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INTERVENTIONAL CARDIOLOGY (S RAO, SECTION EDITOR)

# Current State of Stem Cell Therapy for Ischemic Heart Disease

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**Abstract** Improvements in the care of patients with ischemic cardiovascular disease have led to improved survival but also a burgeoning population of patients with advanced ischemic heart disease. Cell therapies offer a novel approach toward cardiac "rejuvenation" via stimulation of new blood vessel growth, enhancing tissue perfusion, and via preservation or even regeneration of myocardial tissue, leading to improvements in cardiac performance after myocardial infarction and in patients with advanced heart failure. Here, we summarize and offer some thoughts on the state of the field of cell therapy for ischemic heart disease, targeting three separate conditions that have been the subject of significant clinical research: enhancing left ventricular recovery after MI, improving outcomes and symptoms in patients with congestive heart failure (CHF), and treatment of patients with refractory angina, despite maximal medical therapy.

**Keywords** Stem cells · Progenitor cells · Ischemic heart disease · Coronary artery disease · Refractory angina · Congestive heart failure

## Introduction

The survival rate of patients with ischemic heart disease no longer amenable to conventional therapies has increased due to the implementation of highly successful programs to accelerate treatment of acute myocardial infarction (MI), rapid improvements in technologies to treat ischemic heart disease, and development of novel therapies with mortality benefits for patients with congestive heart failure (CHF). Patients with refractory angina are characterized by advanced ischemic heart disease not amenable to revascularization with largely preserved left ventricular (LV) function. These patients have mortality rates similar to those with chronic stable angina (2–4 % per year) [1-3], but are highly symptomatic, requiring frequent use of medical resources including hospitalizations. In contrast, patients with reduced ejection fraction (EF) and symptoms of HF have poorer overall prognosis. Despite these differences, both of these populations represent the significant and growing number of patients with advanced ischemic heart disease in need of new treatment opportunities. Current medical therapy offers some hope; however, it is largely targeted at stabilization of disease and prevention of further deterioration in function. In contrast, regenerative therapies offer new possibilities by providing additional external reparative capacity or by augmenting and stimulating native cell-mediated repair [4-6]. These therapies might affect repair and subsequent reversal of the underlying condition.

There is evidence that native cell-mediated repair is an important process in maintaining homeostasis and tissue integrity. In primitive organisms, regeneration of myocardium indistinguishable from native heart tissue is accomplished after resection of up to 25 % of the left ventricle, but this remarkable cardiac regenerative capacity has been lost in mammalian species [7]. In sex-mismatched cardiac transplant recipients, native host cells that have integrated and presumably transformed into not only endothelial and supportive cells but also cardiac myocytes have been identified by several research groups [8, 9]. More

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recently, rare isotope tracing has been used to demonstrate that low but measurable levels of cardiac regeneration occur throughout adulthood, leading to replacement of almost 50 % of heart tissue with "regenerated" myocardium over the life of an individual [10•]. These observations suggest that continuous myocardial regeneration occurs in humans; however, in order to make this process clinically meaningful, the biology must be understood and applied.

Circulating progenitor cells have been measured and demonstrated in peripheral blood sources [11-14], and mobilization of these cells at times of injury would provide additional exposure of injured myocardium to cells with regenerative capacity [15-17]. As these cells circulate continuously in the myocardium, exposure to these stem cells, even those present at very low levels (0.1 %), far outpaces the dose of stem cells administered in clinical studies. For instance, with a resting coronary blood flow of 250 mL/min, the myocardium is conservatively exposed to approximately 250,000 circulating $CD34^+$ or $CD133^+$ stem cells per minute. How or why the administration of additional similar stem cells might enhance repair is unclear; however, preliminary data are encouraging.

Administration of endogenous cells might more effectively lead to repair via a variety of mechanisms. For instance, cells are most frequently administered by direct injection into the myocardium. Although the heart is exposed to circulating stem cells on a regular basis, these cells may not transit from the circulation effectively if at all, and thus may not localize to myocardial tissue or areas of injury. Second, chronically circulating stem cells are unlikely to be identical to cells used in cell therapy trials. Administration of a purified cell product of concentrated $CD34^+$ cells has been shown to be more effective than an equal dose of $CD34^+$ stem cells in an unpurified state, suggesting that isolation/concentration of stem cell products might be an important step to improving efficacy [18, 19].

As the field evolves, stem cells being tested are increasingly not only purified populations but cells that have been modified to improve their angiogenic or cardiotherapeutic potential [20••, 21•, 22•]. These "second" and "third" generation stem cell products may streamline administration and enhance efficacy of cellular products, leading to the type of regeneration that has drawn such interest.

