Why I prefer IPD based meta-analyses

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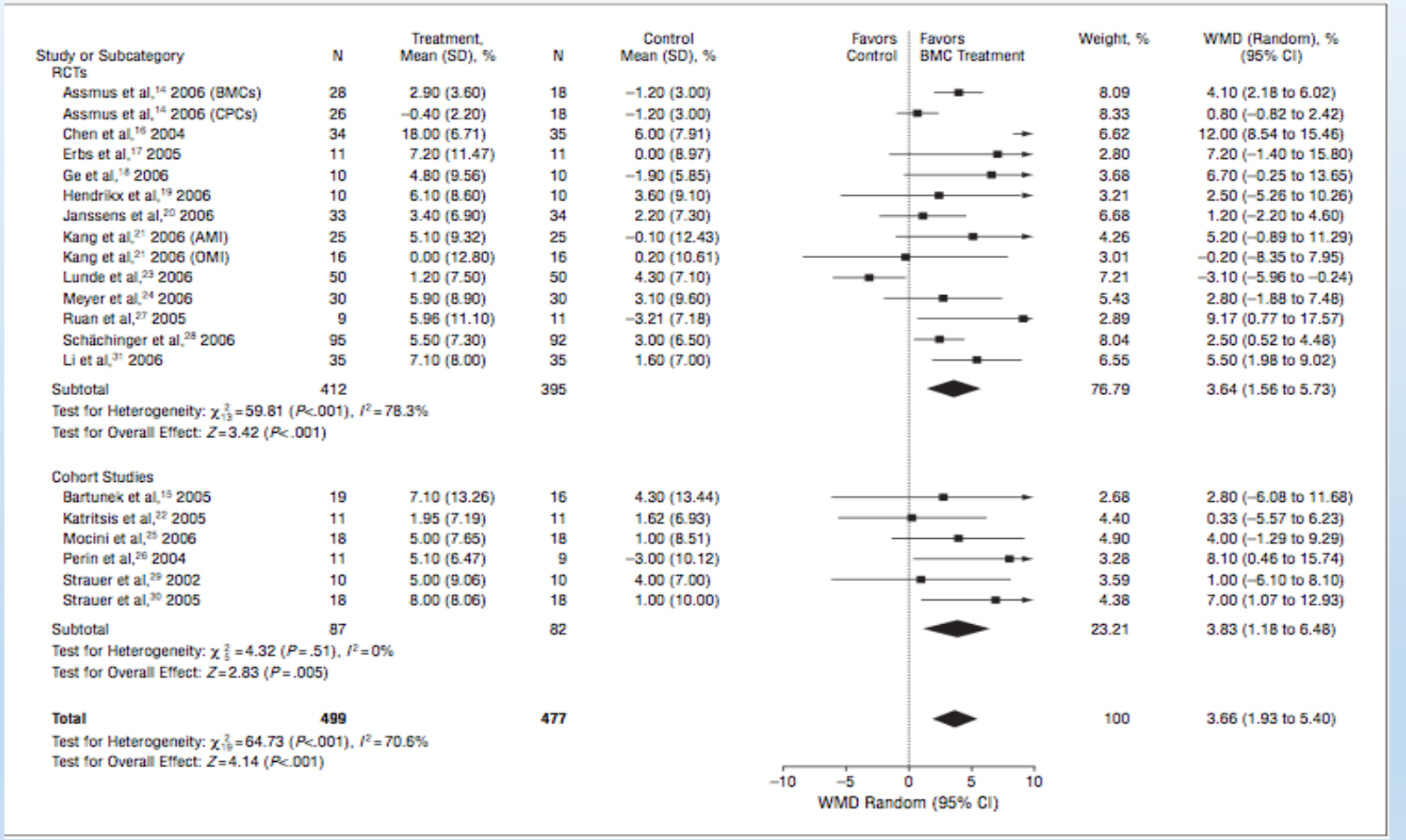
Meta-analysis of trials with intracoronary cell delivery

