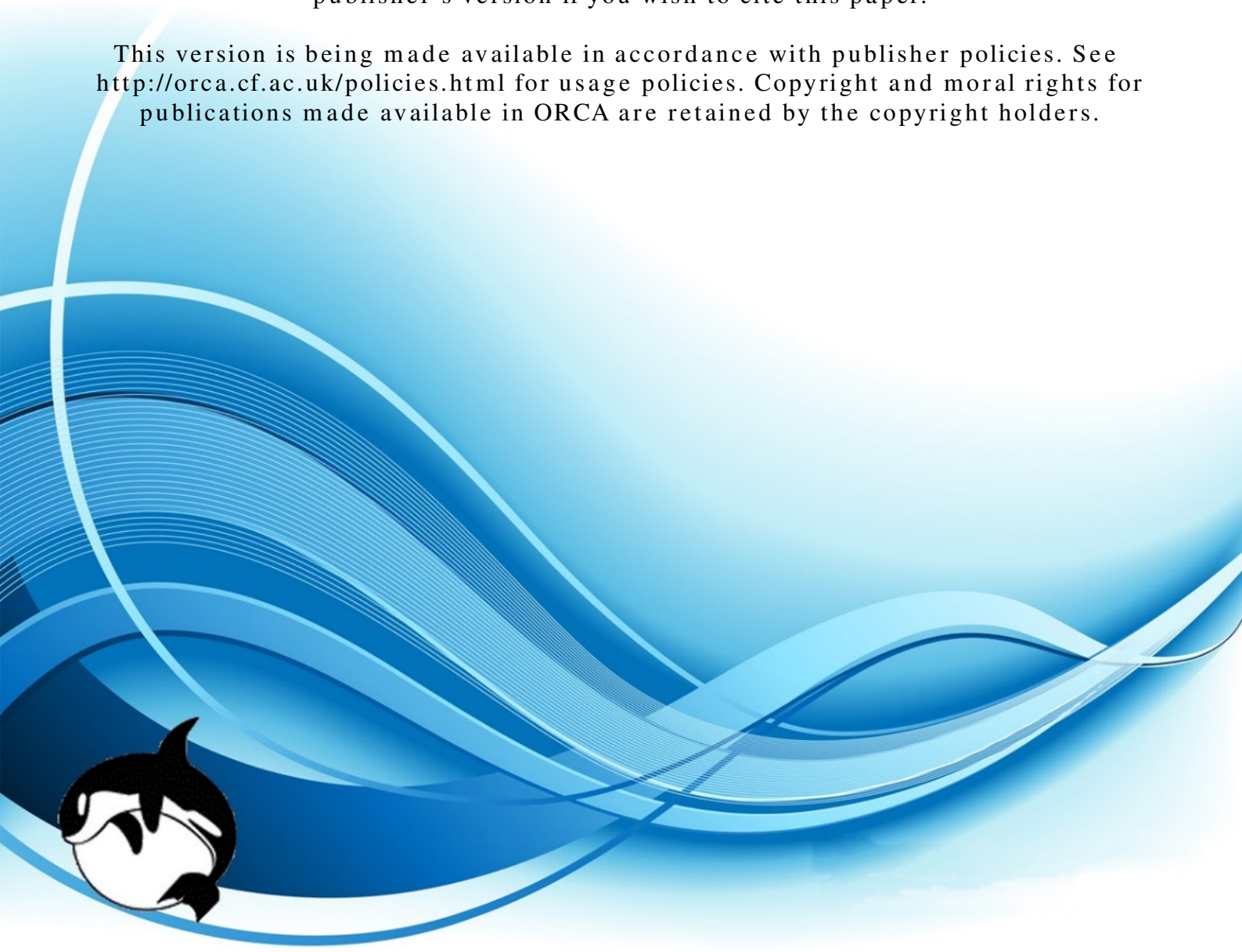

Meta-Analysis of Cell Therapy Studies in Heart Failure and Acute Myocardial Infarction

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Abbreviations

ACCRUE	Meta-Analysis of Cell-based CaRdiac studies
AMI	Acute Myocardial Infarction
AP	Angina pectoris
BMMNCs	Bone Marrow Mononuclear Cells
BMMSCs	Bone Marrow-derived Mesenchymal Stromal Cells
BMSCs	Bone Marrow Stem Cells
CVD	Cardiovascular Disease
CIHD	Coronary Ischemic Heart Disease
G-CSF	Granulocyte-colony stimulating factor
EF	Ejection Fraction
HF	Heart Failure
HFrEF	Heart Failure with reduced Ejection Fraction
IC	Intra-coronary
ICMJE	International Committee of Medical Journal Editors
ICMP	Ischemic Cardiomyopathy
IHD	Ischemic Heart Disease
IM	Intra-muscular
IPD	Individual Patient Data
IS	Information Size
LV	Left Ventricle
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
MRI	Magnetic Resonance Imaging
MSCs	Mesenchymal Stromal Cells
NHLBI	National Heart, Lung and Blood Institute
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
RCTs	Randomized Controlled Trials
RRR	Relative Risk Ratio
TSA	Trials Sequential Analysis

Abstract

Heart failure is one the leading cause of death worldwide and has reached epidemic proportions in most industrialized nations. Despite major improvements in the treatment and management of the disease, the prognosis for patients with heart failure remains poor with approximately only half of patients surviving for five years or longer after diagnosis. The poor prognosis of HF patients is in part due to irreparable damage to cardiac tissue and concomitant maladaptive changes associated with the disease. Cell-based therapies may have the potential to transform the treatment and prognosis of HF through regeneration or repair of damaged cardiac tissue. Accordingly, numerous phase I and II randomized clinical trials have tested the clinical benefits of cell transplant, mostly autologous bone marrow-derived mononuclear cells, in patients with heart failure, ischaemic heat disease and acute myocardial infarction. Although many of these trials were relatively small, meta-analyses of cell-based therapies have attempted to apply rigorous statistical methodology to assess the potential clinical benefits of the intervention. As a prelude to larger phase III trials, meta-analyses therefore remain the obvious means of evaluating the available clinical evidence. Here, we review the different meta-analyses of randomized clinical trials that evaluate the safety and potential beneficial effect of cell therapies in heart failure and acute myocardial infarction spanning nearly two decades since the first pioneering trials were conducted.

