Bone marrow (BM)-derived cell therapy for the damaged heart has now been under investigation for almost 2 decades. Right from the outset, both in vitro and in animal models of cardiac damage, early studies using BM-derived cells showed incredible promise and reported numerous broadly positive findings, driving enthusiasm for the clinical translation of this approach. To mention just a few of those early studies, findings from the late 1990s included the successful differentiation of BM stromal cells into cardiomyocyte-like cells; increased angiogenesis and the formation of cardiomyocyte-like cells in vivo when BM-derived cells were injected into the scarred left ventricular (LV) wall; and the identification that the BM is a reservoir for circulating endothelial progenitor cells that contribute to new vessel formation in the adult. Then, in 2001, it was reported that the intravenous administration of human CD34+ BM-derived cells into immune-deficient rats after acute myocardial infarction (MI) led to the proliferation of pre-existing vasculature and de novo new blood vessel formation in the infarct bed, which contributed to the salvage of viable myocardium and dramatic improvements in LV ejection fraction (LVEF).4 Reduced infarct size, and improved survival in an animal model.6

With these and other remarkable preclinical studies appearing in rapid succession, clinician scientists were swift to begin investigating BM-derived cells to ameliorate cardiovascular disease in humans.7 Indeed, still in 2001, what we think to be the first human report of the use of BM-derived cells in patients with ischemic heart disease appeared in the literature.8 Even though only a pilot with 5 subjects, this study suggested safety and the potential for clinical benefit from BM-derived cells, with improved coronary perfusion observed in 3 of the 5 patients.9

In an attempt to integrate and analyze these many studies of BM-derived cell therapy in patients with ischemic heart disease, a series of meta-analyses were conducted during the past several years. The pattern of the results and conclusions of these meta-analyses has been not dissimilar from that seen in the original studies; that, the previous and even many of the more recent meta-analyses were generally positive in their findings,13,14 The largest of these appeared in 2012 and included 50 studies with 2625 subjects and reported that compared with controls, BM-derived cell therapy was associated with a 3.96% absolute improvement in LVEF, smaller infarct size, and reduced all-cause and cardiac mortality.17 These results warrant cautious interpretation, however, as this analysis combined randomized and cohort data, and documented substantial heterogeneity in the overall treatment effect. A subsequent meta-analysis that only included randomized controlled trials (RCTs) demonstrated a comparable effect with a 2.55% absolute improvement in LVEF, yet also reported significant heterogeneity across studies.19 These limitations notwithstanding, as recently as just ≈18 months ago, for all practical purposes it appeared that the benefits of BM-derived cell therapy were clear and that this approach only required confirmation of efficacy in a phase-III study before it could be widely implemented in the clinic.
and contradictions in the BM-derived cell therapy literature.\textsuperscript{21} This was followed by a weighted regression and meta-analysis from the same group.\textsuperscript{22} In this second article, it was again concluded that discrepancies and inconsistencies were common in the BM-derived cell therapy literature, with 600 discrepancies in 133 reports from 49 trials. Furthermore, there was a significant association between the number of discrepancies and the reported increment in LVEF with BM-derived cell therapy, and that only 5 trials had no discrepancies; among these trials, the mean LVEF effect size was −0.4%.\textsuperscript{22} A third negative report appeared with the meta-analysis of de Jong et al.\textsuperscript{23} When de Jong et al\textsuperscript{23} focused strictly on RCTs of BM-derived cells in the post-MI period that had LV functional end points defined by MRI, rather than the less sensitive measures of LV angiography or echocardiography as was used in many of the previous studies, there was no effect on cardiac function, volumes, or infarct size. Moreover, de Jong et al\textsuperscript{23} found no beneficial effect of BM-derived cell therapy on major adverse cardiac and cerebrovascular event rates after a median follow-up duration of 6 months.\textsuperscript{23} Suddenly, the efficacy of BM-derived cell therapy had been thrown into question.

Although it is possible to debate the relative merits of these many positive and negative meta-analyses and their findings and while in no way belittling the significant efforts that went into these studies, they all have the significant limitations inherent in study-level meta-analyses that are conducted using aggregate or statistical summary data. As a critical aspect of this statistical approach, individual patient data (IPD) are not obtained or used for a study-level meta-analysis, and all of these studies simply extracted the summary study data from the original individual publications or occasionally sourced them directly from the original investigators\textsuperscript{18} and then proceeded to estimate a pooled treatment effect using these aggregate data.

