

Autologous Progenitor Cell Therapy for the Treatment of Ischemic Heart Disease



Assessment
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Executive Summary

Background

Ischemia is the most common cause of cardiovascular disease in the developed world. Despite impressive advances in treatment, ischemic heart disease is still associated with high morbidity and mortality. Treatment with autologous progenitor cells (i.e., stem cells) offers potential benefits beyond those of standard medical care, including the potential for repair and/or regeneration of damaged myocardium.

Objective

To determine whether treatment with autologous progenitor cells improves clinical outcomes for patients with damaged myocardium due to ischemia.

Search Strategy

MEDLINE[®] was searched (via PubMed) using the terms “stem cells” OR “progenitor cells” OR “bone-marrow” OR “peripheral mononuclear.” These terms were cross-referenced with the terms “ischemic cardiomyopathy” OR “myocardial infarction” OR “AMI” OR “congestive heart failure” OR “CHF” OR “atherosclerotic cardiovascular disease” OR “ASCVD” OR “coronary artery disease” OR “CAD.” Search was performed for the time period from January 1995 through August 2008 and was limited to English-language articles on human subjects.

Selection Criteria

Articles were selected for inclusion that had the following characteristics: full-length publications published in a peer-reviewed journal in the English language from 1995 to the present; included patients with damaged myocardium due to ischemia; randomized patients to progenitor cell treatment versus standard medical care; enrolled at least 25 patients per treatment group for acute ischemic heart disease (at least 10 patients per treatment group for chronic ischemic heart disease); and reported on one or more relevant outcome.

Main Results

A total of 15 articles met the inclusion criteria for the Assessment: 9 articles discussed patients with acute ischemic heart disease treated with progenitor cell therapy and 6 articles discussed treatment of patients with chronic ischemic heart disease. The REPAIR-AMI trial, the largest randomized, controlled trial identified, was a double-blinded trial with a sham placebo control infusion that enrolled 204 patients with acute ST-segment elevation. At 12 months of follow-up, there were statistically significant decreases in the progenitor cell group for myocardial infarction (MI; 0 vs. 6, $p<0.03$) and revascularization (22 vs. 37, $p<0.03$) as well as for the composite outcome of death, MI, and revascularization (24 vs. 42, $p<0.009$).



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The ASTAMI trial, the next largest randomized, controlled trial, also reported on clinical events, but had very small numbers of clinical outcomes, precluding meaningful analysis. This trial also included the clinical outcomes of exercise time, symptoms, and quality of life (QOL). There were no group differences in symptoms or QOL. Exercise time increased in both groups, with a greater increase for the bone-marrow-progenitor cell (BMC) treatment group of slightly less than 1 minute (2.1 vs. 1.3 minutes, $p < 0.01$).

The most common physiologic outcome reported was left-ventricular ejection fraction (LVEF). In all studies that reported this outcome, there was a greater increase in the LVEF for the experimental group compared with the control group. In 4 of the 6 studies of acute ischemia, and 4 of 5 studies of chronic ischemia, this difference reached statistical significance. A quantitative meta-analysis that included 10 controlled trials (randomized and nonrandomized) of patients with acute ischemia estimated the incremental improvement in LVEF to be 3.0% (95% CI: 1.9–4.1%, $p < 0.00001$).

Author's Conclusions and Comments

For acute ischemic heart disease, the limited evidence on clinical outcomes suggests that there may be benefits in improving LVEF, reducing recurrent MI, decreasing the need for further revascularization, and perhaps even decreasing mortality. These results indicate that progenitor cell treatment is a promising therapy with the potential to benefit a large population of patients with ischemic heart disease. However, the evidence to date should be viewed as preliminary, rather than definitive. There are numerous reasons why the confidence in these conclusions is not high, and as a result, it is not possible to conclude with adequate certainty that progenitor cell treatment improves clinical outcomes.

The primary limitation is the small quantity of literature that reports on clinical outcomes, with a very small overall number of hard clinical outcomes such as recurrent MI and death across all trials. On formal quality assessment, none of the studies met the criteria for a high-quality trial. Only one trial, REPAIR-AMI, had enough clinical outcomes for meaningful statistical analysis. This trial enrolled a highly selected patient population with acute MI, and thus may not be generalizable to the larger population of patients with acute ischemic heart disease. In the REPAIR-AMI trial, the relative risk reduction (RRR) for individual outcomes had wide confidence intervals, indicating a lack of precision, and, in some cases, point estimates for RRR that may not be clinically plausible (e.g., hazard ratio for recurrent MI or death at 12 months = 0.20; 95% CI: 0.04–0.89). In addition, there were far more revascularization outcomes than other clinical events, and as a result, the composite outcome of major adverse cardiac events (MACE) was driven almost entirely by revascularization rates.

The evidence for a beneficial impact on physiologic outcomes, particularly LVEF, is fairly strong, but the magnitude of effect does not appear to be large. As a result, it is not certain whether the improvement in LVEF translates to meaningful improvements in clinical outcomes. The evidence for a decrease in infarct size is less robust than that for LVEF, but shows a similar pattern of incremental improvement for patients receiving progenitor cell therapy. As with LVEF, the threshold for improvement in infarct size that translates to a clinically meaningful benefit is uncertain.

For chronic ischemic heart disease there is only very scant evidence on clinical outcomes, and no conclusions can be drawn. There are only a handful of clinical outcome events reported across the included studies, too few for meaningful analysis. Other clinical outcomes, such as New York Heart Association (NYHA) class, are confined to very small numbers of patients and not reported with sufficient methodology rigor to permit any conclusions.

Therefore, the evidence is insufficient to permit conclusions with adequate confidence on the effect of progenitor cell therapy on clinical outcomes for patients with ischemic heart disease. While the available evidence suggests a potential benefit on both physiologic and clinical outcomes, the limited amount of clinical outcome evidence combined with uncertainties in the patient populations, mechanism of action, and treatment delivery decreases the confidence of conclusions that can be drawn from this evidence.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of autologous progenitor cell treatment for ischemic heart disease meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Progenitor cell treatment is a procedure that does not require U.S. Food and Drug Administration (FDA) approval, although some of the devices and instruments used during the procedure may be subject to FDA approval. For all trials included in this Assessment, autologous donor cells were used, derived either from the patient's bone-marrow cells or from circulating blood cells, thus avoiding any regulatory issues involved with allogeneic donor cell sources. Devices used during the treatment procedure are generally standard catheter-based devices approved for use in other percutaneous coronary interventions.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The scientific evidence does not permit conclusions to be made with adequate confidence concerning the effect of progenitor cell treatment on clinical outcomes. While the evidence is fairly strong that this treatment improves LVEF, the evidence on the impact on harder clinical outcomes is less compelling. There is only one trial with adequate numbers of clinical events for meaningful analysis, and even this trial had very low numbers of hard events such as recurrent MI and death. This trial enrolled a highly selected patient population that may not be generalizable to most patients with ischemic heart disease. The reported RRRs for the individual clinical outcomes had p values in the 0.03–0.06 range, broad confidence intervals, and point estimates of RRR that may be implausible. Uncertainty about the mechanism of action of progenitor cell treatment and lack of standardization of treatment protocols also contributes to decreased confidence in the validity of the results.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives

It cannot be determined whether progenitor cell treatment for damaged myocardium due to ischemia improves the net health outcome, or whether progenitor cell treatment for damaged myocardium due to ischemia is as beneficial as any established alternatives, since the evidence is not sufficient to permit conclusions on its effect on health outcomes.

5. The improvement must be attainable outside the investigational settings.

It cannot be determined whether any improvement is attainable outside the investigational setting since the evidence is not sufficient to permit conclusions on the effect of progenitor cell treatment for damaged myocardium due to ischemia on health outcomes.

For the above reasons, autologous progenitor cell treatment for damaged myocardium due to ischemia does not meet the TEC criteria.

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Assessment Objective

Ischemic heart disease remains the primary cause of most cardiovascular disease in the developed world. Despite impressive advances in the treatment of ischemic disease over the last two decades, ischemic heart disease remains common and is associated with high morbidity and mortality. For patients with damaged myocardium due to ischemia, treatment with autologous progenitor cells offers potential benefits beyond those of traditional treatment methods. The overall objective of this Assessment is to determine whether treatment with autologous progenitor cells (i.e., stem cells) improves clinical outcomes for patients with damaged myocardium due to ischemia.

Current treatments for damaged myocardium seek to preserve and optimize pump function and to prevent future myocardial damage, but are not able to reverse existing damage to heart muscle. Treatment with progenitor cells offers the potential for regeneration of damaged myocardium following acute or chronic ischemia. In addition, other possible mechanisms of action of progenitor cells may contribute to improvements in cardiac function and health outcomes. Improved perfusion to areas of damaged myocardium has been demonstrated, which may reduce symptoms and preserve healthy myocardium. Release of cytokines by progenitor cells may ameliorate ischemic damage and thus may also contribute to improved outcomes.

There are a number of possible sources of progenitor cells and delivery systems for treatment. Treatment protocols have not yet been standardized for cardiovascular indications. Potential sources of donor cells include embryonic stem cells, adult mesenchymal stem cells, skeletal myoblasts, bone-marrow-derived mononuclear cells, and peripheral mononuclear cells. In cardiology, the most commonly used source of progenitor cells has been autologous bone-marrow-derived mononuclear cells. These cells have been preferentially used due to their availability, potential for differentiation into mature cardiac muscle cells, lack of the need for immunosuppression, and avoidance of ethical issues.

Progenitor cells can be delivered by a variety of mechanisms. Open thoracotomy and direct injection of cells into damaged myocardium

was the first method used, but is also the most invasive and risky method. Percutaneous delivery with catheter-based delivery systems has since been developed. Using percutaneous techniques, donor cells can be injected directly into damaged myocardium with imaging guidance, or can be infused into coronary vessels that supply the area of damaged myocardium. Intravenous infusion of progenitor cells can also be performed, and depends on the ability of the donor cells to target damaged myocardium and exert a local effect.