Introduction

Cardiovascular disease (CVD), of which ischaemic heart disease (IHD) is a major component, is the leading cause of mortality accounting for approximately one third of deaths worldwide [1]. Although the death rate associated with IHD has gradually declined over the last fifty years the incidence and prevalence of heart failure (HF) is on the increase and has become almost a pandemic. Paradoxically, the Center for Disease Control and Prevention have recently reported an increase in the age-adjusted rate for HF-related mortality. [2] The majority of treatment options in HF are palliative or aimed at slowing down disease progression (e.g. the prevention of cardiomyocyte loss or treatment of symptoms). In parallel to the increased incidence of HF, the use of new therapies such as coronary interventions, resynchronization therapy and the implantation of ventricular assist devices has also risen. As a consequence, hospitalisation due to HF has become more frequent, imposing a real economic burden on health care providers across the world. Therefore, there is an unmet clinical need to improve heart performance of patients who suffer IHD and HF and restore heart function.

Unlike many other tissues, heart muscle has a limited capacity to adequately repair itself after injury leading to progressive maladaptive remodelling and left ventricular dysfunction. Given the limited propensity for the heart to repair itself following injury, numerous strategies to repair or regenerate the damaged tissue have been proposed and tested in pre-clinical models and small to medium sized phase I and phase II clinical trials. [3, 4] One of the most promising strategies to repair or regenerate the damaged myocardium involves the use of cell-based therapies. Although several different experimental cell types have been tested in pre-clinical (animal) models and small scale clinical trials, the most commonly used cells are bone marrow-derived stem/progenitor cells (BMSCs) or bone marrow mononuclear cells (BMMNCs), derived from the patient's own bone marrow and are therefore an autologous cell transplant. Bone marrow is a heterogeneous tissue containing multiple cell populations of which approximately 1% are stem/progenitor cell populations of hematopoietic origin, multipotent mesenchymal stromal cells (MSCs) and endothelial progenitors. Unfractionated BMMNCs have been extensively used in clinical trials with the aim of repairing damaged heart tissue. Enriched populations of bone marrow-derived stem or progenitor cells can be isolated from BMMNCs using

antibodies against different cell surface antigens such as CD34 and CD133, through adaption to culture or by mobilisation into the peripheral blood stream following stimulation with cytokines such as G-CSF (Granulocyte-colony stimulating factor). In addition to BMSCs, other cell types such as skeletal myoblasts, adipose tissue-derived stem/progenitor cells, endothelial progenitors and cardiac progenitor cells have been tested in animal models and small clinical trials. [3]

All randomized control trials (RCTs) included in the meta-analyses described herein include a control arm(s) for each of the constituent trials. The control arm or placebo for many RCTs is often heterogeneous (no cells, unconditioned media or vehicle, mock injection etc.). Arguably the most appropriate control for these studies is to use irradiated bone marrow stem cells that are unable to replicate. Although not included in the meta-analyses described herein, Wollert and colleagues have recently published a RCT for myocardial infarction where γ-irradiated stems cells were included in one of the control arms of the trial. [5] Importantly, this trial found that bone marrow stem cell therapy had no significant effect on LVEF improvement in patients treated with viable bone marrow stem cells compared to the control population that received irradiated cells.

The focus of this review is on the meta-analyses of RCTs for cell therapy in heart failure (HF) and acute myocardial infarction (AMI) using ostensibly autologous BMSC transplants.

Meta-analysis in preclinical models

Pre-clinical studies carried out in animal models present a unique opportunity to conduct homogenous trials, e.g. cell-treatment in a pre-specified time, similar animal strain and species, without confounding clinical factors. Recently, meta-analyses of a large number of pre-clinical studies of cell-based therapy in animal models of IHD have been published. [6-9] Frequently, clinical outcomes (e.g. mortality) are not relevant in these studies, mostly due to the limited number of animals included in the studies and short follow-up times. However, efficacy parameters could be comparable to human clinical trials, especially in large animals where LV function and trial outcomes are measured using similar imaging modalities (e.g. magnetic resonance imaging or MRI). A meta-analysis of cell treatment studies in a mouse

model of myocardial ischemia, including only studies using cardiac MRI as functional analytic method of LV performance (21 randomized studies with a total of 583 mice), resulted in a significant improvement in LVEF of 8.59% as compared to the placebo-treated animals. [7] Likewise, two meta-analyses of 52 and 82 large animal trials (pooling data from 888 and 1415 animals, respectively with iatrogenic ischemic heart disease reported an 8.3% LVEF benefit of cell-based therapy in contrast to control animals. [6, 8] Furthermore, a meta-analysis of cardiac progenitor cell (c-kit$^+$, Sca-1$^+$, cardiosphere and cardiosphere-derived cells) therapy studies in AMI (including 80 studies with 1970 rodents and large animals) reported a mean 10.7% LVEF increase in the cell-treated group compared to the control group. [9] Interestingly, cardiac progenitor cell therapy led to a significantly higher effect in rodents than in large animals (increase of LVEF of 11.7% and 5.2% in small and large animals, respectively). The increase in LVEF following cell transplantation in large animals closely relates to the 5-7% improvement in LVEF observed in human clinical trials. Although Zwetsloot *et al*., found that the large animal studies were superior in quality to their small animal counterparts, showed less evidence of publication and attrition biases, the differences in LVEF improvement between large and small animal pre-clinical models are not fully understood. [9] While these unresolved differences may have a methodological or biological origin, it is noteworthy that the smaller effects on LVEF improvement in large animal studies are more closely reminiscent of the trial data derived from human subjects and as such may indicate that large animal are the more appropriate preclinical model for stem cell therapy for cardiac repair. In order to standardize animal studies and to avoid or reduce heterogeneity, and to draw more meaningful conclusions, the NHLBI-sponsored CAESAR consortium and the Working Group on Cellular Biology of the Heart of the European Society of Cardiology have suggested, that pre-clinical studies should also be performed as multi-center randomized blinded studies, similar to human clinical trials. [10, 11]

Meta-analyses of cell therapies in heart failure

Several small or medium-sized Phase I and II cell-based therapy studies have been conducted in HF patients. Currently, approximately 2300 patients with ischemic HF or chronic ischemic heart disease have been treated with different types of cells, mostly with autologous BMMNCs in 45 randomized trials. Other cell types, such as bone marrow-derived MSC, adipose tissue MSC, bone-marrow and peripheral blood

progenitor cells, cardiac progenitor cells (cardiospheres) or myoblasts were also used. HF patients with the characteristics of HFrEF (heart failure with reduced ejection fraction) can mostly be characterized by post-infarction ischemic cardiomyopathy with severe coronary artery disease. Therefore, intramyocardial delivery of cell, either by surgical or percutaneous intervention, seems to be the preferred route of delivery for the intervention. This is in contrast to patients with recent acute myocardial infarction (AMI) enrolled in cell therapy trials and who received cell treatment by intracoronary delivery.

