# Long-Term Effects of Autologous Bone Marrow Stem Cell Treatment in Acute Myocardial Infarction: Factors That May Influence Outcomes

# David M. Clifford<sup>1,2<sup>x</sup></sup>, Sheila A. Fisher<sup>3</sup>, Susan J. Brunskill<sup>3</sup>, Carolyn Doree<sup>3</sup>, Anthony Mathur<sup>4,6</sup>, Mike J. Clarke<sup>5</sup>, Suzanne M. Watt<sup>1,2</sup>, Enca Martin-Rendon<sup>1,2</sup>\*

 Stem Cell Research Laboratory, NHS-Blood and Transplant, John Radcliffe Hospital, Oxford, United Kingdom, 2 Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, United Kingdom, 3 Systematic Review Initiative, Clinical Research Group, NHSBT-Oxford, John Radcliffe Hospital, Oxford, United Kingdom, 4 Department of Clinical Pharmacology, William Harvey Research Institute, London, United Kingdom, 5 All-Ireland Hub For Trials Methodology Research, Queen's University, Belfast, United Kingdom, 6 Barts and the London NIHR Biomedical Research Unit, London, United Kingdom

## Abstract

*Aims:* To investigate whether there are important sources of heterogeneity between the findings of different clinical trials which administer autologous stem cell treatment for acute myocardial infarction (AMI) and to evaluate what factors may influence the long-term effects of this treatment.

*Methods and Results:* MEDLINE (1950-January 2011), EMBASE (1974-January 2011), CENTRAL (*The Cochrane Library* 2011, Issue 1), CINAHL (1982-January 2011), and ongoing trials registers were searched for randomised trials of bone marrow stem cells as treatment for AMI. Hand-searching was used to screen recent, relevant conference proceedings (2005–2010/11). Meta-analyses were conducted using random-effects models and heterogeneity between subgroups was assessed using chi-squared tests. Planned analyses included length of follow-up, timing of cell infusion and dose, patient selection, small trial size effect, methodological quality, loss of follow-up and date of publication. Thirty-three trials with a total of 1,765 participants were included. There was no evidence of bias due to publication or time-lag, methodological quality of included studies, participant drop-out, duration of follow-up or date of the first disclosure of results. However, in long-term follow-ups the treatment seemed more effective when administered at doses greater than 10<sup>8</sup> cells and to patients with more severe heart dysfunction.

*Conclusions:* Evaluation of heterogeneity between trials has not identified significant sources of bias in this study. However, clinical differences between trials are likely to exist which should be considered when undertaking future trials.

Citation: Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, et al. (2012) Long-Term Effects of Autologous Bone Marrow Stem Cell Treatment in Acute Myocardial Infarction: Factors That May Influence Outcomes. PLoS ONE 7(5): e37373. doi:10.1371/journal.pone.0037373

Editor: Giuseppe Biondi-Zoccai, Sapienza University of Rome, Italy

Received January 6, 2012; Accepted March 28, 2012; Published May 24, 2012

**Copyright:** © 2012 Clifford et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** This work was commissioned by the National Health Service Blood and Transplant (NHSBT), Research and Development (SJB, CD and SAF), and the National Institute of Health Research (NIHR), UK, under its Programme Grant Scheme (RP-PG-0310-1001, EMR and SMW). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. DMC was sponsored by the Advanced Medical Science programme, University of Melbourne, Australia. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

\* E-mail: enca.rendon@ndcsl.ox.ac.uk

¤ Current address: University of Melbourne, Melbourne, Australia

#### Introduction

Although advanced therapies have improved short-term survival following acute myocardial infarction (AMI), the incidence of heart failure is steadily increasing worldwide [1]. Current treatments do not address the substantial loss of tissue through injury nor cell death incurred during AMI [2]. In the last decade, autologous bone marrow stem cell (BMSC) treatment has aimed to complement thrombolytic therapies and primary angioplasty in the treatment of AMI (for review see [3]). The hypothesis has been that BMSC would improve heart function delaying the progression of the disease. There is now a substantial body of evidence from randomised trials to assess the effects of this treatment, and a recent update of a Cochrane review by several of the authors of this paper has systematically reviewed this evidence [4].

The first clinical trials were designed to test the safety and feasibility of this new treatment, but were not necessarily powered to assess its efficacy and long-term effects on survival free of major associated cardiac events [5,6,7,8,9]. To date the treatment appears safe and associated with low mortality and morbidity rates (for review see [3,10]). However, there is controversial evidence that a beneficial effect on global heart function is significant and persist long-term (for review see [5,11] and references therein). Clinical evidence from randomised trials of intracoronary infusion of BMSC post-AMI have been evaluated previously in several meta-analyses [10,12,13]. The major limitations in the field that may contribute to these conflicting

results among trials include the small trial sizes and differences in patient selection, participants lost to follow-up, cell isolation protocols, cell dose/type, timing of cell infusion, route of delivery and methodologies used to measure surrogates; as well as variation in data acquisition and data analysis protocols. In addition, new interventions generally raise concerns that early optimism is fuelled by extreme results in early disclosure just to be contradicted by later results [14,15,16]. The rationale of the underlying Cochrane systematic review was to evaluate the efficacy of any dose of autologous BMSC administered to patients with a diagnosis of AMI following revascularisation [4]. In our previous study, sub-group analyses were planned to assess the effect of using different methods (e.g. magnetic resonance imaging (MRI), echocardiography, left ventricular angiography, single positron emission computed tomography (SPECT) or radionucleide ventriculography (RNV)) to measure heart function [4]. The aim of the present study was to conduct further risk of bias and sub-group analyses to explore whether the overall estimate of treatment effect size is a reliable guide to its effect and therefore to address some of the limitations in the field. Here, pre-planned analyses included (i) small trial size effect, (ii) trial quality and participants lost to followup, (iii) length of follow-up in the trial design, (iv) date of publication bias, (v) timing of cell infusion, (vi) cell dose/type, (vii) route of delivery and (viii) differences in patient selection.

#### Methods

#### Eligibility

Inclusion criteria: (i) randomized trials, (ii) participants with a clinical diagnosis of AMI, (iii) within a month of receiving revascularisation by percutaneous coronary intervention (PCI) or thrombolytic therapy or both, (iv) any dose of autologous BMSC, (v) any route of administration, (vi) in the comparator arm participants did not receive BMSC and (vii) any co-interventions provided they were equally applied to each trial arm.

#### Search Strategy

The search strategy is detailed elsewhere [4]. Briefly, databases were searched through to January 31st 2011 for randomised trials in which BMSC were administered as treatment for AMI, including MEDLINE (1950-2011), EMBASE (1974-2011), CEN-TRAL (The Cochrane Library 2011, Issue 1), CINAHL (1982-2011), PubMed, Lilacs, and the Transfusion Evidence Library. Ongoing trial registers (ClinicalTrials.gov, the ISRCTN Register and the WHO International Clinical Trials Platform Registry) were also searched. Searches were combined with adaptations of the Cochrane highly sensitive RCT search filter in MEDLINE, EMBASE and CINAHL [17]. No restrictions by language, year of publication or publication status were imposed. Proceedings from the American Heart Association (2005-2010) and International Society of Stem Cell Research (2005-2011) conferences and the reference lists of identified studies and relevant review articles were hand searched for additional studies.

#### Data Extraction

For each eligible trial, the study and patient population characteristics, the nature of the intervention and comparator, and the outcomes assessed were extracted. The quality of the studies was assessed on the bases of generation of random sequence, concealment of treatment allocation, blinding of outcome assessment and adequacy of follow-up [18]. Eligibility screening, data extraction and assessment of methodological quality were undertaken independently by a total of three reviewers, such that at least two reviewers looked at each potentially eligible trial. Where a trial had used several methods for outcome assessment (e.g. echocardiography, MRI, SPECT, RNV or left ventricular angiography), MRI data were preferentially included in our analysis.

#### Statistical Analysis

Outcome data were analysed quantitatively using RevMan 5 and presented as relative risk (RR) for dichotomous outcomes or weighted mean difference (WMD) for continuous outcomes with 95% confidence interval (CI), two-sided significance tests are reported. Meta-analyses were undertaken using random effects models, due to the high degree of heterogeneity present in these studies [4,10]. Statistical heterogeneity was examined using the I<sup>2</sup> statistic [19] and the chi-squared test.

#### Sensitivity Analysis

Bias related to study size (such as publication bias [20]) was assessed by Funnel plots with Egger's test used to assess asymmetry. Sensitivity analyses were undertaken for all relevant included data to assess the influence of (i) the methodological quality of the trials, (ii) the length of follow-up, (iii) participant drop-out and (iv) publication date. These analyses were specified before they were conducted. In the first instance, trials where the generation of random sequence was rated adequate (marked YES) were analysed separately from those where the generation of random sequence was rated as unclear (marked UNCLEAR) or inadequate (marked NO) as a possible explanation for observed statistical heterogeneity. To assess the effect of length of follow-up on results, trials with short term follow-up periods that have been followed up long term were analyzed separately from those with no long-term follow-up. The influence of participants drop-out was determined by analyzing separately trials with less than 20% drop-out, randomised trials with 20 to 50% drop-out and randomised trials with greater than 50% drop-out for major outcomes measured as dichotomous data (e.g. mortality, reinfarction and target vessel revascularisation). Finally, trials were subgrouped on the basis of their by start date, end date, publication of the main/full article and disclosure or publication of the first results on the primary outcome (LVEF), to assess the possibility of a relationship between publication date and effect size. Other potential reasons for observed heterogeneity were explored via sub-group analysis, with particular emphasis placed on clinical, treatment and outcome measurement differences among the included studies. Sub-groups were stratified by the timing of BMSC transplantation from onset of AMI, dose of BMSC administered, route of administration and baseline LVEF. Differences in effect size between subgroups were assessed using chi-squared tests for heterogeneity between sub-groups as implemented in RevMan 5.

## Results

# Description of the Included Studies and Summary of Previous Findings

The search strategy followed has been described in detail elsewhere [4]. A total of 2,169 citations were identified in the initial search of which thirty-three were primary references to eligible studies (Figure S1). The characteristics of all included studies are detailed in Tables S1 and S5. The thirty-three included randomised trials represent thirty-nine treatment comparisons where BMSC was compared with control in 1,765 patients. Treatment comparisons were defined following the criteria previously described (for review see also [4]). Clinical outcomes and efficacy of BMSC treatment following AMI are fully described in detail in our previous study [4] and are summarised here and in supplementary material for clarity. BMSC administration within a month of AMI has no significant effect on mortality, morbidity, or adverse events. Cumulative figures are presented as  $\leq 61$  months follow-up in supplementary data (Table S2 and reference to studies in Table S5). The statistical heterogeneity in this case was negligible ( $I^2 = 0 - 11\%$ ). However, a statistical power calculation showed that a study with over 5,000 participants in each randomised group would be required in order to achieve 80% power to detect any significant difference in mortality rates given the relatively low incidence of death within the follow-up period for these trials (2.8% in BMSC and 3.6% in Control groups, respectively). BMSC treatment significantly improved left ventricular volumes and ejection fraction in short- and long-term followup periods. However, a considerable degree of statistical heterogeneity ( $I^2 > 75\%$ ) was observed in both infarct size and LVEF comparisons. A summary is presented in supplementary data (Table S3 and reference to studies Table S5). As global LVEF and infarct size have been used as surrogates in many of the included trials, this study was design to explore the observed heterogeneity using these two outcome measures.

#### Exploring Heterogeneity: Risk of Bias

In order to explore the heterogeneity observed above and to dispel concerns raised with novel interventions, risks of bias were assessed according to the criteria described in the Methods.

- (a) Risk of publication bias and small study effect. The possibility of publication bias and study size was assessed by Funnel plot and the Egger's test (Figure 1A&B). The analysis showed no significant small study effects (p = 0.726) and, therefore, little evidence of publication bias.
- (b) Methodological quality of included studies. The quality assessment of the included studies is summarized in supplementary data (Table S4). Sensitivity analysis to estimate the effect of randomization on LVEF was not required as all included studies followed an adequate method of sequence generation during randomization (Table S4) and this could be assessed because of the high quality of reporting of these relatively recent trials.
- Loss of follow-up bias on mortality and morbidity. (c) In 37 trials, 80% or more (ranging from 80%-100%) of randomized participants were analyzed by their randomized treatment group. One trial did not report loss of follow-up [21]. In the remaining trial, only 63.64% of randomized participants were included in the analysis [22]. Sensitivity analyses excluding this trial from the meta-analysis [22] had a negligible effect on the effects on mortality during short term (RR 0.80, 95% CI 0.40 to 1.61, p = 0.52 compared to RR 0.75, 95% CI 0.39 to 1.46, p = 0.40 and long term (RR 0.63, 95% CI 0.20 to 2.00, p = 0.43 compared to RR 0.59, 95% CI 0.22 to 1.56, p = 0.29 follow-up. Similar results were observed for incidence of re-infarction, restenosis, hospital readmission and target vessel revascularization, suggesting a negligible risk of bias. Here the original analyses with all included studies are presented (Table S2).
- (d) Length of follow-up bias on LVEF. For this purpose, the 36 trials that reported short-term LVEF data were divided into two groups: 22 trials were followed-up only for <12 months (Figure 2A) whilst the remaining 14 trials were followed up for 12–61 months (Figure 2B). BMSC treatment effect on LVEF in trials followed up for <12 months (WMD 3.56%, 95% CI 1.74 to 5.37, p = 0.0001- Figure 2A) was not statistically different from the treatment effect in trials

followed-up for 12–61 months (WMD 2.71%, 95% CI 1.35 to 4.06, p < 0.0001- Figure 2B). These results suggest that those trials with long-term follow-up are representative of all included studies (Table S1).

Disclosure or publication date bias on LVEF. The (e) influence of study start date or end date and main publication date on the primary outcome (LVEF) was estimated by sorting the included studies according to those dates. Interestingly, no significant effect was observed in any of these comparisons, indicating a negligible risk of bias on treatment effect. However, when trials were grouped by the year when the first results were disclosed, the studies that disclosed their results first (in 2004) [6,23] showed an average greater effect on LVEF in favour of the treatment than the studies that were designed or reported later (Figure 3A). If we exclude these early trials from the metaanalysis, the overall estimate for the effect on LVEF was reduced (WMD 2.80%, 95% CI 1.83 to 3.77, p<0.001-Figure 3B) compared to the pool of all included studies (WMD 3.26%, 95% CI 2.12 to 4.40, p<0.001- Figure 3A). However, the difference was not substantial and the inclusion of trials with the early, most promising results showed low risk of bias.

#### Exploring Heterogeneity: Sub-group Analysis

- Planned sub-group analyses were carried out to assess the impact of (i) the timing of the BMSC transplantation following AMI, (ii) the dose of BMSC administered, (iii) the route of administration and (vi) the baseline LVEF on infarct size and LVEF for long term follow-up (Table 1). Timing of administration of BMSC infusion was sub-grouped into  $\leq$ 7days and >7days, to reflect the median delay to BMSC infusion from AMI across included studies. Our previous work suggested that doses of  $BMSC > 10^8$  would be required to observe a significant change in LVEF in the treated arm compared with the control arm [10]. Therefore, for the purpose of this study, trials were divided into two groups according to dose:  $\leq 10^8$  BMSC and  $> 10^8$  BMSC. All included trials where the route of administration is detailed in their methods administered BMSC via the infarct related coronary artery. Only one trial compared venus and arterial delivery of BMSC [24]. Therefore, the pre-planned analysis subgrouping the trials by route of delivery was deemed not appropriate in the present study. Finally, further analyses were carried out dividing the trials in two groups to reflect the median value of baseline LVEF in the included trials:  $\leq 40\%$  and  $\geq 40\%$  baseline LVEF.
- (a) **Timing of BMSC infusion.** Table 1 shows statistically significant changes in both infarct size (WMD = -5.2%, p = 0.007) and LVEF (WMD = 4.8%, p = 0.0003), in favour of BMSC, when the treatment was administered within 7 days post-AMI. At present, there are no data available to assess the long term effect on BMSC on infarct size for treatment administered after 7 days, however a significant difference in LVEF in favour of BMSC was maintained when the treatment was administered later than 7 days (WMD = 5.9%, p = 0.01). No significant differences between subgroups were observed for long-term follow-up LVEF (p = 0.68).
- (b) **BMSC dose.** BMSC treatment had a significant effect on infarct size (WMD = -4.3%, p = 0.005) and LVEF (WMD = 4.7%, p = 0.0001) after long-term follow-up when doses  $>10^8$  BMSC were administered. In contrast, the

### (A) Funnel Plot



# (B) Egger's test for small study effects

Egger's test	for small-st	udy effects	(Regre	ess stan	idard norm	al deviate of
intervention	effect estin	nate again s	tits sta	Indarde	error. Numk	perof studies = 36
Root MSE =	2.064. Te	st of H0: no	∣smal⊩	studyef	ffects	P = 0.726
Std_Eff	Coef.	Std. Err.	t	P>	t	[95%) Conf. Interval]
slope	2.819892	1.03708	2.72	0.010	.712292	6 4.927492
bias	.2427289	.687157	0.35	0.726	-1.153742	2 1.6392

Figure 1. Assessment of risk of bias due to publication and study size on LVEF. (A) Funnel plot and (B) Egger's test. No significant risk of publication bias or small study effects was observed.

doi:10.1371/journal.pone.0037373.g001

infarct size and LVEF showed no significant improvement when doses  $\leq 10^8$  BMSC were administered.

