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Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE)

in patients with acute myocardial infarction based on individual patient data

Gyöngyösi. IPD meta-analysis of cell studies

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Additional investigators participating in the ACCRUE database are listed in the Appendix.

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Abstract

Rationale. This meta-analysis of cell-based cardiac studies (ACCRUE) is the first prospectively-declared, collaborative, multinational database of individual patient data (IPD) from patients with ischemic heart disease treated with cell therapy.

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

Methods and Results. The primary endpoint was freedom from combined major adverse cardiac and cerebrovascular events (MACCE; including all-cause death, re-AMI, stroke, and target vessel revascularization). The secondary endpoint was freedom from hard clinical endpoints (death, re-AMI, or stroke), assessed with random-effects meta-analyses and Cox regressions for interactions. Secondary efficacy endpoints included time-related changes in individual end-diastolic volume (ΔEDV), end-systolic volume (ΔESV), and ejection fraction (ΔEF), analyzed with random-effects meta-analyses and analysis of covariance. We reported weighted mean differences between cell therapy and control groups. Cell therapy results were similar to control results, based on MACCE (14.0% vs. 16.3%, hazard ratio 0.86, 95%CI: 0.63, 1.18), death (1.4% vs. 2.1%), death/re-AMI/stroke (2.9% vs. 4.7%), ΔEF (mean difference: 0.96%, 95%CI: -0.2, 2.1), ΔEDV, and ΔESV. These results were not influenced by anterior AMI location, a reduced baseline EF, or the use of MRI for assessing left ventricular parameters.

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

Clinical trial registration: clinicaltrials.gov_NCT01098591

Key words: stem cell, acute myocardial infarction, meta-analysis, heart failure, outcome

Non-standard Abbreviations and Acronyms:

ACCRUE: Meta-Analysis of Cell-based CaRdiac stUdiEs

AMI: acute myocardial infarction

ANCOVA: analysis of covariance

BM-MNCs: bone marrow mononuclear cells

CI: confidence interval

CK: creatine kinase

DM: diabetes mellitus

EDV: end-diastolic volume

EF: ejection fraction

ESV: end-systolic volume

FUP: follow-up

HR: hazard ratio

iCMP: ischemic cardiomyopathy

IDC: Independent Data Committee

IHD: ischemic heart disease

IPD: individual patient data

LV: left ventricular

MACCE: major adverse cardiac and cerebrovascular events

MRI: magnetic resonance imaging

PI: principal investigator

SD: standard deviation

SE: standard error

STEMI: ST-segment elevation myocardial infarction

TVR: target vessel revascularization

Meta-analyses of randomized and cohort cell therapy studies have reported that intracoronary or intramyocardial cell delivery was safe, and it provided 2-8% increases in global, left ventricular (LV) ejection fraction (EF) in patients with acute myocardial infarction (AMI) or ischemic cardiomyopathy.[1-4] Those meta-analyses were based on information from studies that included different patient populations, follow-up (FUP) times, and outcome measures. Consequently, the meta-analysis interpretations were heterogeneous, due to inconsistent clinical definitions and parameters. Additionally, publication-based meta-analyses may include studies that were later withdrawn or that contained publication errors,[5] and they may exclude important trials that reported median values of skewed data. In contrast, individual patient data (IPD)-based meta-analyses contain transparent, controlled data, with unique definitions; this approach allows analyses of specific subgroups and generation of prognostic models.

The largest previous relevant meta-analysis enrolled 50 studies (n=2625 patients). They reported that cardiac transplantation of adult bone-marrow-derived cells (BMCs) provided persistent benefits, in terms of clinical outcome and LV parameters.[3] However, a recent meta-analysis on intracoronary cell treatment trials, which included 30 studies (n=2037 patients), could not confirm data obtained from magnetic resonance imaging (MRI) measurements of LV function[4]; moreover, they were the first to report that cell therapy had no effect on clinical outcome. Both meta-analyses used aggregated data from published studies, but there was considerable heterogeneity across the trials involved.

The ongoing, meta-analysis of cell-based cardiac studies (ACCRUE, NCT01098591, formerly MEta-analysis of Stem cell Studies, MESS) is based on a collaborative, multinational database that comprises IPDs from randomized and cohort studies. The ACCRUE database was established to facilitate exploration of the clinical safety and efficacy of cell therapy in patients with ischemic heart disease (IHD) and to identify subgroups of patients predicted to benefit from cell therapy. The present study represents the first IPD-based meta-analysis of cell treatment in IHD to date.

The objectives of this ACCRUE study were:

1. To estimate the overall treatment effect of cardiac cell-based therapy on clinical outcomes,

including occurrence of major adverse cardiac and cerebrovascular events (MACCE, composite of all-cause death, AMI recurrence [re-AMI], coronary target vessel revascularization [TVR], and stroke) and the occurrence of clinical hard endpoints (death, re-AMI, or stroke);

2. To analyze the effect of cell therapy treatment on LV function and remodeling, including changes in end-diastolic volume (EDV), end-systolic volume (ESV), and EF;

3. To identify predictors of MACCE and of LV function and remodeling improvements in patients with IHD treated with cell therapy;

4. To explore the influence of patient characteristics, including cardiovascular risk factors, on the safety and efficacy of cardiac cell therapy;

5. To identify the characteristics of individual patients with IHD that can predict benefit from cell therapy.

Methods

The main objective of the ACCRUE group is to use IPDs to improve the quality of data used in meta-analyses of cell therapy studies in patients with chronic IHD and AMI. The first collaborative meeting was held in Vienna, 2007, with the investigators of the ASTAMI, REGENT, BOOST, Aalst (Bartunek)-study, BONAMI, REPAIR-AMI, Atsma-study, MYSTAR, STEMMI, the Hamburg and Novosibirsk intramyocardial studies, and the EUROINJECT-ONE cardiac gene therapy study. The meeting aimed to define objectives, to establish data contribution criteria, and to appoint the Independent Data Committee (IDC) and Steering Committee (Online Supplementary Data).

Criteria for considering studies for inclusion in the ACCRUE database

The criteria for contributing data to the ACCRUE database were that the data must be from randomized or cohort clinical studies, and that cardiac regeneration was induced by percutaneous administration of cells- or cell-based products, or by mobilization of BMCs. A continuous literature search was initiated, and principal investigators and study coordinators of recently published studies were prospectively invited to contribute IPDs to the database. Additional study inclusion criteria for randomized studies are included in the Online Supplementary Data.

Outcome measures

The primary outcome measure of the ACCRUE meta-analysis was the safety of the treatment, defined as the freedom from MACCE (the composite of all-cause death, re-AMI, stroke, and TVR). The secondary endpoints were freedom from the combined hard clinical endpoints (all-cause death, re-AMI, or stroke) or freedom from the individual components of MACCE. Another secondary endpoint was efficacy, defined as changes in LV, EDV, ESV, and EF, compared to baseline.

Search methods for identifying studies

Studies were prospectively identified in literature searches, and the identified investigators were invited to participate. The search methods are included in the Online Supplementary Data.

Data collection and management

The data collection method is described in the Online Supplementary Data. The corresponding authors and primary investigators of selected studies were emailed or contacted personally several times with invitations to contribute original data to the central database (Fig. 1). Participants deposited the individual data into the database, which was prepared with predefined terms and conditions (determined and agreed upon at the first investigator meeting). Authors from 39 centers responded, and data were received from 23 centers[6-17] (additional references in Online Supplementary Data, References 18-28). One center later cancelled participation and withdrew their data, due to changes in institutional policy. The current ACCRUE database comprises 1871 IPD sets from 28 studies (15 randomized studies, 10 cohort cell therapy studies, and 3 studies with granulocyte-colony stimulating factor). All patients were classified as "cell-treated" (n=1203) or "control" (n=668).

In accordance with pre-specified plans, analyses carried out in ACCRUE differ from those carried out in the individual papers. Therefore, results from the ACCRUE report may be different from those reported in the individual papers, particularly when different terms were used for event classifications or FUP times. These issues were discussed with the corresponding authors of all papers.

All studies were approved by the local ethics committees. Additional approval was obtained for the meta-analysis. Data quality was evaluated with quality checklists provided in the CONSORT[18] and PRISMA (http://www.prisma-statement.org) statements and guidelines.

The database was controlled by the IDC. It was temporarily closed in June, 2014, to perform the first statistical analysis. The current meta-analysis included data from patients with recent AMIs that were randomized to either intracoronary cell-therapy or control therapy (ASTAMI, Aalst, BONAMI, BOOST, CADUCEUS, FINCELL, LATE-TIME, REGENT, REPAIR-AMI, SWISS-AMI, TIME, SCAMI trials).[6-17] The present analysis excluded all non-controlled studies, the MYSTAR study, which included a combined delivery mode in patients with recent AMI, and all randomized percutaneous intramyocardial cell-based studies in patients with chronic IHD (Fig. 1).

Assessment of risk of bias in included studies

Methods for assessing the risk of bias and quality of the studies are described in the Online Supplementary Data.

Statistics

This IPD-meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Intervention[19] and the guidelines for meta-analysis of IPD for time-to-event outcomes.[20,21] Heterogeneity between the studies was tested with I^2 statistics. Additional sensitivity analyses were performed to detect differences between studies. Two investigators conducted the analyses (EN, MG).

Investigation of heterogeneity and selection bias

The statistics for investigating heterogeneity and selection bias of the included trials are presented in the Online Supplementary Data.