Since the average number of participants in trials are rarely over 50, most of the cell-based therapy studies in HF patients are statistically underpowered. Due to the technical challenges of these trials, namely percutaneous or surgical intramyocardial cell delivery, patient enrolment in randomized trials is usually slow, commonly leading to premature study termination, and/or inconclusive trial results. Hence, systematic reviews and meta-analyses of cell-based regenerative therapies including larger numbers of patients are necessary to evaluate the clinical evidence of cell therapy interventions in this cohort of patients. Table 1 lists the characteristics and results of currently published meta-analyses that included randomized trials involving patients with signs of HF and aimed to assess the effect of cell-therapy on LVEF. [12-24] All trials included in these meta-analyses used autologous cells and no restriction was made with respect to the type of cells used. The summary table shows non-uniform patient populations, including also some studies with recent AMI or refractory angina. The majority of trials delivered the cells intramyocardially via percutaneous intervention. Understandably, therapeutic cell delivery requires coronary artery bypass surgery and injection of the cells into the non-revascularizable (hibernating) areas of the diseased myocardium. Furthermore, intracoronary cell infusion into selected arteries may not be sufficient in cases of multivessel disease or diffuse chronic ischemic myocardium. Most of the meta-analyses reported significant changes in left ventricular parameters (Table 2), namely left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV). However, the clinical outcomes of these meta-analyses are inconclusive (Table 1) since only 5 of the 13 meta-analyses reported a significant reduction in the risk of mortality in favour of the cell treatment in HF patients. [19, 21-24]

Apart from 2 meta-analyses (Cheng *et al.*, 2013 and Fisher *et al.*, 2016), all studies reported a significant increase in LVEF in cell-treated patients compared to the control groups. [18, 24] These discrepancies are potentially explained by differences in statistical power related to the sample size in each study. Cheng *et al.*, included only 5 RCTs in their meta-analysis and could therefore be under-powered to detect statistically significant changes in LVEF. Conversely, Fisher and colleague's meta-analysis included 1114 patients from 38 trials and would therefore have greater statistical power to detect an effect. It appears that with the inclusion of larger number of patients in the meta-analysis, the observed treatment effect on LVEF regresses to a point where the changes are no longer significant. Importantly, this finding is also observed in the largest meta-analyses for AMI. [25, 26] Although LVEF is one of the most commonly used surrogate and prognostic markers in HF and an outcome measure in cell therapy RCTs, differences in the techniques used to measure LVEF are a source of heterogeneity when evaluating different studies. [27] Furthermore, the physiological and clinical significance of the small percentage changes in LVEF reported in most cell therapy RCTs has yet to be established.

Based on several pitfalls of the publication-based meta-analyses, namely the high heterogeneity of the trials, different follow-up times, doubled publications and mixed patient population, an individual data (IPD)-based meta-analysis of HF cell-based therapy trials would be desirable, such as the ACCRUE (Meta-Analysis of Cell-based CaRdiac stUdiEs) study in AMI patients. [25] The IPD-based meta-analysis of percutaneous intramyocardial delivery of regenerative cells in patients with HF is currently under statistical analysis, and some preliminary results have already been presented (Gyongyosi, unpublished data).

Meta-analysis of cell therapy trials in acute myocardial infarction

As is the case with HF and IHD, several small or medium-sized phase I and II cell-based therapy RCTs have been undertaken in patients with AMI. Currently, approximately 2700 patients have been included in meta-analyses of 41 RCTs of autologous cell therapy transplantation in AMI using predominantly BMSCs. It should be noted that many more AMI patients have been treated with cell therapies however, many RCTs and prospective uncontrolled studies do not meet the selection criteria for meta-analyses and were therefore excluded from further analysis. Patients

who suffered AMI underwent revascularization, mostly percutaneous coronary intervention or PCI, and received cell treatment following revascularization. Participants recruited to these trials presented LV dysfunction even after PCI and therefore, the rationale was that LVEF and LV volumes could be improved by cell transplantation. Therefore, changes in LVEF and LV volumes were the primary outcome of these trials. Cells were delivered mostly by infusion into the infarct-related coronary artery (intracoronary cell delivery).

Table 3 summarizes meta-analyses of bone marrow derived cell therapies for AMI published in the last 11 years. The first meta-analysis of cell therapy trials for AMI published in 2006 that included 482 patients enrolled in 5 RCTs, found a significant (P = 0.04) increase in LVEF between baseline and follow-up in the treatment group compared to controls but, more importantly, showed no difference in LVEF between treatment groups at follow-up, on average 5 months later. [28] By contrast, the first large scale meta-analysis of cell therapy for AMI collating data on 811 patients from 13 RCTs found a modest improvement in LVEF (2.99%), and a significantly reduced left ventricular end-systolic volume (LVESV) by 4.74 mL and myocardial lesion area by (3.51%) in patients treated with BMSCs compared to controls (Table 3). Subgroup analysis revealed that there was a statistically significant difference in LVEF in favour of BMSCs when cells were infused within 7 days following AMI and when the BMSC dose administered was higher than 10^8 cells. However, patients in the control group also showed a greater increase in LVEF if they were included into the trial within 7 days post-AMI. [25] In addition, the authors reported anecdotal trends in favour of benefit for most clinical outcomes examined, although none were statistically significant.

Meta-analysis of further trials incorporating increasing numbers of patients and longer follow-ups have produced largely similar results (Table 3), although their conclusions have been equivocal. Broadly speaking, these studies have reported modest but significant changes in LV function allied with no improvement in mortality in patients treated with cell therapies compared to the placebo arm of the trial. Larger meta-analyses such as those reported by Clifford *et al.*, and Zimmet *et al.*, found significant changes in LV function and LVEF (1.78%, Clifford *et al.*) measured using MRI, commonly regarded as the reference method for estimating LV volumes and

ejection fraction. [29, 30] Although the improvements in LVEF may be statistically significant it is unlikely that these small changes are clinically relevant.

