Heart failure (HF), secondary to ischemic and nonischemic cardiomyopathy, remains a major cause of death worldwide. As the long term survival of patients suffering from ischemic and nonischemic cardiomyopathy has increased with recent medical advances, the incidence of HF has also steadily increased. The overall mortality for HF stands at 50% within 4 years of diagnosis, and 50% of patients with severe HF die in the first year. Currently, patients suffering from endstage HF require heart transplantation or are supported by left ventricular assist devices (LVAD). However, both the number of organs for transplantation and the long-term efficacy of LVAD are limited. Additionally, artificial pacemakers or implantable cardioverter-defibrillators are indicated for some patients because they help to improve HF symptoms in the short term. Therefore, there is a need for alternative strategies to mitigate symptoms and decelerate the progression to endstage HF.

Recently, cell therapies have been investigated as a new treatment for patients suffering from acute myocardial infarction (AMI), chronic ischemic and nonischemic cardiomyopathy and HF. Cell-based therapies have the potential to compensate for the limited ability of the adult heart to repair itself following a major injury by improving vascularity, supporting cardiomyocytes or activating endogenous progenitor cells (for review see Behfar et al). There is enough clinical evidence to conclude that cell therapies are safe. However, not all clinical trials show clinical efficacy. Interestingly, cell-based therapy trials are small and therefore conclusions drawn from them have limited statistical power. Systematic reviews and meta-analyses are accepted to be robust and unbiased methods for critical evaluation of clinical evidence and to synthesize results from several clinical trials, thus improving statistical power.

Evidence-based medicine (EBM) aims at bringing closer together clinical research and clinical practice in order to make the best decisions about treating individuals or groups of patients. Randomized controlled trials (RCTs) are one of the more robust tools that EBM uses in modern medicine. It is therefore important that new interventions are evaluated through RCTs whenever possible. RCTs and nonRCTs of cell therapies for heart disease have been appraised recently in a number of systematic reviews and meta-analyses. However, the clinical evidence in this field is widely dispersed and has not been collated. There is a need to assess overall outcomes, including benefits and harms related to cell therapies for heart disease. To date, no assessment of the quality of these systematic reviews...
has been carried out.

Here we present an overview of systematic reviews and meta-analyses that summarizes the current state of the evidence relating to cell therapies for heart disease, with an emphasis on HF. We specified 2 key questions: (1) What is the overall effect of cell therapies on primary outcomes such as left ventricular ejection fraction (LVEF) and mortality? (2) How important is it to define the clinical setting and the length of follow-up when assessing cell-based therapies for heart disease?

**Methods**

**Inclusion Criteria**

Systematic reviews and meta-analyses on cell therapy trials for HF were eligible for inclusion if the studies fulfilled the following: (1) used a systematic approach and included an assessment of the methodological quality of included trials, (2) conducted a meta-analysis of at least 1 outcome including mortality, LVEF, HF, rehospitalization because of HF, adverse events, quality of life (QOL) or exercise tolerance, (3) assessed trials focusing on the administration of any cell therapy as treatment for ischemic heart disease (IHD), including at least 1 trial for HF, and (4) compared cells with no cells (eg, placebo, control, mock intervention). Studies were limited to full-text articles; studies published in any language other than English were excluded. The primary outcomes of this study were LVEF and death. Secondary outcomes included New York Heart Association (NYHA) functional classification, HF symptoms, rehospitalization because of HF, QOL, exercise tolerance and adverse events.

**Search Strategy and Study Selection**

Online medical databases (CENTRAL (The Cochrane Library, 2014, Issue 5), DARE, NHSEED & HTA databases (The Cochrane Library 2014, Issue 2), PubMed (epublications only), MEDLINE (1946 onwards), EMBASE (1974 onwards), CINAHL (1982 onwards), LILACS (1982 onwards), KoreaMed (1997 onwards), PakMediNet (1995 onwards) and IndMed (1985 onwards)) were searched up to 23 June 2014. Detailed search strategies are available from the authors upon request. Two reviewers (S.A.F., E.M.-R.) initially screened all references independently for eligibility. The full text of all potential systematic reviews and meta-analyses was then assessed independently by 2 reviewers (E.H. and E.M.-R.) according to the inclusion criteria. Disagreements were resolved through discussion and agreement. Publications by the same research group that were earlier versions of subsequently updated systematic reviews were excluded.