General Statistics

Normally-distributed, continuous variables are presented as the mean±standard deviation (SD). Continuous parameters with skewed distributions are expressed as the median and first interquartile range. Binary and categorical variables are given as frequencies and percentages. Associations between the number of cells/log number of cells and the changes in EDV, ESV, or EF in the cell-treated group were calculated with linear regression analysis.

All *P* values were based on two-sided tests. For multiple comparisons, *P* values less than 0.01 were considered statistically significant.

IPD meta-analysis

All analyses were based on the intention to treat. Multiple Cox regression models were used to analyze the primary outcome, stratified for the individual studies. The multiple model included cardiovascular prognostic factors for the occurrence of MACCE, such as gender, age, diabetes mellitus (DM), hypertension, hyperlipidemia, and baseline EDV and EF values. This model was used to determine an adjusted, common treatment effect, with baseline hazards that varied across studies.[20,21] To evaluate possible dependencies of the treatment effect on other prognostic factors, all possible interactions were tested within the multiple stratified Cox regression models. Factors were excluded from the analysis when data were missing in at least 50% of cases (e.g., positive family anamnesis for heart disease, baseline infarct size). Adjusted HRs and their 95% CIs are presented with the corresponding *P* values. The Kaplan-Meier method and cumulative hazards were used to display the MACCE-free, death-free, death/re-AMI/stroke-free, and TVR-free survival rates. Pre-specified subgroup analyses for the primary endpoint and the secondary endpoint of death/re-AMI/stroke were carried out for the following subgroup categories: age (> or ≤ 57 years), EF (> or ≤45%), baseline EDV (> or ≤130 ml), anterior AMI (yes or no), maximal creatine kinase (CK, > or ≤ 3450 U/l; CK is associated with infarct size; 3450 U/l was the median value for all patients), gender, DM, hypertension, hyperlipidemia, smoking, and use of MRI.

The secondary endpoints, changes in LV EF, EDV, and ESV, were evaluated with an analysis of covariance (ANCOVA). The treatment effect was adjusted for cardiovascular risk factors, male gender, mode of measuring LV function, anterior location of AMI, baseline EDV, baseline EF, and time between AMI and randomization (sham intervention in controls or cell therapy in cell-treated groups); for these adjustments, the individual studies were considered a block factor. Possible interacting effects with treatment were tested within these ANCOVA models. Changes in EDV, ESV, and EF in the cell therapy and control groups are expressed as the mean ±SD; the mean difference from baseline was reported with the SE, and the relative 95% CIs were reported as effect measures.

Pre-specified subgroup analyses included the effect of FUP time and the effect of baseline EF on changes in LV function, evaluated as dichotomous variables. The numbers of patients in groups that received different subtypes of autologous cells were uneven or low; therefore, we did not perform

subgroup analyses on the effect of cell types on the endpoints.

All statistical computations were performed with Review Manager 5.2 (The Nordic Cochrane Center, Købehvn, Denmark) and Stata/SE, version 12, for Windows (StataCorp, Houston, Texas).

Results

Search results

A systematic search for eligible trials resulted in 1533 clinical reports on cardiac cell therapies. Of these, 921 were excluded based on the pre-clinical nature of the studies or because they were only abstracts or incomplete reports. Thus, 612 clinical studies were eligible, and 149 were selected because they used cell injections or autologous BMC mobilization. A further 94 studies were excluded because they were reviews, descriptions of surgical approaches, or pilot studies for study designs or sub-analyses. Finally, 55 studies were included, and the corresponding authors were contacted. The present analysis included 12 randomized studies on intracoronary cell therapy applied after AMI (Fig. 1).

Study characteristics

Table 1 lists the study characteristics. An average of 104 patients was included in individual studies (n=64 and n=40 for cell treatment and control groups). Most studies used BM mononuclear cells (BM-MNCs), and MRI was used for visualizing and quantifying LV performance. Three studies assessed the timing of cell therapy (CADUCEUS, LATE-TIME, SWISS-AMI); otherwise cell therapies were performed within 2 weeks post-AMI. Most patients were randomized during the first week (65% of patients in the cell-therapy and 79% of patients in the control group), and EF was measured before randomization. The quantitative baseline LV functional parameters were assessed at the time of the primary PCI (e.g., FINCELL), before randomization, 1-3 days post-AMI (e.g., REGENT), or several weeks post-AMI, after resolution of myocardial stunning (e.g., LATE-TIME). Thus, there were different time lapses between the delivery of cell therapy and the measurement of baseline LV function.

All patients received clinical FUPs. Paired LV functional data measured at baseline and at

FUP were available for 1064 (624 cell-therapy and 440 control) patients. Baseline LV function and FUP events were not different for patients that lacked paired LV data for any reason (data not shown).

Infarct size data were available for 114 of 767 subjects (14.9%) that received cell-therapy and for 111 of 485 subjects (22.9%) in the control group. Because these groups did not represent the entire population, we did not analyze changes in infarct size.

Study quality and risk of bias in included studies

Online Table I shows the scales for assessing the quality of the studies on randomized intracoronary cell therapy in AMI that were included in the ACCRUE database. The internal validity was based on results from the external validity criteria and sensitivity analyses; these are described in the Online Supplementary Data.

Baseline patient characteristics

Table 2A shows the baseline clinical data, including measurements of baseline LV function parameters. No differences were observed between the two groups, with the exception of ESV, which was lower in controls. Cardiac MRI was more often used as the imaging modality in the cell therapy group, due to the higher number of patients in cell-therapy group than in the control groups of the SWISS-AMI and REGENT trials (2:1 randomization).

Primary endpoint

MACCE was similar between the groups (HR: 0.86, 95% CI: 0.63, 1.18; Table 2B, Online Figure I). After adjusting for all confounding factors, the Cox regression showed no effect of cell-therapy on MACCE-free survival (Table 2B, Figure 2). The addition of anterior AMI as a confounding factor did not influence the primary outcome (Online Table II). The subgroup analysis did not reveal a prognostic factor for prevention of MACCE (Fig. 2); therefore, we found no factors that influenced the success of cell therapy.

The results of the overall meta-analysis (between-trial analyses) for the primary endpoint were highly consistent in direction and magnitude with those obtained from the individual participant data meta-analyses (within-trial analyses); i.e., there was no significant benefit with cell therapy vs. controls (HR: 0.86, 95% CI:0.63, 1.18; P=0.884). No significant heterogeneity or inconsistency was

found between trials (I^2=0%) (Online Figure I). Additionally, the funnel plot for the primary endpoint did not show asymmetry on visual inspection (Online Figure I), which was confirmed by a non-significant Egger's test.

Secondary endpoints

Similar to the primary endpoint, cell therapy did not improve clinical outcome in terms of the incidence of death, death/re-AMI/stroke, and TVR (Table 2B, Fig. 3A, Online Figure II). No cardiovascular risk factor could be identified that influenced the clinical hard end points (death/re-AMI/stroke). Similarly, the hard endpoints were not impacted by a lower baseline EF, a higher EDV, the location of infarction, the maximal CK, or whether LV function was measured with MRI. Although we observed a trend that different subgroups showed different directions in the effect of cell therapy, as shown in the forest plot (Figure 3B), none was consistently significant (p>0.01), and no interaction was significant.

Both EDV and EF increased slightly in cell-treated and control groups (Table 2B), without a decrease in ESV from baseline to FUP. Cell therapy did not influence the changes in global EF (mean between-group difference of 0.96%, 95% CI: -0.2 2.1), EDV (1.2 ml, 95% CI:-3.4. 5.8), or ESV (0.4 ml, 95% CI: -3.4, 4.1) (Table 2B, Figs. 4A, 4B, 4C).

Table 3 summarizes the ANCOVA results (detailed data in Online Table III). The final changes in EDV, ESV, and EF were not influenced when the model included covariates of gender, age, DM, hypertension, hyperlipidemia, anterior AMI location, MRI imaging modality, baseline EDV, baseline EF, or timing of cell treatment. Cell therapy in older patients led to a greater increase in EDV compared to controls, with no significant changes in ESV or EF (Online Table III).

Sub-analysis of different FUPs

Four studies provided 1-year clinical FUP data (CADUCEUS, REPAIR-AMI, SWISS-AMI, and SCAMI); the other studies reported clinical FUPs of 6 months or shorter. No difference between the groups was identified at the 6-month FUPs or at the 6-to-12-month FUPs regarding MACCE, death, death/re-AMI/stroke, or TVR (Online Figures III-V). The majority of MACCE events were TVR at the 6-month FUP. Trials with a planned 6-month clinical FUP controlled the patients and

performed TVR when in-stent restenosis of the infarct-related artery was documented. This resulted in an increase in the TVR incidence at 6 months, but there was no difference between groups.

Most of the LV functional measurements were performed at the 6-month FUP; the Aalst-study, BONAMI, and REPAIR-AMI provided 3- or 4-month FUP data; the CADUCEUS and SCAMI studies also had control measurements at 1 year. Table 4A shows the FUP time-dependent changes in LV EDV, ESV, and EF in cell-treated and control groups. An increase was observed in EDV from baseline to the 6-month and 12-month FUPs in both the cell-therapy and control groups. Due to the relatively low numbers of patients in these subgroups, and to avoid a type I error, we did not performs statistical comparisons between the 6- and 12-month FUP data. No difference between groups was detected regarding FUP data collected at ≤6 months, or >6 months.

Sub-analysis of baseline EF effects on changes in LV parameters

The sub-classes of baseline EF (>50%, >45%, and >40%) showed no influence of baseline EF on the changes in EDV, ESV, or EF at the FUP (Table 4B).