In addition to the clinical heterogeneity of these trials, early meta-analyses also observed statistical heterogeneity. Many of the larger meta-analyses in AMI have attempted to explain some of the heterogeneity associated with cell therapy for AMI, and have included subgroup analyses to examine the effects of different variables on LV function and clinical outcomes. For example, Delewi and colleagues found that intracoronary delivery of BMSCs led to a moderate improvement of LVEF and a reduction in recurrent AMI and readmission to hospital for heart failure, unstable angina or chest pain. Similarly, patients receiving intracoronary BMSCs within a 3 to 7 day window post-AMI were found have improved LVEF and decreasing end systolic and end diastolic volumes compared to patients treated within 24h or beyond 7 days after AMI suggesting that transplant timing may be a relevant source of heterogeneity in some meta-analyses. [31] A recent meta-analysis focussing on cell therapy trials in both AMI and IHD collated data from 48 RCTs that enrolled a total of 2602 patients (n = 1954 for AMI and n = 648 for IHD) found that LVEF improved by 2.92% and reduced infarct size by 2.25%. [32] The authors also concluded that BMSC therapy improved clinical outcomes, including all-cause mortality and recurrent myocardial Infarction, albeit with differences between AMI and CIHD diagnoses. For example, subgroup analysis found that although cell therapy did not reduce risk of mortality in AMI patients there was a significant reduction in deaths among patients with IHD.

Another major source of heterogeneity in RCTs and therefore subsequent meta-analyses is associated with biological properties or phenotypes of the cell populations used for transplantation. As mentioned above, heterogeneous cell populations have been used in clinical trials including unfractionated BMMNC, enriched CD34-positive or CD133-positive hematopoietic progenitor cells, peripheral blood-derived progenitor cells or bone marrow-derived MSCs. Data derived from the REPAIR-AMI trial suggested that basal migratory capacity or SDF-1 (stromal cell-derived factor-1) -induced migratory capacity of BMSCs may be associated with a range of clinical outcomes. [33] Assmus and co-workers found that the more migratory cells were associated with improved survival free of cardiac, cardiovascular,

unknown death, and re-hospitalization. Robust phenotypic differences in the ability of cardiosphere-derived cells from IHD patients to support vessel formation have recently been reported. [34] These data suggest that not all patients may be suitable for autologous cell transplants. Although current meta-analyses and their associated RCTs have yet to consider the phenotypes of the transplanted cells, this is clearly one of the major sources of trial heterogeneity and may explain why certain patients may benefit from some cell therapy while others do not.

In addition to BMSCs, a meta-analysis of cell therapies from AMI using MSCs has recently been published. Wang and colleagues (Table 3) analysed data from 8 studies containing a total of 449 participants treated with MSCs derived from bone marrow, adipose tissue and umbilical cord (allogenic) reporting no increase in LEVF in the treatment groups compared to controls. [35] Sub-group analysis found that transplantation time, route of delivery and cell dose may affect LVEF in AMI patients treated with MSCs. Specifically, the injection of no more than 10 million mesenchymal stromal cells, via percutaneous coronary intervention, improved left ventricular systolic function when administered within a week of AMI.

Individual patient data and trial sequential analysis

Prior to undertaking large scale clinical trials (Phase III), meta-analyses remain one the most widely used methods to evaluate the benefit of a given intervention. However, findings derived from trial meta-analyses can be misleading if pitfalls in study designs, risk of reporting bias, and variation across studies are not carefully considered. [36, 37] To address some of the limitations and inherent biases associated with meta-analysis of RCTs, meta-analyses of individual patient data (IPD) and trial sequential analysis (TSA) have recently been applied to AMI trials. [25, 26, 38]. In addition to summary statistics derived from meta-analyses of multiple trials similar analyses can performed using IPD. [39] As its name suggests, IPD meta-analyses use prospective data derived from individual patients of all included studies removing the reliance on summary statistics for subsequent analyses. Thus, IPD-based meta-analyses contain transparent controlled data with unique definitions allowing data to be reanalysed *en masse*. Although IPD meta-analyses can help reduce bias associated with data analysis and reporting compared with trial meta-analyses, they cannot avoid bias or pitfalls associated with trial design. The first IPD-based meta-

analysis of cell therapy trials for AMI, ACCRUE (meta-Analysis of Cell-based CaRdiac stUdiEs), collated data from 12 RCTs containing 1252 individuals (767 receiving cell therapy and 485 controls) (Table 3). [25] In agreement with the largest trials-based meta-analyses described above, the ACCRUE study found that intracoronary cell therapy for AMI had no apparent benefit on left ventricular function (including measurements of LV function made by MRI) and clinical outcomes in the treated group compared to the untreated controls.

Trial sequential analysis (TSA) has been used to resolve some of the inherent problems associated with trial meta-analysis such as insufficient statistical power [40, 41]. TSA leverages cumulative data to effectively reduce type I and type II errors and can be used to estimate information size (IS), similar to power calculations used in individual trials. Fisher and colleagues conducted a TSA on 41 AMI trials that included 2739 participants (Table 3). [38] All trials administered BM-derived cells (mononuclear cell, BMMSCs, hematopoietic progenitors, circulating progenitor cells). An '*a priori'* threshold of relative risk reduction (RRR) in mortality of 35% was established as similar figure was empirically associated to percutaneous coronary intervention (PCI) in AMI [42]. In summary, cell therapies as currently tested in clinical trials do not seem to have a beneficial effect on clinical outcomes when administered to AMI patients.

Based upon TSA for AMI, the required IS to detect an effect of 35% RRR in mortality in favour of cell treatment was estimated to be 4,055 participants. Similarly, the required IS to detect a 35% RRR of re-hospitalization was 3,392 participants. However, in practice many more patients will be required to detect smaller effect sizes. This study demonstrates that the current AMI RCTs and meta-analyses lack sufficient statistical power to detect clinically relevant outcomes explaining the inconsistent findings reported in different RCTs and their earlier meta-analyses that used shorter follow-up times.

Concluding remarks

Most meta-analyses reviewed herein seem to agree that the potential beneficial effect of cell therapies for HF and AMI is still inconclusive and statistically underpowered. In AMI, trial meta-analyses (including TSA) and IPD-based meta-

analysis have drawn similar conclusions suggesting that cell-based therapies for AMI had no apparent clinical benefit. In addition, several recently published large RCTs, that have yet to be included in meta-analyses, enrolling patients with ischemic HF and AMI, published neutral results regarding changes in LVEF between the cell treated and control groups. [5, 43-45] Furthermore, the recently published global position paper on cardiovascular regenerative medicine stated that, even if cell-based therapy in HF patients proved to be safe, the results are neither positive nor consistent. [46]

In addition to the concerns regarding statistical power, the quality of the evidence in meta-analyses is confounded by two major sources of variation: (i) pitfalls in trial design and (ii) inconsistencies reporting and interpreting trial results. Therefore, there is a need for trial standardization and deep data sharing to improve reproducibility. To this end, the ACCRUE consortium and guidelines published by the International Committee of Medical Journal Editors (ICMJE) recommend data sharing on publication of trial results (e.g. sharing of the de-identified IPDs in a confidential form within 6 months of the publication). [47, 48] These efforts will hopefully resolve the majority of the controversies in data interpretation and therefore will direct future clinical trials.