**Assessment of the Methodological Quality of the Reviews**

Two independent reviewers (E.H. and E.M.-R.) assessed the methodological quality of the included systematic reviews and meta-analyses using the ‘assessment of multiple systematic reviews’ (AMSTAR) measurement tool (Table S1). Disagreements were resolved through discussion and agreement.

**Data Extraction and Analysis**

Information extracted by 2 independent reviewers (E.H. and E.M.-R.) from each of the included systematic reviews and meta-analyses comprised author, year of publication, date of the search, search characteristics, population of participants included in the original trials, number and type (eg, RCT or nonRCT) of trials included, interventions and comparators, cell delivery strategy, total number of participants included in the meta-analysis, first author and date of publication of included trials and a summary of the study’s outcomes including...
actual measurements and observational data. The analysis included herein was descriptive in nature; results from included systematic reviews are presented with reference to the 2 predefined questions. The effect sizes obtained from meta-analyses for the primary outcomes of LVEF and death in each systematic review were compared visually using forest plots. Continuous data are represented as the mean difference between groups of the total number of participants in the systematic review. All studies lack- ing the control arm accounted for less than 5% (99 participants) of their included trials. This was decided because studies lacking the control arm accounted for less than 5% (99 participants) of the total number of participants in the systematic review. All systematic reviews included trials where cells were delivered intramyocardially (IM); 8 also included trials that administered the treatment via the coronary arteries (IC). These studies were all RCTs of bone marrow mononuclear cell (BMMNC) therapy for CIHD. A summary of the characteristics of the systematic reviews included in this study is presented in Table 1.

### Characteristics of the Included Systematic Reviews

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Date of search</th>
<th>Population</th>
<th>No. and type of trials</th>
<th>Interventions/ comparators</th>
<th>No. of participants</th>
<th>Main data outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng 201327</td>
<td>July 2012</td>
<td>Ischemic HF with LVEF &lt;40%</td>
<td>5 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM</td>
<td>135 in treatment arm; 75 in control arm</td>
<td>LVEF Death</td>
</tr>
<tr>
<td>Donndorf 201115</td>
<td>May 2009</td>
<td>CIHD undergoing CABG</td>
<td>6 trials (4 RCTs and 2 cohorts)</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM</td>
<td>94 in treatment arm; 85 in control arm</td>
<td>LVEF LVESV MACED</td>
</tr>
<tr>
<td>Fisher 201410</td>
<td>March 2013</td>
<td>CIHD and HF</td>
<td>23 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>659 in treatment arm; 478 in treatment arm</td>
<td>LVEF Death</td>
</tr>
<tr>
<td>Jeevanantham 201211</td>
<td>January 2012</td>
<td>IHD (AMI and CIHD)</td>
<td>50 trials (36 RCTs and 14 cohorts)</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>1,460 in treatment arm; 1,165 in control arm</td>
<td>LVEF Scar size Death</td>
</tr>
<tr>
<td>Jiang 201013</td>
<td>June 2009</td>
<td>AMI or CIHD</td>
<td>18 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>490 in treatment arm; 490 in control arm</td>
<td>LVEF LVESV LVEDV</td>
</tr>
<tr>
<td>Kandala 201316</td>
<td>April 2012</td>
<td>Chronic ICM LVEF &lt;45%</td>
<td>10 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>283 in treatment arm; 236 in control arm</td>
<td>LVEF LVESV LVEDV</td>
</tr>
<tr>
<td>Sadat 201414</td>
<td>June 2012</td>
<td>ACS and CAD/HF</td>
<td>32 trials (24 RCTs and 8 nonRCTs)</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>1,300 in treatment arm; 1,006 in control arm</td>
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<tr>
<td>Tian 201428</td>
<td>October 2013</td>
<td>CIHD</td>
<td>11 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM</td>
<td>272 in treatment arm; 220 in control arm</td>
<td>LVEF LVESV LVEDV</td>
</tr>
<tr>
<td>Wen 201117</td>
<td>April 2012</td>
<td>IHD and HF LVEF &lt;40%</td>
<td>13 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>378 in treatment arm; 280 in control arm</td>
<td>LVEF LVESV LVEDV</td>
</tr>
<tr>
<td>Xu 201418</td>
<td>December 2013</td>
<td>CIHD</td>
<td>19 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>440 in treatment arm; 309 in control arm</td>
<td>LVEF LVESV LVEDV</td>
</tr>
<tr>
<td>Zhao 201119</td>
<td>May 2011</td>
<td>CIHD undergoing CABG/PCI</td>
<td>10 RCTs</td>
<td>Autologous cell therapy/no cells or placebo; delivery: IM and IC</td>
<td>250 in treatment arm; 207 in control arm</td>
<td>LVEF LVESV LVEDV</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CIHD, chronic ischemic heart disease; HF, heart failure; IC, intracoronary; ICM, ischemic cardiomyopathy; IM, intramyocardial; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