The limitations of study-level meta-analyses are significant. Indeed, one of the major concerns with study-level meta-analyses is that in trials using repeated measures (ie, LVEF at baseline and follow-up), it is critical to account for the relationship within each subject of these repeated measures. In other words, there is a relationship for each subject between their baseline and follow-up LVEF (and other functional measures) and it is important to account for these intrasubject correlations between time points. However, in a study-level meta-analysis, these intrasubject relationships are ignored.\textsuperscript{24} Furthermore, the amount of missing data at the patient level can further affect these analyses,\textsuperscript{24} and in a study-level meta-analysis, this aspect is again ignored. Moreover, the absence of patient-specific covariates (eg, age) makes standard analytic techniques, such as multivariable regression or examining treatment effects in subgroups challenging, if not impossible at times.\textsuperscript{25} This again is of specific relevance to BM-derived cell therapy, as several claims were made in these study-level meta-analyses of benefits in certain subgroups, such as those with low baseline LVEF.\textsuperscript{15–20} Finally, all of these problems are amplified when a high level of heterogeneity is present among the individual trials—a fact that has been widely acknowledged in the BM-derived cell therapy literature.\textsuperscript{16–19}

Until the meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) of Gyöngyösi et al\textsuperscript{26} published in this issue, there has never been a patient-level meta-analysis of cell therapy (performed using IPD). In brief, for a patient-level meta-analysis, the original data for each individual trial subject are sourced from the primary investigators, harmonized in a common data set, and then analyzed. Although not a substitute for a phase-III RCT, a patient-level meta-analysis overcomes many of the limitations of a study-level approach and is acknowledged as the gold standard methodology for meta-analyses.\textsuperscript{25} However, the challenge with patient-level meta-analyses is that the time, effort, resources, and cost involved are increased exponentially over that of study-level analyses. To their great credit, in 2007, the ACCRUE consortium of investigators was formed to set about the task of gathering and harmonizing IPD from cardiovascular cell therapy studies to perform patient-level meta-analyses.\textsuperscript{26} The criteria for participation in ACCRUE were that the data must be from randomized or cohort clinical studies and that the study involved percutaneous administration of cells or cell-based products, or cytokine mobilization of BM cells, administered with the aim of ameliorating cardiac disease. Importantly, their definitions, end points, and rigorous statistical analysis plans were established prospectively. According to defined terms and conditions, centers and principal investigators were invited to contribute their study data, and the ACCRUE data set now includes 1871 IPD sets from 28 studies.\textsuperscript{26}

Using this gold standard patient-level meta-analysis approach, for the present analysis, the ACCRUE investigators focused on IPD from 12 RCTs of intracoronary cell therapy after acute MI, with a combined total of 767 patients who received cell therapy and 485 controls. The authors appropriately considered study-level effects in their analytic approach by

\textbf{First Generation: BM-derived cell injection}

intra-coronary or intra-myocardial injection

\textbf{Second Generation: Cardiac-derived cell injection}

Purified, specific cardiac-derived populations obtained by biopsy or surgery

\textbf{Third Generation: in situ cell reprogramming, cardiomyocyte dedifferentiation, or stimulation of endogenous cardiac stem cells}

\textbf{Figure.} Author’s impression of current status of cell therapy studies to ameliorate cardiac damage and for cardiac regeneration. BM indicates bone marrow.
stratifying their analyses by trial, thereby generating a singular pooled treatment effect. Unlike previous study-level meta-analyses, Gyöngyösi et al26 found, in summary, no significant effect of cell therapy on either (1) the combined primary end point of freedom from major adverse cardiac and cerebrovascular events and death; (2) another combined end point of freedom from death, re-MI, or stroke; (3) freedom from death alone; (4) freedom from major adverse cardiac and cerebrovascular events alone; and (5) cardiac functional outcomes (LVEF, end-diastolic volume, and end-systolic volume). Furthermore, no predictive factors, subgroups, patient characteristics, or other factors were identified that were associated with a positive effect of cell therapy.26 It is important to note that the overall treatment effect on the end point of major adverse cardiac and cerebrovascular events was in a direction of benefit (hazard ratio, 0.88) and imprecise with a 95% confidence interval between 0.63 and 1.18. As a result, the possibility of more modest, yet clinically meaningful benefit from such therapy cannot be completely excluded based on these findings.

Like any landmark study, this patient-level meta-analysis has raised more questions than it answered. What it has clearly demonstrated is that using the most rigorous statistical methods available, when the bulk of the previous data from well-conducted randomized cell therapy studies are combined, we may conclude that intracoronary cell therapy is safe but that it offers no functional or clinical benefits. Although disappointing, the consistency of the findings across a range of end points, subgroups, and patient characteristics is compelling. We think it would be unlikely that another group would now attempt to perform another patient-level meta-analysis of these data, and therefore, the question of the use of intracoronary cell therapy based collectively on the heterogeneous studies conducted to date has now been put to rest: negative.

