Controversies in Cardiovascular Research

Meta-Analyses of Human Cell-Based Cardiac Regeneration Therapies

What Can Systematic Reviews Tell Us About Cell Therapies for Ischemic Heart Disease?

Enca Martin-Rendon

Abstract: Controversies from basic science, discrepancies from clinical trials, and divergent results from meta-analyses have recently arisen in the field of cell therapies for cardiovascular repair and regeneration. Noticeably, there are almost as many systematic reviews and meta-analyses published as there are well-conducted clinical studies. But how do we disentangle the confusion they have raised? This article addresses why results obtained from systematic reviews and meta-analyses of human cell-based cardiac regeneration therapies are still valid to inform the design of future clinical trials. It also addresses how meta-analyses are not free from limitations and how important it is to assess the quality of the evidence and the quality of the systematic reviews and finally how stronger conclusions can be drawn when several pieces of evidence converge. (Circ Res. 2016;118:1264-1272. DOI: 10.1161/CIRCRESAHA.115.307540.)

Key Words: biomedical research ■ cell- and tissue-based therapy ■ meta-analysis ■ randomized controlled trials as topic ■ regeneration

Cardiovascular disease is a major cause of mortality worldwide. Although death rates associated with cardiovascular disease in general have declined over the past decades, the prevalence and incidence of heart failure (HF) are increasing. The increasing economic burden of the condition, estimated to be $108 billion per annum in 2012. Current standard medical treatment, which includes pharmacological therapy and state-of-the-art revascularization procedures, can significantly improve symptoms and increase long-term survival after myocardial infarction (MI). However, existing treatment regimens do not prevent the progression to ischemic HF. Heart transplantation is the only available option for those patients who have end-stage HF. Therefore, clinicians and scientists have embarked on a quest aiming to develop regenerative treatments for heart disease and HF. Despite the rapid clinical development of such therapies (in phase I and II studies), we are now at crossroads. The past few years have seen controversies in basic science and discrepancies in clinical trials. These discrepancies and controversies, together with the paucity of efficacy data from phase III trials, have spread uncertainty in the field of cardiac regenerative medicine.

Rationale Behind Systematic Reviews and Individual Patient Data Meta-Analyses

Randomized controlled trial (RCT) is one of the most robust tools that modern medicine possesses to deliver the best treatments for patients. However, the evidence from RCTs is not always reliable, especially when phase I/II RCTs include small numbers of participants; then the systematic evaluation of all

Counterpoint, see p 1254
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clinical evidence becomes crucial. Systematic reviews aim to collate all available empirical evidence to answer specific research questions. The early evaluation of clinical evidence in systematic reviews can facilitate the appraisal of benefits and harms of the treatment and the magnitude of treatment effect in a timely manner. It may also generate hypotheses and aid the design of future larger trials.

Systematic reviews provide a transparent means of identifying and evaluating the available evidence from multiple studies with the aim of answering explicit questions. Meta-analyses are the statistical methods used to combine data from individual studies or trials included in systematic reviews. Meta-analyses can be performed for published summary results from multiple trials and individual patient data (IPD). The methodology used in these 2 approaches differs in data collection, data checking, and data analysis. Systematic reviews should have an a priori agreed protocol, which includes eligibility criteria, defines primary and secondary outcomes, and describes methods for data analysis. In IPD meta-analyses, data are derived from individual patients of all included studies, whereas trial-based meta-analyses are based on treatment effect estimates. Trial meta-analyses may seem quicker, easier, and more cost-effective, whereas IPD meta-analyses enable stratification based on IPD and time to event analyses. However, the potential advantages of IPD meta-analyses come with some caveats. There might be circumstances when pooling IPD in a meta-analysis will be crucial, for example, when published data do not allow a good quality review and others where its advantages over trial meta-analysis would be trivial. 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.

In the absence of evidence from large clinical trials, meta-analyses remain the obvious means of evaluating the available evidence. Meta-analyses have the advantage of increasing statistical power, improving precision and giving the opportunity to settle controversies arising from differing findings across studies. They can be used to explore the reason for the variability across studies, not just to derive a mean result. However, meta-analytic findings can be misleading if pitfalls in study designs, risk of reporting bias, and variation across studies are not carefully considered.