We summarize and offer some thoughts on the state of the field of cell therapy for ischemic heart disease, targeting three separate conditions that have been the subject of significant clinical research: enhancing LV recovery after MI, improving outcomes and symptoms in patients with CHF, and treatment of patients with refractory angina, despite maximal medical therapy.

## Myocardial Regeneration After Myocardial Infarction

### Unselected Bone Marrow Cells

Although small feasibility studies with direct surgical injection of bone marrow cells (BMCs) into the myocardium were the initial forays into the field of cardiovascular stem cell therapy [23-26], the first significant and largest clinical experience targeted recovery of myocardium acutely post-infarction [27]. After initial proof-of-concept studies, the BOne MarrOw Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial was the first meaningful randomized study demonstrating an improvement in EF at 6 months [28], although this benefit was no longer apparent at 18-month follow-up [29]. These initial studies stimulated great interest, and perhaps unrealistic expectations, about the use of unselected BMCs to enhance myocardial recovery and regeneration post-MI, and led to a series of largely single- and oligocenter trials of variable size and design to assess the efficacy of this therapy [28, 30-35, 36••, 37, 38••, 39•]. The results of these trials were highly variable, with many reporting no efficacy while others demonstrated immediate and lasting improvements in LV function in patients treated with cell therapy. The variability in results has prompted great debate among scientists in the field, and variables such as cell preparation [40], method of administration, and likely inherent variability in an autologous product each contribute to the efficacy of the therapy and may be responsible for some of the differences in results.

Under the auspices of the National Institutes of Health, the Cardiovascular Cell Therapy Research Network (CCTRN) was organized to conduct cell therapy multicenter studies in the USA. Two of the three trials completed during the first round of funding (2006–2012) sought to provide a definitive answer to the question of this mode of therapy. Using a standardized cell isolation approach and magnetic resonance imaging (MRI) to assess infarct size and EF, the Effect of the Use and Timing of Bone Marrow Mononuclear Cell Delivery on Left Ventricular Function after Acute Myocardial Infarction (TIME), [39•, 41] and the Phase II, Randomized, Double-Blinded, Placebo-Controlled, Pilot Trial Evaluating the Safety and Effect of Administration of Bone Marrow Mononuclear Cells 2 to 3 Weeks after Acute Myocardial Infarction (LATE-TIME) [38••] trials assessed the efficacy of bone marrow stem cell therapy in the days (TIME) and weeks (LATE-TIME) post-MI. These trials showed no benefit for this therapy in improving EF, LV dimensions, or wall motion scores.

The congruity of endpoint assessment (the primary endpoint for all of these trials was change in EF), the common patient populations enrolled, and the relatively similar trial designs employed (intracoronary administration of unselected BMCs) make this topic ideally suited to meta-analysis of the

**Table 1** Meta-analysis of effect of EF of stem cell therapy for ischemic heart disease and/or acute MI

| Source | Studies | Patients | Patient substrate | Trial designs | Change in EF | *P* value |
|---|---|---|---|---|---|---|
| Hristov et al. (2006) [48] | 5 | 482 | AMI | RCT | 4.21 | <0.04 |
| Abdel-Latif (2007) [47] | 20 | 976 | IHD | RCT, cohort | 3.66 | <0.001 |
| | | | AMI | RCT, cohort | 3.95 | |
| | 14 | 807 | IHD | RCT | 3.64 | <0.001 |
| Lipinski et al (2007) [46] | 10 | 698 | AMI | RCT, cohort | 3.00 | <0.00001 |
| Martin-Rendon et al. (2008) [49] | 13 | 715 | AMI | RCT | 2.99 | =0.0007 |
| Jeevanantham et al. (2012) [45•] | 50 | 2625 | IHD | RCT, cohort | 3.96 % | <0.00001 |
| | 36 | 1751 | IHD | RCT only | 3.35 % | <0.00001 |
| | 14 | 874 | IHD | Cohort | 5.68 % | <0.00001 |
| Delewi et al. (2013) [43•] | 24 | 1624 | AMI | RCT | 2.23 % | <0.001 |
| Zimmet et al. (2012) [44•] | 23 | 1480 | AMI | RCT | 2.70 % | <0.0001 |
| De Jong et al. (2014) [50] | 22 | 1513 | AMI | RCT | 3.04 % | p = 0.0008 |