As for the questions raised by Gyöngyösi et al,26 there are many. To first critique the study itself and as a limitation of all meta-analyses, it must be acknowledged that unique design aspects of individual original studies that were aiming to tease out potential beneficial effects in certain patient or cell subgroups may have been lost in the larger analysis. On this note and although we unreservedly applaud the efforts of the ACCRUE investigators, we question the rationale for the inclusion of the CArdiosphere-Derived aUtologous stem CElls (CADUCEUS) study27 in this meta-analysis. CADUCEUS reported positive findings and was the only study in this meta-analysis to inject cardiospheres-derived cells.27 Cardiosphere-derived cells are unique in that they are derived from the heart and not the BM as with all other studies in this meta-analysis. Therefore, it could be said that including CADUCEUS in this meta-analysis is somewhat akin to grouping together apples and oranges. Nevertheless, CADUCEUS was the smallest of all studies included in this meta-analysis (25 subjects of the 1252 analyzed, or only 2%),27 and it is unlikely that it would have significantly affected the overall results. Therefore, for practical purposes, we view the results of this ACCRUE meta-analysis as applying to BM-derived cell therapy. Further possible limitations include the potential for selective inclusion of studies in this analysis. Of the 55 studies deemed eligible for inclusion, only 28 ultimately provided IPD. Thus, only about half of the potentially eligible datasets were included. One is left to wonder if there may have been any biases at play in the decision to submit, or decline to submit, data to the ACCRUE database. However, the majority of the potentially eligible post-MI studies that were not included were relatively small, with a mean of 27 patients in the cell therapy arm and 19 controls when compared with a mean of 64 active study patients and 40 controls for the studies included in ACCRUE. Therefore, it certainly seems that the ACCRUE investigators have made every effort to obtain as much meaningful IPD as possible and that their data set represents the most comprehensive set of cell therapy studies that are likely to be collected, harmonized, and analyzed in this way.

Some will also ask “why did intracoronary cell therapy not show a benefit?” We think there are many possible reasons. To begin with, there are a myriad of potential explanations related to cell type, cell handling and preparation, cell dose, recipient milieu (eg, inflammatory status, timing after MI, and cell homing signals), recipient age, mode of cell delivery, need for multiple cell deliveries, selection of end points, and more. However, there are also many examples of therapies that appeared promising in animal studies, but which failed in the clinic. Perhaps, based on these initial studies, we must be at least prepared to conclude that this first generation BM-derived cell therapy approach may offer no benefit.

Another critical question raised and perhaps the most pressing is “where does this leave the cell therapy field?” As for BM-derived cell therapy, all eyes will now turn to the BAMI study (The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells [BM-MNC] on All Cause Mortality in Acute Myocardial Infarction). BAMI is a multinational, multicenter, phase-III RCT that has been underway for over a year and which aims to demonstrate that the intracoronary administration of autologous BM-derived mononuclear cells is safe and reduces all-cause mortality in patients with reduced LVEF after successful reperfusion for acute MI.28 BAMI aims to recruit 3000 subjects which, notably, is almost 2.5x the total number of subjects in the present meta-analysis of Gyöngyösi et al.26 The BAMI design is based on the original REPAIR-AMI study,5 which showed a beneficial effect in just >200 subjects (and which was included in this ACCRUE meta-analysis). BAMI is expected to complete enrolment in 2017 and to report findings in 2018.27 BAMI will certainly be a pivotal clinical study and, positive or negative, will have a major impact on the field. Beyond BAMI, there remains much to be excited about in the cell therapy arena. Already, what we consider to be second generation cell therapies are being tested in the clinic. As we mentioned, cardiosphere-derived cells have shown promise,27 as too have other novel populations, such as c-kit+ cardiac progenitor cells.28 Furthermore, researchers are already working to refine what we think will be the third generation of studies, based on cell reprogramming, cardiomyocyte dedifferentiation, or in situ stimulation of endogenous cardiac stem cells (Figure). While only time will tell, we think the findings of this laudable meta-analysis by Gyöngyösi et al26 represent the inevitable one step back on the way to taking 2 steps forward.

Acknowledgments

J. Kovacic acknowledges research support from National Institutes of Health (K08HL111330), AstraZeneca, the American Heart

**KEY WORDS:** meta-analysis ■ myocardial infarction ■ stem cells
Cell Therapy For Patients With Acute Myocardial Infarction: ACCRUEd Evidence to Date

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doi: 10.1161/CIRCRESAHA.115.306323

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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