In addition to the quantitative data, syntheses mentioned above, systematic reviews of the literature can provide a more intellectual summary of clinical trials, focusing on trial design, intended population, etc. and give a different but extremely valid perspective of the quality of studies.4,6

### Quality Assurance in Evidence Synthesis

The synthesis of clinical evidence has become an important aspect of modern medicine. Systematic reviews and meta-analyses are conducted not only to generate hypotheses and design new trials but also to inform healthcare decisions. Therefore, they should be of high quality and use robust methodology. Over 2 decades, clinicians and scientists have established quantitative approaches to assess the quality of the evidence provided by systematic reviews and an ethos of continuous improvement.

An example of this is the guidance provided by the Cochrane Collaboration through the publication and regular update of the Cochrane Handbook for Systematic Reviews of Interventions.7 Comparable with any other study type, a study protocol is considered essential and is written in as much detail as an RCT protocol. Prospective registration of review protocols is a growing trend, required by the Cochrane Collaboration and encouraged more widely for all other systematic reviews. Such prospective registration can minimize bias and avoid duplication of systematic reviews. Initiatives that allow prospective registration of systematic review protocols, such as PROSPERO (international prospective register for systematic reviews), are currently available.8 Although deviations from the original protocol are accepted, they are required to be documented with a robust rationale for any changes, which promotes transparency of methods and processes. Furthermore, there is a consensus for the transparent and complete reporting of systematic reviews: the Preferred Items to report Systematic Reviews and Meta-Analyses recommendations.9 Assessment of the validity of findings of each trial included in a systematic review should be undertaken with care and conducted using explicitly systematic methods.7 An important part of any systematic review should be dedicated to assessing risks of bias of the included studies, which consist of selection bias, performance bias, detection bias, attrition bias, publication bias, and reporting bias.

More recently, a formal method of ranking the quality of the evidence for each major outcome measured in a systematic review has been established. The Grades and Recommendations, Assessment, Development and Evaluation approach provides key information about the magnitude of the effect of the intervention and empirical quality of the evidence. It takes into consideration factors, such as within-study risk of bias, directness of the evidence, heterogeneity, precision of effect estimates, and risk of publication bias (http://www.gradeworkinggroup.org). The Grades and Recommendations, Assessment, Development and Evaluation system provides an indication of how confident one can be about the magnitude of any given treatment effect or association. It specifies 4 levels of quality of the evidence and how the quality can be downgraded or upgraded (Table 1).

In addition to assessing the quality of included studies and the quality of the evidence for any given outcome, the quality of systematic reviews can also be appraised. A Measurement Score To Assess Systematic Reviews tool has been recently generated.10 It is based on 11 requirements, which are detailed in Table 2.
The importance of data collection in IPD meta-analyses as part of their quality assurance has to be highlighted. Rigorous data checks are a priority. These include running checks for missing or duplicate data, plausibility of the data, and patterns of randomization.

### Systematic Reviews and Trial Meta-Analyses of Cell Therapies for Ischemic Heart Disease

Strikingly, there are almost as many systematic reviews and meta-analyses in the field of cell therapies for cardiovascular regeneration as there are RCTs. Remarkably, there are not only differing results from individual RCTs but also differing meta-analytic findings reported. Peruzzi et al11 identified 41 trial meta-analyses published by January 2015; of which, 16 involved patients with HF.11,12 There have been 2 overviews of systematic reviews11,12 and at least 3 new systematic reviews and meta-analyses published in 2015, notably including an IPD meta-analysis.13–15