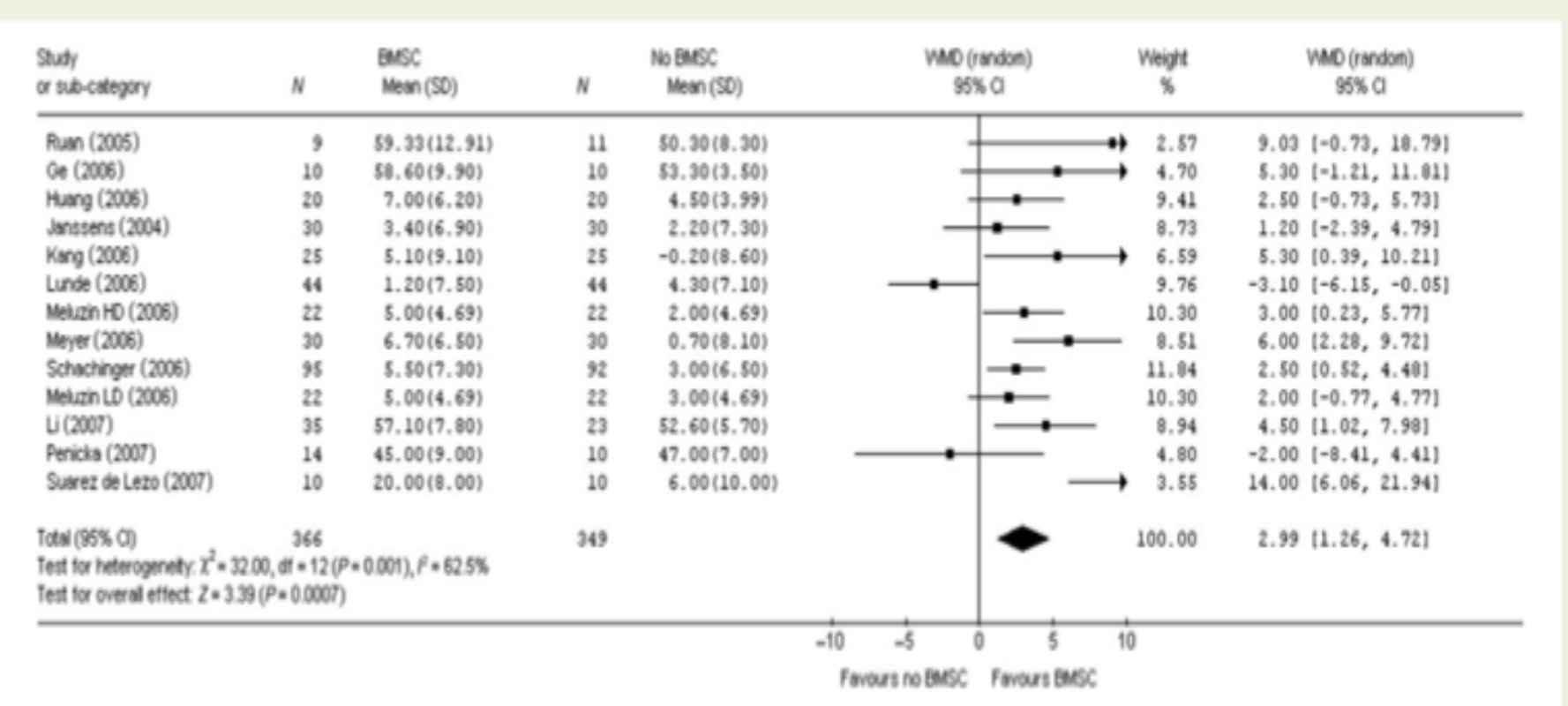


Study or Subcategory	N	Treatment, Mean (SD), %	N	Control Mean (SD), %	Weight, %	WMD (Random), % (95% CI)
RCTs						
Assmus et al,[14] 2006 (BMCs)	28	2.90 (3.60)	18	−1.20 (3.00)	8.09	4.10 (2.18 to 6.02)
Assmus et al,[14] 2006 (CPCs)	26	−0.40 (2.20)	18	−1.20 (3.00)	8.33	0.80 (−0.82 to 2.42)
Chen et al,[16] 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)
Li et al,[31] 2006	35	7.10 (8.00)	35	1.60 (7.00)	6.55	5.50 (1.98 to 9.02)
Subtotal	412		395		76.79	3.64 (1.56 to 5.73)
Test for Heterogeneity: $\chi^2_{13}=59.81$ ($P<.001$), $I^2=78.3\%$						
Test for Overall Effect: $Z=3.42$ ($P<.001$)						
Cohort Studies						
Bartunek et al,[15] 2005	19	7.10 (13.26)	16	4.30 (13.44)	2.68	2.80 (−6.08 to 11.68)
Katritsis et al,[22] 2005	11	1.95 (7.19)	11	1.62 (6.93)	4.40	0.33 (−5.57 to 6.23)
Mocini et al,[25] 2006	18	5.00 (7.65)	18	1.00 (8.51)	4.90	4.00 (−1.29 to 9.29)
Perin et al,[26] 2004	11	5.10 (6.47)	9	−3.00 (10.12)	3.28	8.10 (0.46 to 15.74)
Strauer et al,[29] 2002	10	5.00 (9.06)	10	4.00 (7.00)	3.59	1.00 (−6.10 to 8.10)
Strauer et al,[30] 2005	18	8.00 (8.06)	18	1.00 (10.00)	4.38	7.00 (1.07 to 12.93)
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: $Z=4.14$ ($P<.001$)						

Changes in LV EF: 3.66 %

Abdel-Latif. Arch Intern Med 2007

Meta-analysis of trials with intracoronary cell delivery



Changes in LV EF: 3.39 %

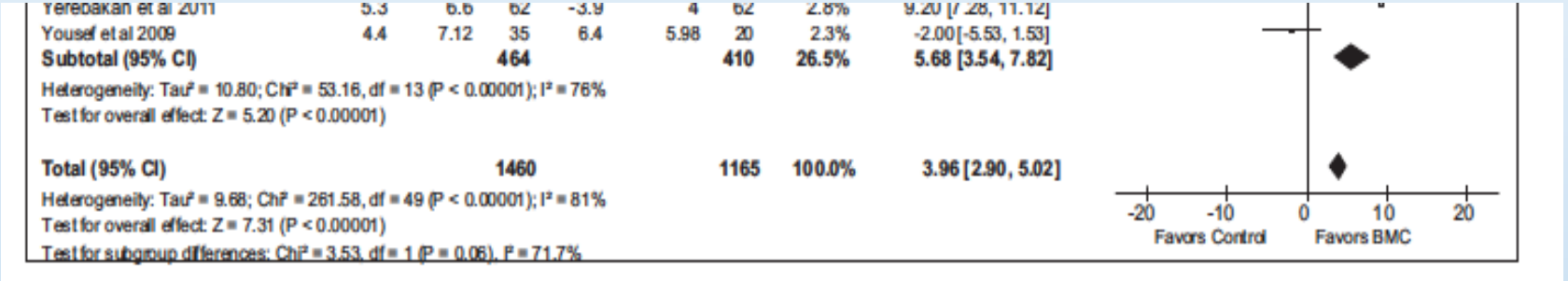
Martin-Rendon. EHJ 2008

Meta-analysis of trials with intracoronary cell delivery

Jeevanantham et al. Circulation 2012

50 studies, 2625 pts treated with cell therapy

EF



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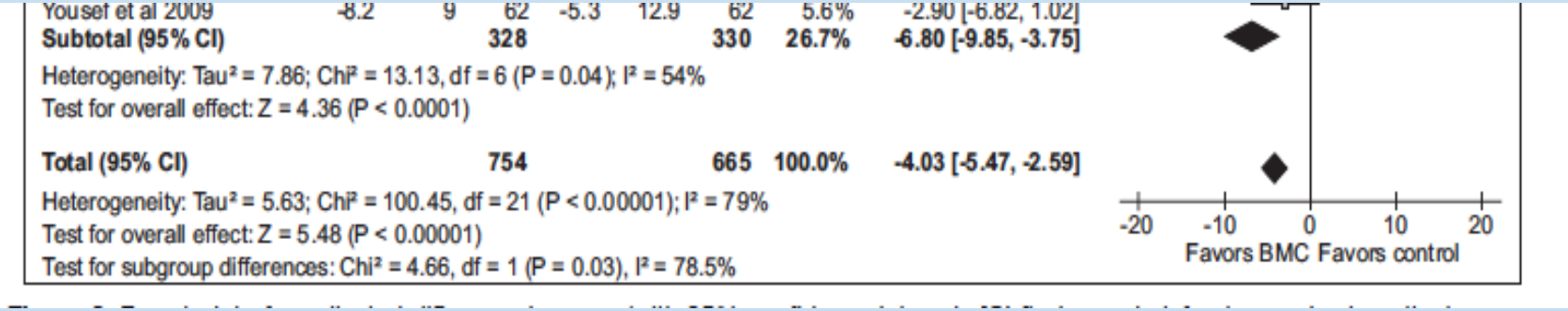


IPD Meta-analysis of trials with intracoronary cell delivery

Gyöngyösi et al. Circ Res 2015

12 studies, 1275 pts treated with cell therapy after AMI

FIRST and ONLY IPD meta-analysis

Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in Patients With Acute Myocardial Infarction Based on Individual Patient Data

Mariann Gyöngyösi, Wojciech Wojakowski, Patricia Lemarchand, Ketil Lunde, Michal Tendera, Jozef Bartunek, Eduardo Marban, Birgit Assmus, Timothy D. Henry, Jay H. Traverse, Lemuel A. Moyé, Daniel Sürder, Roberto Corti, Heikki Huikuri, Johanna Miettinen, Jochen Wöhrle, Slobodan Obradovic, Jérome Roncalli, Konstantinos Malliaras, Evgeny Pokushalov, Alexander Romanov, Jens Kastrup, Martin W. Bergmann, Douwe E. Atsma, Axel Diederichsen, Istvan Edes, Imre Benedek, Theodora Benedek, Hristo Pejkov, Noemi Nyolczas, Noemi Pavo, Jutta Bergler-Klein, Imre J. Pavo, Christer Sylven, Sergio Berti, Eliano P. Navarese, Gerald Maurer; for the ACCRUE Investigators*

Rationale: **The meta-Analysis of Cell-based CaRdiac study is the first prospectively declared collaborative multinational database, including individual data of patients with ischemic heart disease treated with cell therapy.**

Objective: **We analyzed the safety and efficacy of intracoronary cell therapy after acute myocardial infarction (AMI), including individual patient data from 12 randomized trials (ASTAMI, Aalst, BOOST, BONAMI, CADUCEUS, FINCELL, REGENT, REPAIR-AMI, SCAMI, SWISS-AMI, TIME, LATE-TIME; n=1252).**