(c) **Baseline LVEF.** Furthermore, the long-term reduction in infarct size in favour of BMSC treatment was statistically significant when the treatment was administered to participants with baseline LVEF  $\leq 40\%$  (WMD = -5.1%, p = 0.006) whereas no significant effect was observed in participants with baseline LVEF >40% (WMD = -1.4%, p = 0.23). The difference in effect sizes these between subgroups was marginally significant (p = 0.08). The effect of BMSC on LVEF was also greater and more statistically significant when participants had LVEF  $\leq 40\%$  at baseline (WMD = 5.6%, p < 0.0001) compared with participants with baseline LVEF >40% (WMD = 2.4%, p = 0.006), the difference in effect size between these subgroups was clearly significant for this outcome (p = 0.04).

Taken together, these data indicate that the timing of BMSC transplantation following AMI, the dose of BMSC administered and the baseline LVEF are factors that may contribute to the clinical heterogeneity observed among the studies included in this meta-analysis.

#### Discussion

The present study was designed: (i) to assess potential risks of bias and diversity amongst different randomised trials to address major limitations in the field and (ii) to evaluate what factors may influence the long-term effect of BMSC treatment. This meta-analysis confirms the findings of our previous study [4] that BMSC treatment moderately improves heart function and has as yet not been associated with any significant safety concerns, but does not decrease mortality or morbidity significantly in long-term follow-up (with the caveat that there have been no studies designed to address mortality). Our power

#### (A) Length of follow-up <12 months

	1	BMSC		No	BMSC			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Chen 2004	18	4.75	34	6	5.59	35	6.0%	12.00 [9.55, 14.45]	
Ge 2006	4.8	6.76	10	-1.9	4.14	10	4.5%	6.70 [1.79, 11.61]	
Hirsch 2010	3.8	7.4	67	4	5.8	60	6.1%	-0.20 [-2.50, 2.10]	
Huang 2006	7	6.2	20	4.5	3.99	20	5.6%	2.50 [-0.73, 5.73]	
Huang 2007	7.1	3	20	2.9	2.6	20	6.4%	4.20 [2.46, 5.94]	
Huikuri 2008	4	11.3	39	-1.4	10.1	38	4.6%	5.40 [0.62, 10.18]	· · · · · · · · · · · · · · · · · · ·
Kang 2006	5.1	9.1	25	-0.2	8.6	25	4.5%	5.30 [0.39, 10.21]	
Karpov 2005	6.3	7.31	16	4.9	3.85	10	4.9%	1.40 [-2.90, 5.70]	
Li 2007	7.1	5.66	35	1.6	4.95	23	5.9%	5.50 [2.74, 8.26]	
Nogueira AG 2009	6.91	6.59	14	2.01	11.32	6	2.3%	4.90 [-4.79, 14.59]	
Nogueira VG 2009	6.45	7.89	10	2.01	11.32	6	2.1%	4.44 [-5.85, 14.73]	
Plewka 2009	9	6.1	38	5	4.95	18	5.7%	4.00 [1.00, 7.00]	
Quyyumi HD 2011	0.2	0.8	2	1	7.8	10	4.5%	-0.80 [-5.76, 4.16]	
Quyyumi LD 2011	-0.02	13	4	1	7.8	10	1.4%	-1.02 [-14.65, 12.61]	
Quyyumi MD 2011	6.7	4	5	1	7.8	10	3.9%	5.70 [-0.27, 11.67]	
Roncalli 2010	1.9	6.89	47	2.2	6.87	44	5.8%	-0.30 [-3.13, 2.53]	
Ruan 2005	5.96	7.85	9	3.21	5.08	11	3.9%	2.75 [-3.19, 8.69]	
Tendera S 2009	4.2	14.5	51	0.5	9.08	20	4.1%	3.70 [-1.93, 9.33]	
Tendera U 2009	4.4	10.92	46	0.5	9.08	20	4.4%	3.90 [-1.18, 8.98]	· · · · · · · · · · · · · · · · · · ·
Traverse 2010	6.2	9.8	30	9.4	10	10	3.3%	-3.20 [-10.32, 3.92]	
Wohrle 2010	1.8	5.3	28	5.7	8.4	12	4.4%	-3.90 [-9.04, 1.24]	
You 2008	13.3	3.98	7	4	3.58	16	5.5%	9.30 [5.87, 12.73]	
Subtotal (95% CI)			557			434	100.0%	3.56 [1.74, 5.37]	•
Heterogeneity: Tau <sup>2</sup> =	= 12.67; (	Chi² = 9	4.79, di	f = 21 (F	< 0.00	001); I <sup>2</sup>	= 78%		
Test for overall effect	: Z = 3.84	(P = 0.	0001)			372			
		aarta 1853	19 19 19 19 19 19 19 19 19 19 19 19 19 1						
									-10 -5 0 5 10
									Favours no BMSC Favours BMSC

#### (B) Length of follow-up 12-61 months

	B	MSC		No	BMSC	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cao 2009	7.1	2.24	41	5	2.49	45	11.3%	2.10 [1.10, 3.10]	
Grajek 2010	-2.62	6.83	27	-5.96	7.6	12	4.5%	3.34 [-1.67, 8.35]	
Janssens 2006	3.4	6.9	30	2.2	7.3	30	6.5%	1.20 [-2.39, 4.79]	
Jin 2008	4.28	3.53	14	0.28	4.03	12	7.7%	4.00 [1.06, 6.94]	
Lunde 2006	1.2	7.5	44	4.3	7.1	44	7.5%	-3.10 [-6.15, -0.05]	
Meluzin HD 2008	5	4.69	22	2	4.69	22	8.0%	3.00 [0.23, 5.77]	
Meluzin LD 2008	3	4.69	22	2	4.69	22	8.0%	1.00 [-1.77, 3.77]	
Meyer 2006	6.7	6.5	30	0.7	8.1	30	6.3%	6.00 [2.28, 9.72]	
Penicka 2007	6	5.41	14	8	4.03	10	6.2%	-2.00 [-5.78, 1.78]	
Piepoli 2010	12	5.28	17	6.7	6.44	15	5.7%	5.30 [1.19, 9.41]	
Schachinger 2006	3.2	6.8	27	0.8	6.8	27	6.5%	2.40 [-1.23, 6.03]	
Suarez de Lezo 2007	20	8	10	6	10	10	2.3%	14.00 [6.06, 21.94]	
Yao DD 2009	7.3	3.43	15	2.1	1.71	12	9.6%	5.20 [3.21, 7.19]	
Yao SD 2009	5.2	2.72	12	2.1	1.71	12	9.9%	3.10 [1.28, 4.92]	
Subtotal (95% CI)			325			303	100.0%	2.71 [1.35, 4.06]	•
Heterogeneity: Tau <sup>2</sup> = 3	.97; Chi	<sup>2</sup> = 42.	61, df=	: 13 (P <	0.000	1); I <sup>2</sup> =	69%		
Test for overall effect: Z	= 3.92 (	P < 0.0	0001)						

-10 -5 0 5 10 Favours no BMSC Favours BMSC

**Figure 2.** Forest plot of Weighted Mean Difference [WMD, with 95% CI (confidence interval)] in left ventricular ejection fraction (LVEF) in short-term follow-up. (A) Twenty-two randomised trials reporting only short-term follow-up and (B) the remaining 14 trials that reported long-term outcome data as well as short-term data. BMSC treatment significantly improved LVEF in trials with short-term follow-up (3.56%, 95% CI 1.74 to 5.37, p<0.0001) as well as in trials with short- and long-term follow-up (2.71%, 95% CI 1.35 to 4.06, p<0.0001). doi:10.1371/journal.pone.0037373.g002