Interestingly, Peruzzi et al11 observed a significant correlation between the A Measurement Score To Assess Systematic Reviews score and the year of publication of these systematic reviews. This is not surprising as measures of continuous improvement in the reporting of systematic reviews have been progressively introduced since the publication of the first systematic review in the field of cell therapies and cardiac regeneration.16 Left ventricular ejection fraction (LVEF) is a robust predictor of cardiac adverse events and mortality in patients with LV dysfunction. Hence, the majority of RCTs and systematic reviews or meta-analyses report changes in LVEF as a surrogate of heart function. Improvement in LVEF has been observed in patients after acute MI (AMI) and successful percutaneous coronary intervention,17 as well as in the first 30 days after coronary artery bypass graft in patients with chronic ischemic heart disease (CIHD).18 In most systematic reviews and meta-analyses of RCTs administering cell therapies, a moderate but significant improvement of 2% to 4% in LVEF in favor of cell therapy compared with controls has been reported. However, these results are not robust to the risk of performance bias (eg, blinding of participants, clinicians, and outcome assessors).19 The measurement of LVEF has relied on several imaging techniques; of which, magnetic resonance imaging is considered to provide the most accurate measurements. When limited to magnetic resonance imaging, improvement in LVEF and therefore the benefit of cell therapy after AMI seems negligible.5 Performance bias is less likely to have an effect on the reporting of clinical outcomes, such as mortality.

Certainly, a great deal of effort has been made by review authors to compile all clinical evidence that is currently available in the form of systematic reviews and meta-analyses, overview of systematic reviews and systematic analyses of the literature. To enumerate those studies one by one and summarize their findings here will be repeating what is already known and will provide no new perspective or useful mechanistic insight. Instead, an argument for the transitivity assumption, which states that in randomized trials, treatment options are randomized in the same group of patients, is discussed below and justified in the context of systematic reviews and meta-analyses.

To explore the reasons for the differing meta-analytic results, those systematic reviews that have reported trial meta-analysis for both LVEF and mortality have been compared. Those reporting only LVEF or reporting mortality data from individual trials but not conducting meta-analysis have been

<table>
<thead>
<tr>
<th>Quality Level</th>
<th>Type of Study</th>
<th>Factors That Would Downgrade the Quality</th>
<th>Factors That Would Upgrade the Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>RCTs</td>
<td>High likelihood of bias (serious limitations in design or implementation)</td>
<td>Large magnitude of treatment effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Downgraded RCTs or upgraded observational studies</td>
<td>Indirectness of the evidence (indirect population, control, outcomes, or intervention)</td>
<td>Dose-response effect</td>
</tr>
<tr>
<td>Low</td>
<td>Further downgraded RCTs or observational studies</td>
<td>Inconsistent results or substantial unexplained heterogeneity</td>
<td>When results show no effect, all confounding factors suggest spurious results or reduce a demonstrated effect</td>
</tr>
<tr>
<td>Very low</td>
<td>Further downgraded RCTs, downgraded observational studies or case reports</td>
<td>Imprecision of results (underpowered and wide confidence interval)</td>
<td></td>
</tr>
</tbody>
</table>

RCTs indicate randomized controlled trials.

Table 1. Summary of the Grades of Recommendation, Assessment, Development, and Evaluation Approach to Rank the Quality of the Evidence

