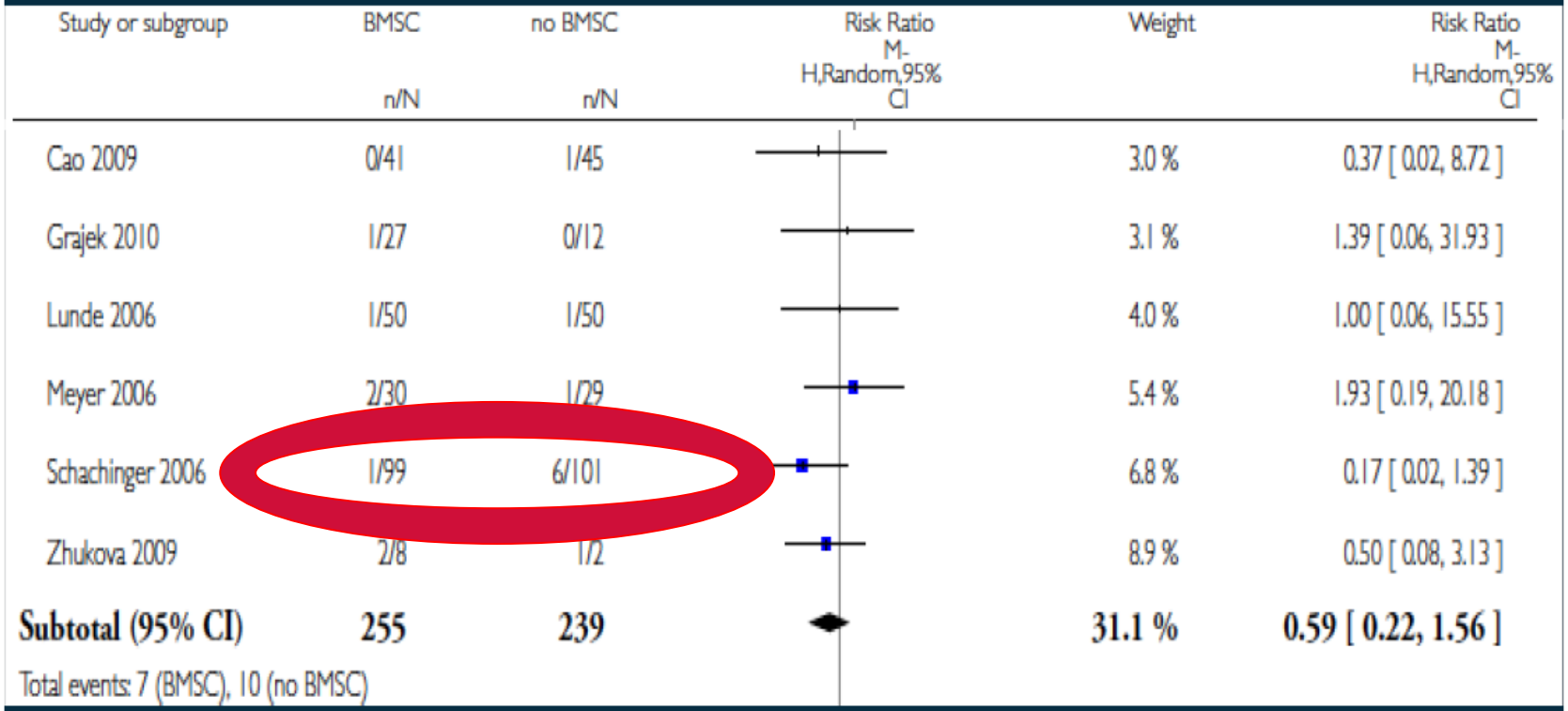
Stem Cells vs no Stem cells – size >12 mo



Stem Cells vs no stem cells - mortality

Study or subgroup	BMSC n/N	no BMSC n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Short term follow-up (<12 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]**
Total events: 16 (BMSC), 15 (no BMSC)					

Stem Cells vs no stem cells – mortality > 12 mo



Study or subgroup	BMSC n/N	no BMSC n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cao 2009	0/41	1/45		3.0 %	0.37 [0.02, 8.72]
Grajek 2010	1/27	0/12		3.1 %	1.39 [0.06, 31.93]
Lunde 2006	1/50	1/50		4.0 %	1.00 [0.06, 15.55]
Meyer 2006	2/30	1/29		5.4 %	1.93 [0.19, 20.18]
Schachinger 2006	1/99	6/101		6.8 %	0.17 [0.02, 1.39]
Zhukova 2009	2/8	1/2		8.9 %	0.50 [0.08, 3.13]
Subtotal (95% CI)	**255**	**239**		**31.1 %**	**0.59 [0.22, 1.56]**
Total events: 7 (BMSC), 10 (no BMSC)					