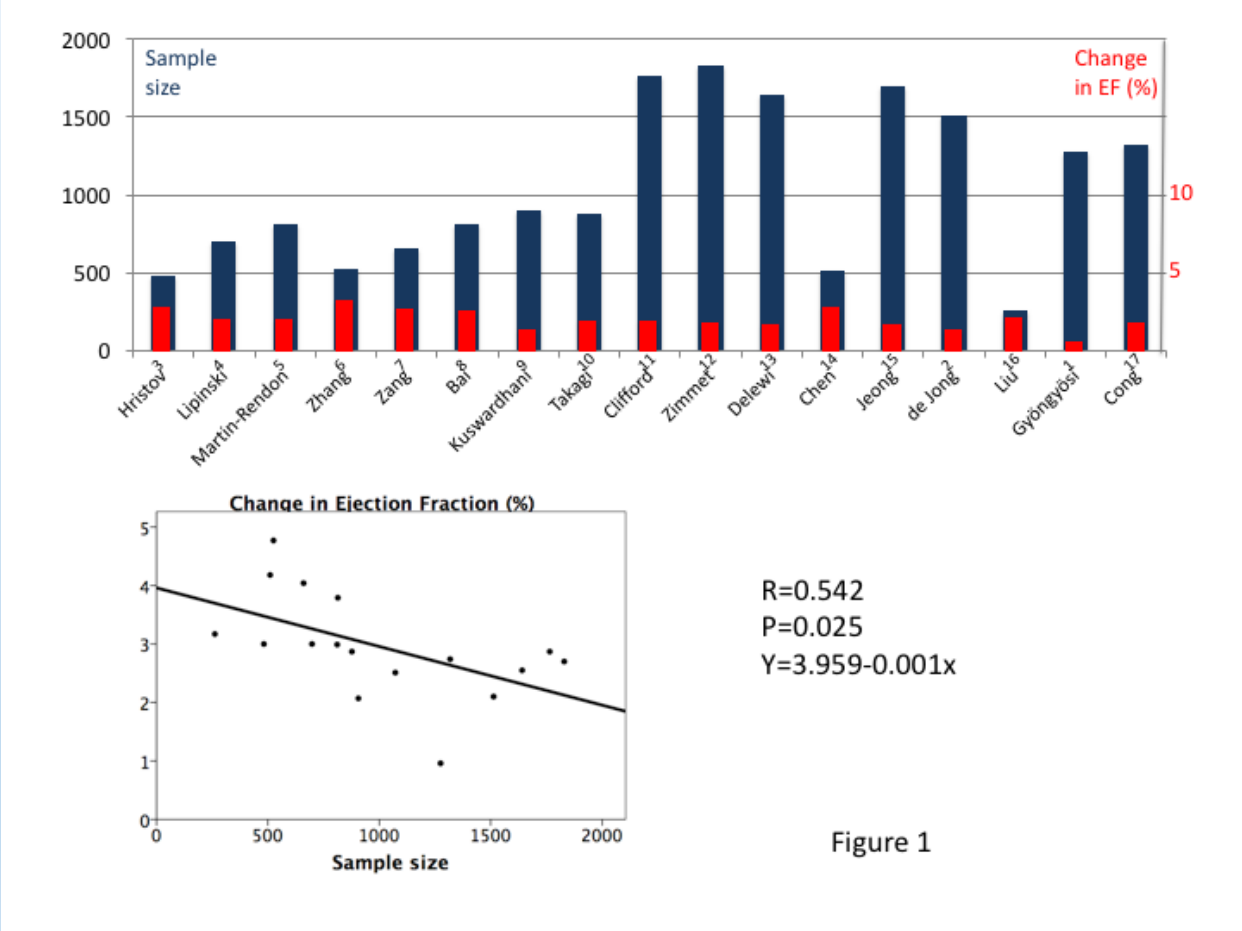
Methods and Results: **The primary end point was freedom from combined major adverse cardiac and cerebrovascular events (including all-cause death, AMI recurrance, stroke, and target vessel revascularization). The secondary end point was freedom from hard clinical end points (death, AMI recurrence, or stroke), assessed with random-effects meta-analyses and Cox regressions for interactions. Secondary efficacy end points included changes in end-diastolic volume, end-systolic volume, and ejection fraction, analyzed with random-effects meta-analyses and ANCOVA. We reported weighted mean differences between cell therapy and control groups. No effect of cell therapy on major adverse cardiac and cerebrovascular events (14.0% versus 16.3%; hazard ratio, 0.86; 95% confidence interval, 0.63–1.18) or death (1.4% versus 2.1%) or death/AMI recurrence/stroke (2.9% versus 4.7%) was identified in comparison with controls. No changes in ejection fraction (mean difference: 0.96%; 95% confidence interval, −0.2 to 2.1), end-diastolic volume, or systolic volume were observed compared with controls. These results were not influenced by anterior AMI location, reduced baseline ejection fraction, or the use of MRI for assessing left ventricular parameters.**

Conclusions: **This meta-analysis of individual patient data from randomized trials in patients with recent AMI revealed that intracoronary cell therapy provided no benefit, in terms of clinical events or changes in left ventricular function.**

Clinical Trial Registration: **URL: http://www.clinicaltrials.gov. Unique identifier: NCT01098591. (*Circ Res*. 2015; 116:1346-1360. DOI: 10.1161/CIRCRESAHA.116.304346.)**

Why I prefer IPD based meta-analyses

Evaluation of the relationship between the sample size of the meta-analyses and the time sequence of publications



Gyöngyösi. Controversies... Circ Res 2016

Published meta-analyses of intracoronary cell therapy in patients with recent MI

Published meta-analyses on cardiac cell-based therapies	Year	Type of meta-analysis	Nr of stu-dies	Sample size	FUP (months)	EDV (ml)	ESV (ml)	EF (%)	if MRI EF
Lipinski	2007	RCT-Pb	10	698	6	-4.6	-7.4*	3.0*	nr
Martin-Rendon	2008	RCT-Pb	13	811	3-6	-2.47	-4.74*	2.99*	nr
Zhang	2009	RCT-Pb	6	525	5	-0.15	n.a.	4.77*	nr
Zhang	2009	RCT-Pb	7	660	6	-0.15	-0.25*	4.04*	nr
Bai	2010	RCT-Pb	10	814	6	nr	nr	3.79*	nr
Kuswardhani	2011	RCT-Pb	10	906	4-60	-3.08*	-5.52*	2.07*	nr
Takagi	2011	RCT-Pb	15	877	nr	-0.18*	-0.35*	2.87*	nr
Clifford	2012	RCT-Pb	33	1765	<12 #	-3.52*	-4.47*	2.87*	1.78*
Zimmet	2012	RCT-Pb	29	1830	3-6	-3.39*	-3.51*	2.7*	nr
Delewi	2012	RCT-Pb	16	1641	3-6	na	na	2.55*	0.16%*
Chen	2013	RCT-Pb	5	510	nr	-2.29	-4.47	4.18*	nr
de Jong	2014	RCT-Pb	22	1513	6	-2.8	-4.05*	2.1*	0.13
Gyöngyösi	2015	RCT-IPD	12	1275	12	1.2	0.4	**0.96**	nr
Cong	2015	RCT-Pb	17	1318	12	-1.69	-3.92*	2.74*	nr

For example, the observed effect sizes beg the question of the clinical relevance of the change in EDV and ESV in this reported range (-4.16 – +1.2 ml).