Outcomes following treatment with progenitor cells include a variety of physiologic measures, incident rates of future adverse cardiovascular events, and functional status/quality of life. Adverse cardiovascular events, which include cardiac mortality, acute myocardial infarction (AMI), and the need for revascularization procedures are the most clinically relevant outcome measures. Functional status, exercise capacity, and quality of life measures are also important clinical outcomes for this condition. Physiologic measures such as left-ventricular ejection fraction (LVEF) and cardiac perfusion are intermediate outcomes that may be useful correlates of clinical outcomes. However, changes in these measures do not by themselves represent improvement in health outcomes.

Background

Ischemic Heart Disease

Ischemic heart disease is the underlying cause of the majority of clinical cardiovascular disease in the developed world. Ischemia, or inadequate blood flow to myocardial tissue, can be either acute or chronic. Acute MI is the classic example of acute ischemia. Acute MI occurs most commonly as a result of thrombotic occlusion of a coronary vessel with underlying atherosclerotic disease. Vessel occlusion leads to infarcted myocardium and impairment of myocardial contractility. Acute MI is a leading cause of overall mortality and cardiovascular morbidity in the developed world. If damage from acute MI is extensive, reduced LVEF and clinical congestive heart failure (CHF) will occur. Clinical CHF is defined as failure of cardiac pump function to meet physiologic demands. This disorder is common and associated with high morbidity and mortality. Mortality in CHF is 20% at 1 year and 50% or greater at 5 years (Mazhari and Hare 2007).

Chronic ischemia results from partial occlusion of coronary vessels causing inadequate blood flow to myocardial tissue. Patients with chronic ischemic heart disease may experience debilitating symptoms such as angina and dyspnea on exertion. As with acute ischemia, loss of myocardial pump function may lead to reduced LVEF and clinical CHF.

Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments are not able to reverse existing damage to heart muscle (Lee and Makkar 2004; Mathur and Martin 2004). Myocardial cells have a limited ability to regenerate following damage. Myocardial muscle mass increases following infarction, in a process known as ventricular remodeling, indicating that some regeneration of myocardium is possible. However, this repair mechanism is incomplete and inadequate to restore normal myocardial function following ischemic damage (Mathur and Martin 2004). Neovascularization of newly formed myocardium is typically not adequate, leading to disordered growth of new muscle cells. This, in turn, can cause increased fibrosis of cardiac tissue, aneurysms of the ventricular wall, and ventricular dilation (Mathur and Martin 2004).

Treatment with progenitor cells is a novel treatment for ischemic heart disease that offers potential benefits beyond those of traditional medical care. In particular, treatment with progenitor cells offers the possibility of reversing and repairing damaged myocardium. As such, this represents a potential line of research that could lead to relatively simple, safe, and inexpensive treatment with important clinical

benefits and wide applicability for patients with ischemic heart disease (Mathur and Martin 2004).

Progenitor Cell Treatment

Donor Cell Source. The commonly used nomenclature “stem cells” is a broad term that refers to a number of progenitor cell lines with varying ability to self-regenerate and differentiate into mature human cells (Mathur and Martin 2004). The ideal donor cell is uncertain; there are scientific as well as ethical concerns involved in choosing the ideal source of donor cells (Mazhari and Hare 2007; Lee and Makkar 2004). The range of potential sources of donor cells and some of their defining characteristics are shown in Table 1.

Embryonic stem cells represent the prototype progenitor cell. These are totipotent cell lines that maintain their ability to differentiate into any cell from each of the three embryonic germ layers (Mazhari and Hare 2007). Embryonic stem cells are capable of differentiating into fully functioning myocytes, as well as cardiac endothelial cells and other cell lines. The use of embryonic stem cells in the U.S. is primarily limited at present by ethical and political concerns.

Fetal cardiomyocytes have been demonstrated to engraft into areas of damaged myocardium and to differentiate into mature myocytes in animal models (Lee and Makkar 2004). The use of these types of cells is limited by ethical issues and the need for immunosuppression in the recipient.

Adult stem cells of mesenchymal origin are multipotent stem cells that can be isolated from

Table 1. Potential Sources of Progenitor Cells for Use in Cardiology

Cell Source	Availability in Sufficient Numbers	Differentiation Potential	Ethical/political Issues	Immunosuppression Required
Embryonic stem cells	+	+++	++	-
Fetal cardiomyocytes	+	++	++	++
Skeletal myoblasts	++	-	-	-
Adult mesenchymal stem cells	+	++	-	-
Bone-marrow-progenitor cells	++	++	-	-
Peripheral-blood-progenitor cells	+	++	-	-

(Adapted from Lee and Makkar 2004)

the bone marrow, umbilical cord blood, adipose tissue, the heart, and possibly other internal organs (Mazhari and Hare 2007). These types of cells have been isolated in small numbers, and the ability to harvest adequate numbers of cells for clinical treatments is currently difficult.

Other types of adult progenitor cells are more accessible than mesenchymal stem cells and avoid the ethical issues surrounding the use of embryonic cells. Skeletal myoblasts can be easily obtained from skeletal muscle biopsies and have high proliferative capacity (Mazhari and Hare 2007). However, these cells do not differentiate into true myocytes and, therefore, may have reduced potential to repair damaged myocardium.

Bone-marrow-derived mononuclear cells are another option. These cells are available in the vast majority of patients via bone marrow aspiration, which is a somewhat invasive but relatively safe procedure. Bone-marrow-derived cells have demonstrated ability to differentiate into mature cardiac cells. Immature mononuclear cells can also be purified from circulating blood cells in the same manner as they are purified from bone-marrow cells. The proportion of such mononuclear cells is smaller in circulating blood as compared to bone marrow, making purification from circulating cells less efficient.

Mechanism of Action. The mechanism of benefit following treatment with progenitor cells is not entirely understood (Mathur and Martin 2004; Murry et al. 2006). Differentiation of progenitor cells into mature myocytes and engraftment of progenitor cells into areas of damaged myocardium has been suggested in animal studies using tagged progenitor cells (Orlic et al. 2001; Murry et al. 2006). However, other research groups have used genetic screening methods and failed to demonstrate differentiation of progenitor cells into myocardial cells with typical myocardial phenotype (Murry et al. 2006). As a result, there is controversy concerning whether injected progenitor cells actually do undergo engraftment and differentiation into mature myocytes in humans (Mathur and Martin 2004).

Other mechanisms of benefit have been hypothesized. Progenitor cells may improve perfusion to areas of ischemic myocardium. Improved perfusion following progenitor cell treatment has been demonstrated in animal

models and in small numbers of humans enrolled in clinical trials (Mazhari and Hare 2007). Basic science research also suggests that injected stem cells secrete cytokines with antiapoptotic and pro-angiogenesis properties (Mazhari and Hare 2007; Uemura et al. 2006). Clinical benefit may result if these paracrine factors are successful at limiting cell death from ischemia. Finally, progenitor cell therapy may activate the intrinsic repair mechanisms of the heart (Mazhari and Hare 2007; Mouquet et al. 2005; Murry et al. 2006). Injection of stem cells peripherally has been shown to increase proliferation of cardiac stem cells, and thus may potentiate the ability of cardiac stem cells to repair damaged myocardium.

Delivery Methods. There are a variety of potential delivery mechanisms for donor cells, encompassing a wide range of invasiveness. Donor cells can be delivered via direct injection into areas of damaged myocardium, as first demonstrated in animal models (Orlic et al. 2001). This can only be performed with open heart surgery and entails the relatively high risks of a thoracotomy. Tse et al. (2003) developed a method for intracardial delivery using a percutaneous catheter-based approach combined with electrochemical mapping.

Injection of progenitor cells directly into the coronary circulation can also be done, using percutaneous, catheter-based techniques. This requires patent intracoronary vessels and intact blood flow to the area of damaged myocardium, and, therefore, cannot be performed following myocardial infarction for which successful revascularization has not been achieved. Finally, progenitor cells can be delivered intravenously via a peripheral vein. With this approach, the cells must be able to target damaged myocardium and concentrate at the site of myocardial damage.

The optimal timing of progenitor cell treatment following acute ischemia is also not known (Murry et al. 2006). Early treatment following acute MI is most likely a more favorable time for cell repair and regeneration, compared with later treatment in which the infarct is complete and scar formation has occurred (Murry et al. 2006). On the other hand, treatment given too early following acute ischemia may be confounded by the intense inflammatory response that accompanies the first several days following acute MI (Lee and Makkar 2004). Furthermore, it is difficult to predict

the extent of left ventricular dysfunction and clinical CHF early in the course of an acute MI (Murry et al. 2006). This makes it difficult to predict which patients will benefit the most from progenitor cell therapy and which patients will have preserved left-ventricular function and, thus, not benefit from this therapy.

Adverse Effects. Adverse effects of treatment with progenitor cells include the risk of the delivery procedure (e.g., thoracotomy, percutaneous catheter-based, etc.) and the risks of the donor cells themselves. Donor progenitor cells can differentiate into fibroblasts rather than myocytes (Lee and Makkar 2004). This can lead to an increase in infarct size, a decrease in ejection fraction, and may create a substrate for malignant ventricular arrhythmias (Lee and Makkar 2004). There is a potential risk of inducing arrhythmias if the progenitor cells integrate into the myocardium in a disorderly fashion, and disrupt the conduction and/or coordination of electrical impulses throughout the myocardium (Lee and Makkar 2004). There is a theoretical risk that tumors, such as teratomas, can arise from progenitor cells, but the actual risk of this occurring in humans is not known at present (Lee and Makkar 2004).