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References

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Arnlov J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Barnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castaneda-Orjuela CA, Castillo-Rivas J, Catala-Lopez F, Choi JY, Christensen H, Cirillo M, Cooper L, Jr., Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C, Kasaeian A, Khader Y, Khan A, Khang YH, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin MJ, Shishehbor M, Shore H, Silva DAS, Sobngwi E, Stranges S, Swaminathan S, Tabares-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70:1-25
2. Ni H, Xu J. Recent trends in heart failure-related mortality: United states, 2000-2014. *NCHS Data Brief*. 2015:1-8
3. Sanganalmath SK, Bolli R. Cell therapy for heart failure: A comprehensive overview of experimental and clinical studies, current challenges, and future directions. *Circ Res*. 2013;113:810-834
4. Lin Z, Pu WT. Strategies for cardiac regeneration and repair. *Sci Transl Med*. 2014;6:239rv231
5. Wollert KC, Meyer GP, Muller-Ehmsen J, Tschope C, Bonarjee V, Larsen AI, May AE, Empen K, Chorianopoulos E, Tebbe U, Waltenberger J, Mahrholdt H, Ritter B, Pirr J, Fischer D, Korf-Klingebiel M, Arseniev L, Heuft HG, Brinchmann JE, Messinger D, Hertenstein B, Ganser A, Katus HA, Felix SB, Gawaz MP, Dickstein K, Schultheiss HP, Ladage D, Greulich S, Bauersachs J. Intracoronary autologous bone marrow cell transfer after myocardial infarction: The boost-2 randomised placebo-controlled clinical trial. *Eur Heart J*. 2017;38:2936-2943
6. Jansen of Lorkeers SJ, Eding JEC, Vesterinen HM, van der Spoel TIG, Sena ES, Duckers HJ, Doevendans PA, Macleod MR, Chamuleau SAJ. Similar effect of autologous and allogeneic cell therapy for ischemic heart disease: Systematic review and meta-analysis of large animal studies. *Circulation Research*. 2014;116:80-86
7. Lang CI, Wolfien M, Langenbach A, Muller P, Wolkenhauer O, Yavari A, Ince H, Steinhoff G, Krause BJ, David R, Glass A. Cardiac cell therapies for the treatment of acute

myocardial infarction: A meta-analysis from mouse studies. *Cell Physiol Biochem*. 2017;42:254-268
8. van der Spoel TI, Jansen of Lorkeers SJ, Agostoni P, van Belle E, Gyongyosi M, Sluijter JP, Cramer MJ, Doevendans PA, Chamuleau SA. Human relevance of pre-clinical studies in stem cell therapy: Systematic review and meta-analysis of large animal models of ischaemic heart disease. *Cardiovasc Res*. 2011;91:649-658
9. Zwetsloot PP, Vegh AM, Jansen of Lorkeers SJ, van Hout GP, Currie GL, Sena ES, Gremmels H, Buikema JW, Goumans MJ, Macleod MR, Doevendans PA, Chamuleau SA, Sluijter JP. Cardiac stem cell treatment in myocardial infarction: A systematic review and meta-analysis of preclinical studies. *Circ Res*. 2016;118:1223-1232
10. Jones SP, Tang XL, Guo Y, Steenbergen C, Lefer DJ, Kukreja RC, Kong M, Li Q, Bhushan S, Zhu X, Du J, Nong Y, Stowers HL, Kondo K, Hunt GN, Goodchild TT, Orr A, Chang CC, Ockaili R, Salloum FN, Bolli R. The nhlbi-sponsored consortium for preclinical assessment of cardioprotective therapies (caesar): A new paradigm for rigorous, accurate, and reproducible evaluation of putative infarct-sparing interventions in mice, rabbits, and pigs. *Circ Res*. 2015;116:572-586
11. Hausenloy DJ, Garcia-Dorado D, Botker HE, Davidson SM, Downey J, Engel FB, Jennings R, Lecour S, Leor J, Madonna R, Ovize M, Perrino C, Prunier F, Schulz R, Sluijter JPG, Van Laake LW, Vinten-Johansen J, Yellon DM, Ytrehus K, Heusch G, Ferdinandy P. Novel targets and future strategies for acute cardioprotection: Position paper of the european society of cardiology working group on cellular biology of the heart. *Cardiovasc Res*. 2017;113:564-585
12. Brunskill SJ, Hyde CJ, Doree CJ, Watt SM, Martin-Rendon E. Route of delivery and baseline left ventricular ejection fraction, key factors of bone-marrow-derived cell therapy for ischaemic heart disease. *Eur J Heart Fail*. 2009;11:887-896
13. Jiang M, He B, Zhang Q, Ge H, Zang MH, Han ZH, Liu JP, Li JH, Zhang Q, Li HB, Jin Y, He Q, Gong XR, Yin XY. Randomized controlled trials on the therapeutic effects of adult progenitor cells for myocardial infarction: Meta-analysis. *Expert Opin Biol Ther*. 2010;10:667-680
14. Donndorf P, Kundt G, Kaminski A, Yerebakan C, Liebold A, Steinhoff G, Glass A. Intramyocardial bone marrow stem cell transplantation during coronary artery bypass surgery: A meta-analysis. *J Thorac Cardiovasc Surg*. 2011;142:911-920
15. Zhao Q, Ye X. Additive value of adult bone-marrow-derived cell transplantation to conventional revascularization in chronic ischemic heart disease: A systemic review and meta-analysis. *Expert Opin Biol Ther*. 2011;11:1569-1579
16. Wen Y, Chen B, Wang C, Ma X, Gao Q. Bone marrow-derived mononuclear cell therapy for patients with ischemic heart disease and ischemic heart failure. *Expert Opin Biol Ther*. 2012;12:1563-1573
17. Kandala J, Upadhyay GA, Pokushalov E, Wu S, Drachman DE, Singh JP. Meta-analysis of stem cell therapy in chronic ischemic cardiomyopathy. *Am J Cardiol*. 2013;112:217-225
18. Cheng K, Wu F, Cao F. Intramyocardial autologous cell engraftment in patients with ischaemic heart failure: A meta-analysis of randomised controlled trials. *Heart Lung Circ*. 2013;22:887-894
19. Fisher SA, Brunskill SJ, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. 2014:CD007888
20. Xiao C, Zhou S, Liu Y, Hu H. Efficacy and safety of bone marrow cell transplantation for chronic ischemic heart disease: A meta-analysis. *Med Sci Monit*. 2014;20:1768-1777