<table>
<thead>
<tr>
<th>AMSTAR Score System</th>
<th>AMSTAR Score System</th>
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<tbody>
<tr>
<td>1. An a priori design or protocol is provided.</td>
<td>1. An a priori design or protocol is provided.</td>
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<tr>
<td>2. Study selection and data extraction is conducted by two independent reviewers.</td>
<td>2. Study selection and data extraction is conducted by two independent reviewers.</td>
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<tr>
<td>3. The systematic review is based in a comprehensive search strategy, searching of at least three electronic databases are required.</td>
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</tr>
<tr>
<td>4. Publication status of the included studies is not restricted (eg, full articles, abstract, no restriction in language).</td>
<td>4. Publication status of the included studies is not restricted (eg, full articles, abstract, no restriction in language).</td>
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<tr>
<td>5. List of included and excluded studies are provided.</td>
<td>5. List of included and excluded studies are provided.</td>
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<tr>
<td>6. Characteristics of the included studies are provided.</td>
<td>6. Characteristics of the included studies are provided.</td>
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<tr>
<td>7. Quality of the included studies is documented in the systematic review.</td>
<td>7. Quality of the included studies is documented in the systematic review.</td>
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<tr>
<td>8. Quality of included studies and quality of the evidence is used appropriately to draw conclusions in the systematic review.</td>
<td>8. Quality of included studies and quality of the evidence is used appropriately to draw conclusions in the systematic review.</td>
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<tr>
<td>9. Detailed methods that are used to combine data and reach findings are also provided.</td>
<td>9. Detailed methods that are used to combine data and reach findings are also provided.</td>
</tr>
<tr>
<td>10. Publication bias is assessed and tested using appropriate statistical methods.</td>
<td>10. Publication bias is assessed and tested using appropriate statistical methods.</td>
</tr>
<tr>
<td>11. Details of any conflict of interest are provided in the included studies.</td>
<td>11. Details of any conflict of interest are provided in the included studies.</td>
</tr>
<tr>
<td>Total: score (of 11)</td>
<td>AMSTAR indicates Measurement Score to Assess Systematic Reviews.</td>
</tr>
</tbody>
</table>
excluded. In the case of systematic reviews that represent updates of previous versions, only the most recent version has been included here for comparison. There are 6 systematic reviews included: 2 in which treatment was administered to patients after AMI and successful revascularization,14,20 3 in which treatment was administered to patients with CIHD and HF (CIHD/HF),19,21,22 and 1 which included trials of both AMI and CIHD/HF.13 The quality of the included systematic reviews has been assessed using the A Measurement Score To Assess Systematic Reviews score (Table 3). Noticeably, all systematic reviews are of moderate to high quality. The most common omissions are related to the provision of a list of excluded trials (reported in 2/6 reviews), the reporting of any conflict of interest of the included trials (reported in 2/6 reviews), the exclusion of studies published in languages other than English (publication status, not limited in 3/6 reviews), the lack of a comprehensive search of the literature (comprehensive search in 5/6 reviews), and the reporting of publication bias using a Funnel plot (reported in 5/6 reviews). A possible justification for such omissions may be that the Cochrane reviews14,19 are required to abide by strict guidelines and have the benefit of no space limitation when published.

In addition, the use of the Grades and Recommendations, Assessment, Development and Evaluation to rank the quality of the evidence for reported outcomes and the existence of a prospective registered protocol is shown in Table 4. The presence of a prospective registered protocol gives confidence in the transparency of processes and methods and allows the documentation of any variation from the original study design. RCTs generally provide the highest level of quality. However, there are factors that could downgrade the quality of the evidence in RCTs (Table 2). The quality of the evidence for outcomes, such as LVEF and mortality, in those reviews that reported them is low to moderate.14,19 This assessment is based on the substantial unexplained heterogeneity, which has been observed particularly for LVEF, and the imprecision (small studies with low numbers of events) observed for the clinical outcomes. It also means that the effect size is likely to change when further evidence becomes available.

The improvement in LVEF in favor of cell therapy in patients with AMI was moderate and significant when pooling all reported data (Table 5).20 However, changes in LVEF were nonsignificant when measured by magnetic resonance imaging.14,20 Neither study showed a significant effect of cell

<table>
<thead>
<tr>
<th>Study ID</th>
<th>de Jong et al20</th>
<th>Fisher et al,14 AMI</th>
<th>Afzal et al13</th>
<th>Fisher et al19</th>
<th>Xu et al22</th>
<th>Fisher et al,21 HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRADE approach provided</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prospective registered protocol available</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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</table>