### Results

#### Search Results

The PRISMA flow chart summarizing study selection is shown in Figure 1. Searches retrieved 5,639 references, which were reduced to 4,265 references when duplicates were removed. Following screening by the 2 independent reviewers, a total of 129 potentially relevant references were identified and fully assessed against the inclusion criteria. Finally, 11 independent systematic reviews and meta-analyses were included. A summary of the characteristics of the systematic reviews included in this study is presented in Table 1.

#### Characteristics of Included Reviews

The included systematic reviews conducted literature searches between May 2009 and December 2013. All reviews included participants with chronic IHD (CIHD) and HF. Three reviews also included participants with AMI or acute coronary syndrome (ACS).13,14 The number of trials included in the systematic reviews ranged from 5 to 50. All systematic reviews included RCTs, and 11 also included RCTs and cohort studies. Sadat et al (2014)14 was included despite lacking controls for some of their included trials. This was decided because studies lacking the control arm accounted for less than 5% (99 participants) of the total number of participants in the systematic review. All systematic reviews included trials where cells were delivered intramyocardially (IM); 8 also included trials that administered the treatment via the coronary arteries (IC). 

The included systematic reviews evaluated data obtained from between 179 and 2,625 participants. There was a core group of trials that were covered by 7 or more of the 11 included systematic reviews.

The included systematic reviews included trials that were covered by 7 or more of the 11 included systematic reviews; 20–26 These studies were all RCTs of bone marrow mononuclear cell (BMMNC) therapy for CIHD. A summary of the trials included in each review is shown in Table S2. All reviews included LVEF as an outcome; only 9 reviews included death or major adverse cardiac events (MACE).10,11,13,15–18,27,28 Five reviews included HF or rehospitalization because of HF as outcomes.10,11,13,16,27

The 11 systematic reviews included in this study present data from trials with different clinical settings and co-interventions;
Table 2. Quality Assessment of the Included Reviews (AMSTAR Score)

<table>
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</thead>
<tbody>
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<tr>
<td>Characteristics of included trials provided</td>
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<tr>
<td>Quality used appropriately in conclusions</td>
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<td>Method of combining findings provided</td>
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<td>7</td>
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<td>7</td>
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</tbody>
</table>

Figure 2. Forest plot of mean difference of left ventricular ejection fraction (LVEF) in response to cell therapy relative to controls from included reviews. All included reviews present data following a random effects model. SC, stem cells; CI, confidence interval; n/r, not reported. For studies that stratified results for different follow-up time points (ST, short term; MT, medium term; LT, long term), these are presented separately (Fisher 2014: ST, <12 months; LT, ≥12 months; Jiang 2010: ST, ≤3 months; MT, 3–6 months; LT, ≥12 months; Zhao 2011: ST, 3–4 months; LT, ≥6 months).
3 systematic reviews included patients with HF or AMI. In addition to this, 2 reviews only included trials that reported revascularization as a co-intervention administered concomitantly to cell therapy. These was either a surgical intervention (eg, coronary artery bypass graft [CABG]) or percutaneous coronary intervention (PCI).