21. Xu R, Ding S, Zhao Y, Pu J, He B. Autologous transplantation of bone marrow/blood-derived cells for chronic ischemic heart disease: A systematic review and meta-analysis. *Can J Cardiol*. 2014;30:1370-1377
22. Tian T, Chen B, Xiao Y, Yang K, Zhou X. Intramyocardial autologous bone marrow cell transplantation for ischemic heart disease: A systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis*. 2014;233:485-492
23. Fisher SA, Doree C, Mathur A, Martin-Rendon E. Meta-analysis of cell therapy trials for patients with heart failure. *Circ Res*. 2015;116:1361-1377
24. Fisher SA, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. 2016;12:CD007888
25. Gyongyosi M, Wojakowski W, Lemarchand P, Lunde K, Tendera M, Bartunek J, Marban E, Assmus B, Henry TD, Traverse JH, Moye LA, Surder D, Corti R, Huikuri H, Miettinen J, Wohrle J, Obradovic S, Roncalli J, Malliaras K, Pokushalov E, Romanov A, Kastrup J, Bergmann MW, Atsma DE, Diederichsen A, Edes I, Benedek I, Benedek T, Pejkov H, Nyolczas N, Pavo N, Bergler-Klein J, Pavo IJ, Sylven C, Berti S, Navarese EP, Maurer G, Investigators A. Meta-analysis of cell-based cardiac studies (accrue) in patients with acute myocardial infarction based on individual patient data. *Circ Res*. 2015;116:1346-1360
26. Fisher SA, Zhang H, Doree C, Mathur A, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2015:CD006536
27. Cikes M, Solomon SD. Beyond ejection fraction: An integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J*. 2016;37:1642-1650
28. Hristov M, Heussen N, Schober A, Weber C. Intracoronary infusion of autologous bone marrow cells and left ventricular function after acute myocardial infarction: A meta-analysis. *J Cell Mol Med*. 2006;10:727-733
29. Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Watt S, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2012:CD006536
30. Zimmet H, Porapakkham P, Porapakkham P, Sata Y, Haas SJ, Itescu S, Forbes A, Krum H. Short- and long-term outcomes of intracoronary and endogenously mobilized bone marrow stem cells in the treatment of st-segment elevation myocardial infarction: A meta-analysis of randomized control trials. *Eur J Heart Fail*. 2012;14:91-105
31. Xu JY, Liu D, Zhong Y, Huang RC. Effects of timing on intracoronary autologous bone marrow-derived cell transplantation in acute myocardial infarction: A meta-analysis of randomized controlled trials. *Stem Cell Res Ther*. 2017;8:231
32. Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy for ischemic heart disease: Evidence and insights from randomized controlled trials. *Circ Res*. 2015;117:558-575
33. Assmus B, Leistner DM, Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Sedding D, Yu J, Corti R, Mathey DG, Barth C, Mayer-Wehrstein C, Burck I, Sueselbeck T, Dill T, Hamm CW, Tonn T, Dimmeler S, Zeiher AM, Group R-AS. Long-term clinical outcome after intracoronary application of bone marrow-derived mononuclear cells for acute myocardial infarction: Migratory capacity of administered cells determines event-free survival. *Eur Heart J*. 2014;35:1275-1283
34. Harvey E, Zhang H, Sepulveda P, Garcia SP, Sweeney D, Choudry FA, Castellano D, Thomas GN, Kattach H, Petersen R, Blake DJ, Taggart DP, Frontini M, Watt SM, Martin-

Rendon E. Potency of human cardiosphere-derived cells from patients with ischemic heart disease is associated with robust vascular supportive ability. *Stem Cells Transl Med*. 2017;6:1399-1411
35. Wang Z, Wang L, Su X, Pu J, Jiang M, He B. Rational transplant timing and dose of mesenchymal stromal cells in patients with acute myocardial infarction: A meta-analysis of randomized controlled trials. *Stem Cell Res Ther*. 2017;8:21
36. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: Pitfalls and hints. *Heart Lung Vessel*. 2013;5:219-225
37. Martin-Rendon E. Meta-analyses of human cell-based cardiac regeneration therapies: What can systematic reviews tell us about cell therapies for ischemic heart disease? *Circ Res*. 2016;118:1264-1272
38. Fisher SA, Doree C, Taggart DP, Mathur A, Martin-Rendon E. Cell therapy for heart disease: Trial sequential analyses of two cochrane reviews. *Clin Pharmacol Ther*. 2016;100:88-101
39. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: Rationale, conduct, and reporting. *BMJ*. 2010;340:c221
40. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol*. 2008;61:763-769
41. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol*. 2009;38:287-298
42. Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, Royle P, Davidson P, Vale L, MacKenzie L. Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: Systematic review and economic evaluation. *Health Technol Assess*. 2005;9:1-99, iii-iv
43. Bartunek J, Terzic A, Davison BA, Filippatos GS, Radovanovic S, Beleslin B, Merkely B, Musialek P, Wojakowski W, Andreka P, Horvath IG, Katz A, Dolatabadi D, El Nakadi B, Arandjelovic A, Edes I, Seferovic PM, Obradovic S, Vanderheyden M, Jagic N, Petrov I, Atar S, Halabi M, Gelev VL, Shochat MK, Kasprzak JD, Sanz-Ruiz R, Heyndrickx GR, Nyolczas N, Legrand V, Guedes A, Heyse A, Moccetti T, Fernandez-Aviles F, Jimenez-Quevedo P, Bayes-Genis A, Hernandez-Garcia JM, Ribichini F, Gruchala M, Waldman SA, Teerlink JR, Gersh BJ, Povsic TJ, Henry TD, Metra M, Hajjar RJ, Tendera M, Behfar A, Alexandre B, Seron A, Stough WG, Sherman W, Cotter G, Wijns W, Program C. Cardiopoietic cell therapy for advanced ischaemic heart failure: Results at 39 weeks of the prospective, randomized, double blind, sham-controlled chart-1 clinical trial. *Eur Heart J*. 2017;38:648-660
44. Patel AN, Henry TD, Quyyumi AA, Schaer GL, Anderson RD, Toma C, East C, Remmers AE, Goodrich J, Desai AS, Recker D, DeMaria A, ix C-DCMI. Ixmyelocel-t for patients with ischaemic heart failure: A prospective randomised double-blind trial. *Lancet*. 2016;387:2412-2421
45. Perin EC, Borow KM, Silva GV, DeMaria AN, Marroquin OC, Huang PP, Traverse JH, Krum H, Skerrett D, Zheng Y, Willerson JT, Itescu S, Henry TD. A phase ii dose-escalation study of allogeneic mesenchymal precursor cells in patients with ischemic or nonischemic heart failure. *Circ Res*. 2015;117:576-584
46. Fernandez-Aviles F, Sanz-Ruiz R, Climent AM, Badimon L, Bolli R, Charron D, Fuster V, Janssens S, Kastrup J, Kim HS, Luscher TF, Martin JF, Menasche P, Simari RD, Stone GW,