FDA Status. Progenitor cell treatment is a procedure that does not require U.S. Food and Drug Administration (FDA) approval, although some of the devices and instruments used during the procedure may be subject to FDA approval. For all trials included in this Assessment, autologous donor cells were used, derived either from the patient's bone marrow cells or from circulating blood cells, thus avoiding any regulatory issues involved with allogeneic donor cell sources. Devices used during the treatment procedure are generally standard catheter-based devices approved for use in other percutaneous coronary interventions.

Methods

Search Methods

MEDLINE® was searched (via PubMed) using the terms, and the term “stem cells” OR “progenitor cells” OR “bone-marrow” OR “peripheral mononuclear.” These terms were cross-referenced with the terms “ischemic cardiomyopathy” OR “myocardial infarction” OR “AMI” OR “congestive heart failure” OR “CHF”

OR “atherosclerotic cardiovascular disease” OR “ASCVD” OR “coronary artery disease” OR “CAD.” The search was performed for the time period from January 1995 through August 2008 and was limited to English-language articles on human subjects. Electronic searches were supplemented with the “related articles” function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies.

Study Selection

Studies were selected for inclusion in this Assessment that met the following criteria:

- full-length publications, published in a peer-reviewed journal in the English language
- included patients with documented damaged myocardium due to ischemia, either acute (acute MI) or chronic ischemic cardiovascular disease of atherosclerotic origin
- randomized, controlled trial comparing usual medical care with progenitor cell treatment using one of the following autologous progenitor donor cells:
 - embryonic stem cells
 - adult mesenchymal stem cells
 - bone-marrow-derived mononuclear progenitor cells
 - peripherally derived mononuclear progenitor cells
- enrolled at least 25 patients per treatment group for acute ischemic heart disease. (at least 10 patients per treatment group for chronic ischemic heart disease)
- reported on one or more relevant clinical outcomes:
 - cardiovascular or all-cause mortality
 - cardiovascular morbidity
 - myocardial infarction
 - revascularization procedure
 - hospitalization for CHF
 - ventricular arrhythmias
 - functional status and/or quality of life

The original article inclusion criterion for minimum patient enrollment was 25 patients per treatment arm for both acute and chronic ischemic heart disease. After it was determined that essentially no trials of chronic ischemic heart disease met this enrollment threshold, the minimum enrollment was modified to 10 patients per treatment arm in order to allow review of the available randomized, controlled trials in this area.

Study Quality Assessment

Study quality for clinical trials was formally assessed as per the approach outlined by the U.S. Preventive Services Task Force (USPSTF; Harris et al. 2001). In this approach, 5 quality indicators are assessed as met or not met. These are:

- Initial assembly of comparable groups (adequacy of randomization, allocation concealment, and equal distribution of confounders among groups);
- Maintenance of comparable groups (attrition, crossovers, contamination, nonadherence);
- Comparable performance of and clear definition of interventions with equivalent attention and quality of care;
- Comparable measurements: unbiased, reliable, and valid (includes blinding of outcome assessment);
- Appropriate analysis of outcomes: Intention-to-treat analysis for randomized, controlled trials, consideration of confounding variables in nonrandomized studies. All important outcomes considered.

An overall level of quality of “good” (meets all criteria), “fair” (does not meet all criteria but no “fatal flaws”), or “poor” (has “fatal flaws”) is assigned based on these 5 parameters.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 10, 2008. In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Formulation of the Assessment

Patient Indications

The relevant patient population is patients with damaged myocardium due to ischemia (Figure). Ischemic heart disease is defined as inadequate blood flow to cardiac myocytes. Acute ischemic heart disease is caused by acute myocardial infarction, which leads to regional

cardiac myocyte death and associated wall-motion abnormalities. This may, in turn, cause depressed LVEF and clinical CHF, depending on the location and extent of myocardial damage. Chronic ischemic heart disease is caused by atherosclerotic cardiovascular disease of the coronary blood vessels. Chronic ischemic disease leads to either regional or generalized damage to myocardial tissue, depending on the location and extent of coronary vessel stenosis, and may also result in reduced ejection fraction and clinical CHF.

Technologies to be Compared

Treatment with progenitor cells will be compared to usual medical care for ischemic heart disease. Usual care for ischemic heart disease includes: risk factor reduction, such as control of blood pressure and cholesterol; medications to alleviate ischemia and/or improve pump function of the heart, and; revascularization of diseased vessels when appropriate.

Health Outcomes

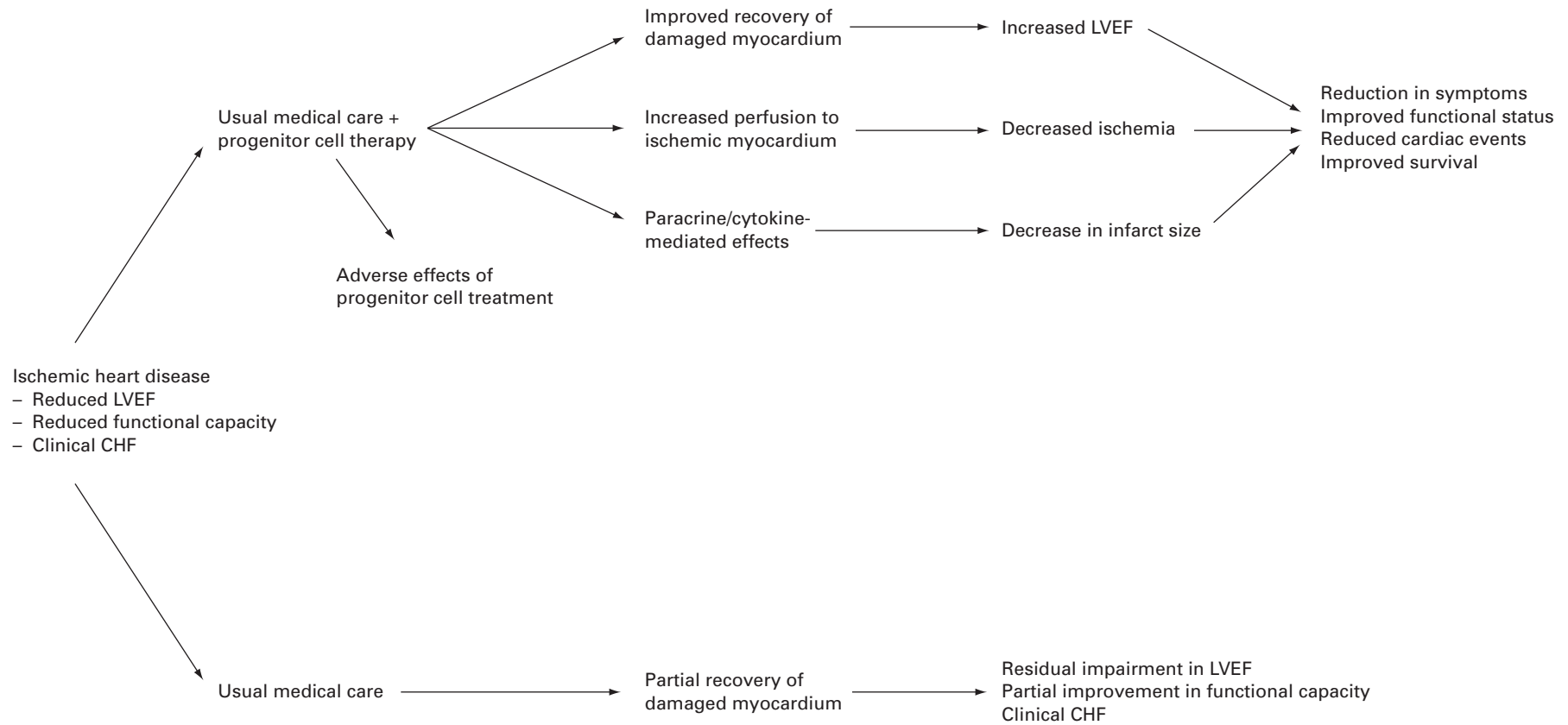
The primary outcomes to be evaluated for this Assessment will be the adverse clinical outcomes associated with ischemic heart disease. Adverse cardiovascular outcomes include:

- cardiovascular death (or all-cause mortality)
- cardiovascular morbidity due to ischemic heart disease:
 - acute MI
 - revascularization procedure
 - hospitalization for CHF
 - functional status and/or quality of life

In addition, ventricular arrhythmias may be associated with progenitor cell treatment, and will be considered a relevant clinical outcome for this Assessment.

Most clinical trials of progenitor cell treatment examine intermediate outcomes related to pump function, myocardial viability, and/or myocardial perfusion. Common methods to measure these intermediate outcomes include echocardiography to estimate ejection fraction, SPECT scanning for myocardial perfusion, and cardiac MRI to measure cardiac viability. Cardiac angiography can also directly measure ejection fraction and myocardial blood flow, but is more invasive and risky than other imaging studies. These intermediate outcomes will be summarized and discussed in order to examine and/or corroborate the physiologic basis for any changes in clinical outcomes reported. However, improvements in these parameters

Figure. Analytic Framework



will not be considered evidence of improved outcomes unless accompanied by improvement in one or more relevant clinical outcomes.

Specific Assessment Question

In patients with damaged myocardium due to ischemia, does treatment with progenitor cells reduce the incidence of adverse cardiovascular outcomes, compared to usual medical care?

Review of Evidence

A total of 15 articles met the inclusion criteria for this Assessment, 9 articles reported on treatment of patients with acute ischemic heart disease, and 6 articles reported on patients with chronic ischemic heart disease. The evidence will be discussed separately for each of these two indications. Both physiologic outcomes and clinical outcomes will be reviewed; however, the focus will be on the impact of treatment on clinical outcomes. The physiologic outcomes will be included in order to corroborate any effects seen on clinical outcomes and to provide insight into the mechanism of effect, magnitude of effect, and durability of effect.