Systematic reviews varied in how they incorporated the different lengths of follow-up used in individual trials in their synthesis of data. Four reviews combined data across trials using the longest follow-up time point provided in each trial, and another 4 reviews selected 6 months follow-up data when multiple time points were available. One systematic review excluded long term data and only analyzed up to 6 months’ follow-up data. Three systematic reviews carried out separate meta-analyses based on the length of follow-up, defined as shorter or longer than 12 months, at 3–4 or 6 months or at 3, 6 and ≥12 months.

Quality of the Evidence

The quality of the systematic reviews and meta-analyses included in this study was estimated by the AMSTAR score (Table 2). All had an ‘a priori’ design, undertook a comprehensive search of the literature, provided characteristics of the included studies, documented the quality of the included trials and provided the methods used to combine findings. All reviews had 2 independent reviewers conducting the study selection and data extraction; however, 3 reviews did not have a procedure in place for reaching a consensus when disagreements arose and Sadat et al (2014) did not report whether they had a consensus procedure or not. Only 6 studies included the status of publication as an inclusion criteria, and one review did not report the status of publication of the included studies. In addition, 4 reviews excluded trials on the basis of language or publication status. All reviews presented a list of included studies, and all but one omitted the list of excluded studies. Only one study did not assess the scientific quality of the included studies when drawing conclusions. That study did not critically highlight the limitations of the systematic review or the included trials (eg, statistical heterogeneity). Only one review included details of funding support for their study and for the included trials. Publication bias was assessed using appropriate statistical methods in 5 reviews.

One systematic review had an AMSTAR score of 6, the lowest score obtained across all included systematic reviews. Jeewanantham et al (2012) did not describe how disagreement procedures were solved, excluded trials on the basis of language, did not provide a list of excluded trials or conflict of interest of the included trials and did not assess publication bias according to the criteria of AMSTAR. One review had an AMSTAR score of 11. Unlike the other studies, this was the only Cochrane systematic review, published in the Cochrane Library database, where restrictions such as number of pages and word count do not apply, and where all conflicts of interest and excluded studies can be easily accommodated.

The key findings of the included systematic reviews and meta-analyses are shown in Table S3.

Primary Outcomes

LVEF All systematic reviews but one demonstrated a moderate but significant improvement in LVEF in favor of cell treatment, with a mean difference in change from baseline between groups ranging from 2.6% to 5.6% (Figure 2). Of note, the CIs from all analyses overlapped within the range of 3.47% and 4.182%, with the smallest CI obtained from the systematic review with the highest AMSTAR score from meta-analysis of 18 trials at short term follow-up. Interestingly, the effect size estimate from this Cochrane review (MD 4.22%) was consistent with the CIs from all other systematic reviews, with the exception of the short term follow-up analysis of Jiang et al (2010), which had an upper confidence limit of 4.18%.