Terzic A, Willerson JT, Wu JC, Group TW, Authors/Task Force Members C, Basic Research S, Translational Research S, Challenges of Cardiovascular Regenerative Medicine S, Tissue Engineering S, Delivery NT, Assessment S, Clinical Trials S, Regulatory, funding strategies s, Delivery NT, Assessment S. Global position paper on cardiovascular regenerative medicine. *Eur Heart J*. 2017;38:2532-2546

47. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, Fletcher J, Frizelle FA, Groves T, Haileamlak A, James A, Laine C, Peiperl L, Pinborg A, Sahni P, Wu S. Sharing clinical trial data: A proposal from the international committee of medical journal editors. *Annals of internal medicine*. 2016;164:505-506
48. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, Hong ST, Haileamlak A, Gollogly L, Godlee F, Frizelle FA, Florenzano F, Drazen JM, Bauchner H, Baethge C, Backus J. Data sharing statements for clinical trials: A requirement of the international committee of medical journal editors. *Jama*. 2017;317:2491-2492
49. Lipinski MJ, Biondi-Zoccai GG, Abbate A, Khianey R, Sheiban I, Bartunek J, Vanderheyden M, Kim HS, Kang HJ, Strauer BE, Vetrovec GW. 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*. 2007;50:1761-1767
50. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: A systematic review. *Eur Heart J*. 2008;29:1807-1818
51. Zhang SN, Sun AJ, Ge JB, Yao K, Huang ZY, Wang KQ, Zou YZ. Intracoronary autologous bone marrow stem cells transfer for patients with acute myocardial infarction: A meta-analysis of randomised controlled trials. *Int J Cardiol*. 2009;136:178-185
52. Zhang S, Sun A, Xu D, Yao K, Huang Z, Jin H, Wang K, Zou Y, Ge J. Impact of timing on efficacy and safetyof intracoronary autologous bone marrow stem cells transplantation in acute myocardial infarction: A pooled subgroup analysis of randomized controlled trials. *Clin Cardiol*. 2009;32:458-466
53. Bai Y, Sun T, Ye P. Age, gender and diabetic status are associated with effects of bone marrow cell therapy on recovery of left ventricular function after acute myocardial infarction: A systematic review and meta-analysis. *Ageing Res Rev*. 2010;9:418-423
54. Kuswardhani RA, Soejitno A. Bone marrow-derived stem cells as an adjunctive treatment for acute myocardial infarction: A systematic review and meta-analysis. *Acta Med Indones*. 2011;43:168-177
55. Takagi H, Umemoto T. Intracoronary stem cell injection improves left ventricular remodeling after acute myocardial infarction: An updated meta-analysis of randomized trials. *Int J Cardiol*. 2011;151:226-228
56. Delewi R, Andriessen A, Tijssen JG, Zijlstra F, Piek JJ, Hirsch A. Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: A meta-analysis of randomised controlled clinical trials. *Heart*. 2013;99:225-232
57. Chen L, Tong JY, Jin H, Ren XM, Jin H, Wang QJ, Ma GS. Long-term effects of bone marrow-derived cells transplantation in patients with acute myocardial infarction: A meta-analysis. *Chin Med J (Engl)*. 2013;126:353-360
58. Jeong H, Yim HW, Cho Y, Park HJ, Jeong S, Kim HB, Hong W, Kim H. The effect of rigorous study design in the research of autologous bone marrow-derived mononuclear cell transfer in patients with acute myocardial infarction. *Stem Cell Res Ther*. 2013;4:82

59. de Jong R, Houtgraaf JH, Samiei S, Boersma E, Duckers HJ. Intracoronary stem cell infusion after acute myocardial infarction: A meta-analysis and update on clinical trials. *Circ Cardiovasc Interv*. 2014;7:156-167
60. Liu B, Duan CY, Luo CF, Ou CW, Sun K, Wu ZY, Huang H, Cheng CF, Li YP, Chen MS. Effectiveness and safety of selected bone marrow stem cells on left ventricular function in patients with acute myocardial infarction: A meta-analysis of randomized controlled trials. *Int J Cardiol*. 2014;177:764-770
61. Cong XQ, Li Y, Zhao X, Dai YJ, Liu Y. Short-term effect of autologous bone marrow stem cells to treat acute myocardial infarction: A meta-analysis of randomized controlled clinical trials. *J Cardiovasc Transl Res*. 2015;8:221-231

Table 1. Meta-analyses of human randomized clinical trials including patients with ischemic heart failure using autologous cells.