Acute Ischemic Heart Disease

Of the 9 articles meeting the inclusion criteria for acute ischemic heart disease, there were 3 studies with multiple publications (Table 2). Two articles were published from the REPAIR-AMI trial (Schachinger et al. 2006a, 2006b), 2 from the ASTAMI trial (Lunde et al. 2006, 2007) and 3 from the BOOST trial (Wollert et al. 2004; Meyer et al. 2006; Schaefer et al. 2006). These multiple publications reported on different outcome measures or the same outcomes at longer follow-up time points. Excluding multiple publications, there were a total of 6 unique studies enrolling 556 patients.

The REPAIR-AMI trial was the largest randomized, controlled trial identified (Table 2). This was a double-blinded trial that employed a sham placebo control infusion of the patients' own serum. This trial enrolled 204 patients with acute ST-segment elevation MI meeting strict inclusion criteria from 17 centers in Germany and Switzerland. Eligible patients had undergone successful PCI with stenting, yet had evidence of residual wall-motion abnormalities and reduced ejection fraction. The primary outcome for the 4-month study results was change in ejection fraction. Clinical

outcomes were secondary outcomes at the 4-month time period. The 12-month follow-up report primarily focused on clinical outcomes at this time point.

The next largest study was the ASTAMI trial, which enrolled 100 patients from two clinical centers in Norway. Eligibility criteria for this trial were similar to that for the REPAIR-AMI trial and included patients with acute MI, successful PCI with stent placement, and 3 or more hypokinetic segments observed on echocardiography. This study screened 1,608 patients with acute ST-elevation MI in order to enroll 100 patients who met the eligibility criteria.

In contrast to the REPAIR-AMI study, the ASTAMI trial was unblinded and did not employ a sham placebo control. The primary outcomes for this trial were LVEF, infarct size, and cardiac perfusion at 6 months' follow-up. The study also reported the number of clinical events in each group, and a separate publication reported on exercise capacity and quality of life at 6 months.

The other included trials enrolled between 50 and 69 patients. These trials primarily focused on the change in LVEF and other physiologic outcome measures. Where clinical events were reported, there were extremely low numbers of events (Table 2), precluding formal statistical analysis.

Formal quality assessment for the individual studies is shown in Table 3. The initial publication from the REPAIR-AMI study (Schachinger et al. 2006a), which reported the main results of the study at 4 months' follow-up, met all quality indicators except for one, i.e., did not include all randomized patients in the analysis and, therefore, received a "fair" rating. The follow-up portion of this study (Schachinger et al. 2006b), which was partially unblinded and reported on clinical events at 12 months of follow-up, also received a "fair" rating.

The ASTAMI trial also did not meet all the quality indicators, with the primary limitation being the lack of double-blinding. This trial was assigned a quality rating of "fair" since it did not contain any major or "fatal" flaws. Similarly, none of the other trials met all quality indicators but most did not contain any "fatal" flaws, and, therefore, each received a quality rating of "fair" (Table 3).

Table 2. Randomized, Controlled Trials of Progenitor Cell Therapy for Acute MI: Study Characteristics

Study/yr	Patients	Study Design	Progenitor Cell Therapy	Outcomes Reported	Comments
ASTAMI Study					
Lunde et al. 2006	100 patients: – age 40–75 years – acute ST-elevation MI – successful reperfusion and stent placement – 3 or more hypokinetic LV segments on echocardiography – CK-MB >3x normal	– RCT from 2 institutions in Norway – Unblinded – No sham placebo control – 6-month follow-up	– Bone-marrow aspiration 4–7 days after acute MI – Progenitor cells isolated and enriched – Infusion of cells using catheter positioned within left anterior descending artery at a median of 6 days post-MI	– Δ LVEF – Δ LVEDV – Δ infarct size	Clinical events reported, but not considered as formal outcome measures and not analyzed statistically
Lunde et al. 2007	same	same	same	– Exercise capacity (bicycle ergometer) – Symptoms (NYHA class) – Physical function (SF-36) – MH function (SF-36)	
REPAIR-AMI Study					
Schachinger et al. 2006a	204 patients: – age 18–80 years – acute ST-elevation MI – successful reperfusion and stent placement – residual LV wall-motion abnormality	– Multicenter RCT from 17 institutions in Europe. – Double-blind – Sham placebo control – 4-month follow-up	– Bone-marrow aspiration 3–6 days after acute MI – Progenitor cells isolated and enriched – Infusion of cells using catheter positioned within stented vessel at 3–7 days post-MI	Primary – Δ LVEF Secondary – Δ LVEDV – Δ LVESV – Δ wall-motion abnormalities – MACE (death, MI, revascularization)	
Schachinger et al. 2006b	same	– 12-month follow-up – Partially unblinded for 4- to 12-month portion (data monitoring center unblinded, pts and clinicians continued blinded)	same	– MACE (death, MI, revascularization)	Reports on 1 year F/U from REPAIR-AMI study

Table 2. Randomized, Controlled Trials of Progenitor Cell Therapy for Acute MI: Study Characteristics (cont'd)

Study/yr	Patients	Study Design	Progenitor Cell Therapy	Outcomes Reported	Comments
BOOST Trial					
Wollert et al. 2004	60 patients: – acute ST-elevation MI – successful reperfusion and stent placement – residual LV dysfunction involving at least 2/3 of LV wall	– RCT from single center in Germany – Unblinded – No sham placebo control – 6-month follow-up	– Bone-marrow aspiration 3–6 days after acute MI – Progenitor cells isolated and enriched by density gradient centrifugation – Infusion of cells using catheter positioned within stented vessel	Primary – Δ LVEF Secondary – Δ LVEDV – Δ LVESV – Δ myocardial perfusion	
Meyer et al. 2006	same	– 18-month follow-up	same	– Δ LVEF – MACE (death, MI, revascularization, rehospitalization) – NYHA class	
Schaefer et al. 2006	same	– 18-month follow-up	same	– Diastolic function by echocardiography	
Janssens et al. 2006	67 patients: – 18–75 years old – acute MI with successful reperfusion and stent placement – residual LV wall motion abnormality	– Randomized, double-blind, placebo controlled at single institution – 4-month follow-up	– Bone-marrow aspiration from every patient – Progenitor cells isolated by Ficoll density gradient centrifugation – Infusion of cells using catheter positioned within stented vessel – Infusion of saline in placebo control group	– Δ LVEF – Δ LVEDV – Δ infarct size	

Table 2. Randomized, Controlled Trials of Progenitor Cell Therapy for Acute MI: Study Characteristics (cont'd)

Study/yr	Patients	Study Design	Progenitor Cell Therapy	Outcomes Reported	Comments
Kang et al. 2006	56 patients: – acute MI with successful reperfusion and stent placement within 14 days	– Randomized, unblinded, no placebo control – 6-month follow-up	– Circulating progenitor cells isolated from peripheral blood and cultured – All pts received G-CSF 10 mcg/kg per day for 3 days prior to treatment – Infusion of cells using catheter positioned within stented vessel	– Δ LVEF – Δ myocardial perfusion – MACE (death, MI, revascularization)	
Chen et al. 2004	69 patients: – younger than 70 years old – acute MI with successful reperfusion and stent placement	– Randomized, double-blind, placebo controlled at single institution – 3-month follow-up	– Bone-marrow aspiration from every patient 8 days after PCI – BM cells cultured and harvested over 10 days period – Infusion of cells using catheter positioned within stented vessel – Infusion of saline in placebo control group	– Δ LVEF – Δ LVEDV – Δ LVESV – Δ infarct size	

Δ : change; BM: bone marrow; F/U: follow-up; G-CSF: granulocyte colony-stimulating factor; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MACE: major adverse cardiac event; MH: mental health; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; RCT: randomized, controlled trial

Table 3. Quality Assessment for Clinical Trials of Acute Ischemic Heart Disease

Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	Overall Quality Level
ASTAMI (Lunde et al. 2006)	YES Randomization adequate; no major baseline differences between groups	YES	NO Intervention in treatment groups; none in control (no sham placebo infusion); Unblinded study	YES	YES 100/101 randomized pts included in final analysis	FAIR Does not meet all quality indicators but no major, or "fatal," flaws
REPAIR-MI (Schachinger 2006a: primary results at 4 months)	YES Central randomization; only minor baseline differences between groups	YES (?) 17/204 patients excluded from analysis, ? differential dropout	YES Sham placebo-control; Double-blinded study	YES	NO 17/204 randomized patients excluded from analysis	FAIR Does not meet all quality indicators but no major, or "fatal," flaws
(Schachinger et al. 2006b: 12-month follow-up)	YES Central randomization; only minor baseline differences between groups	YES (?) 17/204 patients excluded from analysis, ? differential dropout	YES Sham placebo-control; Patients and on-site researchers remained blinded through 12 months	YES	NO 17/204 randomized patients excluded from analysis	FAIR Does not meet all quality indicators but no major, or "fatal," flaws
BOOST (Wollert et al. 2004)	YES Randomization adequate; only minor baseline differences between groups	YES	NO Intervention in treatment groups; none in control (no sham placebo infusion); Unblinded study	YES	YES All randomized pts included in primary analyses	FAIR Does not meet all quality indicators, but no "fatal" flaws
(Meyer et al. 2006)	same	same	same	same	same	FAIR Does not meet all quality indicators but no "fatal" flaws

Table 3. Quality Assessment for Clinical Trials of Acute Ischemic Heart Disease (cont'd)

Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	Overall Quality Level
Janssens et al. 2006	YES (?) Randomization adequate; large difference in baseline rates of hypertension (43 vs. 18%), other baseline characteristics similar	YES (?) 6/66 patients dropped out, ? differential dropout	YES Sham placebo-control	YES	NO 6/66 randomized pts excluded from analysis	FAIR Does not meet all quality indicators but no "fatal" flaws
Kang et al. 2006	YES (?) Randomization not well-described; some baseline differences, e.g., hypertension (60% vs. 36%), hyperlipidemia (24% vs. 12%)	YES (?) 6/56 patients dropped out, ? differential dropout	NO Intervention in treatment groups; none in control (no sham placebo infusion); Unblinded study	YES	NO 6/56 randomized pts excluded from analysis	FAIR Does not meet all quality indicators but no "fatal" flaws
Chen et al. 2004	NO (?) Randomization not well-described; baseline characteristics not well-reported, but no differences noted	NO (?) Uncertain baseline comparability	YES Sham placebo-control	YES	YES All randomized pts included in primary analyses	FAIR Does not meet all quality indicators but no "fatal" flaws

Formal quality assessment for this body of literature on acute ischemic heart disease was performed according to the GRADE method, as shown in Table 4. For the clinical outcomes, this body of literature was judged to be of low overall quality, primarily due to the small numbers of overall clinical outcome events. The quality of the body of evidence was judged to be moderate for the physiologic outcomes of LVEF and infarct size, for which the amount of evidence was higher. The quality for these outcomes was limited primarily by the indirectness of the evidence on clinical outcomes and by the methodologic limitations noted for the individual studies.