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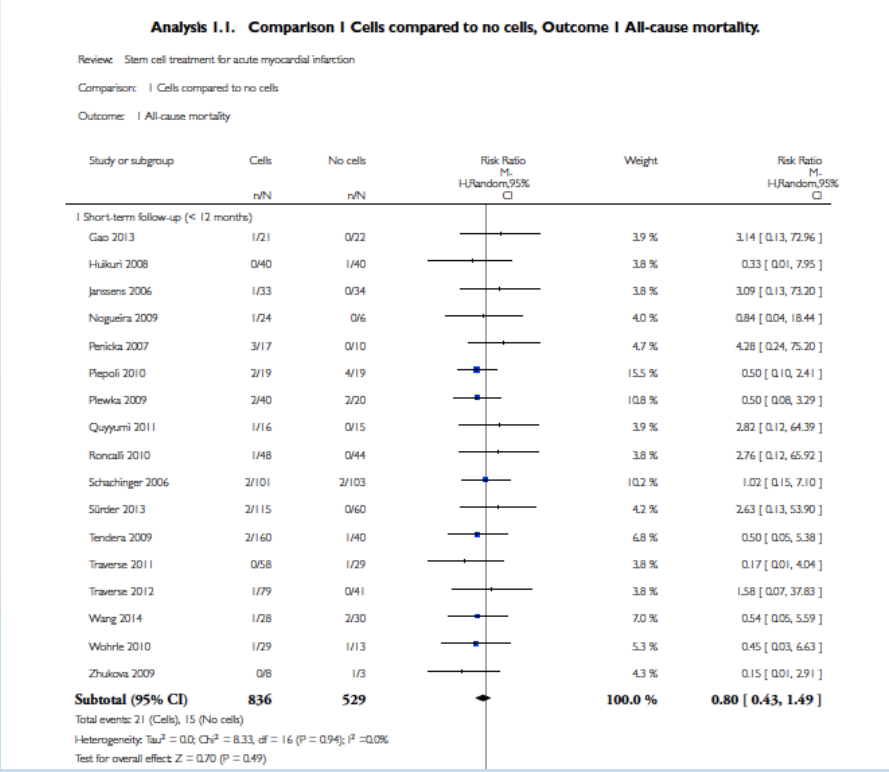
6 months later....

Recent Cochrane meta-analyses outcome NEGATIVE for intracoronary cell-therapy post-AMI

Recent Cochrane meta-analyses outcome NEGATIVE for intracoronary cell-therapy post-AMI



Analysis 1.1. Comparison 1 Cells compared to no cells, Outcome 1 All-cause mortality.

Review: Stem cell treatment for acute myocardial infarction

Comparison: 1 Cells compared to no cells

Outcome: 1 All-cause mortality

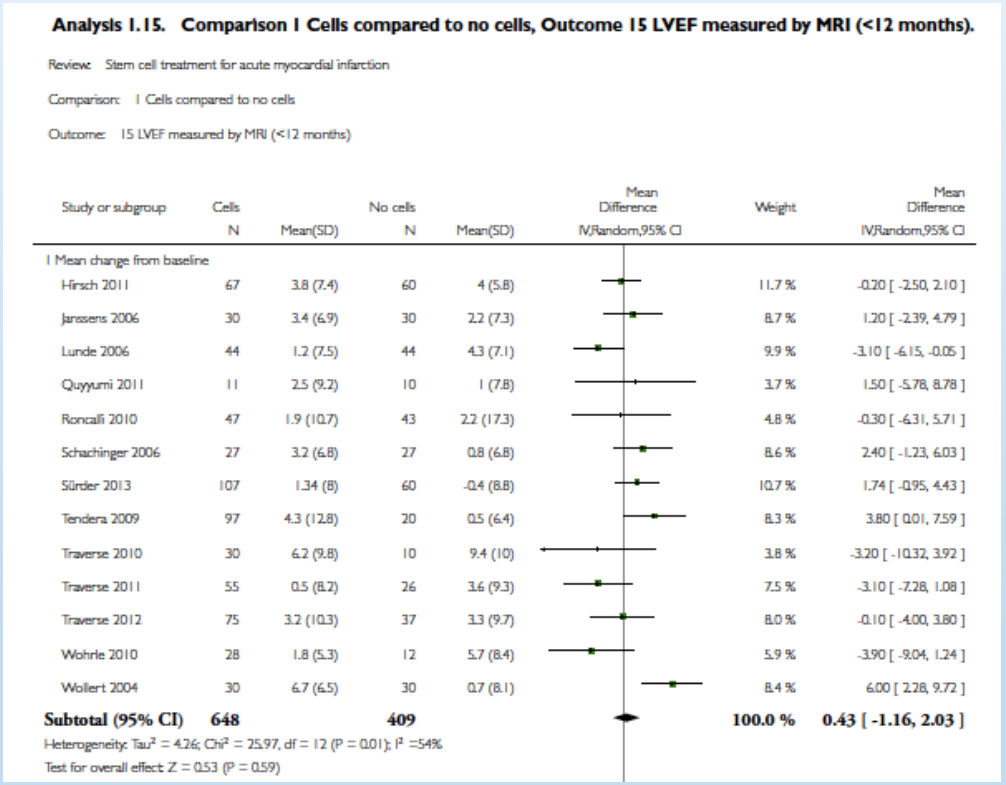
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Short-term follow-up (< 12 months)					
Gao 2013	1/21	0/22		3.9 %	3.14 [0.13, 72.96]
Hukuri 2008	0/40	1/40		3.8 %	0.33 [0.01, 7.95]
Janssens 2006	1/33	0/34		3.8 %	3.09 [0.13, 73.20]
Nogueira 2009	1/24	0/6		4.0 %	0.84 [0.04, 18.44]
Penicka 2007	3/17	0/10		4.7 %	4.28 [0.24, 75.20]
Piepoli 2010	2/19	4/19		15.5 %	0.50 [0.10, 2.41]
Plewka 2009	2/40	2/20		10.8 %	0.50 [0.08, 3.29]
Quyyumi 2011	1/16	0/15		3.9 %	2.82 [0.12, 64.39]
Roncalli 2010	1/48	0/44		3.8 %	2.76 [0.12, 65.92]
Schachinger 2006	2/101	2/103		10.2 %	1.02 [0.15, 7.10]
Sürder 2013	2/115	0/60		4.2 %	2.63 [0.13, 53.90]
Tendera 2009	2/160	1/40		6.8 %	0.50 [0.05, 5.38]
Traverse 2011	0/58	1/29		3.8 %	0.17 [0.01, 4.04]
Traverse 2012	1/79	0/41		3.8 %	1.58 [0.07, 37.83]
Wang 2014	1/28	2/30		7.0 %	0.54 [0.05, 5.59]
Wohrle 2010	1/29	1/13		5.3 %	0.45 [0.03, 6.63]
Zhukova 2009	0/8	1/3		4.3 %	0.15 [0.01, 2.91]
Subtotal (95% CI)	**836**	**529**		**100.0 %**	**0.80 [0.43, 1.49]**

Total events: 21 (Cells), 15 (No cells)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.33$, df = 16 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 0.70 (P = 0.49)

All-cause mortality



Analysis 1.15. Comparison 1 Cells compared to no cells, Outcome 15 LVEF measured by MRI (<12 months).

Review: Stem cell treatment for acute myocardial infarction

Comparison: 1 Cells compared to no cells

Outcome: 15 LVEF measured by MRI (<12 months)

Study or subgroup	Cells N	Mean(SD)	No cells N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mean change from baseline							
Hirsch 2011	67	3.8 (7.4)	60	4 (5.8)		11.7 %	-0.20 [-2.50, 2.10]
Janssens 2006	30	3.4 (6.9)	30	2.2 (7.3)		8.7 %	1.20 [-2.39, 4.79]
Lunde 2006	44	1.2 (7.5)	44	4.3 (7.1)		9.9 %	-3.10 [-6.15, -0.05]
Quyyumi 2011	11	2.5 (9.2)	10	1 (7.8)		3.7 %	1.50 [-5.78, 8.78]
Roncalli 2010	47	1.9 (10.7)	43	2.2 (17.3)		4.8 %	-0.30 [-6.31, 5.71]
Schachinger 2006	27	3.2 (6.8)	27	0.8 (6.8)		8.6 %	2.40 [-1.23, 6.03]
Sürder 2013	107	1.34 (8)	60	-0.4 (8.8)		10.7 %	1.74 [-0.95, 4.43]
Tendera 2009	97	4.3 (12.8)	20	0.5 (6.4)		8.3 %	3.80 [0.01, 7.59]
Traverse 2010	30	6.2 (9.8)	10	9.4 (10)		3.8 %	-3.20 [-10.32, 3.92]
Traverse 2011	55	0.5 (8.2)	26	3.6 (9.3)		7.5 %	-3.10 [-7.28, 1.08]
Traverse 2012	75	3.2 (10.3)	37	3.3 (9.7)		8.0 %	-0.10 [-4.00, 3.80]
Wohrle 2010	28	1.8 (5.3)	12	5.7 (8.4)		5.9 %	-3.90 [-9.04, 1.24]
Wollert 2004	30	6.7 (6.5)	30	0.7 (8.1)		8.4 %	6.00 [2.28, 9.72]
Subtotal (95% CI)	**648**		**409**			**100.0 %**	**0.43 [-1.16, 2.03]**