AMI indicates acute myocardial infarction; GRADE, Grades and Recommendations, Assessment, Development and Evaluation for the quality of the evidence; and HF, heart failure.
therapy on mortality. Thus, there is no conclusive evidence that the treatment affects LVEF or mortality in AMI patients (Table 5). In the 3 systematic reviews of CIHD/HF,20,21,22 all 3 found a significant improvement in LVEF in cell-treated patients compared with controls. In addition, all 3 showed a significant reduction in mortality in favor of cell therapy (Table 5). In the sixth review, which included both AMI and CIHD/HF patients,13 the authors concluded that cell therapies significantly improved LVEF and significantly reduced mortality in treated patients compared with controls. In these systematic reviews and meta-analyses, the improvement in LVEF ranges between 2% and 4%. A recent study has suggested that systematic reviews of cell therapies for heart disease are most likely underpowered to detect changes in LVEF of ≤5%.23 This suggests that the results for LVEF from the systematic reviews and meta-analyses included here (Table 5) may be neither detectable nor clinically relevant and justify the selection of better surrogate outcomes to evaluate treatment effect. In contrast, this study found that the available evidence shows conclusively that cell therapy reduces mortality (risk ratio [RR], 0.42; 95% confidence interval, 0.27–0.64) in patients with CIHD/HF but that AMI reduces mortality (risk ratio [RR], 0.42; 95% confidence interval, 0.27–0.64) in patients with CIHD/HF but that AMI does not reduce mortality risk in patients with AMI, there is a significant reduction in the number of deaths among patients with CIHD/HF, suggesting that patient populations are a confounding factor. If the effect modifiers are clearly different between trials, then the aggregate should not be attempted. The inclusion of RCTs that have recruited participants with dissimilar characteristics may explain the mean results obtained in this meta-analysis.13

**IPD Meta-Analysis**

The Meta-Analysis of Cell-Based Cardiac Studies (ACCRUE) consortium was established in 2007 through collaborative and confidentiality agreements with the aim of evaluating cell therapies as treatment for AMI based on IPD.15 This is the first prospective IPD meta-analysis conducted in the field. It included 12 RCTs, with a total of 1252 participants who received intracoronary administration of cells after a recent AMI and successful revascularization. The ACCRUE IPD meta-analysis evaluates clinical outcomes and heart function parameters. Interestingly, it found no evidence of a beneficial effect of cell therapy on clinical outcomes or LV function and remodeling during short-term follow-ups. IPD meta-analyses maybe crucial to conduct in some instances, and they provide an alternative approach to trial-based systematic reviews that can overcome some of the key limitations of pooling summary trial results. However, the success of the IPD meta-analysis approach relies on obtaining data from all or nearly all studies (>90%) to avoid potential bias. However, the ACCRUE IPD meta-analysis contains ≈60% of the available published studies, which may question our confidence in the conclusions that can be drawn from this study. Furthermore, because of different outcome definitions used in the original studies and in the ACCRUE database, redefinition and recoding of the included variables and outcomes would have been required to

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**Table 5. Changes in LVEF and Mortality Ratios in Patients Treated With Cell Therapies Compared With Controls**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patient Population</th>
<th>LVEF MD, % (95% CI)</th>
<th>LVEF Method</th>
<th>Mortality OR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Jong et al22</td>
<td>AMI</td>
<td>2.10 (0.68 to 3.52)</td>
<td>All methods combined</td>
<td>OR, 0.68 (0.36 to 1.31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.13 (−2.67 to 2.93)</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.93*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al14</td>
<td>AMI</td>
<td>1.27 (−1.14 to 3.68)</td>
<td>MRI</td>
<td>RR, 0.93 (0.58 to 1.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afzal et al13</td>
<td>AMI and CIHD/HF</td>
<td>2.92 (1.91 to 3.92)</td>
<td>All methods combined</td>
<td>OR, 0.55 (0.34 to 0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.000001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al19</td>
<td>CIHD/HF</td>
<td>2.62 (0.5 to 4.73)</td>
<td>All methods combined</td>
<td>RR, 0.28 (0.14 to 0.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al22</td>
<td>CIHD/HF</td>
<td>3.51 (1.65 to 5.38)</td>
<td>All methods combined</td>
<td>RR, 0.49 (0.29 to 0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.00002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al21</td>
<td>CIHD/HF</td>
<td>2.06 (1.10 to 3.01)</td>
<td>All methods combined</td>
<td>RR, 0.48 (0.34 to 0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.00001</td>
<td></td>
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</table>

AMI indicates acute myocardial infarction; CI, confidence interval; CIHD, chronic ischemic heart disease; HF, heart failure; LVEF, left ventricular ejection fraction; MD, mean difference; OR, odd ratio; and RR, risk ratio.
standardize the data before analysis; this necessitates a great deal of effort and negotiation, and the authors should be congratulated for it. This standardization enabled the ACCRUE investigators to check all included data through a thorough data exploration. The main limitation described for the ACCRUE meta-analysis (inclusion of only 60% of the available published studies) may question the validity of its conclusion if it was considered as a stand-alone study. However, the results of the ACCRUE IPD meta-analysis are consistent with the results of other systematic reviews and trial meta-analysis of AMI as described above.5,14,20

Limitations of the Systematic Reviews and IPD Meta-Analyses

Systematic reviews and meta-analyses are restricted by their limitations.