Effect of the number of injected cells on LV function

Linear regression analysis showed no correlation between the number of injected cells or the log number of injected cells and the changes in EDV, EF (Online Figure VI), or ESV (data not shown) in the cell-treated group. There was, however, a large scatter in the number of cells applied (range: 12.5-4303 $\times 10^6$).

Comparison of ACCRUE data with results from non-participating studies

Online Table IV summarizes the results from currently published randomized cell-therapy trials in patients with recent AMI that did not contribute to the ACCRUE database. The reported mean EF± SD and the number of included patients are shown (Online Supplementary Data, References 29-47). These 19 studies included 503 patients (mean = 27) in the cell-treated group and 352 patients (mean = 19) in the control group. In contrast, the ACCRUE intracoronary arm included 767 patients (mean = 64) in the cell-treated group and 485 patients (mean = 40) in the control group. The ACCRUE database currently represents over 70% of all clinical cardiac regeneration studies and approximately 60% of all intracoronary cell studies; it includes all major randomized studies, except

the HEBE trial, the Cao study, and the Chen study (Online Supplementary Data, References 36,40,45).

Discussion

This ACCRUE study was based on the first IPD database, constructed for meta-analyses of cardiac cell therapy. The database comprised a pool of 1871 IPDs from 15 randomized cardiac regeneration studies. Twelve of these studies (with 1252 IPDs) involved intracoronary cell delivery in patients with recent AMIs. This first ACCRUE meta-analysis selected randomized studies on intracoronary administration of reparative cells. We found no effect of cell therapy on clinical events or changes in LV function or remodeling. Based on original data, we could not identify predictive factors or patient characteristics that might indicate patients most likely to benefit from cell therapy.

An important feature of this ACCRUE, which is rarely seen in other meta-analyses, was its prospective nature, in accordance with the Cochrane guidelines for planning and conducting an IPD meta-analysis, involving also the Cochrane Heart Group. The prospective data collection of ACCRUE allowed uniform definitions of endpoints, follow-up periods, and adverse events; this approach ensured the most unbiased, and thus, the most reliable results. It also increased the robustness and accuracy of the findings. The ACCRUE investigators met the goal of this analysis and take advantage of its benefits.

However, some caution should be taken with the interpretation of our results. The negative and, for the health community, disappointing results are not surprising. Six of the included studies (including about two thirds of the study patients), which comprised the largest and most homogeneous clinical populations (ASTAMI, BONAMI, REGENT, TIME, LATE-TIME, SWISS-AMI), reported no benefit from autologous cell-based, intracoronary regenerative treatment.[8,9,11,15-17] One out of three similarly large studies, which were not included in the ACCRUE database (HEBE), also reported a negative outcome.

Potentially, the efficacy of cell therapy could be affected by differences among the studies included in the ACCRUE database. For example, differences in the types of injected cells and the timing of cell administration (acute phase of AMI versus convalescent AMI) may affect the outcomes. We did not evaluate these factors separately, because the individual subgroups would have comprised

statistically unacceptably low numbers of patients, and the analysis may not have provided additional informative value. However, the ANCOVA analysis showed that, when the time to cell/control therapy was considered as an independent covariate, it did not significantly affect the changes in EDV, ESV, or EF. An additional factor that might influence changes in LV function could be the time that baseline EF was measured (if not the same day as the cell therapy). This timing may be consequential, considering that, in the natural course of the reperfused AMI, during the first week, rapid changes were observed in the EF and the size of late enhancement in serial MRIs.[22] Moreover, there was a time-dependent component in the regenerative function of the different types of harvested autologous co-morbid BM-origin cells.[23]

Adverse events, LV function, and LV remodeling related to intracoronary cell therapy

Intracoronary administration of cells proved to be safe, with a low procedural complication rate (2.2%). The composite in-hospital complications were similar between groups. The mortality and incidence of hard clinical endpoints were noticeably low among the patients with STEMI in both groups. This finding may have resulted from the carefully selected patients and the relatively high baseline EFs. Sub-analyses of different FUPs did not change the outcome difference between treated and control patients; the negative results were consistent. We point out that a placebo effect has been observed in blinded randomized trials, although this effect might be less significant than in non-randomized studies. Because the placebo effect is additive to the control treatment effect, it can reduce the observed treatment effect size and the statistical power of the study.

Most patients underwent MRI scanning, which is regarded the gold standard for assessing LV function. Similar to our results, de Jong et al. found that the beneficial effect of cell therapy on LV EF and infarct size disappeared, when MRI was used for quantitative imaging.[4] Additionally, both studies found that the baseline EF did not affect the improvement in LV function over time.[4] Also our data were consistent with a previous study, where serial cardiac MRIs of patients with reperfused, first AMIs showed a gradual increase in LV EDV during the first year after the AMI.[22]

In contrast with previous meta-analyses,[3,4] we did not assess infarct size at FUP, because the majority of trials did not measure infarct size before cell therapy; therefore, no change between baseline and FUP could be reported. Instead, we added the maximal CK as a confounding factor that

could influence the outcome, because maximal CK is highly associated with infarct size.[24]

In contrast with previous meta-analyses, we found no association between the number of cells delivered and the outcomes. It should be mentioned, however, that the numbers of cells used for intracoronary cell therapy varied widely, even without considering trials that assessed the importance of cell number on the clinical or functional outcome. Previous studies reported only the mean or median numbers of injected cells/group. Therefore, the results of those analyses should be considered less exact than results from this ACCRUE study.

One of the objectives of this ACCRUE study was to reveal prognostic factors for clinical events or identify patients that might benefit from cell therapy. We did not achieve this objective, despite the fact that the intracoronary treatment arm of the ACCRUE database included large randomized studies (mean of 104 patients/study) with remarkably low between-trial heterogeneity, compared to the previous largest reported meta-analysis.[3,4] Because we used common definitions of primary endpoints throughout the studies, the heterogeneity for clinical endpoints was 0% among studies. In contrast to previously published meta-analyses, which showed up to 87% heterogeneity among studies, our meta-analysis showed little or no heterogeneity among studies for continuous parameters of the secondary endpoints; i.e., the heterogeneities were 0% for ΔEDV, 11% for ΔESV, and 48% for ΔEF. This highlighted the accuracy of a large-scale IPD-based meta-analysis in characterizing any potential effect in different clinical subgroups and its pivotal role in fully exploring the clinical relevance and adequacy of cell therapy for treating IHD. However, according to de Jong et al., more than 30 000 patients should be included in a study to identify an effect of cell therapy treatment, when mortality is around 2%,[4] similar to our findings.

Advantages of the IPD-based meta-analysis

This ACCRUE IPD-based meta-analysis overcame the major limitations of systematic reviews and conventional meta-analyses. Those approaches extract aggregated data from available publications according to a predefined study protocol, and the random effects are determined by calculating the weighted means (e.g., relative risk) of randomized trials. Accordingly, publication-based meta-analyses must exclude some important trials, where group differences are expressed as the median and interquartile range (e.g., BONAMI, HEBE, MYSTAR, REGENT). Online Table 4 shows

the heterogeneity among reports of LV functional data from studies that did not contribute to the ACCRUE database. All but one study (Ruan et al. Supplemental Reference 47) were included in a recent intracoronary cell therapy AMI meta-analysis.[4] When no original data were available, they re-calculated the mean differences and 95% CIs or SDs with meta-analysis software and a standardized formula. Thus, these re-calculated data were partially discrepant with the published or original data; e.g., Plewka et al. showed changes in EF from baseline to FUP of 10±9% in the cell-therapy group vs. 5±8% in controls (Supplemental Reference 35); in contrast; the calculated random-effect meta-analysis data showed EF changes of 9±5.8 vs. 5±4.9% or 9±7% vs. 5±3.4%, respectively.[3,4] Alternatively, the present IPD meta-analysis included raw data; thus, we could calculate accurate, real means with SDs, mean differences with SEs, and CIs; moreover, these calculations were not influenced by the limited information gained from the publications.

Limitations of the ACCRUE database

A major limitation of the present study was the combination of several different cell types (BM-MNCs, CD133+ -enriched BMCs, CD34+CXCR selected cells, or cardiosphere-derived cells [CDCs]). As in all previous meta-analyses, we assumed that the potency was comparable among different cell types . In fact, different cell populations exert heterogeneous effects, depending on the amount of time passed since the AMI.[23] Additionally, when various clinically-utilized cell types were compared directly in the same mouse infarct model, the rank order of efficacy was CDCs>>BM-MNCs.[25] Only 2% of the ACCRUE database comprised heart-derived cells; thus, heart cells were not well-represented in the present analysis. Additionally, intracoronary infusion of allogeneic mesenchymal stem cells resulted in a 6.28% increase in EF, as reported by de Jong et al.[4] Our meta-analysis contained only studies with autologous cells, which in turn, increased its homogeneity.

Another limitation was that the IPD in the ACCRUE database included fewer studies and patients than the total number of available published studies. Thus, this study did not include all studies that would be typically incorporated into a conventional meta-analysis. This lack was partly due to centers that refused to provide individual data and partly due to the temporary closure of the database, which precluded studies that were published later.

Most previous large medical IPD-based meta-analysis studies were company sponsored.

Those studies implemented a generalized electronic case report form, and the database and data were monitored by external monitoring companies. Therefore, extraction of standardized data from case report forms was *a priori* facilitated. However, to date, no company-sponsored studies on cell-based cardiac regeneration with intracoronary cell delivery have been conducted and controlled centrally. At the time the present study was initiated, no financial support was available for the effort of providing and formatting data in accordance with the ACCRUE database. Additionally, data that did not represent the entire population could not be assessed; we could only analyze data on specific information collected for the database, such as medications during FUP, or specific information provided by the centers, such as data on stent thrombosis. However, the statistical analysis revealed a remarkably low heterogeneity across the trials included in this ACCRUE study (I^2 0% to 48%), compared to previous, largest meta-analyses (I^2 up to 87%),[3,4] due to the pre-specified baseline and outcome parameters.