		100			Duce				
Study or Subgroup	Mean	SD	Total	Mean	BMSC SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
2004 Meyer 2006	6.7	8.5	30	0.7	8.1	30	3.0%	6.00 [2.28, 9.72]	
Chen 2004 Subtotal (95% CI)	18	4.75	34 64	6	5.59	35 65	3.7% 6.7%	12.00 [9.55, 14.45] 9.17 [3.30, 15.04]	-
Heterogeneity: Tau <sup>a</sup> = 1 Test for overall effect: Z	5.42; Chi <sup>p</sup> = 3.06 (P :	= 6.99	, df = 1 2)	(P = 0.)	008); P	= 86%			
2005									
Meluzin HD 2008 Meluzin LD 2008	5	4.69	22	2	4.69	22	3.5%	3.00 [0.23, 5.77]	
Lunde 2006	1.2	7.5	44	4.3	7.1	44	3.3%	-3.10 [-6.15, -0.05]	
Karpov 2005	6.3	7.31	16	4.9	3.85	10	2.7%	1.40 [-2.90, 5.70]	
Heterogeneity: Tau <sup>a</sup> = 3	.97; Chi#=	9.20,	113 df= 4 (	P = 0.0	6); P = 5	109	15.0%	0.81 [-1.56, 3.19]	<b>—</b>
Test for overall effect Z	= 0.67 (P =	= 0.50)							
2006 Huang 2006	7	6.2	20	4.5	3.99	20	3.2%	2.50 [-0.73, 5.73]	
Grajek 2010 Schachinger 2005	-2.62	6.83	27	-5.96	7.6	12	2.4%	3.34 [-1.67, 8.35]	
Kang 2006	5.1	9.1	25	-0.2	8.6	25	2.4%	5.30 [0.39, 10.21]	
Janssens 2006	3.4	6.9	30	2.2	7.3	30	3.1%	1.20 [-2.39, 4.79]	
Li 2007 Subtotal (95% CI)	7.1	5.66	35 174	1.5	4.95	23	3.5% 20.1%	5.50 [2.74, 8.26] 3.71 [2.24, 5.17]	
Heterogeneity: Tau <sup>a</sup> = 0 Test for overall effect: Z	.24; Chi <sup>#</sup> = = 4.96 (P	6.38,	df = 6 ( 001)	P = 0.3	8); I* = 6	%			
2007									
Nogueira AG 2009 Nogueira VG 2009	6.91	6.59	14	2.01	11.32	6	1.1%	4.90 [-4.79, 14.59]	
Tendera U 2009	4.4 1	0.92	46	0.5	9.08	20	2.3%	3.90 [-1.18, 8.98]	
Penicka 2007	6	5.41	14	8	4.03	10	3.0%	-2.00 [-5.78, 1.78]	
Suarez de Lezo 2007 Huang 2007	7.1	3	10 20	2.9	2.6	10 20	1.4%	4.20 [2.46, 5.94]	
Piepoli 2010 Subtotal (95% CI)	12	5.28	17 182	6.7	6.44	15 107	2.8% 17.6%	5.30 [1.19, 9.41] 4.03 [1.41, 6.64]	+
Heterogeneity: Tau <sup>e</sup> = 6 Test for overall effect: Z	77; Chi# =	16.18	, df = 7 30	(P = 0.)	02); 1*=	57%			1000
2008									
Hirsch 2010	3.8	7.4	67	4	5.8	60	3.7%	-0.20 [-2.50, 2.10]	
Plewka 2009	4.28	6.1	38	0.28	4.03	12	3.4%	4.00 [1.06, 6.94]	
Huikuri 2008 Roncalli 2010	4	11.3 6.89	39 47	-1.4	10.1 8.87	38	2.5% 3.5%	5.40 [0.62, 10.18] +0.30 [-3.13, 2.53]	
You 2008 Subtotal (95% CI)	13.3	3.98	212	4	3.58	16 188	3.1%	9.30 [5.87, 12.73] 3.52 [0.59, 6.45]	-
Heterogeneity: Tau <sup>a</sup> = 1	0.74; Chi#	= 27.3	3, df =	5 (P < 0	0.0001);	1*= 824	<b>%</b>		
2000	- 235 (* -	- 0.02)							
Wohrle 2010	1.8	5.3	28	5.7	8.4	12	2.3%	-3.90 [-9.04, 1.24]	
Yao DD 2009 Yao SD 2009	7.3	3.43	15 12	2.1	1.71	12 12	3.9%	5.20 [3.21, 7.19] 3.10 [1.28, 4.92]	
Cao 2009 Subtotal (95% CI)	7,1	2.24	41 96	5	2.49	45 81	4.3% 14.4%	2.10 [1.10, 3.10] 2.53 [0.41, 4.66]	-
Heterogeneity: Tau <sup>a</sup> = 3 Test for overall effect 7	.29; Chi <sup>a</sup> =	13.96	, df = 3	(P = 0.)	003); 1*	= 79%			
2010	- 2.54 0	- 0.02)							
Traverse 2010	6.2	9.8	30	9.4	10	10	1.6%	-3.20 [-10.32, 3.92]	
Heterogeneity: Not appl	licable		30			10	1.0%	-3.20 [-10.32, 3.92]	
Test for overall effect. Z	= 0.88 (P :	= 0.38)							
2011 Quyumi LD 2011	-0.02	13	4	1	7.8	10	0.6%	-1.02  -14.65, 12.61]	
Quyyumi MD 2011 Ouwumi HD 2011	6.7	4	5	1	7.8	10	2.0%	5.70 -0.27, 11.67	
Guiffulli (10/2011					7.0			0 00 06 76 4 161	
Subtotal (95% CI)		0.6	11	1	7.8	30	5.0%	-0.80 [-5.76, 4.16] 1.76 [-2.98, 6.50]	-
Subtotal (95% CI) Heterogeneity: Tau <sup>e</sup> = 5 Test for overall effect. Z	.44; Chi# = = 0.73 (P =	2.85,	11 df = 2	1 P=0.2	7.8 4); P = 3	30 30	5.0%	-0.80 [-5.76, 4.16] 1.76 [-2.98, 6.50]	-
Subtotal (95% CI) Heterogeneity: Tau <sup>a</sup> = 5 Test for overall effect. Z Total (95% CI)	.44; Chi*= = 0.73 (P :	0.8 2.85, = 0.47)	11 df = 2 882	1 (P = 0.2	7.8 4); P= 3	30 10% 737	5.0%	-0.80 [-5.76, 4.16] 1.76 [-2.98, 6.50] 3.26 [2.12, 4.40]	•
Subtotal (95% CI) Heterogeneih: Tau <sup>a</sup> = 5 Test for overall effect. Z Total (95% CI) Heterogeneih: Tau <sup>a</sup> = 7 Test for overall effect. Z	.44; Chi <sup>#</sup> = = 0.73 (P = .66; Chi <sup>#</sup> = = 5.61 (P	2.85, = 0.47) = 145.5 < 0.000	2 11 df = 2 882 1, df = 001)	1  P = 0.2 35 (P <	7.8 4); I* = 3 0.0000	10 30 10% 737 1); I <sup>2</sup> = 1	5.0% 5.0% 100.0% 76%	-0.80 [-5.76, 4.16] 1.76 [-2.98, 6.50] 3.26 [2.12, 4.40]	-10 -3
Subiotal (95% CI) Heterogeneith: Tau <sup>e</sup> = 5 Test for overall effect Z Total (95% CI) Heterogeneith: Tau <sup>e</sup> = 7 Test for overall effect Z	.44; Chi# = = 0.73 (P = .66; Chi# = = 5.61 (P -	0.8 2.85, = 0.47) 145.5 < 0.000	2 11 df = 2 882 1, df = 001)	1  P = 0.2 35 (P <	7.8 4); P* = 3 0.0000	10 30 :0% 737 1); P= 1	5.0% 5.0% 100.0%	-0.80 [-5.76, 4.16] 1.76 [-2.98, 6.50] 3.26 [2.12, 4.40]	-10 -5 10 Favours no BMSC Favours BMSC
Subtotal (95% CI) Heterogeneith: Tau® = 5 Test for overall effect Z Total (95% CI) Heterogeneith: Tau® = 7 Test for overall effect Z (B) Excluding early stu	.44; Chi <sup>#</sup> = = 0.73 (P = .66; Chi <sup>#</sup> = = 5.61 (P - dies	0.8 2.85, = 0.47) 145.5 < 0.000	2 11 df = 2 882 1, df = 001)	1 P = 0.2 35 (P <	7.8 4); I* = 3 0.0000	10 30 0% 737 1); I <sup>2</sup> = 7	5.0% 5.0% 100.0% 76%	-0.80 [-5,76, 4,18] 1.76 [-2.98, 6.50] 3.26 [2.12, 4.40]	10 3 0 10 Favours no BMSC Favours BMSC
Subtotal (95% CI) Heterogeneity: Tau <sup>a</sup> = 5 Test for overall effect Z Total (95% CI) Heterogeneity: Tau <sup>a</sup> = 7 Test for overall effect Z (B) Excluding early stu	.44; Chi <sup>2</sup> = = 0.73 (P = .66; Chi <sup>2</sup> = = 5.61 (P - dies	0.8 2.85, = 0.47) 145.5 < 0.000	2 11 df = 2 ( 882 1, df = 001)	1 (P = 0.2 35 (P <	7.8 4); P = 3 0.0000	10 30 10% 737 1); I*= ;	2.4% 5.0% 100.0% 76%	-0.80 [-5.76, 4.18] 1.76 [-2.98, 6.50] 3.26 [2.12, 4.40]	-10 - 4 0 - 10 Favours no BMSC Favours BMSC
Subtrata (95% C) Heterogeneity: Tau <sup>a</sup> = 5 Test for overall effect Z Total (95% C) Heterogeneity: Tau <sup>a</sup> = 7 Test for overall effect Z (B) Excluding early stu Study or Subgroup 2006	.44; Chi <sup>#</sup> = = 0.73 (P : .66; Chi <sup>#</sup> = = 5.61 (P · dies Bt/ Mean	145.5 < 0.000 145.5 < 0.000	2 11 df = 2 882 1, df = 001)	1 (P = 0.2 35 (P < No Mean	7.8 4); I <sup>a</sup> = 3 0.0000 BMSC SD	10 30 0% 737 1); I <sup>2</sup> = 7	2.4 % 5.0% 100.0% 76% Weight	-0.80 [-5.76, 4.18] 1.76 [-2.98, 6.50] 3.26 [2.12, 4.40] Mean Difference IV, Random, 95% CI	10 5 0 10 Favours no EMSC Favours EMSC Mean Difference M, Random, 955 C
Subtrata (95% C) Heterogeneity: Tau <sup>a</sup> = 5 Test for overall effect Z Total (95% C) Heterogeneity: Tau <sup>a</sup> = 7 Test for overall effect Z (B) Excluding early stu Study or Subgroup 2005 Metuzin LD 2008	44; Chi <sup>a</sup> = = 0.73 (P : .66; Chi <sup>a</sup> = = 5.61 (P · 	4.69	2 11 df = 2 882 1, df = 001) Total	1 P = 0.2 35 (P < <u>No</u> <u>Mean</u>	7.8 4); P = 3 0.0000 BMSC SD 4.69	10 30 0% 737 1); I <sup>2</sup> = 1 Total	2.4% 5.0% 100.0% 76% Weight	-0.80[-5.76, 4.16] 1.76[-2.98, 6.50] 3.26 [2.12, 4.40] Mean Difference <u>IV, Random, 95% CI</u> 1.00 [-1.77, 3.77]	Mean Difference M. Random, 95% Cl
Subtrata (95% C) Heterogeneity: Tau* = 5 Test for overall effect Z Total (95% C) Heterogeneity: Tau* = 7 Test for overall effect Z (8) Excluding early stu Study or Subgroup 2005 Heturin LD 2008 Lunde 2006 Ruan 2005	.44; Chi <sup>a</sup> = = 0.73 (P : .66; Chi <sup>a</sup> = = 5.61 (P · 	4.69 7.85	2 11 df = 2 882 1, df = 001) Total 22 44 9	1 P = 0.2 35 (P < <u>No</u> <u>Mean</u> 2 4.3 3.21	7.8 4); I*= 3 0.0000 BMSC 50 4.69 7.1 5.08	10 30 50% 737 1); I*= 1 Total 22 44 11	2.4% 5.0% 100.0% 76% Weight 4.0% 3.7% 1.8%	-0.80[-5.76, 4.16] 1.76[-2.98, 6.50] 3.26[2.12, 4.40] Mean Difference IV, Random, 95% CI 1.00[-1.77, 3.77] -3.10[-6.15, -0.05] 2.75[-3.16, 8.69]	-10 -5 0 5 10 Favours no EMSC Favours EMSC Mean Difference M, Random, 95 G
Subtat (95% C) Heterogenety, Tau" = 5 Test for overall effect. Z Test (95% C) Heterogenety, Tau" = 7 Test for overall effect. Z (8) Excluding early stu Study or Subgroup 2005 Netzon LO 2008 Lunde 2006 Karpor 2005 Karpor 2005	.44; Chi <sup>#</sup> = = 0.73 (P = .66; Chi <sup>#</sup> = = 5.61 (P - dies <u>Bh</u> <u>Mean</u> 3 1.2 5.96 6.3 5	0.0 2.85,7 145.5 < 0.000 MSC SD 4.69 7.5 7.31 4.69	2 11 11 11 11 11 11 11 11 11 1	1 P = 0.2 35 (P < No Mean 2 4.3 3.21 4.9 2	7.8 4); I*= 3 0.00000 BMSC SD 4.69 7.1 5.08 3.85 4.69	10 30 30 737 1); I <sup>2</sup> = 1 Total 22 44 11 10 22	2.4% 5.0% 100.0% 76% Weight 4.0% 3.7% 1.8% 2.7% 4.0%	-0.80[-5.76, 4.16] -1.76[-2.96, 6.50] 3.26[2.12, 4.40] Mean Difference M. Random, 95% CI 1.00[+1.77, 3.77] -3.10[-6.15, 0.00] 1.40[+2.90, 5.70] 3.00[0.23, 5.77]	Terrence Mean Difference Mean Difference
Subtat (95% C) Heterogenety, Tau" = 5 Test for overall effect 2 Total (95% C) Heterogenety, Tau" = 7 Test for overall effect 2 (B) Excluding early stu Study or Subgroup 2005 Metizin LD 2008 Lunde 2006 Ruan 2005 Subdrad (95% C) Heterogenety 2005	.44; Chi <sup>#</sup> = = 0.73 (P : .66; Chi <sup>#</sup> = = 5.61 (P · dies <u>Mean</u> <u>3</u> 1.2 5.96 6.3 5 97; Chi <sup>#</sup> =	0.0 2.85, = 0.47) 145.5 (0.000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00	22 11 df = 2 ( 882 1, df = 001) Total 22 44 9 16 22 113 df = 4 (	1 P = 0.2 35 (P < <u>No</u> <u>Mean</u> 2 4.3 3.21 4.9 2 2 P = 0.0	7.8 4); P = 3 0.00000 BMSC SD 4.69 7.1 5.08 3.85 4.69 5); P = 5	10 30 30 737 1);   <sup>2</sup> = ; 1);   <sup>2</sup> = ; 22 44 11 10 209 7%	5.0% 5.0% 76% Weight 4.0% 3.7% 4.0% 16.2%	-0.80 (-3.76, 4.16) 1.76 (-2.96, 6.50) 3.26 (2.12, 4.40) Mean Difference M. Random, 95% CI 1.00 (-1.77, 3.77) -3.10 (+5.13, -0.06) 1.40 (-2.90, 5.77) 0.81 (-1.56, 3.19)	Mean Difference Mean Difference
Substat (45% C) Heterogenety, Tau" = 5 Test for overall effect 2 Test for overall effect 2 Heterogenety, Tau" = 7 Test for overall effect 2 (8) Excluding early stu Belican LD 2008 Lunde 2006 Lunde 2006 Melican LD 2008 Melican LD 2008 Meli	.44; Chi <sup>a</sup> = 0.73 (P : .66; Chi <sup>a</sup> = 5.61 (P · dies <u>Bh</u> <u>Mean</u> 3 1.2 5.96 6.3 5 .97; Chi <sup>a</sup> = 0.67 (P ·	0.0 2.85, = 0.47) 145.5 (0.000 4.69 7.5 7.85 9.20, 9.20, 	2 11 11 11 11 11 11 11 11 11 1	1 P = 0.2 35 (P < No Mean 2 4.3 3.21 4.9 2 9 P = 0.0	7.8 4); I <sup>a</sup> = 3 0.0000 BMSC SD 4.69 7.1 5.08 3.85 4.69 5); I <sup>a</sup> = 5	100 30 30 737 1); I <sup>#</sup> = ; 1); I <sup>#</sup> = ; 1); I <sup>#</sup> = ; 22 44 11 10 22 109 77%	2.4% 5.0% 100.0% 76% Weight 4.0% 3.7% 1.8% 2.7% 4.0% 16.2%	-0.80[-2,76,416] -1.76[-2.96,650] 3.26[2.12,4.40] Mean Difference M. Random, 95% CI 1.00[+1.77,377] -3.10[+615,-0.09] -2.76[-3.18,860] 1.40[-2,90,5.70] 3.00[0.22,5.77] 0.81[-1.56,3.19]	Mean Ofference M. Random, 95% C
Substat (45% C) Heterogenety, Tau" = 5 Test for overall effect Z Test for overall effect Z Test for overall effect Z (8) Excluding early stu Study or Subgroup 2005 Network Subgroup Ream 2005 Ream	44; Chi <sup>2</sup> = 0.73 (P) .66; Chi <sup>2</sup> = 5.61 (P) dies <u>Bh</u> <u>Mean</u> 3 1.2 5.96 6.3 5 .97; Chi <sup>2</sup> = 0.67 (P)	0.0 2.85, = 0.47) 145.5 < 0.000 45C SD 4.69 9.20, = 0.500 0.0	11 df = 2 ( 8822 1, df = 2001) Total 22 44 9 16 22 113 df = 4 (	1 P = 0.2 35 (P < <u>No</u> <u>Mean</u> 2 4.3 3.21 4.9 2 2 P = 0.0	7.8 4); I <sup>a</sup> = 3 0.0000 BMSC 50 4.69 7.1 5.08 3.85 4.69 6); I <sup>a</sup> = 5	100 30 737 737 1); I <sup>2</sup> = ; 10; I <sup>2</sup> = ; 10; 109 7%	2.4% 5.0% 100.0% 76% Weight 4.0% 3.7% 1.8% 2.7% 4.0% 16.2%	-0.80 [-2.76, 4.16] -1.76 [-2.96, 6.50] 3.26 [2.12, 4.40] Mean Difference M. Random, 555 CI 1.00 [+ 77, 2.77] -3.10 [+ 51, 53, 650] 2.75 [-3.10, 8.61] -4.0 [-2.00, 5.70] 3.00 [0.23, 5.77] 0.81 [-1.56, 3.19]	Mean Difference M. Random, SS-G
Substat (9%)-C) Heterogenety-Tur" = 5 Test for overall effect 2 Test for overall effect 2 Test for overall effect 2 (8) Excluding early stu 2006 (8) Excluding early stu 2006 Meticatin LD 2008 Lunde 2006 Ruae 2005 Substat (9%)-C) Heterogenety-Tur" = 3 Test for overall effect 2 2000 Substat (9%)-C) Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006	.44; Chi <sup>#</sup> = 0.73 (P = .66; Chi <sup>#</sup> = 5.61 (P - dies <u>Bhi</u> <u>Mean</u> <u>3</u> 1.2 5.96 6.3 5 .97; Chi <sup>#</sup> = 0.67 (P = <u>3.4</u> 7.1	0.0 12.85, 1 145.5 < 0.000 469 7.5 7.31 4.69 9.20, 1 9.20, 500 6.9 5.86	22 11 11 11 11 11 12 11 10 10 10 10 10 10 10 10 10	1 P = 0.2 35 (P < <u>No Mean</u> 2 4.3 3.21 4.9 2 2 P = 0.0 2.2 1.6	7.8 4); (*= 3 0.00000 BMSC SD 4.69 7.1 5.08 3.85 4.69 5); (*= 5 7.3 4.95	100% 300% 737 1); I*= 1 222 44 11 10 229 7%	2.4% 5.0% 100.0% 76% 4.0% 3.7% 1.8% 2.7% 4.0% 4.0% 5.2%	-0.80 [-2.76, 4.16] -1.76 [-2.96, 6.50] 3.26 [2.12, 4.40] Mean Difference M.Random, 95% CI 1.00 [-1.77, 2.77] -3.10 [+4, 15, -0.06] 1.40 [-2.90, 5.77] 0.00 [-2.39, 4.79] 5.50 [2.76, 8, 26]	Mean Difference M. Random, 5% C
Substat (95% C) Heterogenety, Tur" = 5 Test for overall effect. 2 Test for overall effect. 2 Heterogenety, Tur" = 7 Test for overall effect. 2 (B) Excluding early stu Study or Subgroup 2005 2005 Excluding early stu Study or Subgroup 2005 Ruan 2005 Keapor 2005 Metcon HD 2005 Metcon 2006 Metcon 2006 Metcon 2006 Metcon 2006 Metcon 2006	.44; Chi <sup>P</sup> = 0.73 (P .66; Chi <sup>P</sup> = 5.61 (P Mean 3 1.2 5.96 6.3 5 97; Chi <sup>P</sup> = 0.67 (P 3.4 7.1 7 5.1	4.69 5.86 6.9 5.86 6.9 5.86 6.2 9.1	22 11 df = 2 ( 8822 1, df = 001) Total 22 44 9 16 22 113 df = 4 ( 30 35 20 25	1 P = 0.2 35 (P < No Mean 2 4.3 3.21 4.9 2 2 P = 0.0 2 2.2 1.6 4.5 .02	7.8 4); P = 3 0.0000 BMSC SD 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.3 8.85 3.99 8.85 8.6	100% 300% 737 737 1); P= ; 10;	2.4% 5.0% 5.0% 100.0% 76% 4.0% 2.7% 4.0% 3.2% 4.0% 3.2% 4.0% 2.2%	-0.00(5.276,410) -1.76(2.296,650) 3.26(2.12,440) Mean Difference <u>M. Random, 95% CI</u> 1.00(-1.77,277) -3.16(4.15,600) -1.40(2.20,670) 1.40(2.20,670) 1.40(2.20,670) 1.40(2.20,470) 0.01(-1.76,3.30) 1.20(2.2,6,27) 0.01(-1.76,3.30) -5.30(0.30,102) -5.30(0.30,102)	Mean Difference M. Random, 95% C
Substat (95% C) Heterogenety, Tau" = 5 Test for overall effect. 2 Test for overall effect. 2 Test for overall effect. 2 (8) Excluding early stu Because of the state of the state (8) Excluding early stu Because of the state Network of the st	44; Chi <sup>#</sup> = 0,73 (P = 66; Chi <sup>#</sup> = 5.61 (P - dies 1.2 5.96 6.3 5 97; Chi <sup>#</sup> = 0.67 (P = 3.4 7.1 7 1.4 4.8 9.4 7.1	0.0 12.85, 12.8	11 11 11 11 11 11 11 11 11 11	1 P = 0.2 35 (P < <u>Neom</u> 2 4.3 3.21 4.9 2 P = 0.0 P = 0.0 2.2 1.6 6.4.5 -0.2 -1.9 -5.96	7.8 4); (P = 3 0.0000 BMSCC SD 4.69 7.1 5.08 5.08 5.08 5.09 7.3 4.95 5.09 8.6 4.14 4.93 7.3 9.99 8.6 4.14 7.6	100% 300 737 737 1); P= 1 1); P= 1 1; P= 1 22 44 41 11 10 220 23 7% 300 23 20 25 10 12	2.4% 5.0% 5.0% 100.0% 76% 4.0% 3.7% 4.0% 1.8% 1.8% 16.2% 16.2%	-1.00 (27, 2, 410) -1.00 (27, 2, 410) -1.00 (27, 2, 410) 3.20 (2, 12, 440) Motan Difference International Systems -1.00 (1, 7, 3, 77) -1.00 (4, 15, -0.09) -1.20 (2, 29, 4, 70) -5.00 (27, 5, 77) -5.00 (27, 5, 78) -5.00 (27, 5, 78)	Mean Officence IV, Random 95% C
Substat (45%)-C) Heterogenety-Tur" = 5 Test for overall effect 2 Test for overall effect 2 Test for overall effect 2 (8) Excluding early stu 2006 2006 Ruan 2005 Metican LD 2008 Lunde 2006 Ruan 2005 Substat (45%)-C) Heterogenety-Tur" = 3 Test for overall effect 2 2006 Substat (45%)-C) Janssens 2006 Janssens 2006 Janssens 2006 Substat (45%)-C) Substat (45%)-C) Su		**************************************	11 11 11 11 11 11 11 11 11 11	1 P = 0.2 35 (P < <u>Mean</u> 2 4.3 3.21 4.9 2 2 2.2 1.6 6 4.5 -0.2 -5.96 0.8	7.8 4);  *= 3 0.0000 BMSCC SD 4.69 7.1 5.08 3.85 4.69 7.3 4.69 7.3 4.69 7.3 4.95 5.08 8.64 4.14 4.69 7.3 5.08 8.99 8.64 7.6 6.8	10 30 30 737 737 737 737 737 737 737 737	4,0%,3,7%,4,0%,3,5\%,4,0%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,4,0\%,3,5\%,3,5\%,3,5\%,3,5\%,3,5\%,3,5\%,3,5\%,3	-3.00 (27, 24, 14) -1.00 (27, 24, 14) -1.00 (27, 24, 24) 3.26 (24, 24, 440) Mean Difference M, Random, 24, 24, 440 1.00 (17, 27, 27) -1.01 (45, -0.09) -1.40 (22, 25, 24, 24) -1.40 (22, 25, 27) -2.01 (45, -0.09) -2.75 (23, 24, 24) -2.75 (23, 24) -2.75 (2	Mean Difference M. Random, SS G