Three systematic reviews included trials for both CIHD and AMI or ACS and pooled data from these studies for their primary meta-analysis. In subsequent subgroup analysis, 2 reviews suggested that cell therapy significantly improved LVEF in AMI patients but not in CIHD patients. This may be related to the number of included trials for each clinical setting; there were only 4 CIHD studies compared with 14 for AMI in one of the reviews. Although the mean difference in change from baseline LVEF was similar between the AMI and CIHD groups (3.29% and 3.47%, respectively), the 95% CIs were wider for CIHD (2.40–4.55 for AMI, −2.39–8.97 for CIHD). Mean difference values were similar in both clinical
settings as analysed by Sadat et al (2.8% for ACS and 3.0% for CIHD). In their review, meta-analysis restricted to 12 CIHD trials showed that cell therapy had a positive effect on LVEF, but 4 of the CIHD studies lacked control participants and the variation in the number of controls that were included was also large. The remaining review showed a larger treatment effect on LVEF in CIHD than in AMI, but no significant differences were noted between the 2 subgroups. Three reviews included cell therapy trials for CIHD and HF and pooled them in their primary meta-analyses, 2 of which carried out subgroup analysis to compare CIHD and HF. Both reviews found a significant improvement in LVEF associated with cell therapy in patients with CIHD and in those with HF, with the greatest improvement observed for HF. There was a substantial degree of variation in how each of the systematic reviews defined the length of follow-up. Three reviews conducted separate meta-analyses according to the length of follow-up, and 3 other reviews conducted subgroup analyses to assess the effect of cell therapy according to the length of follow-up following the primary meta-analyses. As mentioned above, Cheng et al (2013) found no significant differences in LVEF between treatment groups. Furthermore, no significant differences in LVEF were observed at either 6- or 12-month follow-up. The remaining 5 reviews reported a significant improvement in LVEF in favor of cell therapy at all follow-up time points. One review excluded follow-up ≥12 months and reported that LVEF improved at 3–4 months and 2–6 months follow-up. By contrast, another review reported separate meta-analyses for follow-up at 3, 6 and ≥12 months. One review reported results separately for ≤12 months and >12 months follow-up and another conducted subgroup analysis for length of follow-up at 3–6 months and 12 months. The remaining review reported meta-analyses with follow-up time points defined as 0–3 months, 4–6 months, 7–12 months, 13–24 months and >24 months. These provided mixed results on which follow-up time point gave the most significant improvement in LVEF in response to cell therapy. However, it is difficult to make direct comparisons because the contributing systematic reviews included trials that performed different interventions and treated patients with different clinical diagnosis (eg, AMI, CIHD, HF).

Death Nine systematic reviews reported death as a single or combined outcome, 4 of which estimated the RR for death as a single outcome, including 1 study that reported results separately for short and long term follow-up (Figure 3). Of these 5 meta-analyses, 3 (long term data including 1 study that reported results separately for short and long term follow-up) observed a significant reduction in the risk of death associated with cell treatment. Two reviews reported no change in mortality rate in response to cell therapy but did not report the RR. Three reviews reported death as a major adverse event combined with other outcomes such as HF. No significant differences in major adverse events were associated with the treatment in any of these reviews.

When reporting deaths, all reviews but one combined data from all studies without discrimination of the length of follow-up. There was a substantial variation in the length of follow-up included in individual meta-analyses, which ranged from 3 to 60 months.

Secondary Outcomes NYHA Functional Classification and Rehospitalization Because of HF One review reported a significant increase in odd ratios for improvement in NYHA class in favor of cell therapy, and another reported a direct improvement in NYHA class from baseline in cell-treated participants compared with controls. However, neither study identified a significant difference in the incidence of rehospitalization for HF. By contrast, a third review reported improved NYHA class associated with cell therapy at both short and long term follow-up and a significant decrease in the incidence of rehospitalization for HF in the long term (>12 months). Another review confirmed a significant reduction in the incidence of HF in favor of cell treatment. No significant difference in the incidence of rehospitalization for HF was observed in 2 reviews.

QOL and Exercise Tolerance Two reviews reported a significant improvement in QOL (measured by the Minnesota Living with Heart Failure Questionnaire) in treated patients compared with controls. Both reviews also reported exercise tolerance measured by 6-min walking distance, but although one review noted a significant difference in mean change from baseline in favor of cell therapy (81.85 m), the second review observed no significant difference in mean change from baseline between treated and control participants. The positive effect of cell therapy on QOL was supported by findings from a third review, which demonstrated a significant improvement in exercise capacity at short term follow-up (<12 months) in favor of the treatment.