The results of this IPD meta-analysis revealed some important discrepancies from previous meta-analyses. Our findings highlighted the lack of consistent efficacy in cell-based cardiac regeneration with intracoronary cell delivery in patients with diverse cardiovascular risk factors. Although the ACCRUE database has continued to recruit data contributions, it cannot replace large-volume, prospective randomized studies, such as the ongoing BAMI trial (ClinicalTrials.gov Identifier: NCT01569178) or the CCTRN network.[26,27]

Appendix

Other investigators of the ACCRUE group included: Rayyan Hemetsberger MD, Dietmar Glogar MD, Sasko Kedev MD, Erik Jørgensen MD, Wang Y MD, and Rasmus S. Ripa MD CCTRN.

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The authors declare no conflicts of interest

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Figure legends

Figure. 1. Flow diagram of the ACCRUE database and participating studies

G-CSF: granulocyte colony-stimulating factor; AMI: acute myocardial infarction; iCMP: ischemic cardiomyopathy

Figure 2. Primary endpoint analysis.

2A. Major adverse cardiac events (MACCE)-free survival of patients with recent acute myocardial infarction who were randomized to either cell therapy or control treatment (upper). Hazard ratio and 95% confidence intervals of risk factors that favor cell therapy or control treatment (bottom). MACCE defined as all-cause death, re-infarction, target vessel revascularization, and stroke; DM: diabetes mellitus; EDV: end-diastolic volume, EF: ejection fraction

2B. Forest plot of MACCE-free survival in subgroups, with hazard ratio (Haz), CI: confidence interval, *P* inter: *P* for interaction**,** CK:creatine kinase, MRI: magnetic resonance imaging

Figure 3. Secondary endpoint analysis.

3A. Kaplan-Meier analysis of death/AMI/stroke–free survival of patients randomized either to cell-therapy or controls (upper). Hazard ratio and 95% confidence intervals of risk factors favoring cell therapy or control treatment (bottom). AMI: acute myocardial infarction, DM: diabetes mellitus; EDV: end-diastolic volume, EF: ejection fraction

3B. Forest plot of death/AMI/stroke-free survival in subgroups with hazard ratio (Haz), CI = confidence interval, p inter= *P* for interaction, AMI: acute myocardial infarction, CK: creatine kinase, MRI: magnetic resonance imaging

3C. Kaplan-Meier analysis of target vessel revascularization (TVR)-free survival (upper). Hazard ratio and 95% confidence intervals of risk factors favoring cell therapy or control treatment (bottom). DM: diabetes mellitus; EDV: end-diastolic volume, EF: ejection fraction

Figure 4. Forest plot displaying changes in left ventricular ejection fraction, end-diastolic and end-systolic volumes in patients treated with intracoronary cell therapy after recent acute myocardial infarction.

Unadjusted difference in mean with 95% confidence intervals

4A. Forest plot of changes in ejection fraction

4B. Forest plot of changes in end-diastolic volumes

4C. Forest plot of changes in end-systolic volumes

Table 1. Study characteristics

Name of Study	Sample size (Cell therapy/Controls)	Mean follow-up duration (month)	Cell type	Location of AMI	Time from AMI to cell delivery (days)	Imaging modality
CADUCEUS	17/8	12	Cardiosphere-derived cells	anterior (except 1)	62±11	MRI
BONAMI	52/49	3	BM-MNC	anterior	9±2	SPECT, RNV
Aalst Study	19/16	4	BM-MNC	multiple	12±1	LV Angiography
REPAIR-AMI	101/103	4	BM-MNC	multiple	4±1	LV Angiography
BOOST	30/30	6	BM-MNC	multiple	5±1	MRI
LATE-TIME	58/29	6	BM-MNC	multiple	17±5	MRI
ASTAMI	50/50	6	BM-MNC	anterior	6±1	SPECT, Echocard.
REGENT	160/40	6	BM-MNC, or selected CD34+CXCR	anterior	7±2	MRI
SWISS-AMI	133/67	4	BM-MNC	multiple	13±10	MRI
TIME	79/41	6	BM-MNC	multiple	5±2	MRI
SCAMI	29/13	12	BM-MNC	multiple	6±1	MRI
FINCELL	39/39	6	BM-MNC	multiple	3±1	Echocard.

BM-MNC: Bone marrow mononuclear cells, AMI: acute myocardial infarction, MRI: magnetic resonance imaging, SPECT: single photon emission computed tomography, RNV: radionuclide ventriculography; LV: left ventricular; Echocard.: Echocardiography

Table 2A. Baseline data of patients with recent acute myocardial infarction (AMI) and randomized to cell-therapy or control

	Cell therapy n=767	Control n=485	P value
Baseline			
Age (y)	57.3±10.4	57.0±10.7	0.600
Male gender	614/767 (80.1%)	405/485 (83.5%)	0.136
Diabetes mellitus	111/767 (14.5%)	79/485 (16.3%)	0.419
Hypertension	384/767 (50.1%)	244/485 (50.3%)	0.954
Hyperlipidemia	387/717 (54.0%)	228/435 (52.4%)	0.626
Active smoker	396/708 (55.9%)	243/422 (57.6%)	0.620
Maximal creatine kinase (U/L)	3467±2492	3410±2426	0.235
Number of diseased vessels	1.3±0.6	1.3±0.6	0.952
Anterior AMI	662/767 (86.3%)	415/485 (85.6%)	0.351
Pre-cell therapy			
End-diastolic volume (ml)	146±51	139±48	0.012
End-systolic volume (ml)	84±40	77±36	0.004
Ejection fraction (%)	43.7±11.9	45.5±11.8	0.011
Magnetic resonance imaging	492/767 (64.1%)	257/485 (53.0%)	<0.001
Cell therapy			
Time from AMI to treatment in cell therapy group and randomization/sham intervention in controls (days)	8.0±9.7	6.6±10.9	0.202
Number of cells injected intracoronary (x10^6) (median and 25% and 75% interquartile ranges)	150 (6, 294)		
Intracoronary injection-related procedural complication (%)	14/630 (2.2%)		
In-hospital complication (%)	21/631 (3.3%)	21/413 (5.1%)	0.197

Table 2B. Primary and secondary endpoints

	Cell therapy	**Control**	**P value**
Follow-up	n=767	n=485	
Follow-up time (days)	225±112	231±114	0.375
(median with range)	(180; 90-365)	(180; 90-365)	
MACCE	107/767 (14.0%)	79/485 (16.3%)	0.289
All-cause death (%)	11/767 (1.4%)	10/485 (2.1%)	0.499
Target vessel revascularization (%)	87/767 (11.3%)	65/485 (13.4%)	0.287
Death or Re-AMI or stroke	22/767 (2.9%)	23/485 (4.7%)	0.088
Non-serious adverse events	55/680 (6.5%)	40/472 (8.5%)	0.206
End-diastolic volume (ml)	162±57	153±54	0.008
End-systolic volume (ml)	89±48	82±44	0.012
Ejection fraction (%)	47.3±13.9	48.3±13.4	0.245
Changes from baseline to follow-up	(n=624)	(n=440)	
Δ End-diastolic volume (ml)	15.0±40.1	13.8±33.4	0.614
Mean difference (SE), 95% CI	*1.2 (2.3), -3.4, 5.8*		
Δ End-systolic volume (ml)	5.0±32.5	4.6±27.4	0.853
Mean difference (SE), 95% CI	*0.4 (1.9), -3.4, 4.1*		
Δ Ejection fraction (%)	3.6±9.5	2.6±8.9	0.096
Mean difference (SE), 95% CI	*0.96 (0.58), -0.2, 2.1*		

AMI: acute myocardial infarction, MRI: magnetic resonance imaging, MACCE: major adverse cardiac and cerebrovascular events, SE: standard error, CI: confidence interval.

Table 3. Results of interaction analysis (ANCOVA models) in patients with recent acute myocardial infarction and randomized either to cell treatment of controls

	Changes in end-diastolic volume	Changes in end-systolic volume	Changes in ejection fraction
Cell treatment effect with male gender			
p value	0.919	0.977	0.091
Mean difference	-0.32	-0.08	1.34
SE (95% CI)	3.2 (-6.6, 5.9)	2.6 (-5.2, 5.1)	0.79 (-0.2, 2.9)
Cell treatment effect with diabetes mellitus			
p value	0.483	0.694	0.388
Mean difference	2.30	1.06	0.70
SE (95% CI)	3.3 (-4.1, 8.7)	2.7 (-4.2, 6.3)	0.8 (-0.9, 2.3)
Cell treatment effect with hypertension			
p value	0.603	0.852	0.092
Mean difference	1.22	0.36	0.98
SE (95% CI)	2.3 (-3.4, 5.8)	1.9 (-3.4, 4.1)	0.6 (-0.2, 2.1)
Cell treatment effect with hyperlipidemia			
p value	0.430	0.738	0.067
Mean difference	1.95	0.67	1.09
SE (95% CI)	2.5 (-2.9, 6.8)	2.0 (-3.3, 4.6)	0.6 (-0.1, 2.3)
Cell treatment effect with MRI			
p value	0.604	0.887	0.028
Mean difference	1.26	-0.28	1.31
SE (95% CI)	2.4 (-3.5, 6.0)	2.0 (-4.2, 3.6)	0.6 (0.1, 2.5)
Cell treatment effect with age			
p value	**0.006**	0.029	0.702