First, among the published meta-analyses and systematic reviews, there is a great deal of duplication, which has not been addressed in the overview of systematic reviews.11 Rarely do these systematic reviews or meta-analyses have a prospectively registered review protocol, which can be considered a lack of transparency.

Second, even following the most robust methodology to date, there remains a risk of selection, reporting, and publication bias. Systematic reviews and trial meta-analyses rely on published data and on the response from trial investigators when they are contacted with queries about their original studies. Although formal testing can be conducted for publication bias, reporting bias and publication bias cannot be completely ruled out. Furthermore, agreement (or the lack of) to participate in IPD meta-analyses by the principal investigators of the original studies carries selection bias in itself as IPD meta-analyses should include >90% of all available data to be considered robust.

Third, trial meta-analyses are prone to statistical heterogeneity. Statistical heterogeneity occurs when treatment effect estimates between trials vary beyond the variation expected by chance. When statistical heterogeneity reaches a substantial degree (I² ≥ 50%),24 results from meta-analyses should be interpreted with caution and may trigger sensitivity analyses.

Fourth, there is a risk of observing spurious results. Meta-analyses carry their own risk of observing false-positive (random type I errors) or false-negative (random type II errors) findings. The accumulation of these errors occurs when (1) a low number of trials with a low number of participants is included in the meta-analyses, (2) multiple reviews and review updates are conducted (multiple statistical testing), and (3) when the meta-analyses are underpowered or of insufficient quality. Recently, Fisher et al23 have used trial sequential analysis with cumulative data from 2 Cochrane reviews and meta-analyses to address some of these limitations. Trial sequential analysis helps to reduce the likelihood of observing random errors (type I and type II errors) and estimates the information size, the total number of participants required in a meta-analysis to be confident about its findings. In their study,23 the authors concluded that even these Cochrane reviews are most likely underpowered as they have not reached the required information size. However, although there is insufficient evidence of an effect of cell therapy in patients with AMI to draw firmer conclusions, the existing evidence of a significant improvement in clinical outcomes in patients with HF seems to be conclusive.23

Finally, there is substantial clinical heterogeneity. As mentioned above, the transitivity assumption has to be justified and effect modifiers should be taken into consideration. Such an effect modifier could be the patient population as discussed above, but as more clinical evidence becomes available, other potential modifiers, such as cell type, route of administration (eg, intracoronary, intramyocardial, and transendocardial), and disease severity in the case of HF, should also be taken into account. Although results from meta-analyses suggest that administration of cells into the heart muscle could be more efficacious than via the coronary arteries,25 few trials have compared multiple delivery methods.26,27 Similarly, there are not enough direct comparisons to draw firm conclusions about cell types.

Can Meta-Analyses Inform the Design of Future Trials?

Despite the limitations mentioned above, systematic reviews and meta-analyses have aided decision making in healthcare. Meta-analyses of other interventions have certainly influenced guidelines and recommendations in the prevention of cardiovascular disease.26,28 Examples are the systematic reviews that have evaluated the benefits of cardiac rehabilitation on cardiovascular mortality, morbidity, and quality of life.30,31 Findings from systematic reviews and meta-analyses have also protected patients from harm. Here, it is worth mentioning that a systematic review on the use of rosiglitazone to treat type II diabetes mellitus showed an increase in the risk of MI that led to the suspension of the marketing authorization for this drug in Europe.7,23