Substat (4%)-C) Heterogenety, Tur" = 5 Test for overall effect. 2 Test for overall effect. 2 Test for overall effect. 2 (8) Excluding early stu Study or Subercoup 2016 Metication L0 2006 Hunde 2006 Ruan 2005 Ruanov 2005 Ru	44 Chr# = 8.73 (P : 6.66; Chr# = 6.66; Chr# = 6.66; Chr# = 6.66; Chr# = 8.66; Chr# = 9.536; S = 5.95; S = 5.	4.69 9.2.05, 145.55 (0.000 4.69 9.20, 5.86 6.9 5.86 6.2 9.1 6.9 5.86 6.2 9.1 6.9 5.86 6.83 6.83 6.36,	22 11 df = 2 13 14 df = 2 14 16 10 10 10 10 10 10 10 10 10 10	1 P = 0.2 35 (P < <u>Non Mean</u> 2 4.3 3.21 4.9 2 2 P = 0.0 2 2.2 1.6 4.5 -0.2 -1.9 -5.96 0.8 P = 0.3	7.8 4);  *= 3 0.0000 BBMSC SD 4.69 7.1 5.08 4.69 7.1 3.85 4.69 7.3 3.99 8.6 4.14 7.6 8.8 4.95 3.99 8.6 6.8 8);  *= 5	10 30 30 737 737 1), P=1 1), P=1 1), P=1 10 22 44 44 11 10 222 44 45 10 22 20 25 510 12 27 7%	4.0% 3.2% 4.0% 3.7% 18.2% 4.0% 2.3% 4.0% 2.3% 2.3% 3.2% 2.3% 3.2%	-1.019 (27, 24, 10) -1.019 (27, 24, 10) -1.019 (28, 65, 65) 3.26 (2, 12, 440) -1.019 (15, 65) -1.019 (15, 66) -1.019 (1	Mean Difference Mean Difference
Substat (95% C) Heterogenety, Tur" = 5 Test for overall effect. 2 Test for overall effect. 2 Heterogenety, Tur" = 7 Test for overall effect. 2 (B) Excluding early stu (B) Exc	44 Chr# = 8 Chr# =	0.0 12.85, 1 145.55 (0.000 469 7.85 9.20, 1 0.500 6.9 5.86 6.2 9.1 6.78 6.8 8.8 (6.38, 1 <0.000 (0.000) (0.000	Total 300 355 300 355 100 277 174 46 46 47 47 47 47 47 47 47 47 47 47	1 P = 0.2 35 (P < <u>Nean</u> 2 3.21 4.9 2 2 9 P = 0.0 2.2 1.6 4.5 -0.2 -1.9 -5.96 0.8 P = 0.3	7.8 4); P= 3 0.0000 BMSCC SD 4.69 7.1 5.08 3.85 4.69 7.1 5.08 3.85 4.69 7.1 3.99 8.6 6.8 8.0; P= 5 6.8 9); P= 6	100 300% 737 1); P=1 1); P=1 1); P=1 102 22 44 44 11 10 22 20 25 5 10 10 23 20 25 10 10 27 7%	4.0% 3.2% 4.0% 162% 3.2% 4.0% 16.2% 3.2% 2.3% 2.3% 2.3% 3.2% 2.3% 3.2%	-1.001278,2410 (721230,650) 3.26(212,440) Mona Difference Mona Difference 1.00117,377 3.101415,4009 1.0017,377 3.00123,4791 4.50123,4	Mean Difference M. Random, S9% C
Substat (2%)-C) Heterogenety, Tarl = 5 Test for overall effect. 2 Test for overall effect. 2 Test for overall effect. 2 (8) Excluding early stu 2005 2005 Metizin LD 2008 Lunde 2006 Metizin LD 2008 Lunde 2006 Crask 2006 Crask 2007 Crask 2007 Metizin Control Contro	Bit         Bit           0.73 (P-         66; ChiP=           0.73 (P-         66; ChiP=           0.86; ChiP=         5.66; ChiP=           0.86; ChiP=         5.66; ChiP=           0.87; ChiP=         5.66; ChiP=           0.87; ChiP=         5.67; ChiP=           0.87; ChiP=         4.8; ChiP=           0.87; ChiP=         2.4; ChiP=           0.44; ChiP=         4.96; ChiP=           0.80; ChiP=         5.92; ChiP=           0.80; ChiP=         5.92; ChiP=           0.80; ChiP=         5.93; ChiP=	0.0 2.85, = 0.47) 145.5 < 0.000 4.69 7.5 7.31 4.69 9.20, = 0.50) 6.9 5.86 6.2 9.1 6.76 6.83 6.8 6.38, < < 0.000 6.59	Total 30 35 20 10 11 44 9 113 30 35 20 25 20 27 27 174 4f = 2 10 113 30 35 20 25 20 10 27 27 27 27 27 27 27 27 27 27	1 P = 0.2 35 (P < <u>Nean</u> 2 3.21 4.9 2 2 9 P = 0.0 2 2 2 9 P = 0.0 0 8 P = 0.3 2 0.8 P = 0.2	7.8 4); P= 3 0.00000 BBMSCC SD 4.69 7.1 5.08 3.85 7.3 3.99 8.6 6.8 9); P= 5 6.8 9); P= 6 11.32	100 300% 737 737 737 737 737 737 730 730 22 24 4 11 109 77% 300 23 20 25 510 109 77% 6	2.3% 5.0% 5.0% 100.0% 76% 4.0% 3.7% 4.0% 3.7% 4.0% 5.2% 2.3% 3.2% 2.1% 5.0%	-1.00 (-1.7, 2, 4.10) -1.00 (-1.7, 2, 4.10) -1.00 (-1.7, 2, 4.10) -1.00 (-1.7, 2, 7, 7) -1.00 (-1.7, 3, 7) -1.00 (-1.7, 3	Mean Officence IV. Random, 95% C
Substat (95% C) Heterogenety, Tur" + 5 Test for overall effect. 2 Test for overall effect. 2 Test for overall effect. 2 (8) Excluding early stu 2005 (8) Excluding early stu 2006 Rulas 2005 Rulas 2005 Rulas 2005 Substat (95% C) Janssens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Substat (95% C) Heterogenety, Tur" - 3 Test for overall effect. 2 2006 Crajks 2010 Schartung (95% C) Test for overall effect. 2 2000 Orajks 2010 Substat (95% C) Test for overall effect. 2 2000 Noverall effect. 2 2000 Preside 2005 Substat (95% C) Test for overall effect. 2 2000 Preside 2007	Bit         Bit           0.73 (P-1)         66; ChiP = 5.51 (P)           dies         Bit           Mean         3           3         1.2           5.56 (ChiP = 0.57 (P)           9.97 (ChiP = 0.57 (P)           3.4           7           5.1           3.4           7           3.4           7           5.62           2.42 (ChiP = 4.56 (P)           6.91           4.2           6	0.0 2.85, = 0.47) 145.5 < 0.000 4.69 7.5 7.31 4.69 9.20, 9.20, 9.20, 9.20, 0.500 6.9 5.86 6.2 9.1 6.7 6.83 6.83 6.38, < < 0.000 6.59 14.5 5.41	II           II           II           II           II           II           II           II           BB22           II           III           IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	1 P = 0.2 35 (P < Mean 2 4.3 3.21 4.9 2 2 9 = 0.0 2.2 1.6 4.5 -0.2 9 = 0.3 0.8 P = 0.3 0.8 P = 0.3 0.8 P = 0.2 2.2 1.6 5.9 6 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	7.8 4); (P = 3 0.0000 BMSCC SD 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 8.6 6.8 8.03, (P = 3 0.0000 1.132 8.05 6.0 8.00 1.132 8.05 6.0 8.00 8.00 8.00 8.00 8.00 8.00 8.00	100 300% 737 737 737 737 737 737 737 737 737 73	2.50% 5.0% 5.0% 100.0% 76% 4.0% 3.7% 4.0% 3.7% 4.0% 3.2% 4.0% 3.2% 2.10% 5.0%	-1.001;47,2,410 (761;250,650) 3.26(2;12,440) Mean Difference M. Random, 95; Cl 1.001;7,277 3.016;15,00 2.05;213,00 1.001;470,100 2.05;213,00 1.001;470,100 3.001;470,1000 3.001;470,1000 3.001;470,1000 3.001;470,1000 3	Mean Difference Mandom, 95% Cl
Substat (95% C) Heterogenety, Tur" = 5 Test for overall effect. 2 Test for overall effect. 2 Heterogenety, Tur" = 7 Test for overall effect. 2 (B) Excluding early stu Study Colouroup (90) Biological Colouroup (90) (90) Biological Colouroup (90) (90) (90) (90) (90) (90) (90) (90)		0.0 2.85, 2.85, 145.5 < 0.000 4.69 5.85 4.69 9.20, = 0.500 6.9 5.868 6.76 6.78 6.78 6.83 6.83 6.38, (< 0.000 (< 0.000) 6.9 5.05 0.000 6.9 5.05 6.9 5.55 6.8 6.8 6.9 5.55	22         21           11         df=2;           8822         8832           9001)         001)           222         44           9         166           222         143           df=4;         001)           300         355           200         25           100         27           27         27           174         60001)           14         50           100         46	1 P = 0.2 35 (P < Mean 2 4.3 3.21 4.9 2 2.2 1.6 4.5 -0.2 9 = 0.0 2.2 1.6 4.5 -0.2 -1.9 -5.96 0.8 P = 0.3 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 0.5 8 0.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1	7.8 4); (P = 3 0.0000 BMSCC SD 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 4.69 7.1 5.08 8.6 6.8 80; (P = 5 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	100 300% 737 737 1); P=: 1); P=: 1); P=: 1); P=: 1); P=: 1); P=: 109 7% 30 25 51 109 7% 30 25 51 109 7% 30 20 25 51 109 56 20 20 20 20 20 20 20 20 20 20 20 20 20	100.0% 50% 100.0% 76% 40% 162% 3.2% 40% 162% 162% 0.9% 2.10% 0.9% 2.10% 0.9% 2.10% 0.9% 0.9% 0.9%	-1.001277,410 -1.001277,410 -1.001200,050 -1.000	Mean Difference M. Random, 95% C
Substat (29%) C)           Heterogeneh, Turl * 6           Test for overall effect. 2           Test for overall effect. 2           Heterogeneh, Turl * 7           Test for overall effect. 2           (B) Excluding early stu- steman. 1000           Study or Subgroup.           Matteropereneh, Turl * 7           Test for overall effect. 2           2003           Matteropereneh, Turl * 0           Matteropereneh, Turl * 000           Kampor 2005           Matteropereneh, Turl * 0           Jamissen 2006           L 2007           Studender (55, Turl * 0)           Heteropereneh, Turl * 0           Jamissen 2006           Capos           Schartneger 2006           Grapick 2007           Nogueter Ard 2009           Pencika 2007           Nogueter Ard 2009		0.0 2.85, 2.85, 145.5 < 0.000 4.69 5.86 6.9 5.86 6.38, 6.38, < 0.000 6.9 5.86 6.38, < 0.000 6.9 5.86 6.38, < 0.000 6.9 5.41 7.85 5.85 6.95 5.85 6.95 5.85 6.95 5.85 6.95 5.41 7.85	Total B82 B82 B82 B82 B82 B82 B82 B82 B82 B82	1 P = 0.2 35 (P < Mean 2 3.21 4.9 2 P = 0.0 2.2 1.6 4.5 0.8 0.8 0.8 P = 0.3 2.01 0.5 8 2.01 0.5 6 7 7 7 7 7 7 7 7 7 7 7 7 7	7.8 4); (P= 3 0.0000 BMSCC SD 7.1 5.06 3.85 7.1 4.69 7.1 5.06 3.85 6.8 8 9; (P= 6 8 8); (P= 6 8 8); (P= 6 8 8); (P= 6 8 8); (P= 3 1 3.96 6.8 8); (P= 3 1 5.00 8); (P= 3 7.1 5.00 8) 7.1 7.1 7.3 8,9 8,9 8,9 8,9 8,9 8,9 8,9 8,9 8,9 8,9	100 300% 737 737 1); P=1 1; P=1 22 44 41 11 00 22 237 109 7% 30 25 10 109 7% 30 26 20 26 10 109 7%	2.1% 5.0% 5.0% 100.0% 76% 4.0% 3.7% 4.0% 3.2% 4.0% 4.0% 2.3% 2.3% 2.3% 2.1% 5.0%	-1.00 (-1.77, 4.10) -1.00 (-1.77, 4.10) -1.00 (-1.77, 4.10) -1.00 (-1.77, 3.77) -1.00 (-1	Mean Difference M. Random, 95% C
Substat (9%)-C) Heterogenety: Turl = 6 Test for overail effect. 2 Test for overail effect. 2 Test for overail effect. 2 Test for overail effect. 2 (8) Excluding early stu 2006 2006 Melicanic D. 2008 Lunde 2006 Ruas 2005 Melicanic D. 2008 Lunde 2006 Melicanic D. 2008 Substat (9%)-C) Heterogenety: Turl = 3 Test for overail effect. 2 2006 Janssens 2006 Janssens 2006 Crajk 2010 Sethertunger CO Heterogenety: Turl = 3 Test for overail effect. 2 2007 Melicanic Al 2009 Melicanic Al 2009 Crajk 2010 Melicanic Al 2009 Crajk 2010 Melicanic Al 2009 Crajk 2010 Melicanic Al 2009 Tenders 8 2009		0.0 2.285, 2.285, 14555 4.69 7.65 5.0 4.69 7.7.85 7.31 4.69 7.85 7.31 4.69 7.85 7.31 4.69 9.20, 9.20, 9.1 6.9 9.20, (0.00) 6.9 9.20, (0.00) 6.8 8.83 6.83 6.38, (0.00) 6.541 7.85 5.41 7.89 5.41 7.85 5.41 7.89 5.41 7.85 5.41 7.89 5.41 7.85 7.85	Total B82 B82 B82 B82 B82 B82 B82 B82 B82 B82	1 P = 0.2 35 (P < Mean 2 3.21 4.9 2 P = 0.0 2.2 1.6 4.5 0.8 0.8 0.8 P = 0.3 2.01 0.5 8 2.01 0.5 6,7 2.9 6 6 7 2.9 6 7 2.9 6 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 2.9 7 7 7 7 7 7 7 7 7 7 7 7 7	7.8 4); (P= 3 0.0000 BMSC SD 7.1 5.06 3.85 7.1 4.69 7.1 5.06 3.85 5); (P= 5 5); (P= 5 5); (P= 5 6.8 8); (P= 6 8,8 8,9 6,4 11.32 9.08 6.44 2.56 10	100 300% 737 737 1); P=1 1; P=1 100 22 100 23 25 100 23 25 100 23 25 100 12 27% 30 23 25 100 12 25 100 50 12 25 147 7%	2,2% 5,0% 5,0% 100,0% 76% 4,0% 3,2% 4,0% 3,2% 4,0% 3,2% 4,0% 2,2% 4,0% 3,2% 4,0% 3,2% 4,0% 3,2% 4,0% 3,2% 4,0% 2,2% 3,1% 1,2% 1,2%	-1.00 (-1.77, 4.10) -1.00 (-1.77, 4.10) -1.76 (-2.50, 6.50) 3.26 (2.12, 4.40) Mean Difference 1 Mean Difference 1 Mean Difference 1 -1.00 (-1.77, 3.77) -1.10 (-1.51, -0.09) -1.40 (-2.50, -0.57) -1.20 (-2.30, -1.70) -1.40 (-2.50, -1.70) -1.40 (-2.50, -1.70) -2.30 (-1.70, -1	Mean Officence IN. Random, 95% C
Substat (95% C) Heterogenety, Tur" = 6 Test for overall effect. 2 Test for overall effect. 2 Test for overall effect. 2 (8) Excluding early stu 2005 (8) Excluding early stu 2005 Rular 2005 Rular 2005 Rular 2005 Rular 2005 Rular 2005 Rular 2005 Substat (95% C) Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Substat (95% C) Heterogenety, Tur" = 0 Test for overall effect. 2 2007 Oraşk 2010 Substat (95% C) Heterogenety, Tur" = 0 Test for overall effect. 2 2007 Prediate 32009 Rular 2006 Substat (95% C) Heterogenety, Tur" = 0 Test for overall effect. 2 2007 Prediate 32009 Roguetar 30.2009 Prediate 32009 Prediate 32009 Pre		0.0 2.285, 2.285, 14555 4.69 7.65 5.0 4.69 7.785 7.31 4.69 7.85 7.31 4.69 7.85 7.31 4.69 7.85 5.28 6.2 9.10, 6.9 9.20, - 0.50 6.9 5.88 6.83 6.83 6.59 5.541 7.89 5.541 6.59 14.55 5.41 7.89 5.541 6.59 14.55 5.41 7.89 5.541 6.59 8.541 7.85 5.41 7.85 5.88 6.83 8.638, - 4.69 5.541 6.59 5.545 6.54 6.59 6	Total B822 B822 B822 B822 B822 B822 B822 B82	1 P = 0.2 35 (P < Mean 2 4.9 2 2 1.6 4.5 0.2 -1.9 0.8 P = 0.0 2.2 1.6 0.8 0.8 P = 0.3 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 2.01 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 8 0.5 9 0.5 8 0.5 8 0.5 9 0.5 8 0.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1	7.8 49; P= 3 0.00000 BMSCCSD SD 7.1 5.06 3.85 7.1 5.06 3.85 6.1 4.69 9.7 1 5.06 5.1 P= 5 9.9 8 6 4.69 9.08 8.6 6.8 9); P= 6 11.32 9.08 6.4 4.25 9.08 11.32 9.08 6.44 2.66 10 9.00 00000 00000 000000 000000 000000 0000	100 300% 737 737 1); P=1 1); P=1 109 22 244 111 110 20 23 25 100 23 25 100 23 25 100 12 27 7% 30 25 107 57%	5,0% 5,0% 100,0% 76% 4,0% 1,8% 4,0% 16,2% 16,2% 16,2% 2,3% 2,3% 2,3% 2,1% 5,0% 16,2%16,2% 16,2% 16,2% 16,2% 16,2% 16,2%16,2% 16,2% 16,2% 16,2%16,2% 16,2% 16,2% 16,2%16,2% 16,2% 16,2% 16,2% 16,2%16,2% 16,2% 16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2% 16,2%16,2%	-1.0012-77,4-110 -1.0012-77,4-110 -1.0012-012-012 -1.0	Mean Difference M. Random, 95% C
Substatid (95% C) Heterogenety, Tur" = 5 Test for overail effect. 2 Test for overail effect. 2 Heterogenety, Tur" = 7 Test for overail effect. 2 (B) Excluding early stu Study Cscharoop Distance (100 - 100	44 Chr# = 65 Chr# = 65 Chr# = 556 Chr# = 556 Chr# = 556 63 5 97 Chr# = 6.63 7 3.4 7.1 7 3.4 7.1 7 3.4 7.1 7 5.2 6 6.3 5 9.7 Chr# = 4.2 6 6.9 7.1 7 7 7 7 7 7 7 7 7 7 7 7 7	0.0 2.85,1 = 0.47) 1145.5 < 0.000 4.69 5.85 6.7,85 9.20,1 6.9 5.86 6.2 9.1 6.76 5.83 6.88 6.33, 6.8 6.33, 6.8 6.59 14.5 5.28 14.59 14.53 8 8 8 8 8 8 8 8 8 8 8 8 8	Total           300           25           11           11           df = 2           11           df = 2           11           22           11           22           14           9           16           22           113           300           25           20           25           100           27           174           4f=6           11           14           10           16           177           182           30	1 P = 0.2 35 (P < Neon 2 4.3 3.21 4.3 3.21 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 4); (P = 3 0.0000 4.69 7.1 5.08 4.69 7.1 3.85 3.95 4.65 3.95 6.8 4.55 3.99 6.41 4.76 6.8 50; (P = 5 3.99 6.11 7.3 3.95 3.99 6.41 4.55 50 11.32 9.08 6.11 11.32 9.08 6.43 10.00 11.32 9.00 0.0000 0.0000 0.000000	100 300% 737 737 1); P=; 1); P=; 109 109 109 22 20 22 20 22 20 22 20 22 20 22 27 27 447 % 6 20 10 107 57%	50% 50% 100.0% 76% 40% 1.8% 4.0% 1.8% 4.0% 16.2% 16.2% 16.2% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2	1.001+27,2,410 1.001+27,2410 1.001+17,277	Mean Difference M. Random, S9% C