Mean difference	**9.50**	6.46	0.35
SE (95% CI)	**3.4 (-2.8, 16.2)**	2.9 (-0.7, 12.2)	0.9 (-1.5, 2.2)
Cell treatment effect with anterior infarction			
p value	0.737	0.448	0.074
Mean difference	-1.11	-2.05	1.47
SE (95% CI)	3.3 (-7.6, 5.4)	2.7 (-7.4, 3.3)	0.8 (-0.1, 3.1)
Cell treatment effect with pre-end-diastolic volume			
p value	0.408	0.867	0.238
Mean difference	1.46	0.26	0.76
SE (95% CI)	1.8 (-2.0, 5.0)	1.5 (-2.8, 3.3)	0.6 (-0.5, 2.0)
Cell treatment effect with pre-ejection fraction*			
p value	0.418	0.793	0.304
Mean difference	1.69	0.51	0.76
SE (95% CI)	2.1 (-2.4, 5.8)	1.9 (-3.1, 4.3)	0.7 (-0.7, 2.2)
Cell treatment effect with time to cell therapy[+]			
p value	0.649	0.938	0.435
Mean difference	7.78	8.92	-0.73
SE (95% CI)	4.9 (-1.9, 17.5)	4.0 (1.1, 16.8)	1.2 (-1.6, 3.1)

MRI: magnetic resonance imaging, SE: standard error, CI: confidence interval.

*Sub-analysis between pre-EF groups are displayed in Table 4B.

[+]Effect of the covariate time to cell therapy in cell therapy group or randomization/sham intervention in controls post AMI

Table 4A. Efficacy of cell therapy over time. No significant difference between the groups.

Follow-up time		Changes in end-diastolic volume Mean±SD	Changes in end-systolic volume Mean±SD	Changes in ejection fraction Mean±SD
≤6 months	**Cell therapy (n=383)**	10.2±37.3	2.2±32.6	3.9±10.3
	Controls (n=267)	8.4±28.8	0.31±26.2	2.9±9.6
	Difference in mean (95% CI)	1.9 (-3.4; 7.2)	1.9 (-2.9; 6.6)	0.9 (-0.6; 2.5)
>6-12 months	**Cell therapy (n=241)**	22.4±43.3	9.3±32.0	3.1±8.1
	Controls (n=173)	22.2±37.9	11.3±28.0	2.1±7.8
	Difference in mean (95% CI)	2.6 (-7.8; 8.3)	-2.0 (-8.0; 4.0)	1.0 (-0.6; 2.5)

SD: standard deviation, CI: confidence interval

Table 4B. Impact of baseline ejection fraction on changes in left ventricular parameter. No significant difference between the groups.

Baseline ejection fraction		Changes in end-diastolic volume Mean±SD	Changes in end-systolic volume Mean±SD	Changes in ejection fraction Mean±SD
≥50%	**Cell therapy (n=179)**	14.6±35.2	6.3±26.5	2.2±8.3
	Controls (n=145)	10.6±29.5	4.0±19.8	0.7±8.7
	Difference in mean between cell therapy and controls (95% CI)	4.0 (-3.2; 11.2)	2.2 (-3.0; 7.5)	1.5 (-0.4; 3.3)
<50%	**Cell therapy (n=445)**	15.2±42.1	4.5±34.7	4.1±9.9
	Controls (n=295)	15.5±35.2	4.9±30.5	3.5±9.0
	Difference in mean between cell therapy and controls (95% CI)	-0.3 (-6.1;5.6)	-0.5 (-5.4; 4.4)	0.6 (-0.8; 2.0)
≥45%	**Cell therapy (n=267)**	11.1±34.8	4.2±26.5	2.3±9.0
	Controls (n=212)	9.7±29.6	2.9±20.8	1.3±8.7
	Difference in mean between cell therapy and controls (95% CI)	1.4 (-4.5; 7.39)	1.3 (-3.1; 5.6)	1.0 (-0.6; 2.6)
<45%	**Cell therapy (n=357)**	18.1±43.6	5.6±36.4	4.5±9.8
	Controls (n=228)	17.9±36.4	6.2±32.4	3.8±9.0
	Difference in mean between cell therapy and controls (95% CI)	0.2 (-6.7; 7.1)	-0.6 (-6.5; 5.2)	0.7 (-0.8; 2.3)
≥40%	**Cell therapy (n=381)**	12.1±36.8	4.0±27.1	2.6±9.2

	Controls (n=292)	10.8±31.0	3.3±22.6	1.9±8.5
	Difference in mean between cell therapy and controls (95% CI)	1.4 (-3.9; 6.6)	0.7 (-3.1; 4.6)	0.8 (-0.6; 2.2)
<40%	**Cell therapy (n=243)**	19.7±44.7	6.5±39.7	5.0±9.7
	Controls (n=148)	202±37.2	7.3±35.1	4.1±9.6
	Difference in mean between cell therapy and controls (95% CI)	-0.5 (-9.2; 8.2)	-0.8 (-8.7; 7.1)	0.9 (-1.1; 2.9)

SD: standard deviation, CI: confidence interval

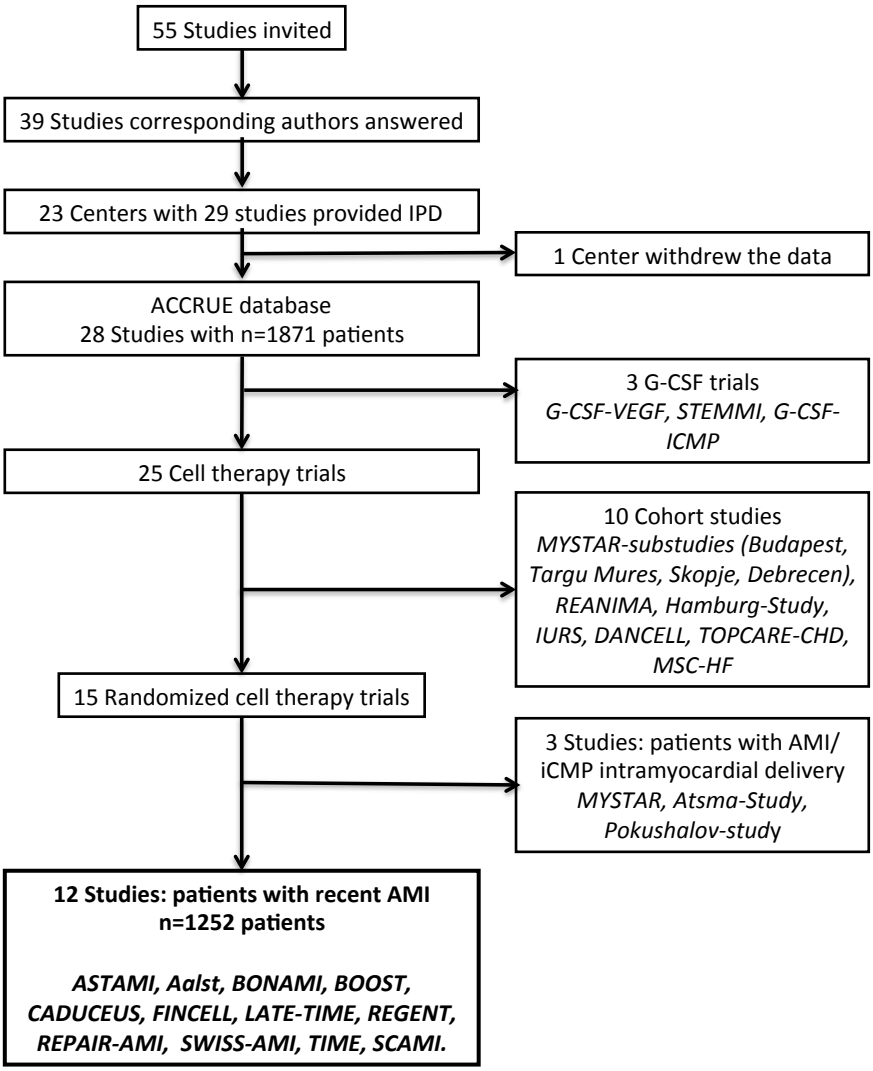
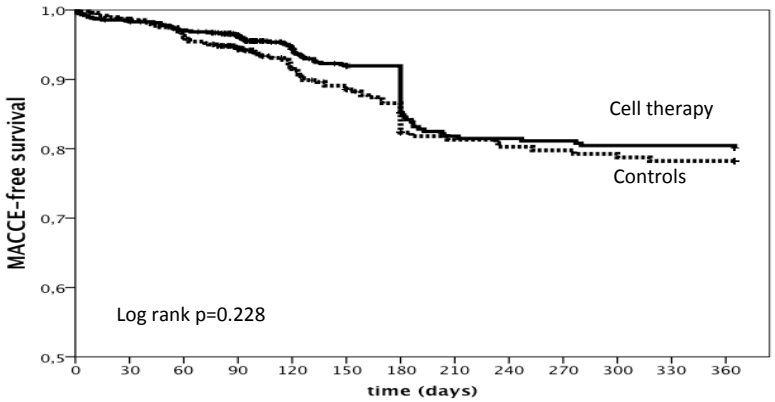

55 Studies invited
39 Studies corresponding authors answered
23 Centers with 29 studies provided IPD
1 Center withdrew the data
ACCRUE database
28 Studies with n=1871 patients
3 G-CSF trials
G-CSF-VEGF, STEMMI, G-CSF-ICMP
25 Cell therapy trials
10 Cohort studies
MYSTAR-substudies (Budapest, Targu Mures, Skopje, Debrecen), REANIMA, Hamburg-Study, IURS, DANCELL, TOPCARE-CHD, MSC-HF
15 Randomized cell therapy trials
3 Studies: patients with AMI/ iCMP intramyocardial delivery
MYSTAR, Atsma-Study, Pokushalov-study
12 Studies: patients with recent AMI
n=1252 patients
ASTAMI, Aalst, BONAMI, BOOST, CADUCEUS, FINCELL, LATE-TIME, REGENT, REPAIR-AMI, SWISS-AMI, TIME, SCAMI.