Physiologic Outcomes. The two physiologic measures that will be discussed in depth for this Assessment are LVEF and infarct size. All 6 included trials reported the change in LVEF and 5 of the 6 trials reported change in infarct size. Other measures of LV function, such as left-ventricular end-diastolic volume and left-ventricular end-systolic volume were less consistently included and less standardized in their reporting. In addition, these other measures have a more uncertain relationship with clinical outcomes. Measures of myocardial perfusion were not commonly reported and were, therefore, not abstracted formally for this Assessment.

The change in LVEF was determined either by echocardiography, cardiac catheterization, or cardiac MRI (Table 5). In all studies, there was a greater increase in the LVEF for the experimental group compared with the control group. In 4 of the 6 studies, this difference reached statistical significance, while in 2 studies there was a nonsignificant increase in favor of the treatment group. However, the incremental change in LVEF was not large in most cases, with 5 of the 6 studies reporting an incremental change of 1.0–6.0%, and the final study reporting a larger incremental change of 18% (Chen et al. 2004).

Change in infarct size was generally measured by SPECT or MRI scanning, and reported as the percent of the LV wall with impaired movement. In the 5 studies reporting these data, infarct size was reduced to a larger extent in the treatment group compared with control (Table 5), with an incremental decrease ranging from 2.2–14%. In 2 of 5 studies, there was a statistically significant greater decrease in the treatment group compared with the

control group, while in 3 studies, the difference did not reach statistical significance.

Lipinski et al. (2007) published a quantitative meta-analysis of studies that evaluated the impact of progenitor cell treatment on LV function for acute ischemic heart disease. This analysis included 10 controlled trials with a follow-up of at least 3 months and that analyzed results by intention-to-treat analysis. Five of the 6 trials included in the present Assessment were included in the Lipinski meta-analysis (Chen et al. 2004 not included), an additional 5 nonrandomized controlled studies were included as well. These trials assigned a total of 698 patients to either progenitor cell therapy or standard medical care and had a mean follow-up of approximately 6 months.

Results for the primary endpoint, change in LVEF, showed a statistically significant greater improvement of 3.0% (95% CI: 1.9–4.1%, $p < 0.00001$) for the progenitor cell group. A similar difference was found when limiting analysis only to studies using a sham intracoronary infusion (3.0%, 95% CI: 0.8–5.2, $p < 0.01$). There was also a statistically significant greater improvement in infarct size for the progenitor cell group with an incremental improvement of -5.6% over the control group (95% CI: -8.7 to -2.5, $p < 0.001$). Other pooled outcomes such as left-ventricular end-diastolic volume and end-systolic volume showed similar patterns of results.

Meta-regression of the results for LVEF found a trend for an association between the volume of cells injected and the improvement in LVEF that did not quite reach statistical significance ($p < 0.07$). There were no associations found for other variables examined in meta-regression: follow-up duration, baseline LVEF, number of injected cells, time to PCI, and time since symptom onset.

Clinical Outcomes. The REPAIR-AMI trial offers the best evidence on clinical outcomes; results from this trial are shown in Table 6. At 4 months, there were a small number of patients who had experienced clinical events such as death ($n=4$), MI ($n=5$), or hospitalization for CHF ($n=2$), and a larger number who had undergone revascularization ($n=47$). There were no statistically significant group differences in these outcomes including the composite outcome of death, MI, and need for revascularization, although the increased

Table 4. Quality Assessment for Body of Literature (GRADE method): Acute Ischemic Heart Disease

Outcome	Studies/ Pts	Study Limitations	Consistency	Directness	Precision	Publication Bias	Overall Quality
Clinical Outcomes							
MACE	2/304	Serious limitations; small numbers of outcomes for all measures except revascularization	No important inconsistency	Direct	Imprecision present; wide CI and implausibly high RRR for some outcomes	Unlikely	LOW Low numbers of outcomes, other flaws are major limitations in overall quality
NYHA class	1/100	Serious limitations; small overall number of patients; incomplete statistical analysis	N/A One study only	Direct	Imprecision present; small overall numbers	Unlikely	LOW Low numbers of outcomes, other flaws are major limitations in overall quality
Exercise capacity	1/100	Serious limitations; one study only with potential bias for outcome	N/A One study only	Direct	Imprecision present; small overall numbers	Unlikely	LOW Low numbers of outcomes, other flaws are major limitations in overall quality
QOL	1/100	Serious limitations; one study only with potential bias for outcome	N/A One study only	Direct	Imprecision present; small overall numbers	Unlikely	LOW Low numbers of outcomes, other flaws are major limitations in overall quality

Table 4. Quality Assessment for Body of Literature (GRADE method): Acute Ischemic Heart Disease (cont'd)

Outcome	Studies/ Pts	Study Limitations	Consistency	Directness	Precision	Publication Bias	Overall Quality
Physiologic Outcomes							
LVEF	6/556	Some limitations	Some heterogeneity of outcomes	Indirect LVEF correlated with improved outcomes; questionable threshold for clinical significance	No important imprecision	Unlikely	MODERATE Quality limited by indirectness of outcome and some methodologic limitations
Infarct size	5/352	Some limitations	Some heterogeneity of outcomes	Indirect questionable threshold for clinical significance	No important imprecision	Unlikely	MODERATE Quality limited by indirectness of outcome and some methodologic limitations

Table 5. Randomized, Controlled Trials of Progenitor Cell Therapy for Acute MI: Physiologic Outcomes¹

Study/yr	F/U	Groups	LVEF ² (%)			Infarct Size (%)		
			Pre	Post	Change	Pre	Post	Change
Lunde et al. 2006	6 mos.	BMC (n=50)	45.7 ± 9.4	48.8 ± 10.7	3.1 ± 7.9	43.8 ± 17.4	32.8 ± 20.4	-11.0 ± 12.7
		Ctrl (n=50)	46.9 ± 9.6	49.0 ± 9.5	2.1 ± 9.2	38.3 ± 21.1	30.5 ± 20.9	-7.8 ± 8.7
		p value			NS			NS
Schachinger et al. 2006a	4 mos.	BMC (n=95)	48.3 ± 9.2	53.8 ± 10.2	5.5 ± 7.3			
		Ctrl (n=92)	48.3 ± 9.2	48.3 ± 9.2	3.0 ± 6.5			
		p value			0.01			
Wollert et al. 2004	6 mos.	BMC (n=30)	50.0 ± 10.0	56.7 ± 12.5	6.7 ± 6.5	33.0 ± 21.1	18.9 ± 12.2	-14.1 ± 13.0
		Ctrl (n=30)	51.3 ± 9.3	52.0 ± 12.4	0.7 ± 8.1	30.3 ± 17.4	19.8 ± 9.8	-10.5 ± 10.6
		p value			0.003			NS
Meyer et al. 2006	18 mos.	BMC (n=30)	50.0 ± 10.0	55.9 ± 14.7	5.9 ± 8.9			
		Ctrl (n=30)	51.3 ± 9.3	54.4 ± 13.0	3.1 ± 9.6			
		p value			NS			
Janssens et al. 2006	4 mos.	BMC (n=33)	48.5 ± 7.2	51.8 ± 8.8	3.4 ± 6.9	20.6 ± 14.3	10.3 ± 8.0	-10.2 ± 7.9
		Ctrl (n=34)	46.9 ± 8.2	49.1 ± 10.7	2.2 ± 7.3	22.3 ± 16.1	14.7 ± 9.3	-7.9 ± 8.5
		p value			NS			NS
Kang et al. 2006	6 mos.	BMC (n=25)	52.0 ± 9.9	57.1 ± 8.7	5.1 ± 9.1	20.6 ± 14.3	10.3 ± 8.0	-12.5 ± 13.3
		Ctrl (n=25)	53.2 ± 13.3	53.1 ± 11.5	-0.2 ± 8.6	22.3 ± 16.1	14.7 ± 9.3	0.8 ± 14.3
		p value			0.05			<0.01
Chen et al. 2004	3 mos.	BMC (n=34)	49 ± 9	67 ± 11	18	32 ± 11	13 ± 5	-19
		Ctrl (n=35)	48 ± 10	53 ± 13	5	33 ± 10	28 ± 10	-5
		p value			0.01			0.001

¹ p-value for comparison of change between experimental and control groups, unless otherwise specified² Values for LVEF reported from echocardiography; LVEF also calculated from SPECT imaging and MRI with slightly different values

number of recurrent MI in the control group (5 vs. 0) approached statistical significance ($p < 0.06$).