*AMI* acute myocardial infarction, *EF* ejection fraction, *IHD* ischemic heart disease, *RCT* randomized controlled trial

multitude of trials completed in this field [42, 43•, 44•, 45•, 46-48]. The results of a series of analyses are remarkably consistent in their conclusions and clearly demonstrate several lessons (Table 1). First, and perhaps most importantly, the therapy appears safe. There was no evidence, with the exception of a single study using granulocyte colony stimulating factor (G-CSF) mobilized cells, that there was a safety concern with stent restenosis, thrombosis, or arrhythmic events [51]. Second, when assessing all trials combined, there appears to be a small but demonstrable effect on EF (Table 1). Further analysis indicated that similar findings were observed on other imaging endpoints, including LV volumes (both end-systolic and end-diastolic), infarct size, and regional contractility. In the larger studies, which included the more recent randomized trials, the effects were highly statistically significant. In addition, the effect on EF consistently appeared to be more pronounced in the studies for which 12-month follow-up was available; however, the number of patients available for analysis was frequently significantly lower than the primary analysis results analyzed most frequently 4–6 months after cell administration. Third, stem cell therapy may be associated with a reduced risk of hard cardiovascular endpoints, including cardiovascular mortality and rehospitalization (Table 2). In some analyses, these effects were highly statistically significant [45•], suggesting that even small effects on EF may translate into significant clinical importance.

The compelling impact on clinical events has led to the European Commission-funded Bone Marrow for Acute Myocardial Infarction (BAMI) trial, which will assess the impact of BMCs on cardiovascular mortality. This 3000-patient trial uses an open-label design to minimize costs and is powered to detect a 25 % mortality reduction as its primary endpoint; enrollment is ongoing.

## Second Generation Cell Therapies

Given the mixed results with unselected BMCs, as well as the lack of commercial opportunities with these cells,

**Table 2** Meta-analysis of effect on cardiac endpoints of stem cell therapy for ischemic heart disease

| Source | Patients | Death | CV death | CHF/rehospitalization | Re-MI | Revascularization | Arrhythmia |
|---|---|---|---|---|---|---|---|
| Lipinski (2007) [46] | 669 | 0.52 (0.26) | | | 0.22 (0.04) | 0.97 (0.9) | |
| Martin-Rendon et al. (2008) | | 0.62 (0.37) | | | 0.61 (0.54) | 0.55 (0.28) | |
| Jeevanantham et al. (2012) [45•] | 2625 | 0.39 (<0.00001) | 0.41 (0.005) | 0.52 (0.05) | 0.25 (0.001) | 0.83 (0.35) | 1.14 (0.74) |
| Delewi et al. (2013) [43•] | 1624 | 0.6 | | 0.60 | 0.41 | 0.82 | |
| Zimmet et al. (2012) [44•] | 383 | 0.64 (0.46) | 0.74 (0.78) | 0.62 (0.59) | | 0.68 (0.10) | 1.42 (0.77) |

*CHF* congestive heart failure, *CV* cardiovascular, *MI* myocardial infarction

attention has turned to the use of selected BMCs from other sources. In a small study, Bartunek et al. demonstrated an improvement in EF in $CD133^+$ cell-treated patients compared with controls [52]. In Poland, the 200-patient REGENT trial demonstrated that both $CD34^+CXCR4^+$ and unselected BMCs led to a small (3 %) improvement in EF compared with control [37]. The improvement was limited to those with baseline EF below the median (37 %), mirroring observations from other studies that benefit is largely limited to those patients with large infarctions [31, 36••, 37]. More recently, Caladrius, formerly NeoStem, reported the results of a 195-patient trial evaluating $CD34^+$ cells. The study demonstrated that in patients receiving over 14 million $CD34^+$ cells, there was a significant improvement in the number of cardiac events [53]. These findings were consistent with a phase I study that showed a dose effect [54].

While these studies build support for the role of autologous bone marrow-derived cells, Marban et al. have studied the use of cardiac stem cells, which might be particularly attractive given their derived source. Building on a wealth of preclinical data, these authors have demonstrated the superiority of cardiosphere-derived cells (CDCs) for myocardial regeneration in a large animal model [55, 56]. A phase I study using autologous cells derived from endomyocardial biopsy specimens were derived 2–4 weeks after MI, expanded, and then reintroduced via an intracoronary route into the infarct-related artery. Using MRI imaging, the authors demonstrated a reduction in infarct size in patients treated with cardiac stem cells with a corresponding increase in viable myocardium, demonstrating true regeneration for the first time. While the exact mechanisms for such results remain unclear and need to be substantiated in additional clinical trials, these findings demonstrate the promise of regenerative medicine and illustrate why this field has received so much attention. The phase II study ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration (ALLSTAR) trial is a randomized, double-blind, placebo-controlled trial, notable for its transition to the use of allogeneic cell product (CDCs). ALLSTAR will assess efficacy in both an acute (<3 months) and subacute (>3–12 months) cohort of patients with acute MI. The initial phase I 14-patient open-label study showed no safety concerns, and ALLSTAR has now progressed to the randomized, double-blind phase [57•].