Heterogeneity: $Tau^2 = 4.26$; $Chi^2 = 25.97$, df = 12 (P = 0.01); $I^2 = 54\%$

Test for overall effect: Z = 0.53 (P = 0.59)

LV EF measured by MRI

Why I prefer IPD based meta-analyses

IPD-based meta-analysis

ID	age	gender	group	DM	Base-EF	Base_EDV
221233	56	male	Cell therapy	yes	55	130

1. Each study can be included
2. Consistent terms and conditions
3. **Controlled and transparent data** (independent data monitoring board)
4. Analysis of predictive factors for different outcomes
5. Analysis of patient subgroups

Study	Mean change	SD	Nr of treated	Mean change	SD	Nr of controls
Study	5	1	50	3	2	50

Publication-based meta-analysis

1. Random-effect meta-analysis can include only studies with published means, thus studies with reported medians are automatically excluded (eg. HEBE, MYSTAR, REGENT, etc)
2. Not prevented by publication errors and bias (eg. Strauer studies with over 700 patients were included in every meta-analyses until 2015; or studies withdrawn later, or double publications)
3. Heterogeneity (up to 92.2%) of end points and clinical definitions (eg. cardiac death or all-case death, etc),
4. Not useful for analysis of subgroups

Why I prefer IPD based meta-analyses

Data collection bias

IPD-based meta-analysis

1. Selected studies are included in ACCRUE; results depend on:
   1. Arbitrary willingness to send data
   2. Insitutional policy to participate in the ACCRUE consortium
   3. Agreement with the aim and methods of ACCRUE
   4. Due to different definitions, unavoidable discrepancies raised in terms and result interpretation – vulnerable target for international critics; PIs want to avoid that.
2. Focus on most important parameter: keeping the DB as simple as possible

ID	age	gender	group	DM	Base-EF	Base_EDV
221233	56	male	Cell therapy	yes	55	130

Publication-based meta-analysis

Publication-based meta-analyses can evaluate all published parameters, such as
- different follow-up times,
- injected cell volume,
- infarct size,
- bone marrow aspiration in the control group,
- different cells
- details on cell preparation,
- quality of life scores, or any subjective or semiobjective parameter.

Some of these data are evaluated even if they are only reported in a fraction of the collected trials, leading to contradictory results.

Study	Mean change	SD	Nr of treated	Mean change	SD	Nr of controls
Study	5	1	50	3	2	50

Why I prefer IPD based meta-analyses

Data collection bias

IPD-based meta-analysis

Using IPDs avoids data conflicts.

Publication-based meta-analysis

ID	age	gender	group	DM	Base-EF	Base_EDV
221233	56	male	Cell therapy	yes	55	130

Study	Mean change	SD	Nr of treated	Mean change	SD	Nr of controls
Study	5	1	50	3	2	50

1. Can include all studies, can analyse all parameters, such as QOL, injected cell volume, even if the data are reported only in a fraction of the studies, resulting in conflicting results:

Fisher 2015	**Restenosis**	**TVR**
Short-term	11.3%	11.9%
9 studies		
Long-term	2.7%	14.3%
4 studies		

WMSC		**Nr of pts**	**WMSC**	**Signif**
Short-term <12mo				
Clifford	2012	747	-0.06	n.s.
Chong	2015	793	-0.06	0.002
Long-term <12 mo				
Clifford	2012	279	-0.12	0.004

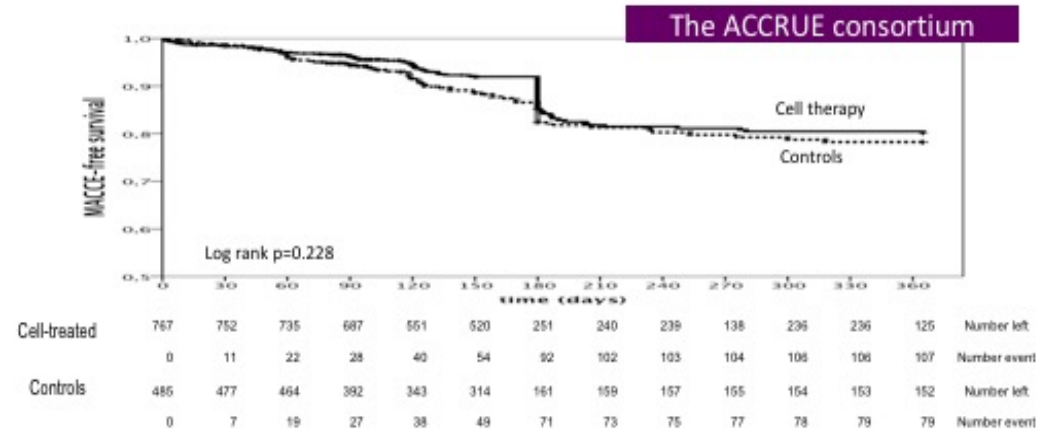
Infarct size		**Nr of pts**	**Infarct size**	**Signif**
Short-term <12mo				
Martin-Rendon	2008	240	-3.51%	0.004
Clifford	2012	670	-1.9%	n.s.
Long-term <12 mo				
Martin-Rendon		na	na	
Clifford	2012	353	-3.36%	0.0021

Why I prefer IPD based meta-analyses

Data collection bias

IPD-based meta-analysis

Ultimate benefit: Time to event: Survival curve



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ID	age	gender	group	DM	Base-EF	Base_EDV
221233	56	male	Cell therapy	yes	55	130

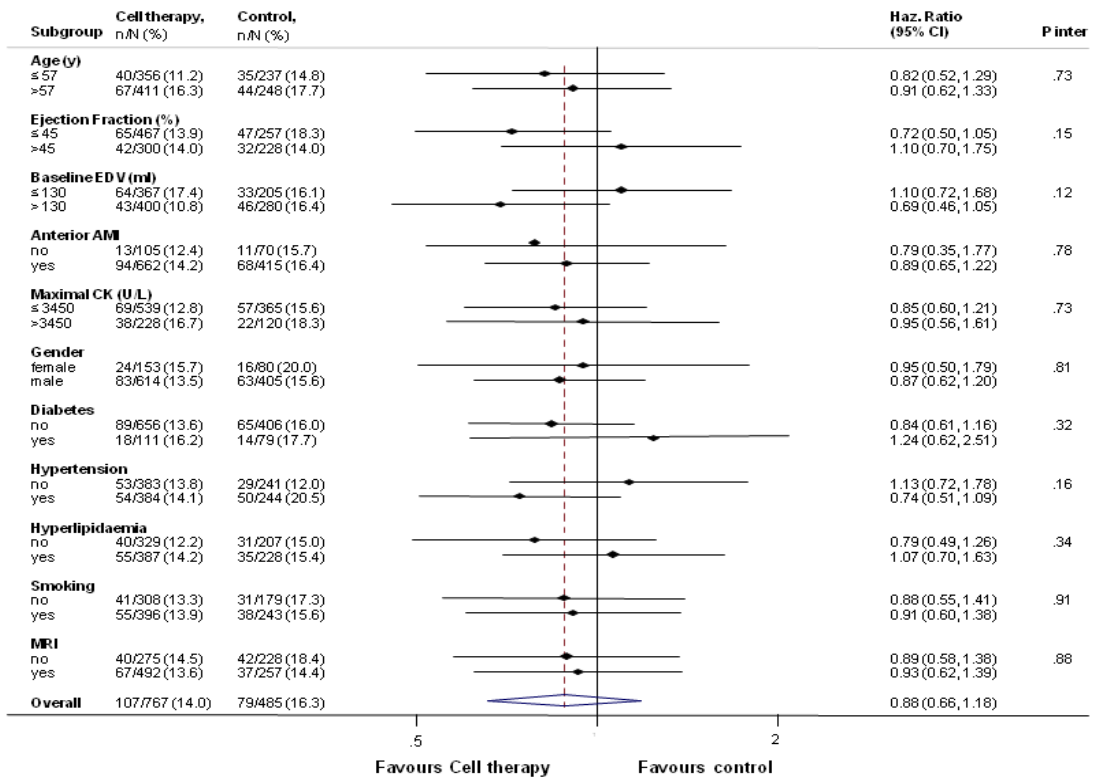
Study	Mean change	SD	Nr of treated	Mean change	SD	Nr of controls
Study	5	1	50	3	2	50