HF trials	No. of studies	Patients treated/controls	Patient population	Mortality	Application (No. of trials)	Conclusion
Brunskill *et al.* 2009 [12]	21	565 / 526	AMI, CIHD	n/r	i.m. surgical (4), i.m. perc.(1), i.c. (17)*	only i.m. delivery was effective
Jiang *et al.* 2010 [13]	18	490 / 490	AMI, CIHD	n.s.	i.m. surgical (2), i.c. (16)	cell therapy was effective only in patients with AMI
Donndorf *et al.* 2011[14]	6	94 / 85	CIHD	n.s.	i.m. surgical (6)	safe and effective
Zhao *et al.* 2011 [15]	10	250 / 207	CIHD	n/r	i.m. surgical (5), i.c. (6)*	cell therapy was effective only with CABG but not with PCI
Wen *et al.* 2012 [16]	13	378 / 280	IHD, HF	n/r	i.m. surgical (4), i.m. perc. (6), i.c. (4)*	cell therapy is more effective in patients with IHF
Kandala *et al.* 2013 [17]	10	283 / 236	ICMP	n.s.	i.m. surgical (7), i.c. (4)*	cell more effective with i.m. delivery
Cheng *et al.* 2013 [18]	5	135 / 75	Ischemic HF	n.s.	i.m. surgical (1), i.m. or perc. (4)	6 min walking distance † NYHA decrease †
Fisher *et al.* 2014 [19]	23	659 / 478	CIHD, HF	sig.	i.m. surgical (3), i.m.perc. (9), i.c. (12)*	NYHA class and rehospitalization sig.
Xiao *et al.* 2014 [20]	20	453 / 322	CIHD	n.s.	i.m. surgical (8), i.m. perc.(8), i.c. (5)*	route of delivery, baseline EF and type of cells influence significance
Xu *et al.* 2014 [21]	19	440 / 309	CIHD	sig.	i.m. surgical (7), i.m. perc.(7), i.c. (6)*	safe and effective
Tian *et al.* 2014 [22]	11	272 /220	CIHD	sig.	i.m. surgical (5), i.m. perc. (6)	more effective if revascularization was possible
Fisher *et al.* 2015 [23]	31	626 / 895	HF	sig.	i.m. surgical (7), i.m. perc.(12), i.c. (12)	sig. for rehospitalization
Fisher *et al.* 2016 [24]	38	1114 / 793	CIHD, HF, refractory AP	sig.	i.m. surgical (7), i.m. perc (17), i.c. (13)	low quality of evidence

Abbreviations: AMI, acute myocardial infarction; AP, angina pectoris; CABG, coronary artery bypass graft; CIHD, chronic ischemic heart disease; HF, heart failure; ICMP, ischemic cardiomyopathy; i.c., intracoronary application; i.m., intramyocardial; n/r, not reported; n.s., not significant; NYHA, New York Heart Association; perc., percutaneous; * including trials with more than one delivery route; † statistical significance between groups in subgroup analyses.

Table 2. Results of the left ventricular function parameters in meta-analyses including patients with ischemic heart failure.

HF trials	Patient population	LVEF difference (%)	LVESV difference (mL)	LVEDV difference (mL)
Brunskill *et al.* 2009 [12]	CIHD	3.71*	n/r	n/r
Jiang *et al.* 2010 [13]	AMI and CIHD	2.93*	-10.67*	8.61*
Donndorf *et al.* 2011[14]	CIHD	5.4*	n.s.	9.55
Zhao *et al.* 2011 [15]	CIHD	4.59*	-0.36*	-0.38*
Wen *et al.* 2012 [16]	IHD and HF	3.83*	-16.29	-13.76
Kandala *et al.* 2013 [17]	ICMP	4.48*	-20.64*	-16.71*
Cheng *et al.* 2013 [18]	Ischemic HF	0.11 (n.s.)	n/r	n/r
Fisher *et al.* 2014 [19]	CIHD and HF	2.62*	-14.64*	n.s.
Xiao *et al.* 2014 [20]	CIHD	3.05*-3.35*	-11.75*	-7.8*
Xu *et al.* 2014 [21]	CIHD	3.54*	-8.96*	-0.75
Tian *et al.* 2014 [22]	CIHD	4.91*	-10.66*	-7.82
Fisher *et al.* 2015 [23]	HF	4.02 - 4.66*	n/r	n/r
Fisher *et al.* 2016 [24]	CIHD, HF, refractory AP	-1.6 (n.s.)	n/r	n/r

Abbreviations: AMI, acute myocardial infarction; AP, angina pectoris; CIHD, chronic ischemic heart disease; HF, heart failure; ICMP, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; n/r, not reported; n.s., not significant; * $p<0.05$.

Table 3. Meta-analyses of human randomized clinical trials for patients with acute myocardial infarction.

AMI Trials	Sample Size (No. of studies)	Follow-up (months)	Mortality	LVEDV changes (mL)	LVESV changes (mL)	% change in EF (by MRI)
Hristov *et al.* 2006 [28]	482 (5)	4–6	n/r	n/r	n/r	n/r
Lipinski *et al.* 2007 [49]	698 (10)	6	n.s.	-4.6	−7.4*	n/r
Martin-Rendon *et al.* 2008 [50]	811 (13)	3–6	n.s.	-2.47	−4.74*	n/r
Zhang *et al.* 2009 [51]	525 (6)	5	n/r	-0.15	n/r	n/r
Zhang *et al.* 2009 [52]	660 (7)	6	n.s.	-0.15	−0.25*	n/r
Bai *et al.* 2010 [53]	814 (10)	6	n/r	n/r	n/r	n/r
Kuswardhani and Soejitno 2011 [54]	906 (10)	4–60	n.s.	−3.08*	−5.52*	n/r
Takagi and Umemoto 2011 [55]	877 (15)	n/r	n/r	−0.18*	−0.35*	nr
Clifford *et al.* 2012 [29]	1765 (33)	<12	sig.	−3.52*	−4.47*	1.78*
Zimmet *et al.* 2012 [30]	1830 (29)	3–6	n.s.	−3.39*	−3.51*	n/r
Delewi *et al.* 2013 [56]	1641 (16)	3–6	n/r	n/r	n/r	0.16*
Chen *et al.* 2013 [57]	510 (5)	n/r	n/r	-2.29	-4.47	n/r
Jeong *et al.* 2013 [58]	1072 (17)	3–6	n/r	-3.46	−4.98*	n/r
de Jong *et al.* 2014 [59]	1513 (22)	6	n.s.	-2.8	−4.05*	0.13 (n.s.)
Liu *et al.* 2014 [60]	262 (8)	6–24	sig.	0.69	-0.99	n/r
Fisher *et al.* 2015 [26]	2732 (41)	6-60	n.s.	n/r	n/r	1.05 (n.s.)
Gyöngyösi *et al.* 2015 (IPD) [25]	1275 (12)	12	n.s.	1.2	0.4	n/r
Cong *et al.* 2015 [61]	1318 (17)	12	n.s.	-1.69	−3.92*	n/r
Wang *et al.* 2017 (MSC) [35]	449 (8)	1-24	n/r	n/r	n/r	n/r
Xu *et al.* 2017 [31]	2307 (34)	3-61	n.s.	n/r	n/r	n/r

Abbreviations: AMI, acute myocardial infarction; EF, ejection fraction; HF, heart failure; IPD, individual patient data; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; MSC, mesenchymal stem cells; MRI, magnetic resonance imaging; n/r, not reported; n.s., not significant; * $p<0.05$.