

Clinical aspects for cell-based therapies for cardiac repair

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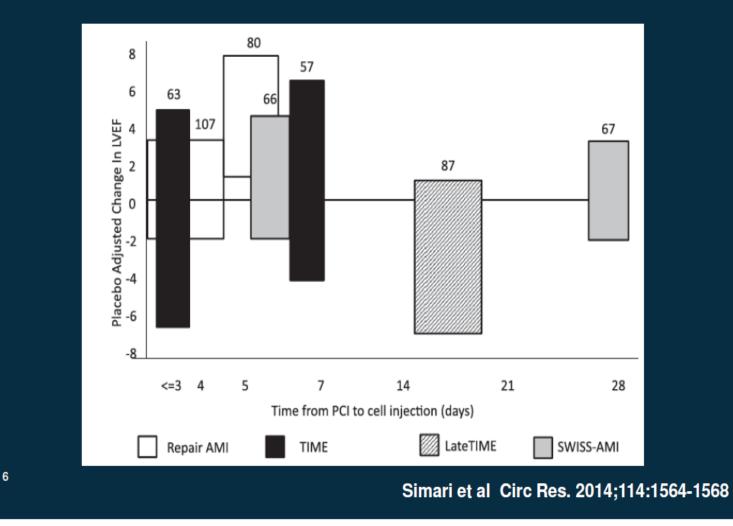
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Efficacy of Stem cell applications? What we learned from clinical trials today!

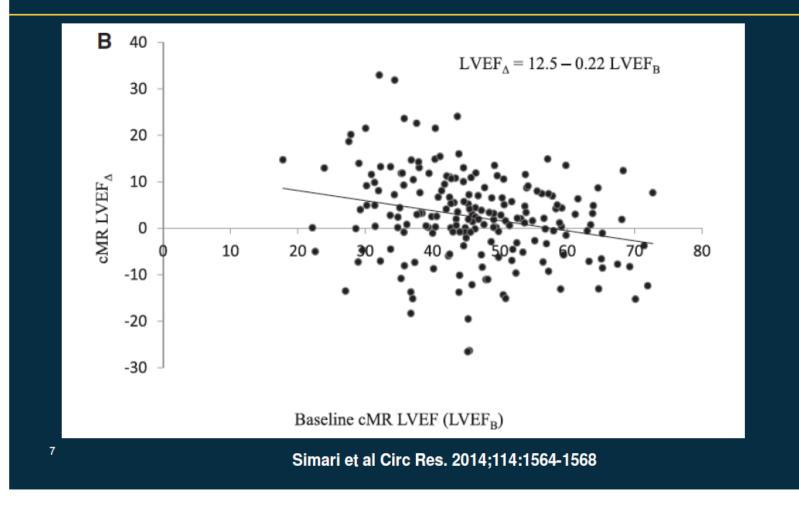
- Not clear when, what, how and how much.
- Much debate on efficacy and reliability of the data reported.
- No standardization of products and assessments in vitro and in vivo.



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

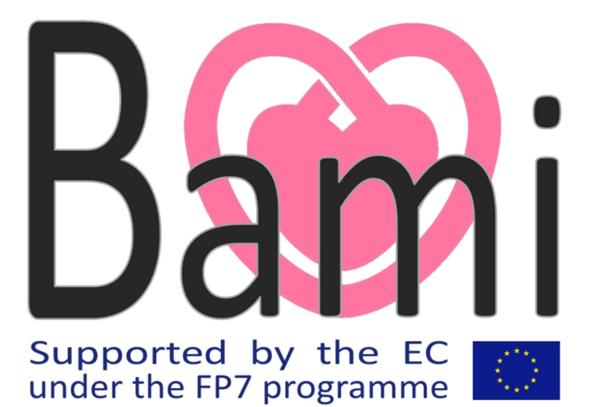
| Study or subgroup | BMSC | | Control | | Mean Difference | Weight | Mean Difference |
|--|--------------------------|----------------------|---------------------------|-------------|-------------------------|---------|--------------------------|
| | N | Mean(SD) | N | Mean(SD) | IV/Random,95% CI | _ | 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

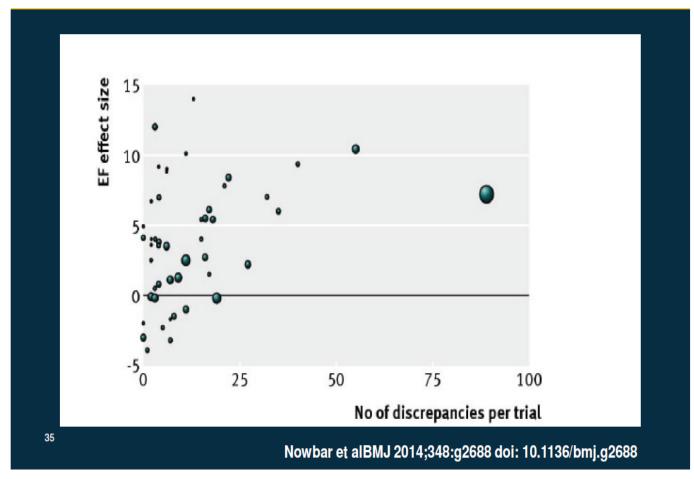


Over 1700 pts in 33 trials



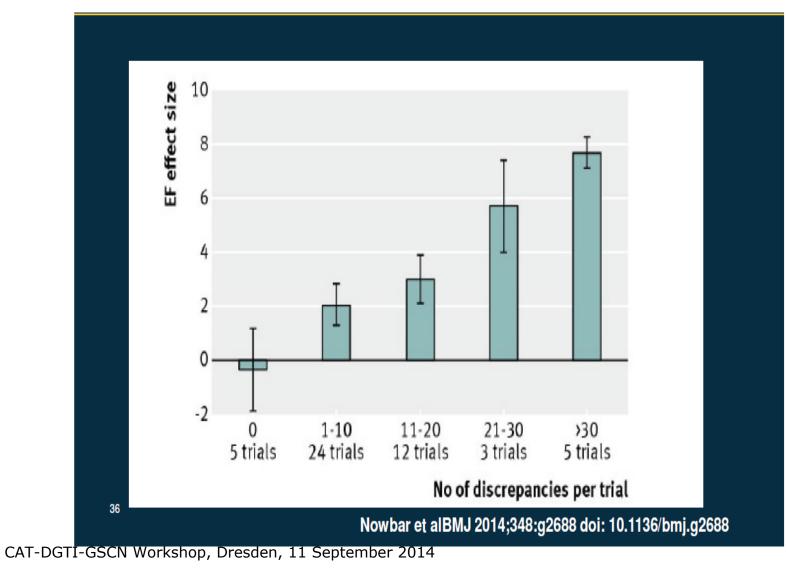
"Overall, bone marrow stem cell therapy improved left ventricular ejection fraction (LVEF) by 2.87%" Sustained after 12 months and dependant on the dose

Discrepancies vs functional outcome





Effect vs discrepancies



15

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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