Substat (9%)-C1 Heterogenety, Turl = 6 Test for overail effect. 2 Test for overail effect. 2 Test for overail effect. 2 (8) Excluding early stu 2005 2005 Metizani. D. 2008 Lunde 2006 Metizani. D. 2008 Lunde 2006 Graph. 2006 Graph. 2007 Metizani. C. 2006 Graph. 2007 Metizani. C. 2006 Metizani. C. 2007 Metizani. C. 2006 Metizani. C. 2007 Metizani. C. 2006 Metizani. C. 2006 Metizani. C. 20		0.0 2.85,1 = 0.47) 1145.5 < 0.000 4.69 5.85 9.20,1 6.76 5.28 6.33 6.8 6.33,6,2 (0.000 6.59 14.5 5.28 8 14.618 = 0.000 3.98	Total 8822 11 8822 11 8822 11 8822 11 8822 11 8822 11 12 12 12 13 14 15 10 10 10 10 10 10 10 10 10 10	1 P = 0.2 35 (P < Mean 2 4.3 3.21 4.9 2 P = 0.0 2.2 1.6 4.5 -0.2 -1.9 -5.96 0.8 P = 0.3 2.01 0.5 8 2.01 0.5 6.7 2.9 6.7 2.9 4.3 2.1 1.5 6.7 2.9 4.5 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 1.5 6.7 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.1 2.1 1.5 6.7 2.5 6.7 7.5 6.7 7.5 6.7 7.5 6.7 7.5 6.7 7.5 6.7 7.5 6.7 7.5 6.7 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7	7.8 4);  *= 3 0.00000 BBMSCC SD 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.1 1.02 8.6 6.9 8 6.6 9.02 8.0 8 6.0 9.02 8.0 9.00 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.0 9.02 8.00 8.0 8.0 8.0 8.0 8.0 8.0 8.0 8.0 8.	100 300% 737 737 1); P=; 1); P=; 109 109 22 24 44 11 10 22 20 22 20 23 20 20 23 20 20 23 20 20 23 20 20 20 20 20 20 20 20 10 10 10 10 10 10 10 10 10 10 10 10 10	5.0% 5.0% 100.0% 76% Weight 4.0% 3.2% 4.0% 3.2% 4.0% 3.2% 4.0% 2.3% 2.2% 4.0% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3% 4.0% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3	-1.00   27,2 4 10 -1.00   27,2 4 10 -1.00   27,2 4 00 -1.00   17,3 27 -1.00   17,3 27 -1.00   17,3 27 -1.00   17,3 27 -1.00   15,0 00 -2.77   5.10 00 -0.00   2,5 27 -0.01   1.65,3 10 -0.01   25,3 10 -0.01   25,3 10 -0.01   25,1 10 -0.01   25,1 10 -0.01   27,1   20,1   27,1   27,1   20,1   27,1   27,1   20,1   27,1   27,1   27,1   27,1	Mean Difference M. Random, 955 C
Substat (95% C) Heterogenety, Tur" = 5 Test for overall effect 2 Test for overall effect 2 Test for overall effect 2 Test for overall effect 3 (8) Excluding early stu 2005 2005 Meticalin LD 2008 Lunde 2006 Runa 2005 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2006 Galance 100 Substat (95% C) Janssens 2006 Jansens 2006 Jansens 2006 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2006 Graphs 2010 Schartinger 2005 Substat (95% C) Test for overall effect 2 2007 Test for overall effect 2 2007 Substat (95% C) Heterogenety, Tur" = 0 Test for overall effect 2 2007 Substat (95% C) Heterogenety, Tur" = 0 Test for overall effect 2 2007		0.0 2.85,7 145,55 (0.000 145,55 50 50 50 50 50 50 50 50 50	Total B882 B882 B882 B882 B882 B882 B882 B882	1 P = 0.2 35 (P < Mean 2 4.3 3.21 4.9 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 4);  * = 3 0.00000 BBMSCC SD 4.69 7.1 4.69 7.1 4.69 7.1 4.69 7.3 4.69 8.3,85 4.69 8.0;  * = 5 8.8 8);  * = 5 8.8 8);  * = 6,8 8);  * = 3 9.08 4.11 7.2 9.08 4.11 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 8.44 9.08 9.08 9.08 9.08 9.08 9.08 9.08 9.08	100 300% 737 737 737 737 737 22 44 41 110 22 20 22 20 22 20 25 109 7% 6 6 20 10 107 57% 6 6 20 107 167 44 4 4 4 107 107 107 107 107 107 107 107 107 107	5,0% 5,0% 100,0% 76% 4,0% 2,7% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 4,0% 2,2% 2,2% 2,2% 2,2% 2,2% 2,2% 2,2% 2	1.001 ± 77, 2.110 1.001 ± 77, 2.10 1.001 ± 77, 2.170 1.001 ± 77, 2.177 1.001 ± 77, 1.460 1.001 ± 70, 1.460 1.001 ± 70, 1.460 1.001 ± 70, 1.271 1.001 ± 70, 1.271 1.001 ± 70, 1.271 1.001 ± 70, 1.460 1.001 ± 70, 1.271 1.001 ± 70, 1.271 ± 70, 1.271 1.001 ± 70, 1.271 ± 70, 1.271 ± 70, 1.271 ± 70, 1.271 ± 70, 1.271 ± 70, 1.271	Mean Difference Mandom, 95% C
Substat (95% C) Heterogenety, Tur" = 6 Test for overall effect 2 Test for overall effect 2 Test for overall effect 2 (8) Excluding early stu 2005 (8) Excluding early stu 2005 Ruan 2005 Ruan 2006 Ruan 2007 Ruan 2007 Ruan 2006 Ruan 2007 Ruan 2007 R		0.0 2.85, 2.85, 0.001 145,5 4.69 7.85 7.31 4.69 9.20, 0.50 6.9 9.20, 0.50 6.8 8.38, 4.69 9.20, 0.50 6.8 8.38, 4.69 9.20, 0.000 6.59 14,5,5 4.69 9.20, 0.000 6.9 14,5 5.08 6.83 6.	Total B882 B882 B882 B882 B882 B882 B882 B882	1 P = 0.2 35 (P < Noo Mean 2 2 3 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 40; I*= 3 0.00000 BBMSCC SD 7.3 4.69 7.1 5.08 4.69 6.0; I*= 5 3.99 8.6 4.14 4.55 8.6 6.8 11.32 9.08 4.69 8.6 6.8 11.32 9.08 4.05 11.32 9.08 4.05 11.32 9.08 4.45 11.32 9.08 4.45 11.32 9.08 4.45 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 9.08 11.32 1.35 1.35 1.35 1.35 1.35 1.35 1.35 1.35	100 300% 737 737 737 737 737 737 737 737 737 73	100.0% 5.0% 100.0% 76% 4.0% 3.7% 4.0% 3.7% 4.0% 3.7% 4.0% 3.2% 5.2% 3.2% 5.2% 9.20%	-1.001247,24.10 -1.001247,24.10124	Mean Difference M.Random, 595 C
Substat (95% C) Heterogenety, Tur" = 5 Test for overall effect 2 Test for overall effect 2 (B) Excluding early stu (B) Excluding early stu (C) Excludi		0.0 2.285,1 = 0.477 145.55 < 0.000 4.69 7.85 7.31 4.69 7.85 7.31 9.20,1 = 0.500 6.9 5.86 6.2 9.1 (< 0.000 6.59 14.5 5.28 3.8 (< 0.000 (< 0.59) 14.5 5.28 3.8 (< 0.000 (< 0.59) 11.5 5.28 3.8 (< 0.59) 11.5 5.28 3.8 (< 0.59) 11.5 5.28 3.8 (< 0.000 (< 0.59) 11.5 5.28 3.8 (< 0.59) 11.5 5.28 3.8 (< 0.59) 11.5 5.28 5.	Total           11           #882           8832           11           8832           11           12           130           14           14           14           14           14           14           14           14           15           16 <t< td=""><td>1 P = 0.2 35 (P &lt; No Mean 2 2 3 3.21 4.9 2 2 2 2 2 2 2 2 2 2 2 2 2</td><td>7.8 40; I*= 3 0.00000 BEMSCC SD 7.3 4.69 7.1 5.06 4.69 6.8 6.9 6.9 11.32 9.06 8.6 4.14 7.6 8.9 9.06 8.6 11.32 9.06 8.6 11.32 9.06 8.6 11.32 9.06 9.02 11.32 9.02 11.32 9.05 10.02 11.32 10.02 10</td><td>100 300% 737 737 737 737 737 737 730 730 732 737 730 730 735 735 735 735 735 735 735 735 735 735</td><td>00.0% 5.0% 100.0% 4.0% 3.7% 1.0% 3.7% 16.2% 16.2% 2.1% 5.2% 2.1% 5.2% 2.1% 5.2% 2.1% 5.2% 1.2% 4.9% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5</td><td>1.00   27,2 4.10 1.00   27,2 4.10 1.00   17,2 12,0,0 50 1.00   17,3 77 1.00   17,3 77 1.0</td><td>Mean Difference M. Random, 59% C</td></t<>	1 P = 0.2 35 (P < No Mean 2 2 3 3.21 4.9 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 40; I*= 3 0.00000 BEMSCC SD 7.3 4.69 7.1 5.06 4.69 6.8 6.9 6.9 11.32 9.06 8.6 4.14 7.6 8.9 9.06 8.6 11.32 9.06 8.6 11.32 9.06 8.6 11.32 9.06 9.02 11.32 9.02 11.32 9.05 10.02 11.32 10.02 10	100 300% 737 737 737 737 737 737 730 730 732 737 730 730 735 735 735 735 735 735 735 735 735 735	00.0% 5.0% 100.0% 4.0% 3.7% 1.0% 3.7% 16.2% 16.2% 2.1% 5.2% 2.1% 5.2% 2.1% 5.2% 2.1% 5.2% 1.2% 4.9% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5	1.00   27,2 4.10 1.00   27,2 4.10 1.00   17,2 12,0,0 50 1.00   17,3 77 1.00   17,3 77 1.0	Mean Difference M. Random, 59% C
Stabitized (25%) C1           Heterogrenety, Tau" = 6           Test for overail effect, 2           2006           2006           Stabit or Subgroup, Tau", 2           2006           Metagonethy, Tau", 2           2006           Metagonethy, Tau", 2           2006           Subgroup, 2006           Metagonethy, 2006           Subgroup, 2006           Subgroup, 2006           Subgroup, 2006           Subgroup, 2006           Capote           Capote     <		0.0 2.285,1 = 0.477 1145.55 < 0.000 <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>ISSC</b> <b>IS</b> SC <b>IS</b> SCC <b>IS</b> SCC <b></b>	Total           11           #882           8832           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           12           12           12           12           13           14           10           13           14           14           10           10           11           11           11           11           11           11           12           13           14           14           14           14           14           14           14           14           14	1 P = 0.2 35 (P < No Mean 2 4,3 3,21 4,3 3,21 2 P = 0.0 2,2 1,6 4 5,2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7.8 4);  P = 3 0.00000 BBMSCC SD 7.1 5.08 4.59 7.1 5.08 4.59 5);  P = 5 7.3 3.95 4.45 3.99 6, 2 7, 3 3.95 4.45 3.99 6, 2 7, 3 3.95 6, 2 7, 3 3.95 6, 2 9, 2 9, 0 8 4, 1 9, 2 9, 2 9, 2 9, 2 9, 2 9, 2 9, 2 9, 2	100 300% 737 737 737 737 737 737 730 730 722 244 111 122 244 111 122 244 111 122 245 245 200 223 225 225 227 75% 50 10 10 22 227 75% 50 10 10 10 10 10 10 10 10 10 10 10 10 10	100.0% 5.0% 100.0% 76% 4.0%, 3.2%, 4.0%, 2.3%, 2.3%, 2.3%, 2.3%, 2.3%, 2.3%, 2.3%, 2.3%, 2.3%, 3.2%, 3	1.00 (5.7, 2.4) (0) 1.00 (5.7, 2.4) (0) 1.00 (5.7, 2.4) (0) 1.00 (5.7, 2.7) 1.00 (5.7,	Mean Difference M. Random, 955 C
Substat (95% C) Heterogenety, Tur" + 5 Test for overall effect 2 Test for overall effect 2 Test for overall effect 2 (8) Excluding early stu 2005 (9) Excluding early stu 2005 Meticatin LD 2008 Lunde 2006 Runa 2005 Substat (95% C) Heterogenety, Tur" + 3 Test for overall effect 2 2000 Substat (95% C) Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Substat (95% C) Heurog 2006 Substat (95% C) Pencida 2007 Nogueta AD 2009 Pencida 2007 Nogueta AD 2007 Pencida 2007 Nogueta AD 2007 Nogueta AD 2007 Nogueta AD 2009 Pencida 2007 Nogueta AD 2009 Pencida 2007 Nogueta AD 2009 Pencida 2007 Nogueta AD 2007 Pencida 2007 Nogueta AD 2007 Pencida 2007 Nogueta AD 2007 Pencida 2007 Pen		0.0 2.285,1 0.477 1145,55 0.000 1145,55 0.000 1145,55 0.000 1145,55 0.000 1145,55 0.000 0.000 0.9 0.9 0.9 0.9 0.9	Total BB2 211 BB2 2	1 P = 0.2 35 (P < Mean 2 4,3 3.21 4,3 3.21 4,3 2 P = 0.0 2.2 1.6 4.5 0.8 0.8 0.8 0.8 0.8 0.9 0.0 0.5 0.6 0.7 2.9 6 0.2 0.1 0.5 0.6 0.8 0.8 0.9 0.8 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9	7.8 4);   *= 3 0.00000 BBMSCC SD 7.1 5.08 5.3 4.89 7.1 5.08 5.3 4.89 7.1 5.08 5.3 4.89 5.1   *= 5 7.3 4.85 5.0 8.6 6.8 6.8 6.8 6.8 6.8 6.8 6.8 11.32 9.06 6.44 2.9 0.0000 022;   *= 3 5.5 8 6.87 10.5 8 5.0 8 10 8 10 8 8 5.0 8 10 8 8 10 8 10 8 10 8 8 10 8 10 8 8 10 8 8 8 8	100 30 30 30 50% 737 22 24 41 11 109 109 22 22 24 41 11 109 22 22 20 25 25 20 100 107 57% 57% 57% 16 6 20 107 10 10 10 10 10 10 10 10 10 10 10 10 10	100.0% 5.0% 100.	1.30 (277, 2410) 1.30 (277, 2410) 1.70 (250, 650) 3.20 (2.12, 440) 1.30 (2.12, 4	Mean Difference M.Random, 95% C
Substat (95% C) Heterogenek): Tur" = 6 Test for overall effect: 2 Test for overall effect: 2 Test for overall effect: 2 (B) Excluding early slu Statuty or Suberroup 2005 Metication LD 2006 Lunde 2006 Ruan 2005 Ruancy 2007 Ruancy 2007 Ruanc		0.0 2.285,1 = 0.477 1145.55 < 0.000 1145.55 5.0 1145.55 5.0 6.9 1.145.55 5.0 6.9 1.145.55 5.0 6.9 1.15 5.0 6.9 1.145.55 5.0 6.0 0.000 6.59 1.145.55 5.0 6.0 0.000 6.59 1.145.55 5.141 7.092 5.28 8.000 6.59 1.145.55 5.141 7.092 5.28 8.000 6.09 1.145.55 5.141 7.15 5.141 7.15 5.141	Total BB2 22 11 BB2 23 14 17 17 17 17 17 17 17 17 17 17	1 P = 0.2 35 (P < Mean 2 4.3 3.21 4.5 4.5 4.5 7.9 9 0.0 2.2 1.6 5.7 2.0 1.6 5.7 2.5 8 1.6 5.7 2.5 8 1.6 5.7 2.5 1.6 5.7 2.5 1.6 5.7 5.7 5.8 1.6 5.7 5.7 5.8 7 5.7 5.8 7 5.9 5.8 7 5.7 5.8 5.7 5.7 5.8 5.7 5.7 5.7 5.7 5.7 5.7 5.7 5.7	7.8 45; P= 3 0.00000 50 50 7.3 4.69 7.1 4.69 7.3 4.59 8.6 6.8 8); P= 5 7.3 4.95 8.6 6.8 8); P= 5 7.3 4.95 8.6 6.8 8); P= 5 0 11.32 9.08 4.14 4.59 9.08 6.84 4.59 9.08 4.14 4.55 9.00 8.54 4.55 9.00 8.54 4.55 9.00 8.54 4.55 9.00 8.55 8.55 8.55 8.55 8.55 8.55 8.55 8	100% 30 30 30 737 737 22 24 41 11 12 22 24 41 11 12 22 23 25 10 25 10 25 20 10 25 20 10 25 20 10 25 20 20 25 20 25 20 20 25 20 20 25 20 20 25 20 20 20 20 25 20 20 20 20 20 20 20 20 20 20	20% 200% 100.0% 10.	-1.001 [-77, 2-10] -1.001 [-77, 2-10] -1.001 [-77, 2-17] -1.001 [-77, 2-77] -1.001 [-77, 2-77] -1.001 [-77, 2-77] -1.001 [-77, 2-77] -1.001 [-77, 2-77] -1.001 [-73, 2-77] -1.001 [-74, 2-78] -1.001	Mean Difference M. Random, 95% C
Substat (2%)-C) Heterogenety, Turk = 6 Test for overail effect. 2 Test for overail effect. 2 Test for overail effect. 2 (8) Excluding early stu 2005 Melizin LD 2008 Lunde 2006 Melizin LD 2008 Lunde 2006 Graph 2006 Graph 2006 Graph 2007 Melizin LD 2008 Lunde 2006 Graph 2007 Melizin LD 2008 Lunde 2006 Graph 2007 Melizin LD 2008 Lunde 2006 Graph 2007 Melizin LD 2008 Lunde 2006 Graph 2007 Melizin LD 2008 Melizin LD 2008 Melizin LD 2008 Melizin LD 2008 Melizin LD 2007 Melizin 2008 Melizin 2008		0.0 2.2.85,1 2.2.85,1 0.2.05,1 1.145.55 4.6.9 9.2.0,1 6.7.85 9.2.0,1 0.500 1.145.55 9.2.0,1 0.500 1.4.59 1.4.51 5.4.61 0.920 1.4.51 5.4.63 0.920,1 0.920,1 0.500 1.4.51 5.4.63 0.920,1 0,	Total           222           41           8882           1, df = 2;           9862           1, df = 1001)           1           222           24           44           99           2001)           102           202           213           314           510           102           201)           14           51           14           100           100           100           14           51           14           67           39           38           144           67           200           77           39           338           14           67           212           307           212           307           212           307           212           307           214           147           1410	1 P = 0.2 35 (P < Mean 2 4 3 3.21 4.5 -0.2 1.6 4.5 -0.2 -1.9 -5.96 0.8 P = 0.0 2.22 1.6 6.5 -0.2 -1.9 -5.96 0.8 P = 0.2 -0.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -1.9 -5.96 0.8 -0.2 -0.2 -1.9 -5.96 0.8 -0.2	7.8 45; P= 3 0.00000 900000 469 7.1 550 4.69 7.1 4.69 7.1 4.69 7.1 4.69 8.6 6.8 8 80; P= 5 7.3 4.95 8.6 6.8 8 9; P= 5 7.3 4.95 8.6 6.8 8 9; P= 5 7.3 4.95 9, P= 5 9, P	100% 300% 737 737 1); P = ; 1009 1000 1009 100	2100.0% 5.0% 100.0% 76% 4.0% 3.7% 12.7% 4.0% 3.2% 4.0% 3.2% 4.0% 3.2% 5.2% 4.0% 3.2% 4.0% 3.2% 4.0% 3.2% 4.0% 3.2% 5.2% 5.5%	1.00   5.7 & 1.10 1.00   5.7 & 1.20 1.00   5.7 &	Mean Difference M. Random, 95% C
Substat (9%) C) Heterogrene(*, Tur" + 5 Test for overall effect; 2 Test for overall effect; 2 Test for overall effect; 2 Test for overall effect; 3 (8) Excluding early stu 2005 Meticalin, LD 2008 Lunde; 2006 Ruan; 2005 Substat (9%) C) Heterogrene(*, Tur" + 3 Test for overall effect; 2 2006 Janssens 2006 Janssens 2006 Janssens 2006 Janssens 2006 Graph; 2010 Substat (9%) C) Heterogrene(*, Tur" + 3 Test for overall effect; 2 2006 Graph; 2010 Substat (9%) C) Heterogrene(*, Tur" + 3 Test for overall effect; 2 2007 Tenders 3; 2009 Tenders 3; 2009 Tenders 3; 2009 Tenders 3; 2009 Tenders 4; 2009 Heterogrene(*, Tur" + 3 Test for overall effect; 2 2000 Heterogrene(*, Tur" + 3 Test for overall effect; 2 2000 Heterogrene(*, Tur" + 3 Test for overall effect; 2 2009 Wohl 2007 Substat (9%) C) Heterogrene(*, Tur" + 5 Test for overall effect; 2 2009 Wohl 2009 Heterogrene(*, Tur" + 1 Test for overall effect; 2 2009 Wohl 2010 Yas DD 2009 Yas DD 20		0.0         0.0           22.85,1         0.47           2.05,1         0.40           1145.5         0.000           46.9         0.20           4.69         9.20,1           5.06         6.2           9.20,1         0.50           6.9         5.86           6.38,0         0.000           6.59         11.3           6.59         116.18           9.00,2         2.24           2.724         2.72           2.242         2.72	Total           11           12           130           14           151           161           177           133           14           151           161           17           17 <t< td=""><td><math display="block">\begin{array}{c} 1 \\ P = 0.2 \\ \hline \text{Neon} \\ 4 \\ 325 (P &lt; 0 \\ 4 \\ 3.21 \\ 4.9 \\ 2 \\ 2 \\ 4.3 \\ 3.21 \\ 4.9 \\ 2 \\ 2 \\ 2 \\ 1.6 \\ 4.5 \\ 0.2 \\ 0.8 \\ 0.8 \\ 0.9 \\ 0.</math></td><td>7.8 4); [P = 3 0.00000 BEMSCC SD 4.69 7.1 5.08 3.98 6, 4.69 7.1 4.55 3.99 8.6 4.14 4.7 6.8 50; [P = 5 3.99 8.6 4.14 4.7 6.8 50; [P = 5 3.99 8.6 4.14 4.7 4.5 5 3.99 8.6 4.13 4.09 4.03 4.03 5 3.95 5 50; [P = 5 3.99 8.6 4.14 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 11.32 5 5 5 11.32 5 5 8 11.32 5 5 8 11.32 5 5 8 11.32 5 8 5 8 11.32 5 8 8 6 8 4.03 8 5 8 4.03 8 5 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8</td><td>100 30 30 737 737 1); P = ; 1); P = ; 109 7% 30 22 24 41 109 7% 30 23 23 20 25 10 109 7% 6 6 20 27 107 109 7% 6 6 20 27 107 109 109 109 109 109 109 109 109</td><td>2.2% 5.0% 100.0% 76% 4.0% 1.5% 4.0% 3.5% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 2.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4</td><td>1.001 ; 27, 2 4 10 (721 ; 256, 524 ; 10 (721 ; 256, 524 ; 10 3.20 [ 2, 12, 440] 1.20 ; 2, 20 ; 21 1.01 ; 77, 277 1.01 ; 77, 277 1.01 ; 77, 277 1.01 ; 77, 277 1.01 ; 17, 277 1.01 ; 17, 277 1.01 ; 17, 277 1.00 ; 2, 2577 0.001 ; 2, 577 0.001 ; 2, 577 ; 2, 577</td><td>Mean Difference M. Random, 95% C</td></t<>	$\begin{array}{c} 1 \\ P = 0.2 \\ \hline \text{Neon} \\ 4 \\ 325 (P < 0 \\ 4 \\ 3.21 \\ 4.9 \\ 2 \\ 2 \\ 4.3 \\ 3.21 \\ 4.9 \\ 2 \\ 2 \\ 2 \\ 1.6 \\ 4.5 \\ 0.2 \\ 0.8 \\ 0.8 \\ 0.9 \\ 0.$	7.8 4); [P = 3 0.00000 BEMSCC SD 4.69 7.1 5.08 3.98 6, 4.69 7.1 4.55 3.99 8.6 4.14 4.7 6.8 50; [P = 5 3.99 8.6 4.14 4.7 6.8 50; [P = 5 3.99 8.6 4.14 4.7 4.5 5 3.99 8.6 4.13 4.09 4.03 4.03 5 3.95 5 50; [P = 5 3.99 8.6 4.14 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 3.99 8.6 4.13 4.03 5 3.95 5 5 11.32 5 5 5 11.32 5 5 8 11.32 5 5 8 11.32 5 5 8 11.32 5 8 5 8 11.32 5 8 8 6 8 4.03 8 5 8 4.03 8 5 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	100 30 30 737 737 1); P = ; 1); P = ; 109 7% 30 22 24 41 109 7% 30 23 23 20 25 10 109 7% 6 6 20 27 107 109 7% 6 6 20 27 107 109 109 109 109 109 109 109 109	2.2% 5.0% 100.0% 76% 4.0% 1.5% 4.0% 3.5% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 2.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4	1.001 ; 27, 2 4 10 (721 ; 256, 524 ; 10 (721 ; 256, 524 ; 10 3.20 [ 2, 12, 440] 1.20 ; 2, 20 ; 21 1.01 ; 77, 277 1.01 ; 77, 277 1.01 ; 77, 277 1.01 ; 77, 277 1.01 ; 17, 277 1.01 ; 17, 277 1.01 ; 17, 277 1.00 ; 2, 2577 0.001 ; 2, 577 0.001 ; 2, 577 ; 2, 577	Mean Difference M. Random, 95% C