Adverse Effects In all reviews that reported adverse events it was found that cell therapy did not lead to an increased incidence of events such as in-stent restenosis, in-stent thrombosis or cerebrovascular accidents. Jeevanantham et al (2012) noted a significantly decreased risk of developing in-stent thrombosis (RR 0.34) in favor of cell therapy. None of the 8 reviews that investigated the incidence of arrhythmia as an adverse effect detected any significant difference between treatment and control.}

Discussion

This study presents the first overview that collates and synthesizes data from systematic reviews and meta-analyses on cell therapies for HF. It is based on a comprehensive search strategy and conducted according to the principles and methods described in the Cochrane handbook of systematic reviews. Our search identified 11 systematic reviews and meta-analyses of HF published between 2010 and 2014. In the present study, we set out to assess the quality of the current evidence and defined 2 key questions: (1) What is the overall effect of cell therapies on primary outcomes such as left ventricular ejection fraction (LVEF) and mortality? (2) How important is it to define the clinical setting and the length of follow-up when assessing cell-based therapies for heart disease?

The systematic reviews and meta-analyses included in the present study were assigned AMSTAR scores between 6 and 11, indicating that they were of moderate to high quality. Surprisingly, only one review was awarded a score of 11; this was a Cochrane systematic review that abided by strict guidelines and methodology and had the benefit of no space limitations for additional data to be included.

The overall effect of cell-based therapies on LVEF seems consistent across systematic reviews and meta-analyses and ranged from 2.6% to 5.6%, despite the differences among the reviews in eligibility criteria and methodology. Only one of 11 reviews reported no significant improvement in LVEF. That review included only 5 trials and a total of 151 participants, which represented 10% of the number of studies included in the largest systematic review (50 trials). Notably, this moderate improvement in LVEF in favor of cell therapies emerged (1) irrespective of baseline LVEF, (2) when compared with controls and (3) in addition to current treatments, such as med-
Cell Therapies for HF

ical treatment and revascularization, which are administered to all participants. Clearly, cell-based therapies were not being assessed as stand-alone treatments in the included systematic reviews, indicating that the improvement of LVEF over current treatments may be promising and clinically relevant. Although all reviews included participants with IHD, not all participants were selected on the basis of a baseline LVEF cut-off. Baseline LVEF has been documented as a predictor of treatment effect.10 In the included trials, baseline LVEF varied greatly (from 21% to 62%), suggesting that a larger treatment effect may be more apparent if patient selection is included in future trial designs.

Improvement in global LVEF has been directly correlated with improved long-term survival in patients with LV dysfunction. The available data from the reviews included in this study suggest that cell therapy is safe, because they consistently report the lack of adverse events and no increase in mortality rates. The fact that 3 reviews reported a significant reduction in the risk of death in favor of the treatment may be also promising. However, in our opinion, there is not enough evidence from the included systematic reviews that cell-based therapies have an overall beneficial effect on survival.

There are several important limitations associated with the systematic reviews and meta-analyses, which include, but are not limited to, pooling together trials from different clinical settings, sample size, the inclusion of RCTs and nonRCTs in the same review, the high degree of unexplored heterogeneity and duplication, estimation and misreporting of data.

One of the major limitations of the included systematic reviews is that data from trials assessing cell-based therapies in different clinical settings (eg, AMI and CHD or HF) were pooled in combined meta-analyses. Evidently, mortality rates are very different in patients diagnosed with AMI and treated for revascularization compared with patients diagnosed with more severe HF. Therefore, the effect size estimates from those systematic reviews on overall clinical efficacy may be meaningless. These results should be taken with caution and need to be confirmed in appropriately powered clinical trials. We can conclude that it is important to define the clinical setting when discussing cell-therapy trials for heart disease. Clinical trials are designed to treat a particular syndrome or disease (eg, ACS, AMI, refractory angina, etc). Therefore, when synthesizing clinical evidence in a systematic review or meta-analysis, the same principle should apply. Justifiably, this may reduce the number of clinical trials assessed and may reduce statistical power. However, this could achieve (1) a reduction in clinical and statistical heterogeneity in the analyses, and (2) a more accurate measure of the treatment’s effect size.