However, citing an eminent cardiologist, meta-analyses are not replacements for large trials nor are large trials replacements for meta-analyses.34 Historically, meta-analyses have been used to design further clinical trials when the meta-analytic findings have been promising. Nonetheless, there are examples of large RCTs in cardiology that have either contradicted the results of meta-analyses35 or observed a much smaller treatment effect than that observed in meta-analyses.36 There are also examples of large RCTs in cardiology that have confirmed the results of a meta-analysis.37 The apparent discrepancies could be explained by the samples size in the meta-analyses and the number of events observed. The latter meta-analysis showed that thrombolytic therapy significantly reduced mortality and included ≈5000 participants and about 1000 deaths (events).37 In contrast, the former meta-analysis on the use of magnesium for AMI included a much smaller sample size (1300 patients) and the number of events (78 deaths).35

Survival rates after AMI have improved in the past 2 decades because of thrombolytic therapy and advanced revascularization techniques. Therefore, a moderate treatment effect is more plausible than a large effect in the field of cell therapies and heart disease. Not surprisingly, the results from trial sequential analysis suggest that the recent Cochrane review and
meta-analysis on bone marrow cell therapy trials for patients with AMI is underpowered to detect a relative risk reduction (RRR) in mortality of ≤35%. This meta-analysis is based on 81 observed deaths. Assuming a mortality rate of 5% in the control group as previously observed, ~4055 patients with AMI will need to be included to observe an RRR in mortality of 35% and 8400 patients with AMI if the RRR associated with bone marrow cell therapy was 25%. In the setting of HF and assuming a mortality rate of 15% in the control group, ~1236 patients with HF will need to be included to observe an RRR of 35% in mortality, whereas 2546 patients with HF will be required to observe an RRR of 25% in mortality associated with bone marrow cell therapy. However, whereas the results for AMI are not robust because the meta-analysis cumulative data for a beneficial effect did not reach significance, there is firm evidence that bone marrow cell therapy reduces the risk of mortality when administered to patients with HF. There is probably no merit in designing another phase III clinical trial of bone marrow cells for patients with AMI until the BAMI trial (The Effect of Intracoronary Reinfusion of Bone Marrow-Derived Mononuclear Cells [BM-MNC] on All Cause Mortality in Acute Myocardial Infarction) is completed (NCT01569178). Efforts may be better placed designing a large RCT for patients with HF to confirm the results of the meta-analyses. An assumption that treatment effect is likely to be smaller than that predicted by the meta-analyses should be made as the meta-analytic results are based on the small number of events (~75 observed deaths).

Furthermore, to detect a difference of 4% in LVEF (measured by magnetic resonance imaging) in favor of bone marrow cell therapy ≈841 patients with AMI will need to be recruited, whereas 206 patients with HF will need to be included to detect a difference of the same magnitude. If the difference in LVEF is halved (2%), ≈3367 patients with AMI or 827 patients with HF will be required to observe this difference. Trial sequential analysis has shown that recent meta-analyses have reached the required number of patients and therefore are sufficiently well powered to detect an improvement in LVEF of 4%. This provides conclusive evidence that bone marrow cell therapy does not improve LVEF by 4% when administered to patients with AMI or HF. The implication is that LVEF may not be an acceptable end point/surrogate in future trials of cell therapies for heart disease.

In separate analyses by route of administration (intracoronary versus intramyocardial administration), the recent study showed that both trials in which cells were administered intracoronarily and those in which cells were administered intramyocardially showed a significant beneficial effect in mortality in patients with HF. In addition, evidence for comparison of cell doses or cell types is still sparse and trialists may consider to include these comparisons in future RCTs.

**Conclusions**

Although no replacements for large clinical trials, systematic reviews and meta-analyses (both trial and IPD meta-analyses) are powerful tools to evaluate clinical efficacy in healthcare. However, they are as informative as the studies on which they are based. When meta-analytic findings combine small studies or low-quality studies, they can be misleading and hence, those findings should be taken cautiously. Robust methodology is currently available to assess the quality of included studies (risk of bias), the quality of the evidence for any given outcome measured (the Grades and Recommendations, Assessment, Development and Evaluation approach), and the quality of the systematic reviews on which meta-analyses are based. Taken together, all these methodologies should help evaluating clinical efficacy of most medical interventions. Here, the benefits and risks of cell therapies in heart disease are summarized.