Substat (49%)-C) Heterogenek, Tur" + 5 Test for overall effect 2 Test for overall effect 2 (8) Excluding early stu 2006 (8) Excluding early stu 2006 (9) Excluding early stu 2006 Metication 2006 Ruan 2005 Substat (49%)-C0 Heterogenek/Tar" + 3 Test for overall effect 2 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Jansens 2006 Substat (49%)-C0 Heterogenek/Tar" + 3 Test for overall effect 2 2007 Press 2006 Substat (49%)-C0 Heterogenek/Tar" + 3 Test for overall effect 2 2007 Press 2009 Press 2009 Pres		0.0 2.2.95,1 2.2.95,1 0.477 1145.55 3.0001 5.0001 5.00 5.0	Total           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           12           22           24           9           101           12           22           244           9           133           35           200           27           27           27           27           27           27           27           27           27           27           27           277           14           10           10           11           14           17           200           10           11           14           15	1 P = 0.2 35 (P < Mean 2 2 3 2 3 2 2 3 5 9 6 8 7 2 9 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 7 5 2 6 7 5 2 6 7 5 2 6 7 5 7 6 5 7 6 7 5 7 6 7 5 7 6 7 5 7 6 7 5 7 6 7 5 7 6 7 5 7 6 7 5 7 6 7 7 2 9 6 7 5 7 6 7 7 2 7 8 7 7 7 7 7 8 7 7 7 7 7 7 7 7 7 7 7 7 7	7.8 6); (P = 3 0.00000 BEMSCC SD 0.00000 4.69 9.1 5.00 4.69 9.08 4.64 4.03 5.85 1.32 5.85 8.68 7.10 1.32 5.85 8.68 7.10 1.32 5.85 8.68 7.10 1.32 5.85 8.68 7.10 1.132 5.85 8.68 7.10 1.132 5.85 8.68 7.10 1.132 5.85 8.68 7.10 1.132 5.85 8.68 7.10 1.132 5.85 8.87 1.0001 1.71 5.85 8.87 1.71 1.71 5.85 8.87 1.01 1.95 8.44 4.95 8.87 1.02 1.95 8.87 1.01 1.95 8.87 1.71 1.95 8.87 1.71 1.95 8.87 1.71 1.71 1.71 1.71 1.72 1.71 1.71 1.72 1.71 1.72 1.71 1.72 1.71 1.72 1.71 1.72 1.71 1	100% 300 300 737 737 737 737 757 300 222 444 111 102 223 205 223 205 223 205 223 205 205 205 205 205 205 205 205	2.2% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2%	-1.30) [-7, 2, 410] (-7, 2) [-2, 50, 65] 3.20 [2, 12, 440] 3.20 [2, 12, 440] (-7, 12, 12, 12, 12, 12, 12, 12, 12, 12, 12	Mean Difference M.Random, 95% C
Substat (9%)-C) Heterogenety, Turl ~ 5 Test for overail effect. 2 Test for overail effect. 2 Test for overail effect. 2 (8) Excluding early stu 2005 Melizin LD 2008 Lunde 2006 Melizin LD 2008 Lunde 2006 Graph 2016 Graph 2016 Melizin LD 2008 Lunde 2006 Graph 2016 Graph 2016 Melizin LD 2008 Lunde 2006 Graph 2016 Graph 2016 Melizin LD 2008 Lunde 2006 Graph 2016 Graph 2016 Graph 2016 Melizin LD 2008 Lunde 2007 Tenders 8 2009 Tenders 2006 Metrogenety, Turl ~ 1 Metrogenety, Turl ~ 1 Metrogenety, Turl ~ 1 Metrogenety, Turl ~ 1 Test for overal effect. 2 2000 Works 2010 Substat (9%)-C) Heterogenety, Turl ~ 1 Test for overal effect. 2 2009 Yao ED 2009 Yao ED 2009		0.0 2.2.95,1 2.2.95,1 0.001 1145.5 0.001 1145.5 0.001 1145.5 0.001 1145.5 0.001 1145.5 0.001 1145.5 0.001 0.9 0.9 0.69 0.69 0.69 0.69 0.69 0.69 0.69 0.69 0.69 0.60 0.69 0.60 0.69 0.60 0.50 0.60 0.50 0.60 0.50	Total           11           11           11           11           11           11           11           11           11           11           11           11           122           13           122           133           141           10           252           20           250           2001)           1474           51           1474           51           1474           51           1474           51           1474           67           77           77           77           77           77           77           338           14           67           77           77           77           77           77           77           77           77           77           77	1 P = 0.2 35 (P < Note Mean 2 4.3 3.2 4.9 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 6); [P = 3 0.00000 EBMSCC SD 4.69 7.3 4.69 7.3 4.69 6.8 6.8 6.8 7.3 9.00 9.0 11.32 9.00 9.0 11.32 9.00 9.0 11.32 9.00 9.0 11.32 9.00 11.32 1.35	100% 100% 737 737 737 737 737 22 22 77 107 75  6 20 23 23 23 23 24 27 109 10 22 27 109 10 22 27 109 10 20 23 20 10 10 20 10 10 10 10 10 10 10 10 10 10 10 10 10	2.2% 0.9% 2.2% 0.9% 2.2% 0.9% 2.2% 0.9% 2.2% 0.9% 2.2% 0.9% 2.2% 0.9% 2.2% 0.9% 2.3% 0.9% 2.3% 0.9% 2.3% 0.9%	1.001-17.2, 4.10 1.001-17.2, 4.10 1.001-17.2, 4.10 1.001-17.2, 4.10 1.001-17.2, 4.10 1.001-17.2, 4.10 1.001-17.2, 3.101-14.10 1.001-17.2, 3.101-14.10 1.001-17.2, 3.101-14.10 1.001-17.2, 3.101-14.10 1.001-17.2, 3.101-14.10 1.001-17.2, 3.101-14.10 1.001-17.2, 3.101-14.10 1.001-17.2, 5.101-14.10 1.001-17.2, 5.101-14.10 1.001-14.10 1.001-14.10 1.001-14.10 1.001-14.10 1.001-14.10	Mean Difference M. Random, 95% C
Substat (9%)-C) Heterogenety, Turk = 6 Test for overail effect 2 Test for overail effect 2 Test for overail effect 2 (8) Excluding early stu 2006 Substat (9%)-C) Heterogenety, Turk = 1 2006 Melicatin LD 2008 Lunde 2006 Melicatin LD 2008 Lunde 2006 Melicatin LD 2008 Lunde 2006 Substat (9%)-C) Heterogenety, Turk = 0 Test for overail effect 2 2006 Oraşk 2010 Graphs 2010 Graphs 2010 Graphs 2010 Heterogenety, Turk = 0 Test for overail effect 2 2007 Nogueta Ac 2009 Tenders 8 2009 Penetics 2000 Tenders 8 2009 Penetics 2000 Romal 2010 Heterogenety, Turk = 0 Test for overail effect 2 2007 Nogueta Ac 2009 Tenders 8 2009 Penetics 2000 Heterogenety, Turk = 0 Test for overail effect 2 2002 Wohle 2010 Heterogenety, Turk = 0 Test for overail effect 2 2002 Wohle 2010 Con 2008 Penetics 2009 Heterogenety, Turk = 0 Test for overail effect 2 2009 Wohle 2010 Con 2009 Yao E010 Con 2009 Yao E010 Con 2009 Yao E010 Con 2009 Yao E010 Con 2009 Yao E010 Heterogenety, Turk = 1 Test for overail effect 2 2009 Wohle 2010 Heterogenety, Turk = 0 Test for overail effect 2 2009 Wohle 2010 Con 2009 Yao E010 Heterogenety, Turk = 1 Test for overail effect 2 2000 Wohle 2010 Con 2009 Yao E010 Heterogenety, Turk = 1 Test for overail effect 2 2000 Wohle 2010 Con 2009 Yao E010 Heterogenety, Turk = 1 Test for overail effect 2 2000	$\begin{array}{c} & & & & & & \\ & = 0.73 \ \varphi \cdot \varphi \\ = 0.73 \ \varphi \cdot \varphi \\ = 0.73 \ \varphi \cdot \varphi \\ = 0.66; \ ChP = \\ & & & & \\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	Total           11           11           11           11           11           11           11           11           11           11           11           11           11           122           13           122           14           10           25           20           20           25           20           25           20           25           20           25           26           27           27           27           27           27           27           27           27           27           27           2001)           14           51           14           16           17           30           30           30	1 P = 0.2 35 (P < Mean 2 2 3.321 4 2 2 2 2 2 1.6 4.5 -0.2 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 40; P= 3 0.00000 BMSCC SD 7.3 4.69 7.1 5.08 4.69 7.3 3.85 4.69 6.8 7.3 3.99 8.6 6.8 11.32 9.00 4.14 7.6 6.8 10.000 11.32 9.00 4.14 4.59 8.6 6.8 10.000 11.32 9.00 8.6 6.8 10.000 11.32 9.00 8.6 6.8 10.000 11.32 9.00 8.6 6.8 10.000 11.32 9.00 8.6 6.8 10.000 11.32 9.00 8.6 6.8 10.000 10.000 11.32 9.00 8.6 6.8 10.000 11.32 9.000 8.6 6.8 10.000 10.000 10.000 10.000 10.000 10.000 10.000 10.000 10.000 10.000 10.000 10.000 10.000 11.32 10.0000 10.0000 10.00000 10.00000 10.0000	100 100% 737 737 737 737 737 737 222 222	2.2%, 2.4%, 2.2%, 2.4%,	1.001547, 4.10 1.001547, 4.10 1.001542, 4.00 1.001542, 4.001 1.001542, 4.001542, 4.001 1.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001542, 4.001	Mean Difference Mean Difference
Substat (29%) C)           Heterogenek): Tul" + 5           Test for overall effect: 2           Test for overall effect: 2           Test for overall effect: 2           2005           2005           2005           2005           2005           2005           2005           2005           2005           2005           2005           2005           2005           2005           Substat (29%) C)           Jansens 2006           2005           Substat (29%) C)           Heterogenek) Tul" - 3           2006           Calaber 2005           Substat (29%) C)           Heterogenek) Tul" - 3           2006           Substat (29%) C)           Heterogenek) Tul" - 3           2007           Nogues A2:009           Nogues A2:009           Presks 2007           Nogues A2:009           Presks 2007           Nogues A2:009           Presks 2007           Nogues A2:009           Presks 2007           Nogues A2:009           Presks 2		0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	Total           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           12           130           22           44           9           15           22           44           30           25           2001)           144           1001)           144           1001)           144           1001)           144           17           38           144           67           212           28           411           12           15           16           27           28           411           12           130           300           300           300	1 P = 0.2 35 (P = 0.1 2 2 3 321 2 2 3 321 2 2 3 321 2 2 2 2 2 2 2 2 2 2 2 2 2	7.8 45, [P = 3 0.0000 BBMSCC SD 7.1 5.08 4.69 7.1 5.08 4.69 50, [P = 5 7.3 4.89 50, [P = 5 7.3 4.95 50, [P = 5 7.3 4.95 8.6 6.8 8.0 11.32 9.08 4.14 7.6 6.8 8.0 11.32 9.08 4.14 7.6 6.8 8.0 11.32 9.08 4.14 7.6 6.8 8.0 11.32 9.08 4.14 7.6 6.8 8.0 11.32 9.08 4.14 7.6 6.8 8.05 11.32 9.08 4.14 7.6 6.8 8.05 11.32 9.08 4.14 7.6 6.8 8.05 11.32 9.08 4.14 7.6 6.8 8.05 11.32 9.08 4.14 7.6 6.8 8.05 11.32 9.08 4.14 7.6 6.8 8.05 1.13 9.08 6.4 4.03 5.8 9.08 6.4 4.03 5.8 9.08 6.4 4.03 9.08 6.4 4.03 9.08 6.4 4.03 9.08 6.4 4.03 9.08 6.4 4.03 9.08 6.4 4.03 7.5 1.13 9.08 6.4 4.03 5.8 7.3 9.08 6.4 4.03 7.5 1.13 9.08 6.4 4.03 5.8 6.8 8.6 8.6 8.6 8.6 8.6 8.6 8	100 100% 737 737 1); P = - 1); P = - 100 100 100 100 100 100 100 10	2.2% 2.2% 2.2% 2.2% 3.3% 4.0%	-1.00  -17, 2.10   .100  -17, 2.10  -20  -20  -20  -20  -20  -20  -20  -2	Mean Difference M.Random, 95% C
Substat (95% C) Heterogenety, Tur" = 5 Test for overall effect 2 Test for overall effect 2 Test for overall effect 2 (8) Excluding early stu Status or Substroup 2005 2005 Relation D 2005 Heterogenety, Tur" = 7 Test for overall effect 2 2006 Heterogenety, Tur" = 7 Test for overall effect 2 2006 Jansens 2006 Lange 2005 Substat (95% C) Heterogenety, Tur" = 7 Test for overall effect 2 2007 Plasma 2006 Substat (95% C) Heterogenety, Tur" = 3 2007 Plasma 2008 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2007 Plasma 2008 Substat (95% C) Heterogenety, Tur" = 0 Test for overall effect 2 2007 Vou 2009 Plasma 2010 Heterogenety, Tur" = 0 Test for overall effect 2 2009 Vou 2009 Plasma 2010 Heterogenety, Tur" = 0 Test for overall effect 2 2009 Vou 2008 Roncall 2010 Heterogenety, Tur" = 0 Test for overall effect 2 2009 Von 2009 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2009 Vonthe 2010 Cao 2009 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2009 Vonthe 2010 Cao 2009 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2017 Taverses 2010 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2017 Taverses 2010 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2017 Taverses 2010 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2017 Taverses 2010 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2017 Taverses 2010 Substat (95% C) Heterogenety, Tur" = 3 Test for overall effect 2 2017 Heterogenety, Tur" = 3 Test for overa		0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	Total           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           11           12           13           14           12           130           32           2001)           14           10           14           10           14           10           11           14           10           11           14           10           11           14           10           11           14           17           200           10           114           10           114           12           130           300           300	1 P = 0.2 35 (P = 0.2 35 (P = 0.2 2 4.3 3.21 1.6 2.2 1.6 0.5 0.8 P = 0.0 0.5 0.8 P = 0.0 0.5 0.5 0.5 0.5 0.5 0.5 0.5	7.8 40; P= 3 0.00000 EBMSCC SD 7.3 4.69 0; P= 5 7.3 4.69 0; P= 5 7.3 4.69 0; P= 5 7.3 4.69 0; P= 5 0; P= 5 11.32 0,000 0; P= 5 11.32 0,000 0; P= 5 11.32 0,000 0; P= 5 11.32 0,000 0; P= 5 11.32 0; P= 5 11.32 11.	100 100% 737 737 1); P= 1); P= 1); P= 1); P= 109 102 22 23 23 23 23 23 23 23 23 2	22% 3.0% 4.0% 3.1% 4.0% 3.1% 4.0% 3.1% 4.0% 2.2% 4.0% 3.1% 2.2% 4.0% 3.2% 2.2% 4.0% 3.2% 4.0% 3.2% 4.0% 3.1% 3.1% 4.0% 2.2% 4.0% 3.1% 4.0% 3.1% 4.0% 3.1% 4.0% 3.1% 4.0% 5.2% 4.0% 5.2% 4.0% 5.2% 5.2% 5.5% 5.5% 5.5% 5.5% 5.5% 5.5	-1.30   2.78, 2.410 (7.78   2.36, C.54 3.26   2.12, 2.440] Moan Offreenece M. Random, 955 Cl 1.30   2.71, 2.71 1.30   2.73, 2.71 1.30   2.73, 2.71 1.30   2.73, 2.71 1.30   2.73, 2.71 3.30   2.24, 2.51 3.30   2.24, 5.77 3.30   2.24, 5.77 3.30   2.24, 5.77 3.30   2.24, 5.77 3.30   2.24, 5.77 3.31   2.73, 2.54, 2.45 3.37   2.24, 2.54, 7.77 3.30   2.24, 5.77 3.37   2.24, 5.177 3.37   3.3	Mean Difference M. Random, 955 C