## Congestive Heart Failure

Increasing attention has been focused on the use of stem cell therapy to treat CHF. This interest is driven by the exponential growth of this patient population, the poor outcomes and prognosis, and the hope that regeneration represents a path to stabilization and eventual reversal of this condition. While there have been some initial experiences with surgical administration of cell therapy for the treatment of CHF [24], it is unlikely that even minimally invasive surgical methods are reasonable approaches to cell administration given the high morbidity and mortality of such procedures in patients with advanced HF. In contrast to therapies for acute MI in which cell delivery is almost exclusively via an intracoronary route, intramyocardial delivery has been favored in patients with HF given the presence of advanced and variable coronary disease, the need to diffuse administration of cell throughout the myocardium, and studies that have demonstrated great cell retention when given intramyocardially.

The earliest cell types to be developed for this indication were derived from autologous peripheral muscle [58], and a series of early studies demonstrated significant improvement in EF and patient symptoms [59-65]. Unfortunately, the largest study to date demonstrated no change in EF [66], and a subsequent phase III randomized trial was stopped prematurely for financial reasons [67]. While unselected BMCs have been studied in Europe [27] and the USA [68], unselected BMCs failed to show any signs of efficacy in a CCTRN-sponsored multicenter US-based study [69••].

### Second Generation Cell Therapies

Commercial opportunities have driven the development of second generation modified cells. For the first time, there are large-scale studies aimed to definitively asses the efficacy and safety of these therapies. Two programs warrant specific attention.

Allogeneic mesenchymal stem cells (MSCs) are particularly attractive because of their “off-the-shelf” properties and small but provocative studies indicating that MSCs and mesenchymal-like cells might be more efficacious at affecting cardiac repair. These cells are capable of multilineage differentiation, perhaps promoting growth of both myocytes and their supporting structures in the heart, and secrete multiple paracrine factors contributing to neovascularization and apoptosis [4, 70-72]. Li et al. compared four stem cell types that were or are being evaluated clinically in an acute MI model, including CDCs, bone marrow MSCs, and adipose-derived MSCs. Angiopoietin-2, basic fibroblast growth factor, human growth factor, insulin-like growth factor-1, stromal-derived factor-1, and vascular endothelial growth factor (VEGF) were each expressed at higher levels in the various MSC populations compared with unselected BMCs. These findings translated into enhanced in vitro tube formation, a marker of angiogenesis and greater improvement in EF (in comparison with bone marrow-derived cells) [56]. In a permanent ligation acute MI model,

Armiñán et al. demonstrated greater improvements in anterior wall thickening and reduction in scar tissue with MSCs compared with $CD34^+$ bone marrow [73].

Small studies have compared MSCs with other cell sources in humans. In the TAC-HFT trial, Heldman et al. randomized 65 participants with ischemic cardiomyopathy to treatment with autologous MSCs or autologous unselected BMCs. While the study was too small to be definitive, there were intriguing signals that MSC therapy might be more potent than the use of unselected BMCs, as reflected in improvements in distance walked in 6 min, infarct size as measured using MRI, and regional recovery [74].

The ongoing DREAM-HF trial builds on findings from a phase I dosing study exploring the feasibility of an allogeneic MSC precursor selected based on expression of the STRO-3 stromal cell surface antigen, selecting for MSC populations which include all the multipotent subpopulations. A phase I study demonstrated feasibility, suggesting that the highest cell dose tested (150 million cells) was associated with a reduction in cardiac events. Based on these findings, a phase III $1700^+$-patient study is underway, powered to detect a reduction in cardiac events. When completed, this would be a landmark study in the field, evaluating for the first time the effect of cell therapy on hard cardiac endpoints. Enrollment is proceeding in the USA, with plans for expansion to a global trial.