Several of the systematic reviews included a small number of trials, and many of the trials had relatively small numbers of participants. This is particularly apparent for 1 review,27 which only included 5 trials. In this trial, meta-analyses of the less commonly reported outcomes, such as 6-min walking distance and NYHA functional class yielded comparisons between 2 trials. Although these issues were highlighted by the authors, caution should be taken when assigning clinical relevance to these findings. The largest number of trials included in a systematic review was 50.11 The potential increase in statistical power resulting from the high number of included trials in that review is confounded by the substantial degree of clinical and statistical heterogeneity (I^2=81%), most likely related to differences in diagnosis (both AMI and CHD), duration of follow-up (ranging from 3 to 60 months) and/or baseline cardiac function (mean LVEF between 21% and 62%).

In 3 systematic reviews, data from RCTs and nonRCTs were pooled in their meta-analyses.11,14,15 Six reviews conducted meta-analyses pooling data from trials with participants suffering from CHD and AMI11,13,14 or CHID and HF,10,17,27 However, all but 1 review27 conducted subgroup analysis to identify the importance of the clinical setting on LVEF.

Six systematic reviews included trials with multiple intervention arms and a single comparator group (control or placebo).10,11,16–19 Four of those reviews included multiple intervention arms in their meta-analyses and duplicated the control group.10,16–18 Furthermore, 1 systematic review11 included data from 2 publications,3,12 which in fact described the same trial with the same participants. This review13 and 5 others15,16,18,19,28 also included a trial that we have previously deemed to lack appropriate randomization and therefore should not be classed as an RCT.10

Several reviews used estimation methods to obtain the required data for meta-analyses, including estimating means and standard deviations from median values, and estimating mean change from baseline data where only baseline and endpoint data are reported. These estimated data may introduce a risk of bias, the extent of which is unclear.

It is also important to define the length of follow-up to assess whether the treatment has a short or long-lasting effect, as some trials suggested that the effect of cell therapies on LVEF was temporary.14 Six reviews included in this study examined the effect of cell therapies on LVEF at different lengths of follow-up,10,11,13,17,19,27 Of note, 5 of those systematic reviews showed significant improvement in LVEF in favor of cell therapy at all follow-ups,10,11,13,17,19 suggesting a sustained beneficial effect of cell therapies on LVEF. However, systematic reviews that assessed mortality as a primary outcome combined data from short and long term follow-up. In view of the current data from individual trials, a moderate improvement in LVEF cannot explain the positive effect on mortality rate that some systematic reviews and trials have observed. Therefore, it may be beneficial for further reviews and trials to better define the length of follow-up in their methods (eg, 0–6 months, 7–12 months and ≥13 months) to assist comparisons of major outcomes and between systematic reviews and meta-analyses.

Clinical and statistical heterogeneity seems to be present to a substantial degree in both trials and systematic reviews, suggesting that care should be taken during the design of trials, and that the questions to be addressed in systematic reviews should be carefully considered in order to minimize such heterogeneity. Perhaps then, the assessment of cell therapies as treatment for HF and the evidence for their clinical effect will become more apparent. Systematic reviews allow the pooling of clinical data to increase participant numbers and add statistical power to the defined outcomes. This is essential for forming critically assessed opinions on emerging novel therapies. Reliable, unbiased opinions are needed for EBM to develop the best possible treatments for patients. Therefore, systematic reviews must be robust and comply with guidelines to avoid the production of misleading information. A core part of this is to correctly present all data and detailed methodology and trial authors themselves should be forthcoming with clarification when discrepancies are identified or when data queries arise. Ultimately, trialists should be prepared to disclose individual patient data so that the gold standard of meta-analysis can be performed.

In summary, the present study describes a systematic approach to assessing the current clinical evidence of cell therapies as treatment for HF in order to answer 2 key questions about the efficacy of the treatment. Despite the publication of 11 systematic reviews of cell-based therapies in HF, the qual-
ity of the evidence could be improved and the heterogeneity reduced by standardizing the methods used.

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Disclosures

The authors have none to declare.

References


Supplementary Files

Supplementary File 1

Table S1. Assessment of multiple systematic reviews (AMSTAR) questionnaire

Table S2. Trials included in each systematic review

Table S3. Main findings of the included systematic reviews

Please find supplementary file(s) at http://dx.doi.org/10.1253/circj.CJ-14-1415