Figure 3. Forest plot of Weighted Mean Difference [WMD, with 95% CI (confidence interval)] in left ventricular ejection fraction (LVEF) in short-term follow-up sub-grouped by the year of the first results' disclosure. (A) Including early studies reporting data in 2004 (3.26%, 95% CI 2.12 to 4.40, p<0.00001).and (B) excluding studies with early reporting in 2004 (2.80%, 95% CI 1.83 to 3.77, p<0.00001). BMSC treatment significantly improved LVEF in both meta-analyses. WMD had overlapping CI and were not significantly different.

doi:10.1371/journal.pone.0037373.g003

calculation estimates that a trial with several thousand participants would be needed to detect significant differences in mortality between treatment and control groups. Recently, the first trial to address mortality associated with BMSC treatment in patients who suffered AMI has been designed and funded by the European Union (EU FP7-BAMI). The BAMI trial will be administering unfractionated bone marrow mononuclear cells to patients who have suffered from AMI, similarly to the majority of trials included in the present study. The results of this trial should allow us to directly answer the question of whether BMSC therapy following AMI can change the prognosis of this disease.

As the results of the present study are not always consistent with those of large randomised trials [7,8,25,26,27], we have conducted extensive sensitivity analyses to evaluate potential factors that may account for the discrepancies observed. Major limitations in the field have been enumerated earlier in the Introduction. Importantly, the underlying Cochrane systematic review for this study is unique and superior to others previously reported in a number of ways and has allowed us to address some of those issues. Firstly, it is based on a comprehensive search strategy and a protocol approved by the Cochrane Collaboration prior to starting the search. Although the majority of randomised trials were identified through searching the main databases (MEDLINE, EMBASE, CENTRAL and CINAHL), hand-searching identified several crucial references used to assess risk of bias that would have otherwise been missed [7,21,26,28,29,30,31]. Secondly, the robustness of the original systematic review has been tested extensively within this study through a comprehensive sensitivity analysis and risk of bias assessment to explore the presence and impact of heterogeneity. Finally, the large number of trials included here allows particularly powerful assessments of heterogeneity through planned sub-group analysis.