Figure 1



Cell-treated	767	752	735	687	551	520	251	240	239	138	236	236	125	Number left
	0	11	22	28	40	54	92	102	103	104	106	106	107	Number event
Controls	485	477	464	392	343	314	161	159	157	155	154	153	152	Number left
	0	7	19	27	38	49	71	73	75	77	78	79	79	Number event

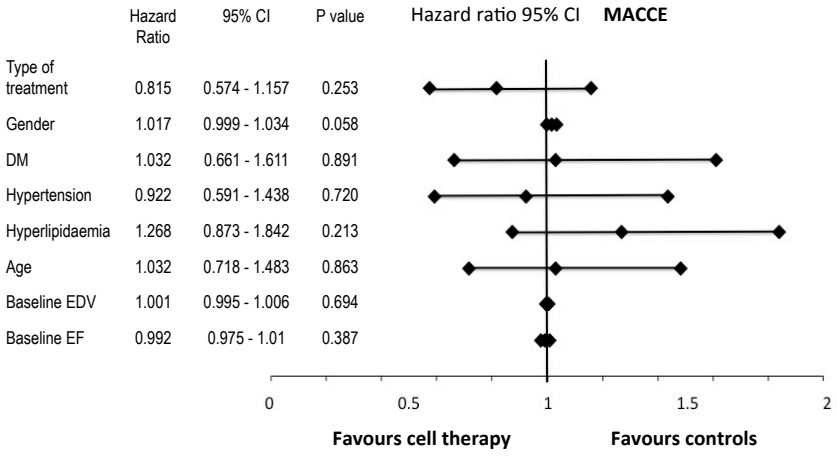


Figure 2A

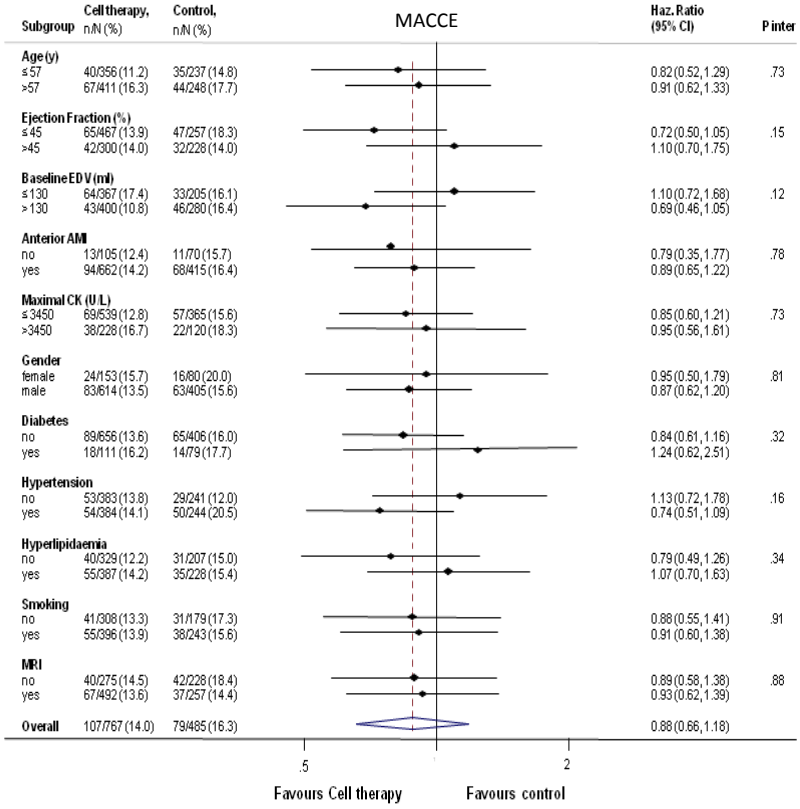
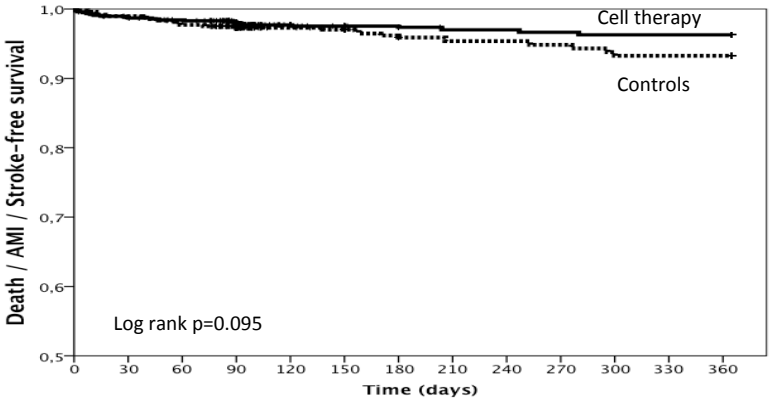

Subgroup
Cell therapy, n/N (%)
Control, n/N (%)
MACCE
Haz. Ratio (95% CI)
P inter
Age (y)
≤57 40/356 (11.2) 35/237 (14.8) 0.82 (0.52, 1.29) .73
>57 67/411 (16.3) 44/248 (17.7) 0.91 (0.62, 1.33)
Ejection Fraction (%)
≤45 65/467 (13.9) 47/257 (18.3) 0.72 (0.50, 1.05) .15
>45 42/300 (14.0) 32/228 (14.0) 1.10 (0.70, 1.75)
Baseline EDV (ml)
≤130 64/367 (17.4) 33/205 (16.1) 1.10 (0.72, 1.68) .12
>130 43/400 (10.8) 46/280 (16.4) 0.69 (0.46, 1.05)
Anterior AMI
no 13/105 (12.4) 11/70 (15.7) 0.79 (0.35, 1.77) .78
yes 94/662 (14.2) 68/415 (16.4) 0.89 (0.65, 1.22)
Maximal CK (U/L)
≤3450 69/539 (12.8) 57/365 (15.6) 0.85 (0.60, 1.21) .73
>3450 38/228 (16.7) 22/120 (18.3) 0.95 (0.56, 1.61)
Gender
female 24/153 (15.7) 16/80 (20.0) 0.95 (0.50, 1.79) .81
male 83/614 (13.5) 63/405 (15.6) 0.87 (0.62, 1.20)
Diabetes
no 89/656 (13.6) 65/406 (16.0) 0.84 (0.61, 1.16) .32
yes 18/111 (16.2) 14/79 (17.7) 1.24 (0.62, 2.51)
Hypertension
no 53/383 (13.8) 29/241 (12.0) 1.13 (0.72, 1.78) .16
yes 54/384 (14.1) 50/244 (20.5) 0.74 (0.51, 1.09)
Hyperlipidaemia
no 40/329 (12.2) 31/207 (15.0) 0.79 (0.49, 1.26) .34
yes 55/387 (14.2) 35/228 (15.4) 1.07 (0.70, 1.63)
Smoking
no 41/308 (13.3) 31/179 (17.3) 0.88 (0.55, 1.41) .91
yes 55/396 (13.9) 38/243 (15.6) 0.91 (0.60, 1.38)
MRI
no 40/275 (14.5) 42/228 (18.4) 0.89 (0.58, 1.38) .88
yes 67/492 (13.6) 37/257 (14.4) 0.93 (0.62, 1.39)
Overall 107/767 (14.0) 79/485 (16.3) 0.88 (0.66, 1.18)
.5
2
Favours Cell therapy
Favours control

Figure 2B



Cell-treated	767	754	746	701	567	473	272	270	270	269	268	268	267	Number left
	0	9	12	15	17	16	19	20	20	21	22	22	22	Number event
Controls	485	479	472	399	362	342	182	181	181	180	177	177	176	Number left
	0	5	11	13	13	14	18	19	19	20	23	23	23	Number event