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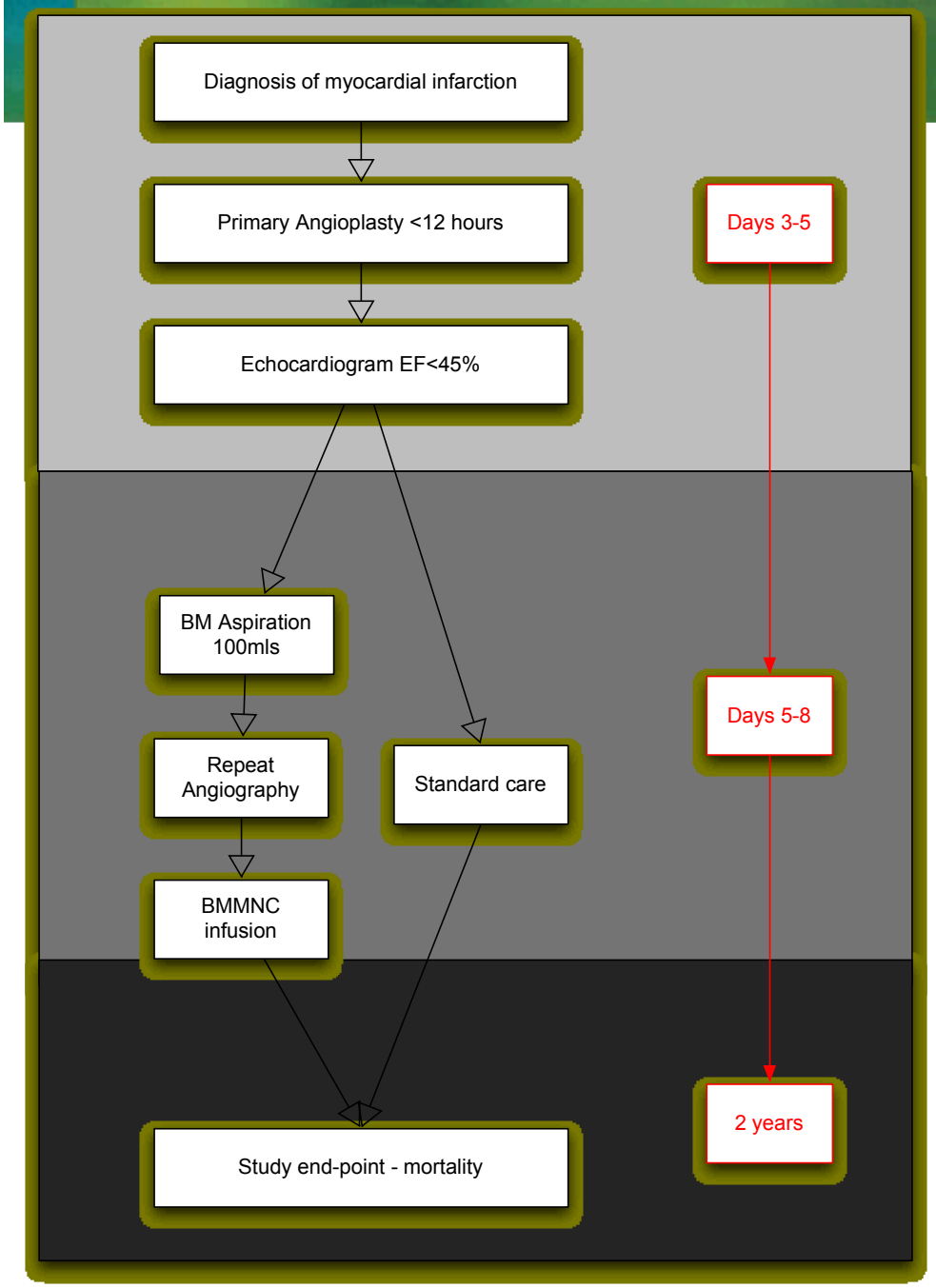
Bami