Considering that a phase III trial has not yet been completed in this field and that the quality of most published reports is relatively high, the conclusions from systematic reviews and meta-analyses can inform about treatment benefits and harms. Currently, evidence provided by systematic evaluation of the literature using qualitative assessment of RCTs, trial-based meta-analyses, and an IPD meta-analysis is in agreement that there is insufficient evidence of a beneficial effect of bone marrow cell therapies over placebo/control when administered to patients after AMI and revascularization although systematic reviews and meta-analyses are most likely underpowered to detect an RRR of ≤35% in mortality and <4% improvement in LVEF in this clinical setting. It is plausible that the significant positive effect on LVEF (ranging from 2% to 4%) shown in some meta-analyses may represent too optimistic or spurious results.

In contrast, there is robust evidence of a beneficial effect of bone marrow cell therapies on reducing mortality in patients with HF. Although promising, the meta-analytic findings are based on a small number of events (75 observed deaths), and therefore, these results should be considered with caution and will need to be confirmed in a large phase III trial. Suggestions that may help the design of a larger trial have been given above. With the ethos of continuous improvement, the design of such a trial should also aim at standardizing methodology, reducing performance bias, measuring robust and relevant surrogate outcomes, and clearly defining the patient population.

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**Disclosures**

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**References**


Although the author, E. Martin-Rendon, cited several quality criteria for publication-based meta-analyses, other major issues were omitted. First, if the data for meta-analytic pooling are not available or some outcomes not reported, then even the highest quality meta-analysis based on such aggregate (but not individual) data will necessitate an artificial recalculation of outcomes. Such an operation increases the risk of statistical bias by entering virtual data into the analysis, or selection biases by omission end-point analysis parameters that cannot be readily extracted from the original publication, or omission of studies not reporting arithmetic means and SDs of end-point parameter. In such cases, the reliability of the results is questionable and potentially subject to the data-dredging phenomena that can favor cell-therapy effects through artificial statistical methodologies.

Secondly, only small numbers of patients are included in the subgroup analyses based on unique outcome parameters in the publication-based meta-analyses. Although it is true that Meta-Analysis of Cell-Based Cardiac Studies (ACCRUE) included only 1252 patients (although all corresponding authors and principal investigators of relevant trials were invited to participate), a complete data set for all parameters were available for the ACCRUE patients. In contrast, the recently published Cochrane study, including 41 studies of 2732 patients with recent acute myocardial infarction treated with autologous bone marrow cells, analyzed all-cause mortality (within 12 months) in a subset of patients (836 cell treated and 529 controls), for whom this clinical outcome was clearly presented. These figures are comparable with those reported for ACCRUE (767 versus 485, respectively). In addition, at 12 months of follow-up, information on target vessel revascularization were available for a total of 789 patients (of 2732 patients) in the Cochrane database, in contrast to all 1252 patients in ACCRUE.

Finally, an evaluation of the time-dependent occurrence of adverse events or changes in left ventricular performance are not possible for aggregate data in meta-analyses, in which individual follow-up times are not reported; this could potentially lead to unpredictable bias. Furthermore, only data based on individual patients can enable subgroup analyses of prespecified patient criteria (eg, diabetic or female or diabetic female patients), which are now critical in the era of personalized medicine.

Finally, the ACCRUE data set provides the largest patient level database analyzed and represents the most robust database with which to reliably interpret the clinical effects of cell therapy in patients with recent acute myocardial infarction, randomized to cell therapy or control groups. ACCRUE continues to evaluate cell-based or cell-related cardiac regenerative therapies, with the aim of identifying promising methods, and individual patients for whom they have been beneficial. Although science is in continuous flux, there is clear evidence that only the rigorous application of scientific, clinical, and statistical methods facilitates the preservation of data integrity and derive reliable conclusions.
Meta-Analyses of Human Cell-Based Cardiac Regeneration Therapies: What Can Systematic Reviews Tell Us About Cell Therapies for Ischemic Heart Disease?
Enca Martin-Rendon

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