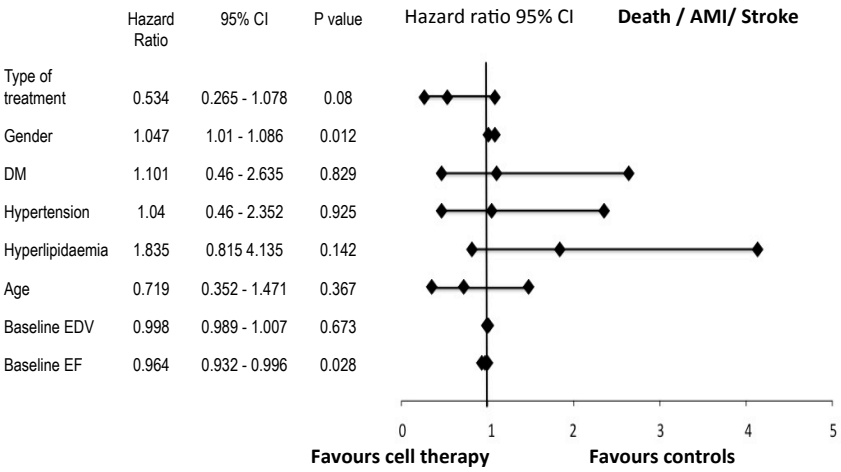


Figure 3A

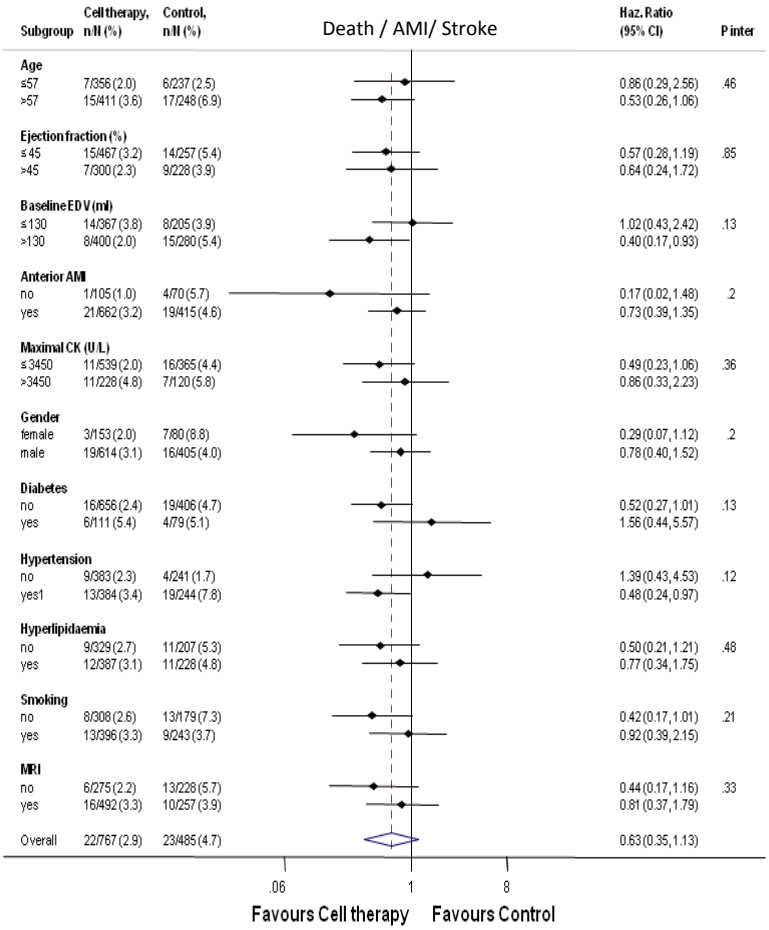
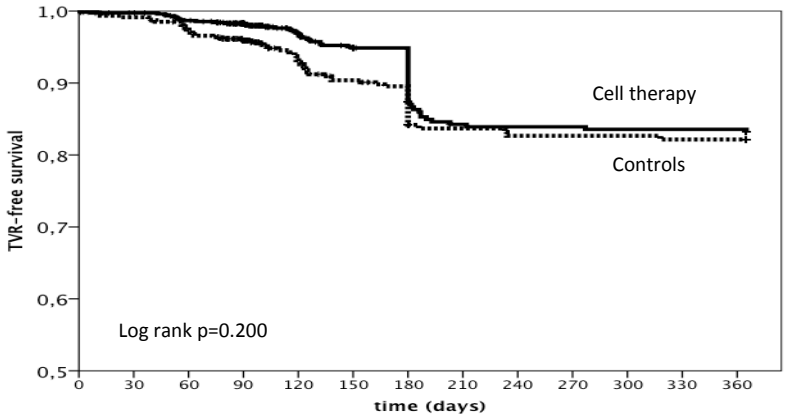

Subgroup
Cell therapy, n/N (%)
Control, n/N (%)
Death / AMI/ Stroke
Haz. Ratio (95% CI)
P inter
Age
≤57 7/356 (2.0) 6/237 (2.5) 0.86 (0.29, 2.56) .46
>57 15/411 (3.6) 17/248 (6.9) 0.53 (0.26, 1.06)
Ejection fraction (%)
≤45 15/467 (3.2) 14/257 (5.4) 0.57 (0.28, 1.19) .85
>45 7/300 (2.3) 9/228 (3.9) 0.64 (0.24, 1.72)
Baseline EDV (ml)
≤130 14/367 (3.8) 8/205 (3.9) 1.02 (0.43, 2.42) .13
>130 8/400 (2.0) 15/280 (5.4) 0.40 (0.17, 0.93)
Anterior AMI
no 1/105 (1.0) 4/70 (5.7) 0.17 (0.02, 1.48) .2
yes 21/662 (3.2) 19/415 (4.6) 0.73 (0.39, 1.35)
Maximal CK (U/L)
≤3450 11/539 (2.0) 16/365 (4.4) 0.49 (0.23, 1.06) .36
>3450 11/228 (4.8) 7/120 (5.8) 0.86 (0.33, 2.23)
Gender
female 3/153 (2.0) 7/80 (8.8) 0.29 (0.07, 1.12) .2
male 19/614 (3.1) 16/405 (4.0) 0.78 (0.40, 1.52)
Diabetes
no 16/656 (2.4) 19/406 (4.7) 0.52 (0.27, 1.01) .13
yes 6/111 (5.4) 4/79 (5.1) 1.56 (0.44, 5.57)
Hypertension
no 9/383 (2.3) 4/241 (1.7) 1.39 (0.43, 4.53) .12
yes1 13/384 (3.4) 19/244 (7.8) 0.48 (0.24, 0.97)
Hyperlipidaemia
no 9/329 (2.7) 11/207 (5.3) 0.50 (0.21, 1.21) .48
yes 12/387 (3.1) 11/228 (4.8) 0.77 (0.34, 1.75)
Smoking
no 8/308 (2.6) 13/179 (7.3) 0.42 (0.17, 1.01) .21
yes 13/396 (3.3) 9/243 (3.7) 0.92 (0.39, 2.15)
MRI
no 6/275 (2.2) 13/228 (5.7) 0.44 (0.17, 1.16) .33
yes 16/492 (3.3) 10/257 (3.9) 0.81 (0.37, 1.79)
Overall 22/767 (2.9) 23/485 (4.7) 0.63 (0.35, 1.13)
.06
1
8
Favours Cell therapy
Favours Control

Figure 3B



Cell-treated	767	757	743	642	560	531	255	244	243	243	242	242	241	Number left
	0	2	10	13	22	33	75	84	85	85	86	86	87	Number event
Controls	485	464	453	377	334	323	166	165	163	163	163	162	162	Number left
	0	4	13	19	30	39	61	62	64	64	64	65	65	Number event