## Third Generation Cell Therapies?

A key limitation of autologous therapies is the variability and perhaps impairment in activity of cells derived from patients most in need of effective repair. There have been several demonstrations that patients with advanced ischemic heart disease have functional impairment in their BMCs [75-79], especially in those with HF [80]. A "third generation" approach to this problem is reprogramming of cells to enhance and revitalize their therapeutic potential. One approach to this limitation is "guided cardiopoiesis," in which patient-derived BMCs are programmed via expansion in a cardiogenic conditioning medium toward a cardiopoietic phenotype, resulting in a biotherapeutic with uniform therapeutic value [81]. The feasibility of such an approach was evaluated in the 45-patient phase II Cardiopoietic stem Cell therapy in heart failURE (C-CURE) trail of patients with ischemic HF. Although this was an open-label study, the randomized multicenter trial demonstrated improvement in LV EF and volumes, as well as in 6-min walk distance [82••]. Based on these initial results, a phase III European study has recently completed enrollment, and will offer important insights into the efficacy and safety of this approach. A follow-up international study including enrollment in North America is planned.

## Refractory Angina

The improvements in mortality in patients with ischemic heart disease has led to a growing population of patients with "end-stage" disease, manifesting as either advanced ischemic HF or advanced "refractory" angina. This latter population represents an underserved, highly symptomatic, health care resource-intensive group of patients who have exhausted their options for revascularization and medial therapy, and represent up to 25 % of patients undergoing cardiac catheterization [1]. While there is some debate about the outcomes in these patients, a plethora of recent analyses have described the overall low incidence of mortality and hard cardiovascular events among these patients, suggesting that symptom relief should be the primary goal of therapy [1-3, 77, 83]. The lack of treatment options has stimulated exploration of a number of new therapies for these patients [84], including regenerative therapies.

Since the primary deficit in these patients is diffuse inadequate perfusion and as the vast majority of stem cell products used are felt to affect repair in large part via enhanced angiogenesis, stem cell therapy appears ideally suited for this indication. It is notable that the results in this field, predominantly but not exclusively from randomized, double-blind studies, are remarkably and consistently positive. Several meta-analyses have suggested that stem cell therapy may reduce symptoms and enhance exercise capacity, quality of life, and even mortality [85-87].

Under the leadership of Atsma, a group from Leiden University has published a series of studies. The first was an open-label 25-patient study [88] which led to an important 50-patient randomized placebo-controlled study of injection of 100 million unselected BMCs via an intramyocardial approach using the NOGA-Myostar injection catheter system (Biosense-Webster, Diamond Bar, CA). Cell therapy was associated with improvements in Canadian Cardiovascular Society (CCS) angina class, quality of life, EF as assessed by MRI, and myocardial perfusion [89]. Sixteen of the 25 control patients were subsequently treated in a crossover study, which again led to similar benefits [90]. A follow-up study at 4 years confirmed the low mortality (only one death) that has been reported from observational databases, with some attenuation in the effect on symptoms [91]. The results were also supported by an effort from Tse et al. who demonstrated improvements in EF, HF class, and exercise time, although angina class did not change [92].

A recent publication from the Leiden University group tackled an interesting and largely unanswered question in the field: what are the long-term outcomes after single administration of stem cells and is repeat dosing an option? They found that that there was some attenuation of benefit with a return of symptoms at 5 years. Encouragingly, however, the effect of repeat treatment replicated that observed after the

initial therapy [93•]. While there are several caveats with this open-label study [94], these data add to the remarkably positive outcomes observed in these patients.

Kastrup et al. have explored the use of MSCs for this indication [95, 96]. As noted previously, some have found that MSCs may produce higher levels of pro-angiogenic cytokines than other stem cells [56]. In an initial 31-patient experience, bone marrow MSCs were isolated and culture expanded, then stimulated with VEGF for 1 week. Twelve months after treatment, patients experienced an increase in maximal metabolic equivalent (MET) during exercise (4.23 MET to 4.72 MET at 12-month follow-up; $p < 0.001$), a reduction in CCS angina class from 3.0 to 0.8, a >75 % reduction in the number of angina episodes per week (13.8 to 3.2), an almost 70 % reduction in nitroglycerin consumption (0.7 to 3.4 per week; $p < 0.001$), and marked improvement in Seattle Angina Questionnaire parameters.

The largest body of literature comes from the efforts of Losordo, Henry, and colleagues, who built on the initial finding that $CD34^+$ cells represent a population of endothelial progenitor cells capable of revascularization in various ischemic models [11, 18, 97, 98]. Included in this preclinical work is an intriguing experiment in which the benefits of cell purification and isolation are demonstrated. In an acute MI model, Kawamoto et al. showed that a preparation of isolated purified $CD34^+$ cells was more efficacious than a cellular product containing equal numbers of angiogenic $CD34^+$ cells as an unselected bone marrow preparation [19].