It has been suggested that measurement of surrogates such as LVEF by different methodology may be a risk of bias because of the known limitations of some methods [32]. Analysis of the included studies sub-grouped by the methodology used to measure surrogate outcomes has been addressed elsewhere [4]. It has also been suggested that stopping or reporting early results in randomised trial may affect the perception that the public has of the treatment efficacy in novel interventions [33]. As early results are more limited than the results of a final analysis, concerns have been raised as treatment effects seen early may either not be real or may be overly optimistic. In this study, we have had a unique opportunity to assess whether factors such as short versus long follow-up or early reporting of results may contribute to bias amongst the pooled results of all included trials. The risk of bias due to length of follow-up for LVEF was negligible indicating that those trials with long term follow-up data are representative of all included studies. This conclusion may have implications interpreting early results from trials with long-term follow-up or trials with short term follow-up only. In addition, low risk of bias was observed when studies were grouped by study start date, study end date or publication of main reference to the studies. There were no significant differences of treatment effect on LVEF when two early

Subaroun Analycic	Cubratemory	No. studies (No. staticinante)	Infarct size (%) WMD (05% C1) o value	Bef to study	No studies	L VEF (%) WMD (95%	Daf to ctudu
Timing of SCT <sup>a</sup>	≤7 days	3 (99)	-5.16(-8.87, -1.44) P=0.007	[9,45]	6 (241)	4.76 (2.18, 7.33) P<0.001	[7,9,23,30,45,47]
,	>7 days	0 (0)	N/A		3 (56)	5.87 (1.24, 10.51) P=0.01	
	Difference in subcategorie	es				P=0.68	
Dose	≤10 <sup>8</sup>	3 (168)	-1.96 (-5.23, 1.32) P=0.24	[8,44]	6 (228)	2.66 (-0.07, 5.38) P=0.06	[8,22,44,45,48]
	>10 <sup>8</sup>	4 (185)	-4.28 (-7.29, -1.27) P=0.005	[9,45,47]	9 (407)	4.72 (2.68, 6.76) P<0.001	[7,9,23,28,30,45,47,49,50]
	Difference in subcategori:	S	P=0.31			P=0.23	
Baseline LVEF <sup>b</sup>	≤40%	3 (91)	-5.12 (-8.76, -1.48) P = 0.006	[44,45]	7 (177)	5.62 (2.95, 8.29) P<0.001	[22,30,44,45,49,50]
	>40%	3 (222)	-1.37 (-3.62, 0.88) P=0.23	[8,9,47]	7 (418)	2.36 (0.67, 4.04) P= 0.006	[7,8,9,23,28,44,47,48]
	Difference in subcategori	es	P=0.09			P=0.04	
Cl, confidence interval; <sup>a</sup> studies classified acco <sup>b</sup> Mean%, Melzuin LD w	: LVEF, left ventricular ejecti rding to timing of stem cel /as excluded as treatment a	ion fraction; N/A, not applica II administration in at least 7/ and control groups in this sti	ible; SCT, stem cell transplantation; W 0% of patients (as estimated from the udy could not be classified into the sa	AD, weighted me mean and stand me baseline LVEF	an difference. ard error or median anc erroup.	l interquartile range).	

Stem Cell Treatment in Acute Myocardial Infarction

studies [5,6] where either included or excluded from the metaanalysis and negligible risk of bias due to quality of included studies or loss of participant's follow-up. This may also imply that trial design and methodology has not changed drastically amongst trials in the last decade for significant differences to be observed. Although no significant risk of bias was observed in the present study, one cannot exclude the possibility that discrepancies between the different studies may be explained by variability in factors such as cell isolation, data acquisition or data analysis protocols amongst others. Hence the importance of agreeing to standardised protocols in the future. Part of the remit of the BAMI trial (EU-BAMI mentioned above) is to consider the methodologies used to date and produce a standardised technique for bone marrow processing and delivery.

Here, a parallel significant improvement on LVEF and reduction of infarct size was observed. Although caution is advisable in interpreting results from surrogate outcomes, the moderate improvement in LVEF over short- (3.26%) and longterm (3.91%) follow-up is similar to that obtained in previous trials where AMI patients were treated with a combination of thrombolytic therapy and PCI [34,35]. In the CADILLAC trial, improvement of LVEF correlated with better long-term survival rate [35,36]. The results of the CADILLAC trial were also consistent with those of the Netherland's trial, where thrombolytic therapy was administered to patients suffering from AMI [37]. Consequently, the moderate but significant improvement in LVEF in favour of BMSC treatment reported in the present study could be clinically very relevant providing that limitations such as study size could be overcome. Improvement in long-term survival has been suggested by the results of two recent randomised trials [28,38]. When sub-group analyses were conducted, greater effects on infarct size were observed when BMSC were administered earlier ( $\leq$ 7days). Effects on both infarct size and LVEF were greater when BMSC were administered at doses  $>10^8$  and to patients with larger infarcts or lower baseline LVEF. This is in agreement with previous published results [10,39]. Administering cells earlier may reduce infarct size and reduce damage during ventricular remodelling thus preventing or delaying the onset of heart failure. The requirement for a larger dose of BMSC to reduce infarct size and improve LVEF can be explained by the low rates of cell retention in the heart after BMSC infusion [29,40]. This supports the idea that the treatment may have a paracrine effect [41]. A number of randomised trials are currently addressing the effects of timing of stem cell transplantation [42,43], cell dose [44,45,46], cell delivery [24] and cell composition [27] on global left ventricular function. Although global LVEF has been a primary surrogate measured in the majority of included trials, the results presented here should be carefully considered, as there is still no evidence of clinical efficacy.

In summary, we have addressed some of the limitations present in the field here and elsewhere [4]. However, other limitations such as small study sizes, patient-related factors and variability in protocols still remain. This study shows that risk of bias due to publication, quality of the studies, loss of follow-up, duration of follow-up and date of disclosure of early results is minor among randomised trials that administer BMSC as treatment for AMI. BMSC treatment significantly reduces infarct size and improves LVEF long-term. Factors such as timing of BMSC transplantation, cell dose and baseline LVEF could affect the successful outcome of this treatment. An attempt has now been made with the design of the BAMI trial to standardise the techniques of BMNC isolation and delivery to man and to measure clinically significant end-points such as mortality.

doi:10.1371/journal.pone.0037373.t001

#### Supporting Information

**Figure S1 PRISMA diagram.** (DOC)

Table S1 Characteristics of the included studies.  $\left(\mathrm{DOC}\right)$ 

Table S2 Relative risk of dichotomous clinical outcomes.

(DOC)

Table S3 Weighted mean differences of continuousoutcomes measured.

 $\left( \text{DOC} \right)$ 

Table S4Quality assessment of included studies.(DOC)

#### References

- Velagaleti RS, Pencina MJ, Murabito JM, Wang TJ, Parikh NI, et al. (2008) Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 118: 2057–2062.
- 2. McMurray JJ, Pfeffer MA (2005) Heart failure. Lancet 365: 1877–1889.
- Wollert KC, Drexler H (2010) Cell therapy for the treatment of coronary heart disease: a critical appraisal. Nat Rev Cardiol 7: 204–215.
- Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, et al. (2012) Stem cell treatment for acute myocardial infarction. Cochrane Database Syst Rev 2: CD006536.
- Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, et al. (2004) Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet 364: 141–148.
- Chen SL, Fang WW, Ye F, Liu YH, Qian J, et al. (2004) Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 94: 92–95.
- Janssens S, Dubois C, Bogaert J, Theunissen K, Deroose C, et al. (2006) Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet 367: 113–121.
- Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, et al. (2006) Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 355: 1199–1209.
- Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, et al. (2006) Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med 355: 1210–1221.
- Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, et al. (2008) Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. Eur Heart J 29: 1807–1818.
- Janssens SP (2011) Cardiac bone marrow cell therapy: the proof of the pudding remains in the eating. Eur Heart J 32: 1697–1700.
- Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, et al. (2007) Adult bone marrow-derived cells for cardiac repair: a systematic review and metaanalysis. Arch Intern Med 167: 989–997.
- Lipinski MJ, Biondi-Zoccai GG, Abbate A, Khianey R, Sheiban I, et al. (2007) Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a collaborative systematic review and meta-analysis of controlled clinical trials. J Am Coll Cardiol 50: 1761–1767.
- Ioannidis JP, Trikalinos TA (2005) Early extreme contradictory estimates may appear in published research: the Proteus phenomenon in molecular genetics research and randomized trials. J Clin Epidemiol 58: 543–549.
- Hopewell S, Clarke M, Stewart L, Tierney J (2007) Time to publication for results of clinical trials. Cochrane Database Syst Rev. MR000011 p.
- Trikalinos TA, Churchill R, Ferri M, Leucht S, Tuunainen A, et al. (2004) Effect sizes in cumulative meta-analyses of mental health randomized trials evolved over time. J Clin Epidemiol 57: 1124–1130.
- Robinson KA, Dickersin K (2002) Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol 31: 150–153.
- Higgins J, Green S (2008) Cochrane Handbook for Systematic Reviews of Interventions 5.0.0; Higgins J, Green S, editors. Chichester, UK: John Wiley & Sons Ltd..
- Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539–1558.
- Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K (2009) Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev. MR000006 p.
- Fernandez-Pereira C, Vigo C, Bataglia S, De la Hoz R, Vetulli H, et al. (2006) Autologous bone marrow stem cell transplant after myocardial infarction. In-

Table S5Reference to studies.(DOC)

#### Acknowledgments

We thank Drs. Fengjuan Lu and Huajun Zhang for the translation of papers from Mandarin to English, Sarina Agkatsev for the translation from German to English, Dr. Sally Hopewell for advice with the publication bias tests.

#### **Author Contributions**

Conceived and designed the experiments: SJB AM MC EMR. Performed the experiments: DMC SAF CD SJB EMR. Analyzed the data: DMC SAF EMR. Contributed reagents/materials/analysis tools: SMW. Wrote the paper: DMC EMR. Approved final version of the manuscript: DMC SAF CD SJB AM MC SMW EMR.

hospital and long-term follow-up results of the randomised argentina trial (STAR AMI). Eur Heart J August. 279 p.

- Zhukova NS, Staroverov, II, Stukalova OV, Samoleinko LE, Romanov Iu A, et al. (2009) An experience of the use of stem cells in the treatment of patients with myocardial infarction and low ejection fraction. Kardiologiia 49: 19–24.
- Meyer GP, Wollert KC, Lotz J, Steffens J, Lippolt P, et al. (2006) Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' followup data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. Circulation 113: 1287–1294.
- Nogueira FB, Silva SA, Haddad AF, Peixoto CM, Carvalho RM, et al. (2009) Systolic function of patients with myocardial infarction undergoing autologous bone marrow transplantation. Arq Bras Cardiol 93: 374–379, 367–372.
- 25. Hirsch A, Nijveldt R, van der Vleuten PA, Tijssen JG, van der Giessen WJ, et al. (2011) Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. Eur Heart J 32: 1736–1747.
- Roncalli J, Mouquet F, Piot C, Trochu JN, Le Corvoisier P, et al. (2011) Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial. Eur Heart J 32: 1748–1757.
- 27. Tendera M, Wojakowski W, Ruzyllo W, Chojnowska L, Kepka C, et al. (2009) Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial. Eur Heart J 30: 1313–1321.
- 28. Grajek S, Popiel M, Gil L, Breborowicz P, Lesiak M, et al. (2010) Influence of bone marrow stem cells on left ventricle perfusion and ejection fraction in patients with acute myocardial infarction of anterior wall: randomized clinical trial: Impact of bone marrow stem cell intracoronary infusion on improvement of microcirculation. Eur Heart J 31: 691–702.
- Karpov RS, Popov SV, Markov VA, Suslova TE, Ryabov VV, et al. (2005) Autologous mononuclear bone marrow cells during reparative regeneratrion after acute myocardial infarction. Bull Exp Biol Med 140: 640–643.
- Piepoli MF, Vallisa D, Arbasi M, Cavanna L, Cerri L, et al. (2010) Bone marrow cell transplantation improves cardiac, autonomic, and functional indexes in acute anterior myocardial infarction patients (Cardiac Study). Eur J Heart Fail 12: 172–180.
- Li ZQ, Zhang M, Jing YZ, Zhang WW, Liu Y, et al. (2007) The clinical study of autologous peripheral blood stem cell transplantation by intracoronary infusion in patients with acute myocardial infarction (AMI). Int J Cardiol 115: 52–56.
- Arnesen H, Lunde K, Aakhus S, Forfang K (2007) Cell therapy in myocardial infarction. Lancet 369: 2142–2143.
- Kumar A, Galeb S, Djulbegovic B Treatment of patients with multiple myeloma: an overview of systematic reviews. Acta Haematol 125: 8–22.
- Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, et al. (2001) Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 344: 1895–1903.
- Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, et al. (2002) Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 346: 957–966.
- Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, et al. (2005) Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 45: 1397–1405.
- 37. Simoons ML, Vos J, Tijssen JG, Vermeer F, Verheugt FW, et al. (1989) Longterm benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. J Am Coll Cardiol 14: 1609–1615.

- Assmus B, Rolf A, Erbs S, Elsasser A, Haberbosch W, et al. (2010) Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. Circ Heart Fail 3: 89–96.
- Brunskill SJ, Hyde CJ, Doree CJ, Watt SM, Martin-Rendon E (2009) Route of delivery and baseline left ventricular ejection fraction, key factors of bonemarrow-derived cell therapy for ischaemic heart disease. Eur J Heart Fail 11: 887–896.
- Schachinger V, Aicher A, Dobert N, Rover R, Diener J, et al. (2008) Pilot trial on determinants of progenitor cell recruitment to the infarcted human myocardium. Circulation 118: 1425–1432.
- Gnecchi M, Zhang Z, Ni A, Dzau VJ (2008) Paracrine mechanisms in adult stem cell signaling and therapy. Circ Res 103: 1204–1219.
- 42. Traverse JH, Henry TD, Vaughan DE, Ellis SG, Pepine CJ, et al. (2009) Rationale and design for TIME: A phase II, randomized, double-blind, placebocontrolled pilot trial evaluating the safety and effect of timing of administration of bone marrow mononuclear cells after acute myocardial infarction. Am Heart J 158: 356–363.
- 43. Traverse JH, Henry TD, Vaughan DE, Ellis SG, Pepine CJ, et al. (2010) LateTTME: a phase-II, randomized, double-blinded, placebo-controlled, pilot trial evaluating the safety and effect of administration of bone marrow mononuclear cells 2 to 3 weeks after acute myocardial infarction. Tex Heart Inst J 37: 412–420.
- Meluzin J, Janousek S, Mayer J, Groch L, Hornacek I, et al. (2008) Three-, 6-, and 12-month results of autologous transplantation of mononuclear bone

- 45. Yao K, Huang R, Sun A, Qian J, Liu X, et al. (2009) Repeated autologous bone marrow mononuclear cell therapy in patients with large myocardial infarction. Eur J Heart Fail 11: 691–698.
- Quyyumi AA, Waller EK, Murrow J, Esteves F, Galt J, et al. (2011) CD34(+) cell infusion after ST elevation myocardial infarction is associated with improved perfusion and is dose dependent. Am Heart J 161: 98–105.
- Cao F, Sun D, Li C, Narsinh K, Zhao L, et al. (2009) Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up. Eur Heart J 30: 1986–1994.
- 48. Jin B, Yang Y, Shi H, Luo X, Li Y, et al. (2008) Autologous intracoronary mononuclear bone marrow cell transplantation for acute anterior myocardial infarction: Outcomes after 12-month follow-up. Journal of Clinical Rehabilitative Tissue Engineering Research 12: 2267–2271.
- Suarez de Lezo J, Herrera CP, M., Romero M, Pavlovic D, Segura J, et al. (2007) Tratamiento regenerativo en pacientes con infarto agudo anterior revascularizado y funcion ventricular deprimida. Rev Esp Cardiol 60: 357–365.
- Penicka M, Horak J, Kobylka P, Pytlik R, Kozak T, et al. (2007) Intracoronary injection of autologous bone marrow-derived mononuclear cells in patients with large anterior acute myocardial infarction: a prematurely terminated randomized study. J Am Coll Cardiol 49: 2373–2374.