Supported by the EC under the FP7 programme

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



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

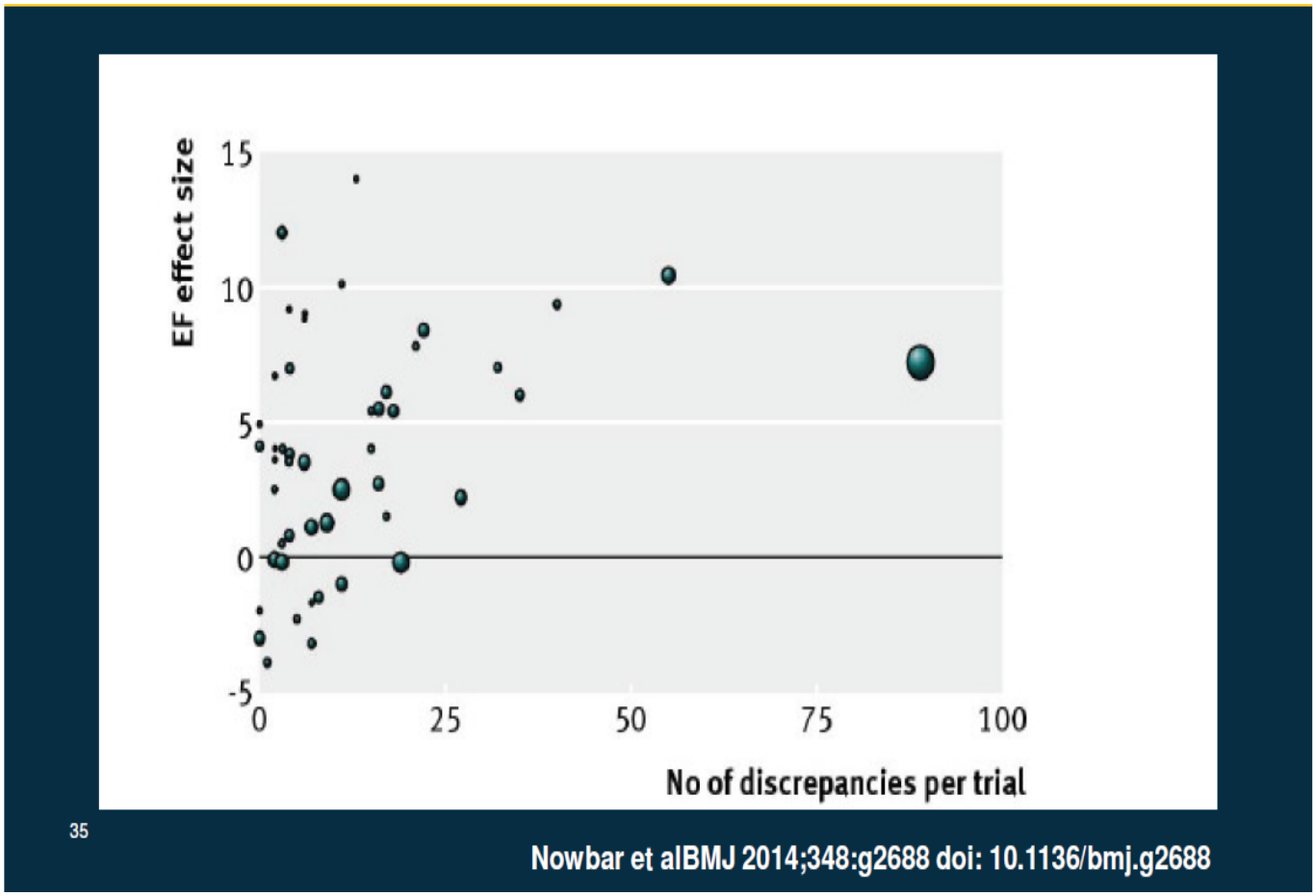
Over 1700 pts in 33 trials

THE COCHRANE COLLABORATION®

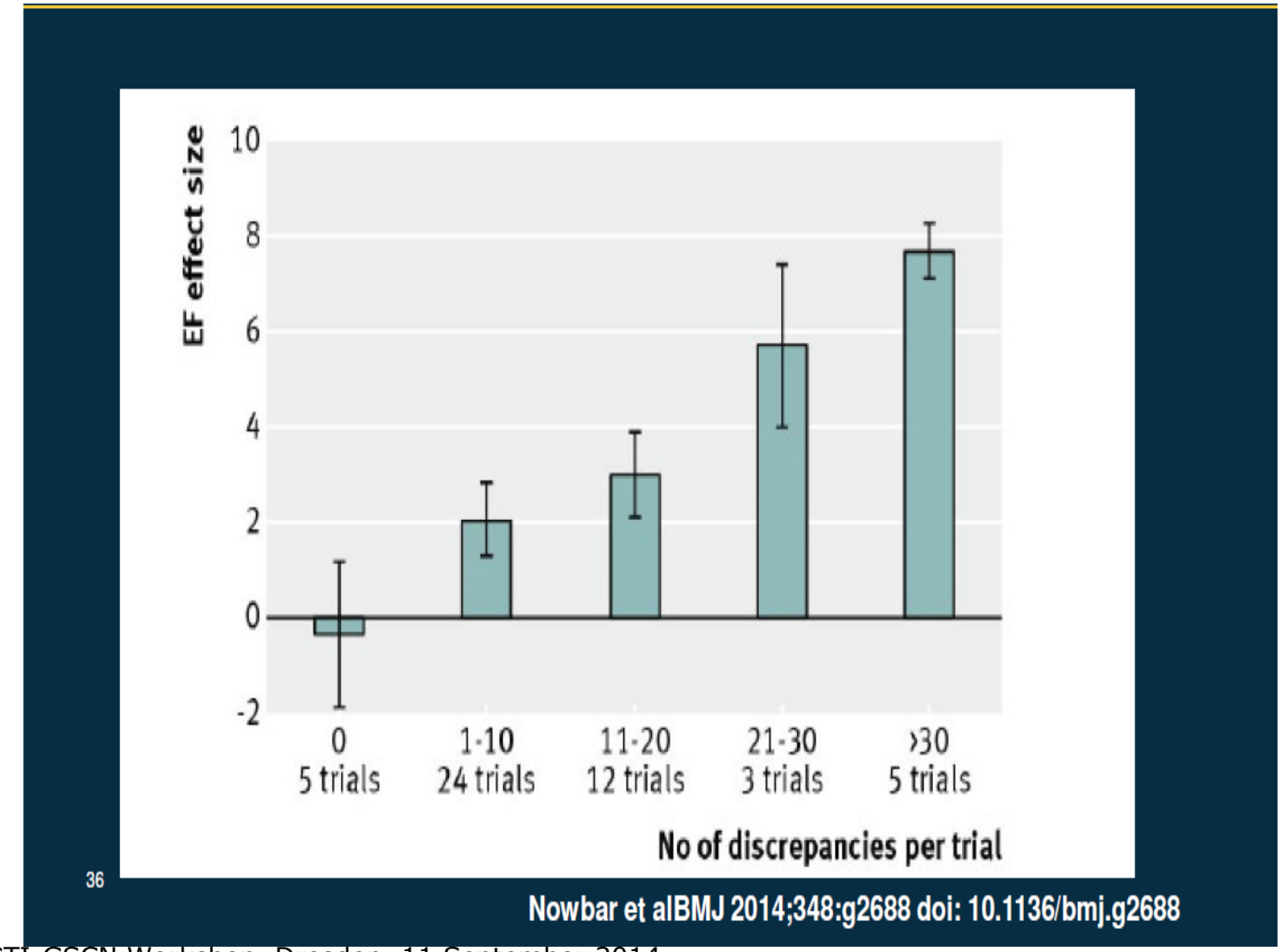
"Overall, bone marrow stem cell therapy improved left ventricular ejection fraction (LVEF) by **2.87%**"