The promise seen in these preclinical models and the theoretical attractiveness of targeting a population in which the predominant deficit is ischemia led to a series of studies exploring the effectiveness of this therapy on symptoms of angina. A phase I study demonstrated the feasibility of harvesting up to 500,000 $CD34^+$ cells/kg utilizing G-CSF mobilization and apheresis [99]. Cell procurement and injection appeared safe, and there were signs of efficacy in endpoints such as the number of angina episodes experienced by these patients [99]. The follow-up ACT-34 study, although considered a phase II study, remains one of the largest stem cell studies completed to date, and our largest experience in the treatment of refractory angina [100••]. In addition, this is one of the few dose-finding studies of sufficient size to reasonable compare the effectiveness of two doses of a cell therapy. Perhaps somewhat surprisingly, this study suggested a threshold effect of cell dose, with no difference in efficacy between the two doses of 1- and $5 \times 10^5$ $CD34^+$ cells/kg. The study was remarkable in the benefit demonstrated by cell therapy, with an improvement of over 140 s in exercise time using a modified Bruce protocol in cell therapy-treated patients, compared with approximately 60-s improvement in placebo-controlled patients [100••]. The significant improvement observed in the placebo group speaks to the blinded controlled nature of this trial, as placebo effects of this degree on subjective endpoints like exercise time are expected and support the need for double-blinded trials in this field. In addition, patients experienced statistically significant improvements in the numbers of angina episode experiences. These findings are especially notable when compared with other therapies that have been approved for the treatment of angina, notably Ranexa. The Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial demonstrated improvements in exercise times of 23.8 and 45.9 s at doses of 500 and 1500 mg twice daily of Ranexa [101], and the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial showed 24-s improvements in exercise time [102]. The benefits of enhanced external counterpulsation (EECP), the only other recently approved treatment for angina, appear even more limited (16 s) in the only randomized blinded study of this treatment (multicenter study of enhanced external counterpulsation- MUST-EECP trial) [103]. The effectiveness of auto-$CD34^+$ cells on angina episodes appears similarly appealing, as the decrease of 5.6 episodes per week noted in ACT-34 compared favorably with decreases of 0.4 to 0.8 angina episodes per week noted for Ranexa [102, 104] and 1.4 episodes per week noted in MUST-EECP [103].

Importantly, these trials add to the growing body of evidence that cell therapy may be associated with improvements in cardiac outcomes, including favorable trends in reduction in mortality as well as rehospitalizations [100••]. These encouraging findings led to the design and implementation of the phase III trial RENEW, which aimed to definitively determine both the safety and efficacy of this therapy for treatment of refractory angina. After discussions with regulatory authorities about safety assessment, this trial was mandated to include two control arms: (1) an open-label standard of care arm to assess the safety of the combined cell harvesting and administration procedure, and (2) a double-blind active control arm in which patients underwent full cell mobilization and isolation (apheresis) as well as a fully blinded intramyocardial injection procedure [20••]. Comparison of these arms with the full treatment arm would allow assessment of the efficacy of delivery of the cell product on outcomes measured. Unfortunately, enrollment in RENEW was stopped by the sponsor. While this study will add to the growing body of data in this patient population, it is not likely to meet its initial substantive goals. This was a blow to the field because this would have been the first trial designed with regulatory authorities and of adequate power to support clinical approval of a cell therapy for a cardiovascular indication.

## Conclusions

Cell therapy for ischemic heart disease has progressed from excitement to an appreciation for the significant efforts required to bring the promise of this therapy to fruition. While

the initial excitement may have led to overly ambitious expectations, the conduct of carefully designed and conducted clinical trials is bringing greater clarity to the field. While unselected bone marrow stem cells appear to have modest effects and continue to undergo investigation, a greater amount of energy is now being invested in the development of next generation therapies engineered to affect more robust cardiac repair. The results of sufficiently powered studies aiming to assess the impact of these therapies on both patient-centered outcomes as well as hard cardiac endpoints are eagerly anticipated.

**Compliance with Ethical Standards**

**Conflict of Interest** Thomas J. Povsic reports personal fees from Pluristem Inc., Capricor, and Amorcyte, and grants from Baxter Healthcare, Cardio3 Biosciences, and Janssen Pharmaceuticals.

**Human and Animal Rights and Informed Consent** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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