Why I prefer IPD based meta-analyses

IPD-based meta-analysis

Data collection bias

Ultimate benefit: Subgroup analysis



ID	age	gender	group	DM	Base-EF	Base_EDV
221233	56	male	Cell therapy	yes	55	130

Study	Mean change	SD	Nr of treated	Mean change	SD	Nr of controls
Study	5	1	50	3	2	50

Why I prefer IPD based meta-analyses

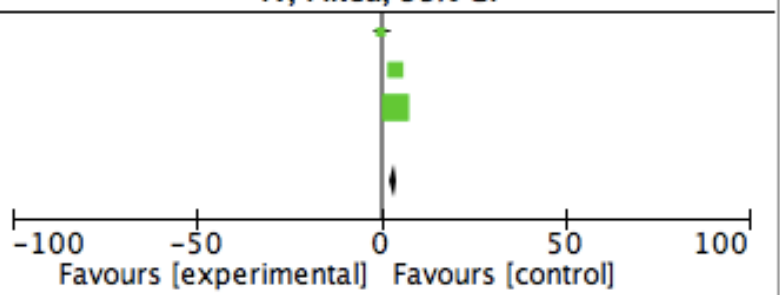
Data analysis bias

The statistical paradox

Study or Subgroup	Stem cell treated Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Study 1	0	5	50	0	5	50	11.8%	0.00 [-1.96, 1.96]
Study 2	5	1	5	1	1	5	29.4%	4.00 [2.76, 5.24]
Study 3	5	1	10	1	1	10	58.8%	4.00 [3.12, 4.88]
Total (95% CI)			**65**			**65**	**100.0%**	**3.53 [2.86, 4.20]**

Heterogeneity: $Chi^2 = 14.12$, $df = 2$ ($P = 0.0009$); $I^2 = 86\%$

Test for overall effect: $Z = 10.29$ ($P < 0.00001$)



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Why I prefer IPD based meta-analyses

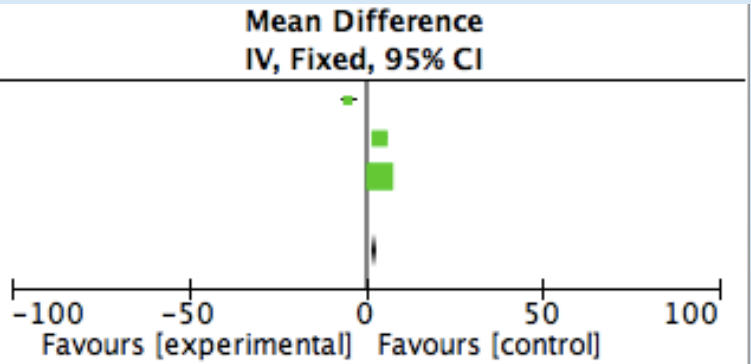
Data analysis bias

The statistical paradox

Study or Subgroup	Stem cell treated Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Study 1	0	5	50	5	5	50	11.8%	-5.00 [-6.96, -3.04]
Study 2	5	1	5	1	1	5	29.4%	4.00 [2.76, 5.24]
Study 3	5	1	10	1	1	10	58.8%	4.00 [3.12, 4.88]
Total (95% CI)			**65**			**65**	**100.0%**	**2.94 [2.27, 3.61]**

Heterogeneity: $Chi^2 = 71.47$, $df = 2$ ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: $Z = 8.57$ ($P < 0.00001$)



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Why I prefer IPD based meta-analyses

Data analysis bias

Intracoronary cell injection	FUP time	Number of patients	Changes in EF from baseline to FUP mean ±SD	Number of controls	Changes in EF from baseline to FUP mean ±SD	Comments
Ge[29]	6 mo	10	4.8	10	3.5	*a*
Janssens[30]	4 mo	30	3.4±6.9	30	2.2±7.3	
Penicka[31]	4 mo	14	15.4	10	20.5	*a*
Meluzin[32]	3 mo	44	2±1 and 5±1	22	2±1	
Suarez[33]	3 mo	10	20±8	10	6±10	
Noguira[34]	6 mo	14	6.7±5.5	6	2±11.5	*b*
Plewka[35]	6 mo	38	10±9	18	5±8	
Cao[36]	6 mo	41	9.4	45	7.1	*a*
Yao[37]	12 mo	27	NA	12	2.9±2	*c*
Grajek[38]	6 and 12 mo	31	NA	14	NA	*a*
Piepoli[39]	12 mo	19	13.1±1.9	19	5.3±2	
Hirsch[40]	4 mo	67	3.8±7.4	60	4.0±5.8	*d*
Turan[41]	3 mo	42	NA	20	NA	
Liepic[42]	6 mo	26	3±7.3	10	3.8±4.6	
Quyyumi[43]	6 mo	11	2.5±9	10	1±7.8	*e*
Colombo[44]	12 mo	10	3±2.7	5	-3±3.9	*f*
Chen[45]	3 mo	34	NA	35	NA	*a*
Houtgraaf[46]	6 mo	9	4.6	4	NA	*g*
Ruan[47]	6 mo	9	NA	11	NA	*a*

a: SD of changes at FUP were not reported;
b: 10 patients received retrograde intravenous cell therapy; separate SD of changes were not reported;
c: data of repeated intracoronary injection of cells 3 months post-AMI in Group B were pooled to the single injection Group A, but significant difference between Group A and B was reported.
d: patients with intracoronary infusion of peripheral blood mononuclear cells are not included
e: dose escalation study with 3 different doses
f: data of bone marrow (Group A) and peripheral blood mononuclear cells (Group B) were pooled
g: 3:1 randomization of 14 patients with 1 drop-out; SD of changes in cell therapy group not available, no data of changes in EF in control group