Sustained after 12 months and dependant on the dose

Discrepancies vs functional outcome



Effect vs discrepancies



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 ?

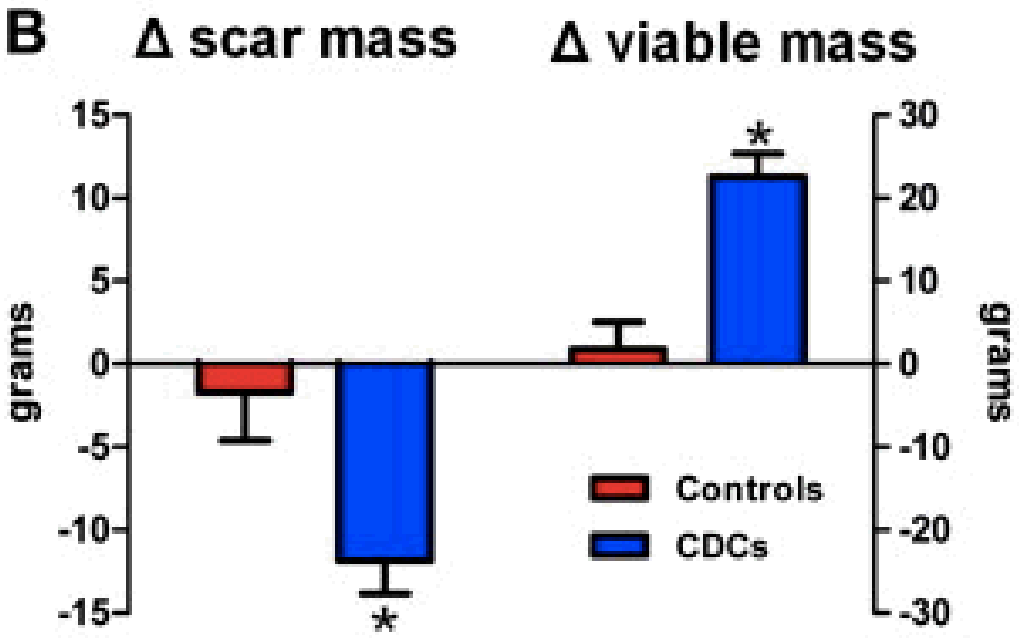
Solution: registration of ongoing studies

www.preclinicaltrials.eu

UMC Utrecht

Morphology:
Infarct size MRI LGE

Caduceus: cardiospheres



Scipio: cardiac stem cells