The study was partially unblinded after the 4-month follow-up and patients continued to be followed for clinical outcomes. The study analysis center that ascertained outcomes was unblinded, but the patients and clinicians treating the patients remained blinded to treatment assignment. The 12-month results for clinical outcomes are also shown in Table 6. At this time point, there were still relatively small numbers of hard events for death ($n=8$), MI ($n=6$), and hospitalization for CHF ($n=3$), with higher numbers for revascularization ($n=59$). However, at this time point, there were statistically significant increases in the control group for MI (6 vs. 0, $p < 0.03$) and revascularization (37 vs. 22, $p < 0.03$) as well as for the composite outcome of death, MI, and revascularization (42 vs. 24, $p < 0.009$). There was no increase in ventricular arrhythmias at either time point, and no other adverse events reported for patients undergoing treatment with progenitor cells.

Clinical results of the ASTAMI trial are also shown in Table 6. There were very low numbers of hard clinical events, with no deaths and only one recurrent MI. A total of 2 patients were hospitalized for CHF, one in each group. A larger number of patients underwent target-vessel revascularization within 6 months ($n=22$), with an equal number in each group (11/50).

The ASTAMI trial reported exercise capacity measured by bicycle ergometry and quality of life measured by the SF-36 scale at 6 months' follow-up (Lunde et al. 2007), as shown in Table 6. Exercise time increased in both groups, with a greater increase for the BMC group of slightly less than 1 minute (2.1 vs. 1.3 minutes). Somewhat more patients in the BMC group reported symptom improvement of at least one NYHA class (18 vs. 12) but this difference did not reach statistical significance. There were no differences in physical functioning or mental health functioning as measured by SF-36.

Some of the other trials reported on clinical events, but the small numbers of events precluded any meaningful analysis. Data from these other trials are not shown in the tables as there were too few reported events for a meaningful analysis.

Chronic Ischemic Heart Disease

A total of 6 trials met the inclusion criteria for treatment of chronic ischemic heart disease (Table 7). Three trials randomized 125 patients to progenitor cell therapy vs. standardized medical care. The other 3 trials randomized 106 patients undergoing coronary artery bypass grafting (CABG) to CABG plus progenitor cell treatment versus CABG alone. Four trials employed bone-marrow-derived progenitor cells as the donor cell source, one trial used circulating progenitor cells (CPC), and the final trial included both a CPC treatment group and a BMC treatment group.

The largest trial was Assmus et al. (2006), which enrolled 75 patients to 3 groups: treatment with bone-marrow-derived progenitor cells, treatment with circulating progenitor cells, or usual medical care. This was a single-center, randomized, controlled trial that did not include a sham placebo control. Primary outcomes were reported at 3 months and included change in LVEF, as well as clinical outcomes of NYHA class and adverse cardiac events.

Formal quality assessment for the individual trials is shown in Table 8. The Assmus trial received a formal quality assessment of "fair," since it did not meet all quality indicators but did not contain any "fatal" flaws. One other trial received a "fair" rating (Losordo et al. 2007), while all the other trials received a "poor" rating. "Poor" ratings were assigned for trials with very low numbers of patients and/or other major flaws such as failure to randomize entire population.

Formal quality assessment for this body of literature on acute ischemic heart disease was performed according to the GRADE method, as shown in Table 9. For clinical outcomes, this body of literature was judged to be of low overall quality, primarily due to the very small numbers of overall clinical outcome events. The quality of the body of evidence was also judged to be low for the physiologic outcomes of LVEF and infarct size, due to the small quantity of evidence and other methodologic limitations noted for the individual studies.

Physiologic Outcomes. The primary physiologic measurement reported in these trials was change in LVEF. In all 6 trials there was a greater improvement in LVEF for the treatment group compared with the control group (Table 10), and in 4 of 6 trials, this difference

Table 6. Randomized, Controlled Trials of Progenitor Cell Therapy for Acute MI: Clinical Outcomes

Study/yr	F/U	Groups	Outcomes					
			Death	MI	Revasc	Hosp CHF	Composite MACE ¹	Arrhythmias
REPAIR-AMI Study								
Schachinger et al. 2006a	4 mos.	BMC (n=101)	2.0% (2/101)	0% (0/101)	19% (19/101)	0% (0/101)	21% (21/101)	4.0% (4/101)
		Control (n=103)	2.0% (2/103)	4.9% (5/103)	27% (28/103)	1.9% (2/103)	29% (30/103)	3.9% (4/103)
			p=NS	p<0.06	p=NS	p=NS	p=NS	p=NS
Schachinger et al. 2006a	12 mos.	BMC (n=101)	2.0% (2/101)	0% (0/101)	22% (22/101)	0% (0/101)	24% (24/101)	5.0% (5/101)
		Control (n=103)	5.8% (6/103)	5.8% (6/103)	36% (37/103)	2.9% (3/103)	41% (42/103)	3.9% (4/103)
			p=NS	p<0.03	p<0.03	p=NS	p<0.009	p=NS
ASTAMI Study								
Lunde et al. 2006	6 mos.	BMC (n=50)	0% (0/50)	2% (1/50)	22% (11/50)	2% (1/50)	NR	4% (2/50)
		Control (n=50)	0% (0/50)	0% (0/50)	22% (11/50)	2% (1/50)	NR	2% (1/50)
			p=NS	p=NS ²	p=NS	p=NS		p=NS ²
			Δ Exercise Time		Δ Symptoms ³	Δ Physical Function ⁴		Δ MH Function ⁴
Lunde et al. 2007	6 mos.	BMC (n=50)	2.1 \pm 1.9 min		36% (18/50)	5.8 \pm 11.2		1.2 \pm 11.4
		Control (n=50)	1.2 \pm 1.3 min		24% (12/50)	6.0 \pm 9.3		2.1 \pm 11.9
			p<0.01		p=NS	p=NS		p=NS

¹ Composite of death, recurrent MI and any revascularization procedure, unless otherwise indicated² Chi-square calculated from raw data using Fischer's exact test³ Percent of patients with improvement of at least one NYHA class⁴ Absolute difference as measured by SF-36 on 0-100 scale

BMC: bone-marrow cells; MH: mental health; NS: not significant

Table 7. Randomized, Controlled Trials of Progenitor Cell Therapy for Chronic Ischemic Heart Disease: Study Characteristics

Study/yr	Patients	Study Design	Progenitor Cell Therapy	Outcomes Reported
Medical Therapy vs. Medical Therapy + Progenitor Cell Treatment				
Losordo et al. 2007	24 patients: – >21 years old – CCS class III or IV – On optimal medical therapy – Ischemia on stress testing with SPECT imaging – Not a candidate for conventional revascularization	– Randomized, double-blind, placebo controlled dose-escalating trial from 3 clinical centers in U.S. – ?3 mos. follow-up	– Autologous CD34+ stem cells isolated by leukopheresis. – Direct injection of cells into ischemic myocardium – Three dosage groups: – 5×10 ⁴ cells/kg – 1×10 ⁵ cells/kg – 5×10 ⁵ cells/kg – All pts received G-CSF 5 mcg/kg for 5 days	– Change in LVEF – Angina frequency – Nitroglycerin use – Exercise tolerance – CCS class – QOL measure – SPECT imaging
Assmus et al. 2006	75 patients: – 18–80 years old – MI at least 3 mos. prior, with patency of infarct-related artery – Region of chronic LV dysfunction	– Single-center RCT – Pts randomized to BMC infusion, CPC infusion, or no cell infusion – Primary outcomes measured at 3 mos. – Crossover phase from 3–6 mos. in which patients receive alternative treatment	BMC – 50 mL BM aspirate obtained – Mononuclear cells isolated by Ficoll density-gradient – Mean 205×10 ⁶ cells/pt infused CPC – 270 mL peripheral blood obtained – Mononuclear cells isolated by Ficoll density-gradient and culture. – Mean 22×10 ⁶ cells infused	– Change in LVEF – NYHA functional status – Clinical events – Survival – MI – Stroke – Rehospitalization for CHF
Erbs et al. 2005	26 patients: – Chronic, total occlusion for at least 30 days, TIMI flow 0–1 – LV wall motion abnormality in region of ischemia	– Randomized, double-blind, placebo controlled from single centers in Germany – Sham intracoronary injection of saline in control group – 3 mos. follow-up	– All pts received G-CSF 300 mcg/d for 4 days prior to treatment – CPCs isolated from peripheral blood and cultured – Cells injected into coronary vessel supplying area of ischemia	– Change in LVEF – Myocardial perfusion

Table 7. Randomized, Controlled Trials of Progenitor Cell Therapy for Chronic Ischemic Heart Disease: Study Characteristics (cont'd)

Study/yr	Patients	Study Design	Progenitor Cell Therapy	Outcomes Reported
CABG Alone vs. CABG + Progenitor Cell Treatment				
Stamm et al. 2007	43 patients: – MI at least 14 days prior to enrollment – Indication(s) for CABG on vessels other than infarcted vessel – Area of LV dysfunction in area of prior infarct	– Randomized, unblinded with no placebo control from single clinical center in Germany – 12-mos. follow-up	– BMC harvested from iliac crest 1 day prior to treatment – CD133+ cells isolated by magnetic separation with ferrite-conjugated antibody – Direct injection of cells into ischemic myocardium	– Change in LVEF – Change in myocardial perfusion by SPECT imaging – Mortality – Major cardiac events – Ventricular arrhythmias
Hendrikx et al. 2006	43 patients: – Prior transmural MI with residual LV dysfunction – Scheduled for elective CABG	– Randomized, double-blind, placebo controlled trial from single clinical center in Belgium	– BMC harvested from iliac crest 1 day prior to treatment – CD34+ cells isolated by density-gradient centrifugation – Direct injection of cells into ischemic myocardium	– Change in LVEF – Change in wall thickness of infarcted area – Change in infarct size by thallium scan
Patel et al. 2005	20 patients: – CHF of ischemic origin with LVEF <35% – NYHA class III–IV – Optimal medical management – Scheduled for elective CABG	– Randomized, unblinded with no placebo control from single clinical center in Argentina	– BMC harvested from iliac crest during surgery – CD34+ cells isolated by density-gradient centrifugation – Direct injection of cells into border areas of ischemic myocardium following completion of CABG	– Change in LVEF – Change in LVEDV