Why I prefer IPD based meta-analyses

Data analysis bias

Intracoronary cell injection	FUP time	Number of patients	Changes in EF from baseline to FUP mean ±SD	Number of controls	Changes in EF from baseline to FUP mean ±SD	Comments	Changes in EF pts (J. Circ 2012)	Changes in EF controls (J. Circ 2012)	Changes in EF pts (de J, Circ HeartF 2014)	Changes in EF controls (de J, Circ HeartF 2014)
Ge[29]	**6 mo**	**10**	**4,8**	**10**	**3,5**	***a***	**4,8±9.6**	**-1.9±5.9**	**4.8±5.2**	**3.0±6.5**
Janssens[30]	4 mo	30	**3.4±6.9**	30	2.2±7.3		**3.4±6.9**	2.2±7.3	**3.4±6.9**	2.2±7.3
Penicka[31]	4 mo	14	**15,4**	10	20,5	*a*	**15.4±5.5**	20.5±4.6	**6±5**	8±4.8
Meluzin[32]	3 mo	44	**2±1 and 5±1**	22	2±1		**4.0±4.7**	2.0±4.7	**5±6.6**	0±8.9
Suarez[33]	3 mo	10	**20±8**	10	6±10		**21±8**	6±10	**21±8**	6±5.2
Noguira[34]	6 mo	14	**6.7±5.5**	6	2±11.5	*b*	**6.9±6.2**	2±11	**6.7±5.5**	2±11.5
Plewka[35]	6 mo	38	**10±9**	18	5±8		**9±7**	3±3.6	**9±5.8**	5±4.9
Cao[36]	6 mo	41	**9,4**	45	7,1	*a*	**11.5±3.2**	7.9±3.4	**9.4±1.8**	7.1±2.6
Yao[37]	12 mo	27	**NA**	12	2.9±2	*c*	**2.4±3.1**	1.6±2.1	**6.2±2.4**	2.2±1.8
Grajek[38]	**6 and 12 mo**	**31**	**NA**	**14**	**NA**	***a***	**-3.4±5.9**	**-6.4±7.9**	**-2.5±5.6**	**0±7.8**
Piepoli[39]	**12 mo**	**19**	**13.1±1.9**	**19**	**5.3±2**		**9.5±2.6**	**3.5±2.9**	**8.4±9.2**	**2.2±12.6**
Hirsch[40]	4 mo	67	**3.8±7.4**	60	4.0±5.8	*d*			**3.8±7.4**	5.2±5.8
Turan[41]	3 mo	42	**NA**	20	NA		**11±6**	1±6.3	**11±6**	1±6.3
Liepic[42]	6 mo	26	**3±7.3**	10	3.8±4.6		**3±7.3**	3.8±4.6		
Quyyumi[43]	6 mo	11	**2.5±9**	10	1±7.8	*e*	**2.5±9**	1±7.8		
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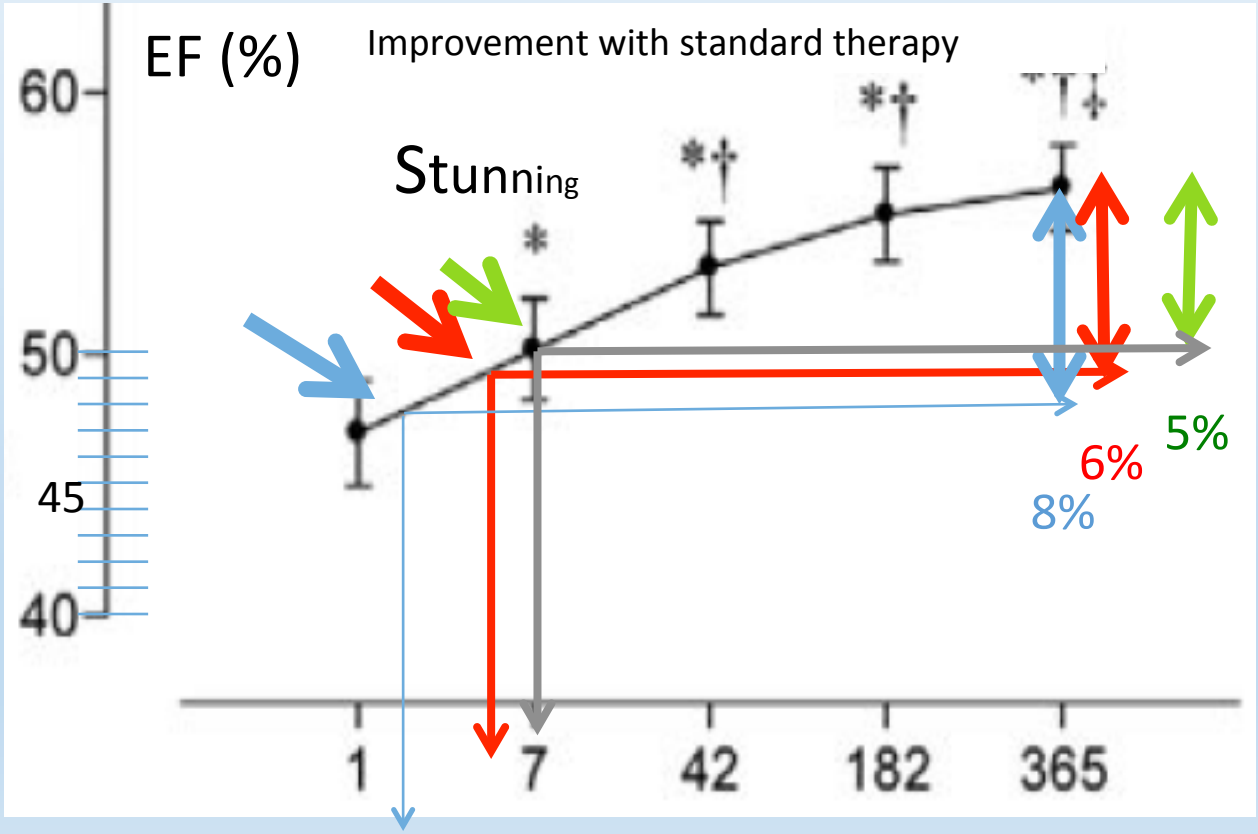
Chen[45]	3 mo	34	**NA**	35	NA	*a*	**18±6.8**	6±6.9		
Houtgraaf[46]	6 mo	9	**4,6**	4	NA	*g*				
Ruan[47]	6 mo	9	**NA**	11	NA	*a*				

Why I prefer IPD based meta-analyses

Data analysis bias

„Lower EF is associated with more increase in EF in cell treatment group."

Lower EF with subsequent more increase in EF is associated with the *time* of the EF measurement, and randomization.
Accordingly, patients in placebo group have also higher increase in EF if they have low EF at the randomization)



ACCRUE	Changes in EF from baseline to FUP	
	Cell-treated group	Controls
Baseline EF		
<50%	4.1±9%	3.5±9.0%
<45%	4.5±9.8%	3.8±9.0%
<40%	5.0±9.7%	4.1±9.6%

Gyöngyösi. Controversies... Circ Res 2016

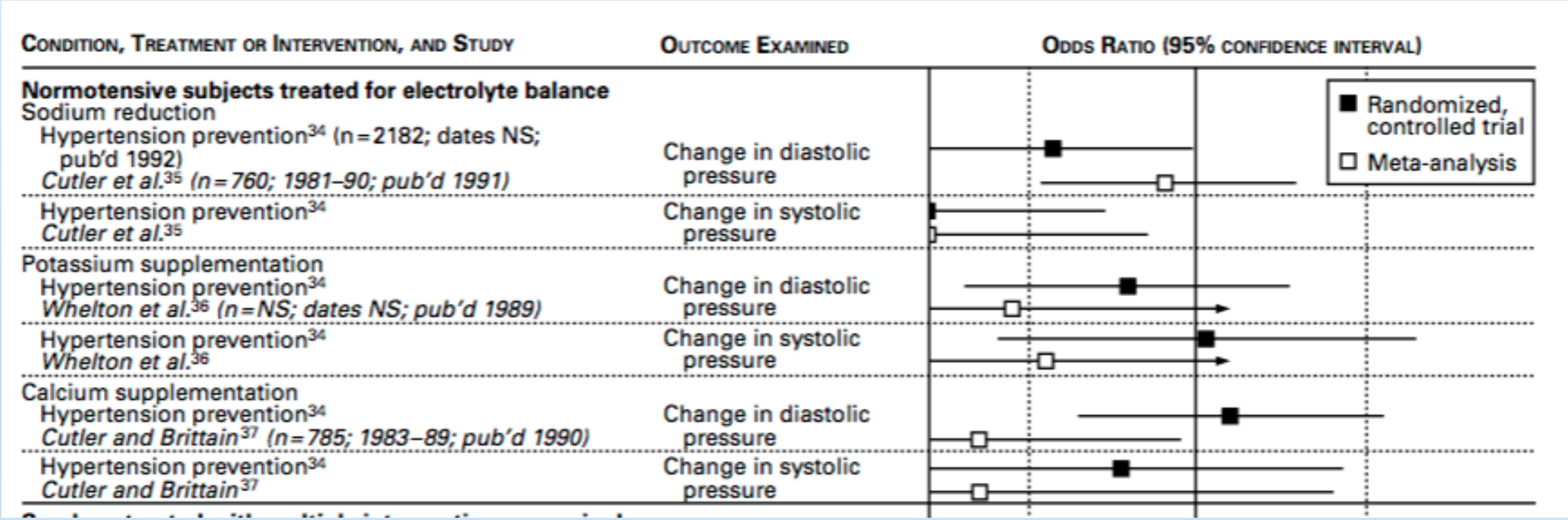
Adapted from Engblom et al. Circ Cardiovasc Imaging. 2009