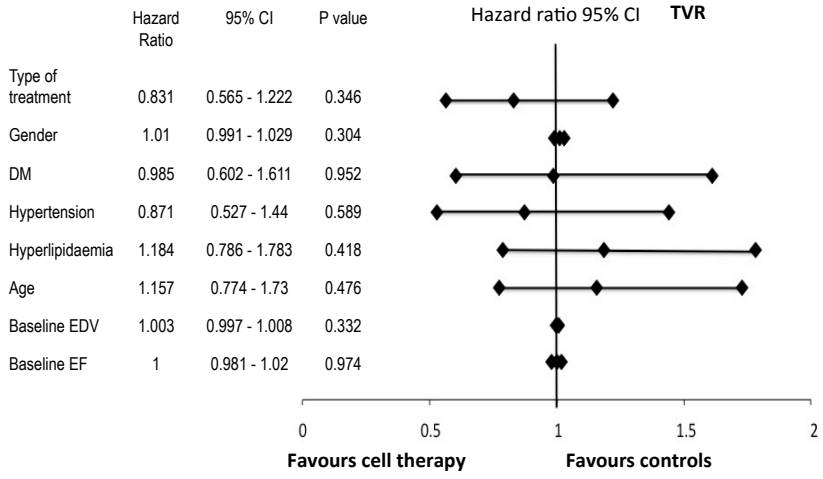


Figure 3C

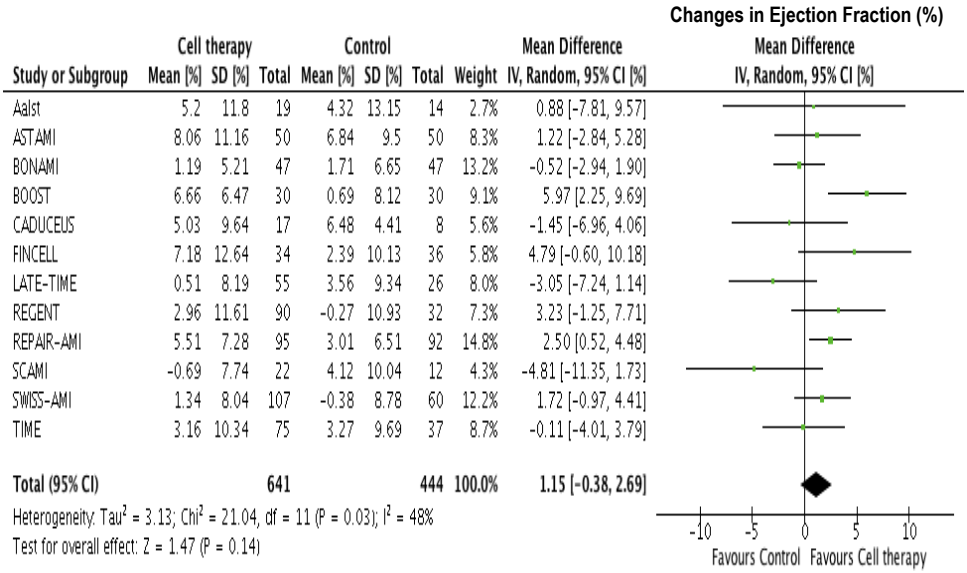

Changes in Ejection Fraction (%)
Cell therapy
Control
Mean Difference
Mean Difference
Study or Subgroup Mean [%] SD [%] Total Mean [%] SD [%] Total Weight IV, Random, 95% CI [%]
IV, Random, 95% CI [%]
Aalst 5.2 11.8 19 4.32 13.15 14 2.7% 0.88 [-7.81, 9.57]
ASTAMI 8.06 11.16 50 6.84 9.5 50 8.3% 1.22 [-2.84, 5.28]
BONAMI 1.19 5.21 47 1.71 6.65 47 13.2% -0.52 [-2.94, 1.90]
BOOST 6.66 6.47 30 0.69 8.12 30 9.1% 5.97 [2.25, 9.69]
CADUCEUS 5.03 9.64 17 6.48 4.41 8 5.6% -1.45 [-6.96, 4.06]
FINCELL 7.18 12.64 34 2.39 10.13 36 5.8% 4.79 [-0.60, 10.18]
LATE-TIME 0.51 8.19 55 3.56 9.34 26 8.0% -3.05 [-7.24, 1.14]
REGENT 2.96 11.61 90 -0.27 10.93 32 7.3% 3.23 [-1.25, 7.71]
REPAIR-AMI 5.51 7.28 95 3.01 6.51 92 14.8% 2.50 [0.52, 4.48]
SCAMI -0.69 7.74 22 4.12 10.04 12 4.3% -4.81 [-11.35, 1.73]
SWISS-AMI 1.34 8.04 107 -0.38 8.78 60 12.2% 1.72 [-0.97, 4.41]
TIME 3.16 10.34 75 3.27 9.69 37 8.7% -0.11 [-4.01, 3.79]
Total (95% CI) 641 444 100.0% 1.15 [-0.38, 2.69]
Heterogeneity: Tau² = 3.13; Chi² = 21.04, df = 11 (P = 0.03); I² = 48%
Test for overall effect: Z = 1.47 (P = 0.14)
-10 -5 0 5 10
Favours Control Favours Cell therapy

Figure 4A

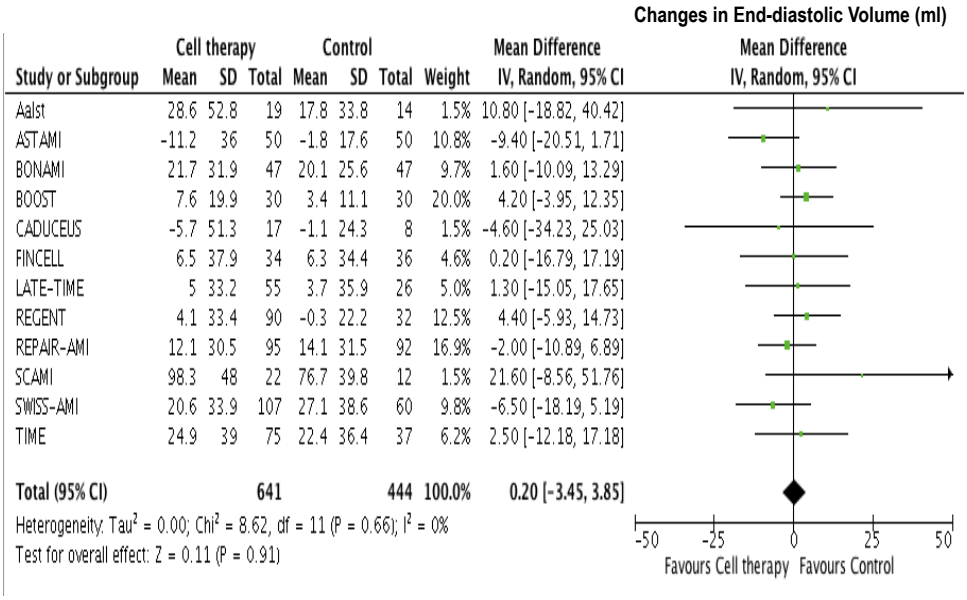

Changes in End-diastolic Volume (ml)
Cell therapy
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Aalst 28.6 52.8 19 17.8 33.8 14 1.5% 10.80 [-18.82, 40.42]
ASTAMI -11.2 36 50 -1.8 17.6 50 10.8% -9.40 [-20.51, 1.71]
BONAMI 21.7 31.9 47 20.1 25.6 47 9.7% 1.60 [-10.09, 13.29]
BOOST 7.6 19.9 30 3.4 11.1 30 20.0% 4.20 [-3.95, 12.35]
CADUCEUS -5.7 51.3 17 -1.1 24.3 8 1.5% -4.60 [-34.23, 25.03]
FINCELL 6.5 37.9 34 6.3 34.4 36 4.6% 0.20 [-16.79, 17.19]
LATE-TIME 5 33.2 55 3.7 35.9 26 5.0% 1.30 [-15.05, 17.65]
REGENT 4.1 33.4 90 -0.3 22.2 32 12.5% 4.40 [-5.93, 14.73]
REPAIR-AMI 12.1 30.5 95 14.1 31.5 92 16.9% -2.00 [-10.89, 6.89]
SCAMI 98.3 48 22 76.7 39.8 12 1.5% 21.60 [-8.56, 51.76]
SWISS-AMI 20.6 33.9 107 27.1 38.6 60 9.8% -6.50 [-18.19, 5.19]
TIME 24.9 39 75 22.4 36.4 37 6.2% 2.50 [-12.18, 17.18]
Total (95% CI) 641 444 100.0% 0.20 [-3.45, 3.85]
Heterogeneity: Tau² = 0.00; Chi² = 8.62, df = 11 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
-50 -25 0 25 50
Favours Cell therapy Favours Control

Figure 4B

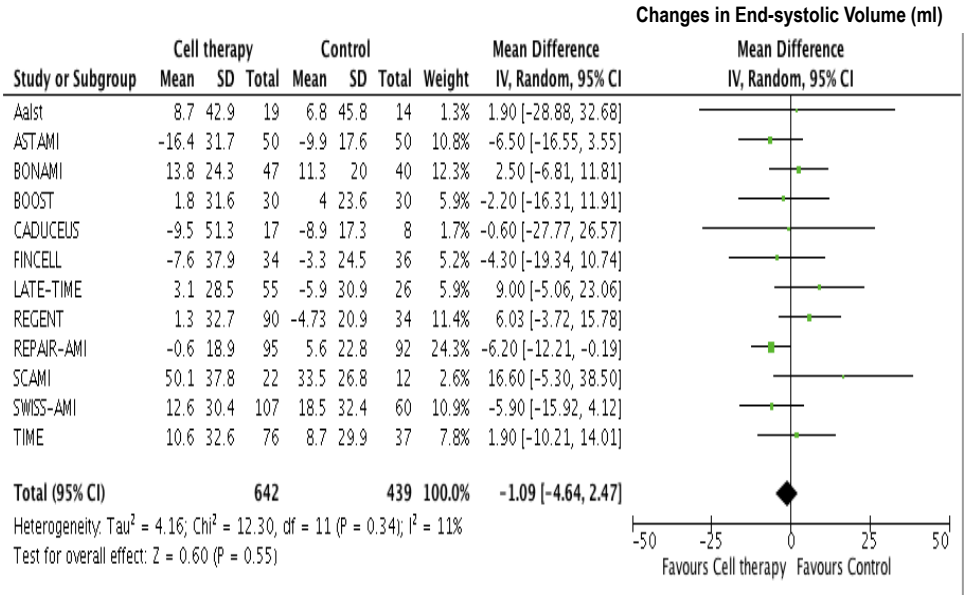

Changes in End-systolic Volume (ml)
Cell therapy
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Aalst 8.7 42.9 19 6.8 45.8 14 1.3% 1.90 [-28.88, 32.68]
ASTAMI -16.4 31.7 50 -9.9 17.6 50 10.8% -6.50 [-16.55, 3.55]
BONAMI 13.8 24.3 47 11.3 20 40 12.3% 2.50 [-6.81, 11.81]
BOOST 1.8 31.6 30 4 23.6 30 5.9% -2.20 [-16.31, 11.91]
CADUCEUS -9.5 51.3 17 -8.9 17.3 8 1.7% -0.60 [-27.77, 26.57]
FINCELL -7.6 37.9 34 -3.3 24.5 36 5.2% -4.30 [-19.34, 10.74]
LATE-TIME 3.1 28.5 55 -5.9 30.9 26 5.9% 9.00 [-5.06, 23.06]
REGENT 1.3 32.7 90 -4.73 20.9 34 11.4% 6.03 [-3.72, 15.78]
REPAIR-AMI -0.6 18.9 95 5.6 22.8 92 24.3% -6.20 [-12.21, -0.19]
SCAMI 50.1 37.8 22 33.5 26.8 12 2.6% 16.60 [-5.30, 38.50]
SWISS-AMI 12.6 30.4 107 18.5 32.4 60 10.9% -5.90 [-15.92, 4.12]
TIME 10.6 32.6 76 8.7 29.9 37 7.8% 1.90 [-10.21, 14.01]
Total (95% CI) 642 439 100.0% -1.09 [-4.64, 2.47]
Heterogeneity: Tau² = 4.16; Chi² = 12.30, df = 11 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.60 (P = 0.55)
-50 -25 0 25 50
Favours Cell therapy Favours Control

Figure 4C