Δ: change; BM: bone marrow; BMC: bone marrow progenitor cells; CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; CHF: congestive heart failure; CPC: circulating progenitor cells; F/U: follow-up; G-CSF: granulocyte colony-stimulating factor; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MACE: major adverse cardiac event; MH: mental health; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; RCT: randomized, controlled trial; SPECT: single photon emission computed tomography

Table 8. Quality Assessment for Clinical Trials of Chronic Ischemic Heart Disease

Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	Overall Quality Level
Losordo et al. 2007	YES Randomization adequate; only minor baseline differences between groups	YES	NO Different doses of donor cells given within treatment group	YES	NO Inadequate power for analysis of clinical outcomes	FAIR Does not meet all quality indicators but no "fatal" flaws
Assmus et al. 2006	YES (?) Randomization not well-described; baseline imbalance in number of pts, no other differences noted	YES (?) Baseline comparability uncertain	NO Intervention in treatment group only; no sham placebo infusion; Unblinded study	YES	YES All randomized pts included in primary analyses	FAIR Does not meet all quality indicators but no "fatal" flaws
Erbs et al. 2005	YES (?) Randomization adequate; very small numbers raise likelihood of unreported group imbalances	YES (?) Baseline comparability uncertain	YES (?) All pts underwent PCI; experimental group also underwent cell injection, no sham placebo injection	YES	NO 3/26 randomized pts excluded from analysis	POOR Very small numbers constitute "fatal" flaw
Stamm et al. 2007	NO Randomization scheme modified mid-trial to accommodate scheduling	NO Baseline comparability not demonstrated	NO (?) All pts underwent CABG; experimental group also underwent cell injection, no sham placebo injection; Unblinded study	YES	NO (?) 3/43 pts excluded from analysis	POOR Failure to randomize entire population, and multiple other flaws constitute "fatal" flaws
Hendrikx et al. 2006	YES (?) Randomization adequate; very small numbers raise likelihood of group imbalances	YES (?) 3/23 randomized pts dropped out, ? differential dropout	YES Sham placebo-control	YES	NO 3/23 randomized pts excluded from analysis	POOR Very small numbers constitute "fatal" flaw
Patel et al. 2005	NO (?) Randomization possibly adequate; baseline characteristics not reported, and very small numbers	NO	NO (?) All pts underwent CABG; experimental group also underwent cell injection, no sham placebo; Unblinded study	YES	YES All randomized pts included in primary analyses	POOR Very small numbers constitute "fatal" flaw

Table 9. Quality Assessment for a Body of Literature (GRADE Method) – Chronic Ischemic Heart Disease

Outcome	Studies/ Pts	Study Limitations	Consistency	Directness	Precision	Publication Bias	Overall Quality
Clinical Outcomes							
MACE	1/92	Serious limitations; small numbers of outcomes for all individual measures except revascularization	N/A One study only	Direct	Imprecision present; small overall numbers and wide confidence intervals	Unlikely	LOW Low numbers of outcomes and other methodologic flaws major limitations in overall quality
NYHA class	2/112	Serious limitations; small overall number of patients; incomplete statistical analysis	N/A One study only	Direct	Imprecision present; small overall numbers and variable magnitude of effect	Unlikely	LOW Low numbers of outcomes and other methodologic flaws major limitations in overall quality
Physiologic Outcomes							
LVEF	5/247	Serious limitations Small overall numbers and some methodologic limitations	Some heterogeneity of outcomes	Indirect LVEF correlated with improved outcomes; questionable threshold for clinical significance	No important imprecision	Unlikely	LOW Quality limited by small numbers, indirectness of outcome, and some methodologic limitations
Infarct size	1/20	Some limitations Very small overall numbers	N/A One study only	Indirect questionable threshold for clinical significance	Imprecision present; small overall numbers and wide confidence intervals	Unlikely	LOW Quality limited by small numbers, indirectness of outcome, and some methodologic limitations

Table 10. Randomized, Controlled Trials of Progenitor Cell Therapy for Chronic MI: Physiologic Outcomes¹

Study/yr	F/U	Groups	LVEF (%)			Infarct Size (%)		
			Pre-	Post-	Change	Pre-	Post-	Change
Medical Therapy vs. Medical Therapy + Progenitor Cell Treatment								
Assmus et al. 2006	3 mos.	BMC (n=28)	41 ± 11	43 ± 10	2.9 ± 3.6			
		CPC (n=24)	39 ± 10	39 ± 10	-0.4 ± 2.2			
		Ctrl (n=23)	43 ± 13	42 ± 13	-1.2 ± 3.0			
		p value			0.001			
Erbs et al. 2005	3 mos.	CPC (n=13)	50 ± 6.0 ⁴	57 ± 7	7			
		Ctrl (n=13)	54 ± 6	55 ± 5	1			
		p value			0.01			
CABG Alone vs. CABG + Progenitor Cell Treatment								
Stamm et al. 2007	6 mos.	BMC (n=20)	37.4 ± 8.4	47.1 ± 8.3	9.7			
		Ctrl (n=20)	37.9 ± 10.3	41.3 ± 9.1	3.4			
		p value			0.03 ²			
Hendrikx et al. 2006	4 mos.	BMC (n=10)	42.9 ± 10.3	48.9 ± 9.5	6.1 ± 8.6	4.0 ³	3.3 ± 1.0	-0.7
		Ctrl (n=10)	39.5 ± 5.5	43.1 ± 10.9	3.6 ± 9.1	4.0	3.7 ± 0.4	-0.3
		p value			NS			NS
Patel et al. 2005	6 mos.	BMC (n=34)	29.4 ± 3.6	46.0 ± 1.9	16.6			
		Ctrl (n=35)	30.7 ± 2.5	37.2 ± 3.4	6.5			
		p value			<0.001 ²			

¹ p-value for comparison of change between experimental and control groups, unless otherwise specified² p-value for difference between final LVEF values at 6 mos.³ Infarct size reported as mean defect score for individual LV segments on 0–4 scale, with eligible segments all having baseline score = 4 (<50% uptake)⁴ Values estimated from graphical representation

reached statistical significance. For the 3 trials of progenitor cell treatment versus standard medical care, the range of incremental improvement in LVEF was 2.7–6.0%. For the trials of progenitor cell treatment plus CABG versus CABG alone, the range of improvement in LVEF was 2.5–10.1%. Only one trial reported comparative analysis of data on the change in size of ischemic myocardium (Hendrikx et al. 2006). This trial reported that there was no difference in size of ischemic myocardium between treatment groups.

Clinical Outcomes. There are limited data from this group of studies on clinical outcomes (Table 11), with only 2 studies report any clinical outcomes (Assmus et al. 2006; Patel et al. 2005). Assmus reports on adverse cardiac events, but there were extremely small numbers of any of these clinical outcomes, and no differences between groups.

Both trials reported on change in NYHA class between groups. Assmus et al. reported an improvement in mean NYHA class of 0.25 (0–4 scale) for the BMC group and an improvement of 0.23 for the CPC group, compared with a worsening of 0.18 for the standard medical therapy group ($p < 0.01$).

Patel reported a greater improvement in mean NYHA class for patients in the CABG plus progenitor cell group compared to CABG alone (2.7 vs. 0.7, p value NR), but no statistical testing for this outcome was reported (Table 11).

Discussion

The evidence base consists largely of small randomized, controlled trials that focus on the impact of autologous progenitor cell treatment on physiologic outcomes such as change in LVEF. The available evidence suggests that progenitor cell treatment results in a modest increase in LVEF. The direct evidence on clinical outcomes is more limited. The limited evidence on clinical outcomes suggests that there may be benefits in reducing MI, decreasing the need for further revascularization, and perhaps even decreasing mortality for patients with acute ischemic heart disease. For chronic ischemic heart disease, there is only very scant evidence on clinical outcomes.

Most of the conclusions on clinical outcomes are from the REPAIR-AMI trial. This trial

reported statistically significant differences in favor of the progenitor cell group on clinical outcomes such as recurrent MI and revascularization procedures, as well as composite major adverse cardiac events. These represent improvements in important clinical outcomes of a magnitude that are clinically meaningful. Furthermore, these clinical benefits are plausible effects of improvements in myocardial pump function, limiting infarct size, and/or improving perfusion to ischemic myocardium.

Other evidence on clinical outcomes is scant. The ASTAMI trial reported an improvement in exercise capacity for patients treated with progenitor cell therapy, but reported no differences in other clinical outcomes such as symptoms or QOL. There was a potential for bias on this outcome since the trial was unblinded, and the outcome of exercise time is an effort-dependent measurement that could be influenced by knowledge of group assignment. This trial also reported adverse cardiovascular events but did not have adequate numbers of events for statistical analysis.

These results on clinical outcomes indicate that progenitor cell treatment is a promising therapy with the potential to benefit a large population of patients with ischemic heart disease. However, the evidence to date should be viewed as preliminary, rather than definitive. There are numerous reasons why the confidence in these conclusions is not high, and as a result the available evidence is insufficient to determine whether or not progenitor cell treatment improves clinical outcomes with an adequate degree of certainty.

The primary limitation in the data is the small quantity of literature reporting on clinical outcomes. Although numerous trials report clinical outcomes, the overall numbers for clinical events is very low relative to the large number of individuals with ischemic heart disease. Only one trial, the REPAIR-AMI trial, has enough clinical outcomes for meaningful analysis. Conclusions concerning the impact of progenitor cell treatment on clinical outcomes for patients with acute ischemic heart disease are largely derived from this single trial. Even for this trial, the overall numbers of hard clinical events such as death and MI is very small. There are larger numbers of revascularization outcome and as a result revascularization drives the results of composite adverse cardiac events.