Why I prefer IPD based meta-analyses

Data analysis bias

Pitfalls of Evidence-Based Medicine:
Negative Outcome of a Randomized Clinical Study Based on Positive Meta-Analysis Results

1. Results of meta-analyses can differ from subsequent large randomized clinical trials; the observed effect could be overestimated.
2. Positive meta-analysis results can pave the way to initiating a large randomized clinical study with a neutral or negative outcome, as has been observed several times in medical literature and practice.



Gyöngyösi. Controversies... Circ Res 2016

LeLorier J. NEJM 1997

Why I prefer IPD based meta-analyses

Data analysis bias

Pitfalls of Evidence-Based Medicine:
Negative Outcome of a Randomized Clinical Study Based on Positive Meta-Analysis Results

1. Large randomized trials are considered the gold standard with the highest quality level I evidence for application of the study results in clinical practice based on the evidence-based medicine grading system.

2. Importantly, the prespecified data collected in IPD-based meta-analyses (eg, ACCRUE) allow the results to truly reflect the original data, as well as pool them in a database in similar form as clinical trial case reports.

Center	Name_of_study	Patient_Identifiaction	Age	Gender	Randomized_yes_or_no	Randomized to group	Main_Diagnosis (post_Acute_Myocardial_Infarction/ischemic_Cardiomyopathy)	Canadian_Society_of_Cardiology_Angina_Score-before_Cell_treatment	New_York_Heart_Assotiation_Heart-Failure_Score_before_Cell_treatment	Diabetes mellitus (yes/no)	Hypertension (yes/no)	Hyperlipidaemia (yes/no)	Smoking (yes/ex/no)	Family history of Coronary_Artery_Disease (yes/no)	No of diseased vessel beore Cell therapy (1/2/3)
Test1	Test	1234	56	m	yes	cell thera	iCMP	2	3	yes	yes	no	no	yes	2

Thus, IPD collection may be considered a novel prospective multicenter large randomized clinical trial and the IPD meta-analyses as evidence-based medicine.

Gyöngyösi. Controversies... Circ Res 2016

Why I prefer IPD based meta-analyses

1. Your life is not boring:

It takes much longer time to gather the IPDs and analyse, than the analysis of the publication-based data

ACCRUE:

1. Busy 7 years to gather over2000 IPDs, fully exhausting 2 GB email box capacity with round 100 email partners for appr. 10.000 emails,

considering that and inbetween several other meta-analyses with positive outcome are published with much higher number of data

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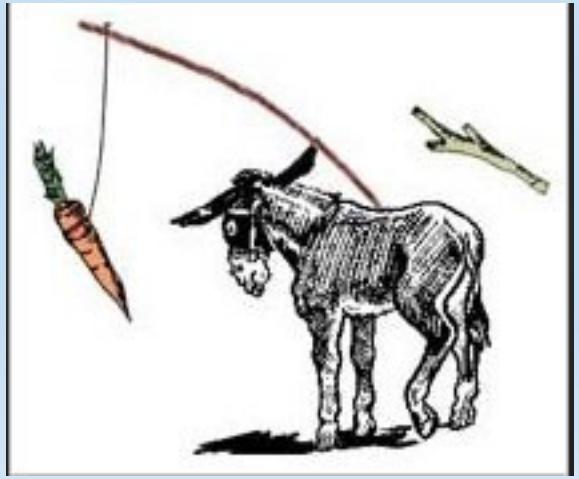
You have the feeling, never reach the target



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2. At the end of the story you are satisfied with yourself, because, you have learnt a lot of things, such as
   1. understanding and performance of the most complicated statistics,
   2. you can handle your frustration about the negative outcome of the analysis.

- The IPD meta-analysis is currently considered the gold standard for meta-analyses assessing the impact of a treatment on clinical outcomes, especially in the case of small and medium-sized clinical cardiac regeneration studies.

- This meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) represents the first prospective meta-analysis in this field to be based on individual patient data (IPD).

- This approach generates time-to-event data for estimating survival, can explore heterogeneity at the patient level, and allows subgroup analyses.

- Using pre-specified terms and conditions, the database is similar to that of a prospective multicenter randomized clinical trial with similar statistical assessment modalities combined with standardized approaches to evaluating meta-analyses.

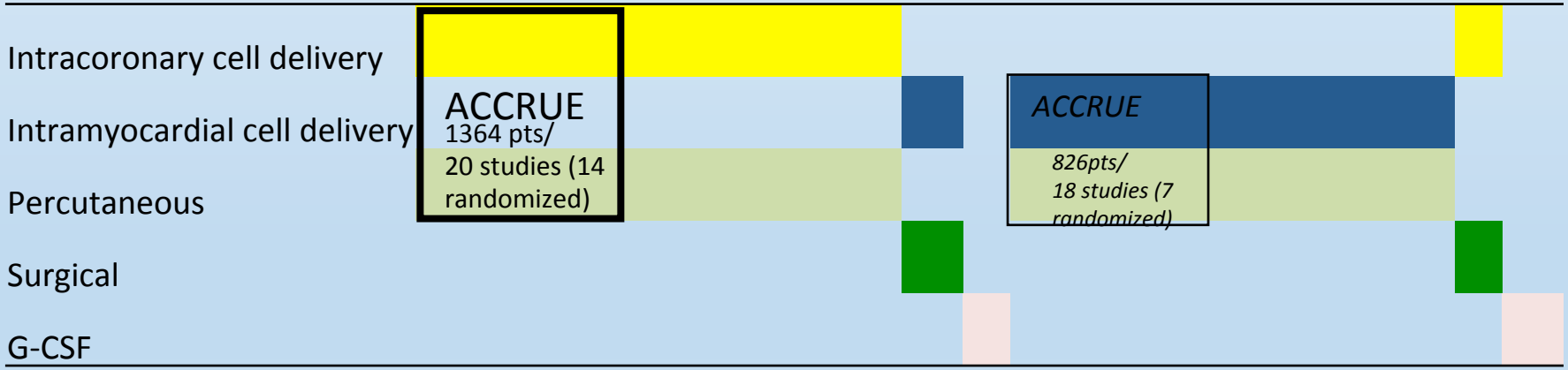
- Collection of IPDs is going-on, including further studies, G-CSF studies, and long-term FUP data.

Summary of Why I prefer IPD based meta-analyses

Thank you for the valuable support of all ACCRUE participants

Cardiac cell-based regeneration studies

	Acute STEMI	Chronic IHD
Number of studies	41	39
Number of included patients	2732	1921
Randomized studies	41	39



Source: Fisher et al. Cochrane Library 2015

Source: Fisher et al. Cochrane Library 2016