Table 11. Randomized, Controlled Trials of Progenitor Cell Therapy for Chronic MI: Clinical Outcomes

Study/yr	F/U	Groups	Outcomes					
			Death	MI	Revasc	Hosp CHF	Composite MACE ¹	Arrhythmias
Assmus et al. 2006	3 mos.	BMC (n=35)	0% (0/35)	0% (0/35)	11% (4/35)	0% (0/35)	0% (0/35)	0% (0/35)
		CPC (n=34)	0% (0/34)	0% (0/34)	5.9% (2/34)	2.9% (1/34)	8.8% (3/34)	0% (0/34)
		Control (n=23)	4.3% (1/23)	0% (0/23)	0% (0/23)	4.3% (1/23)	4.3% (1/23)	0% (0/23)
			p=NS	p=NS	p=NS ²	p=NS	P=NS	p=NS
	3 mos.	NYHA Class (mean)						
			Pre	Post	change	p value		
		BMC (n=35)	2.23 ± 0.6	1.97 ± 0.7	-0.25	0.005		
CPC (n=34)		2.16 ± 0.8	1.93 ± 0.8	-0.23	0.13			
	Control (n=23)	1.91 ± 0.7	2.09 ± 0.9	+0.18	0.27			
Patel et al. 2005	6 mos.	NYHA Class (mean)						
			Pre	Post	change	p value		
		BMC (n=10)	3.5	0.7	-2.7	NR		
		Control (n=10)	3.4	2.7	-0.7	NR		

¹ Composite of death, recurrent MI and any revascularization procedure, unless otherwise indicated

² Chi-square calculated from raw data using Fischer's exact test

³ Percent of patients with improvement of at least one NYHA class

⁴ Absolute difference as measured by SF-36 on 0–100 scale

BMC: bone marrow progenitor cells; CHF: congestive heart failure; CPC: circulating progenitor cells; F/U: follow-up; Hosp: hospitalization; MACE: major adverse cardiac events; MI: myocardial infarction; NR: not reported; NS: not significant; NYHA: New York Heart Association; Revasc: revascularization

None of the included studies met the formal criteria for a high-quality trial. The REPAIR-AMI met all but one criterion, which was failure to include all randomized patients in the analysis. The other trials had additional limitations including lack of double-blinding and lack of placebo control. Thus, it is not possible to exclude bias as a cause of the treatment differences reported.

Related to the small number of outcomes, the relative risk reduction (RRR) for individual outcome measures cannot be estimated with precision. The RRR for all outcomes except revascularization have wide confidence intervals, and in some cases point estimates that may not be clinically plausible, such as the RRR for recurrent MI or death at 12 months (HR 0.20; 95% CI: 0.04–0.89). The composite outcome of MACE is driven by revascularization, with nearly identical RRR for revascularization (HR 0.55; 95% CI: 0.32–0.93) as the RRR for combined death, MI, or revascularization (HR 0.52; 95% CI: 0.32–0.86). This decreases confidence in the validity of the composite MACE outcome (Kip et al. 2008).

The populations included in the clinical trials likely represent highly selected patient populations, with areas of ischemic myocardium vulnerable to further damage following successful PCI with stenting. Most studies did not provide a flow chart for patient screening and inclusion. One trial that did, the ASTAMI trial, screened over 1,600 patients with acute ST-elevation MI in order to enroll 100 patients who met the inclusion criteria. Other trials with similar inclusion/exclusion criteria, including the REPAIR-AMI trial are therefore likely to have had a similar selection process. The populations included, patients with successful PCI and stent placement but with areas of ischemic myocardium vulnerable to further damage, may derive the greatest potential benefit from progenitor cell treatment. However, this benefit may not be generalizable to broader populations with ischemic heart disease.

There is uncertainty as to mechanism of effect. The original theory that progenitor cells engraft onto areas of damaged myocardium may or may not be true, and there are other potential mechanisms of benefit such as released of cell mediators, and/or an improvement in myocardial perfusion. As a result, there is also uncertainty concerning the optimal mechanism of delivery. This uncertainty includes the type of

donor cell used and the manner in which treatment is delivered. For example, if engraftment and replacement of myocytes is the goal, then cells with the greatest differentiation potential would be expected to have the greatest effect (Table 1). On the other hand, if clinical benefit is achieved by release of cell mediators, then more mature donor cells may be favored.

While the evidence for a beneficial impact on physiologic outcomes, particularly LVEF, is fairly strong, the magnitude of effect does not appear to be large. The included trials consistently report an improvement in LVEF for the progenitor cell treatment group. Because the magnitude of this effect is not large it is uncertain whether the improvement in LVEF translates to meaningful improvements in clinical outcomes. The evidence on other clinical outcomes, such as infarct size and myocardial perfusion, is less robust. The available evidence does suggest that these outcomes may be improved, but the confidence in this conclusion is limited.

The modest magnitude of benefit and the uncertain mechanism of action create difficulties in extrapolating a benefit in LVEF to improvement in clinical outcomes. While there is a correlation between LVEF and outcomes in a wide range of cardiovascular disorders, the threshold of improvement in LVEF that represents a clinical benefit is uncertain. Some experts have suggested a threshold of 5% for a meaningful improvement in LVEF. The estimated pooled impact of progenitor cell treatment on LVEF by Lipinski et al. (2007) was an improvement of 3.0%, which would be somewhat lower than this definition of clinically important improvement.

It is also not possible to directly equate an improvement in LVEF from one modality of treatment such as medications, with a similar improvement in LVEF from a novel treatment such as progenitor cells. There may be different and/or additional mechanisms of actions for both medications and progenitor cells on cardiac function, resulting in overall effects that may be different despite similar improvements in LVEF.

Therefore, the evidence is insufficient to permit conclusions on the effect of progenitor cell therapy on clinical outcomes for patients with damaged myocardium due to ischemia. While the available evidence is consistent in

suggesting a potential benefit on both physiologic and clinical outcomes, the limited amount of evidence on clinical outcomes and uncertainties in patient populations, mechanism of action, and delivery of treatment, all combine to decrease confidence in any conclusions that can be drawn from the available evidence.

Future Research Recommendations

The first and primary priority for future research is for larger trials with sufficient power to fully evaluate the impact of progenitor cell treatment on important clinical outcomes. Trials need to be substantially larger than the largest trial to date, the REPAIR-AMI trial, in order to have enough clinical events for a more precise estimate of treatment effect. Trials should also be longer in length, several years or more, in order to accumulate more events and evaluate the durability of the treatment. Hard clinical outcome events, such as MI and cardiac death, are the optimal clinical outcomes. Other measures of clinical morbidity such as symptoms, functional status, and quality of life are also important clinical outcome measures. Composite outcomes should be viewed somewhat more critically, especially if the overall composite rate is driven primarily by softer clinical outcome(s) such as revascularization or hospitalization.

Trials with broader patient populations are desirable in order to determine whether benefit is confined to subset of patients or generalizable to all patients with ischemic heart disease. The populations in the current trials are highly selected and may represent patients with the greatest potential benefit. Other related populations, such as patients with successful percutaneous coronary intervention and revascularization without evidence of residual LV wall dysfunction, or patients with completed infarcts who do not have evidence of myocardial viability, may benefit less or not at all. It is therefore important to determine whether progenitor cell treatment is appropriate only for a subset of patients with indications as defined by the current inclusion criteria, or whether this treatment may benefit a broader population of patients.

Other priorities include better understanding on the mechanism of action, standardization of donor cell source, and standardization of treatment delivery protocols. Further basic research into the mechanism of action would be helpful in understanding the rationale for treatment

and would also help direct decisions as to the optimal cell source and treatment protocol. The ideal donor cell is not known at present, with multiple potential sources each with its own pros and cons. The primary donor cell source tested has been bone-marrow-derived mononuclear cells, it is not known whether other types of cells would result in similar outcomes.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of autologous progenitor cell treatment for ischemic heart disease meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Progenitor cell treatment is a procedure that does not require U.S. Food and Drug Administration (FDA) approval, although some of the devices and instruments used during the procedure may be subject to FDA approval. For all trials included in this Assessment, autologous donor cells were used, derived either from the patient's bone-marrow cells or from circulating blood cells, thus avoiding any regulatory issues involved with allogeneic donor cell sources. Devices used during the treatment procedure are generally standard catheter-based devices approved for use in other percutaneous coronary interventions.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The scientific evidence does not permit conclusions to be made with adequate confidence concerning the effect of progenitor cell treatment on clinical outcomes. While the evidence is fairly strong that this treatment improves LVEF, the evidence on the impact on harder clinical outcomes is less compelling. There is only one trial with adequate numbers of clinical events for meaningful analysis, and even this trial had very low numbers of hard events such as recurrent MI and death. This trial enrolled a highly selected patient population that may not be generalizable to most patients with

ischemic heart disease. The reported RRRs for the individual clinical outcomes had p values in the 0.03–0.06 range, broad confidence intervals, and point estimates of RRR that may be implausible. Uncertainty about the mechanism of action of progenitor cell treatment and lack of standardization of treatment protocols also contributes to decreased confidence in the validity of the results.

- 3. The technology must improve the net health outcome; and**
- 4. The technology must be as beneficial as any established alternatives**

It cannot be determined whether progenitor cell treatment for damaged myocardium due to ischemia improves the net health outcome, or whether progenitor cell treatment for damaged myocardium due to ischemia is as beneficial as any established alternatives, since the evidence is not sufficient to permit conclusions on its effect on health outcomes.

- 5. The improvement must be attainable outside the investigational settings.**

It cannot be determined whether any improvement is attainable outside the investigational setting since the evidence is not sufficient to permit conclusions on the effect of progenitor cell treatment for damaged myocardium due to ischemia on health outcomes.

For the above reasons, autologous progenitor cell treatment for damaged myocardium due to ischemia does not meet the TEC criteria.

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