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Autologous bone marrow cell transplantation for myocardial infarction

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Executive Summary

Heart failure is a disease characterised by a severe deficiency in ventricular pump function. It can arise from a variety of causes, however in western society its most common cause is myocardial infarction. Myocardial infarction itself is caused by the narrowing of epicardial blood vessels resulting from build-up of atheromatous plaque, which can lead to partial or total occlusion of vessels, creating imbalances in the oxygen supply and demand of the myocardium. In patients who have suffered myocardial infarction, a process known as myocardial remodelling, characterised by myocyte apoptosis, cardiomyocyte replacement by fibrous tissue in the ventricular wall, progressive expansion of infarct area and dilation of the left ventricular lumen, leads to heart failure.

In Australia, coronary heart disease deaths are used as a measure of acute myocardial infarction death. Between 1999 and 2000 there were 29,731 coronary heart disease events (deaths plus non-fatal hospital admissions) in men and 18,582 coronary heart disease events in women aged between 40 and 90 years. This makes coronary heart disease responsible for 21% of all deaths among people in this age group. In 1995 results from the National Health Survey revealed that 506,461 Australians or 2.8% of the population reported to have heart disease.

Autologous bone marrow cell transplantation is designed to improve cardiac function and inhibit cardiac remodelling by replacing the fibrous scar tissue (created by myocardial infarction) with viable myocardium. The procedure involves the harvest of bone marrow cells and their delivery into the infarcted myocardial region. Harvest of bone marrow cells can be performed under general or local anaesthesia while delivery is performed under general anaesthesia by a cardiologist or cardiac surgeon (depending on the delivery method).

Currently, the best treatment option for patients suffering from heart failure is heart transplantation. However due to the severe worldwide lack of available donor hearts and large number of sufferers this is not a widely available option. Alternative treatment options are limited to the treatment of the established disease and at best are able to slow down the progression of heart failure. There are currently no treatment strategies which address the underlying cause of the disease or aim to replace damaged cardiomyocytes. Therefore the prevention of heart failure in patients who have suffered myocardial infarction would present a significant advantage over current treatment options which treat the already established disease.

Autologous bone marrow cell transplantation appears to be a safe procedure when cell transplantation is performed via either a transvascular approach or direct injection into

the infarcted region. Few serious short term adverse events are associated with autologous bone marrow cell transplantation. Unfortunately transplantation via bone marrow cell mobilisation is associated with a high rate of restenosis making this option dangerous and much less favourable than the transvascular or direct injection transplantation approaches.

Autologous bone marrow cell transplantation has lead to significant improvements in various indicators of cardiac function in patients receiving cell transplantation via a transvascular approach. Transplantation via direct injection into the infarct-related region also demonstrated improvements in cardiac function but the positive effects were not as evident as the transvascular approach. Results were generally reported for short follow-up periods of four to six months. Therefore the long term benefits (if any) remain unknown.

Coronary heart disease has costly consequences for the Australian healthcare system. In 1993-1994 it was estimated that direct healthcare expenditure on coronary heart disease was $894 million or 2.8% of the total recurrent health expenditure. Recent data (2006) reports that heart failure accounts for 11% of the $3,719 million utilised for the treatment of cardiovascular disease in Australia.

Further investigation is required to determine the long term safety and efficacy of autologous bone marrow cell transplantation. This would indicate whether the significant short term benefits experienced by patients could be maintained over the long term and determine which group of patients stand to benefit the most from this potentially revolutionary treatment.

Autologous bone marrow cell (ABMC) transplantation for the treatment of acute and chronic myocardial infarction, and resultant heart failure, has the potential for clinical application. Studies to date report that ABMC transplantation is safe and is associated with modest improvement in cardiac function and morphology. However, the variety of diagnostic tests used to assess cardiac function and the differences in reported outcome measurements limit its potential applicability. Standardised evaluation and outcomes measurement is required to inform the ongoing applicability of this technology.

It is anticipated that this technology will be regulated as a pharmaceutical in Australia. Consequently, its introduction into Australia is likely to require consideration by the existing pharmaceutical process.

Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures - Surgical, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (HealthPACT) on the state of play of the introduction and use of autologous bone marrow cell transplantation for myocardial infarction.

Autologous bone marrow cell transplantation is designed to improve left ventricular function among patients with acute or old myocardial infarction. The procedure would be offered through cardiologists or cardiac surgeons (depending on delivery method) and is currently not in use in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of autologous bone marrow cell transplantation for the treatment of myocardial infarction, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with autologous bone marrow cell transplantation for the treatment of myocardial infarction.

Background

Cardiovascular disease (CVD) is a term coined to describe diseases affecting the heart and blood vessels and is one of the many health problems that prevail in society today. Research has revealed that CVD has emerged as one of the major health concerns throughout the world, to the extent that it exceeds infection as the leading cause of death worldwide (Ott *et al.* 2005). Numerous efforts has been initiated to treat CVDs, however there has been little progress in treating one key CVD, heart failure. Defined as a severe deficiency in ventricular pump function, heart failure arises from a finite number of terminal effector mechanisms, regardless of the cause. These include defects intrinsic to cardiac muscle cell contractility (due to altered expression or operation of calcium-cycling proteins), components of the sarcomere, enzymes for cardiac energy production, defects extrinsic to cardiac muscle cells (such as interstitial fibrosis, affecting organ-level compliance) and myocyte loss unmatched by myocyte replacement (Dimmeler *et al.* 2005).

In western societies, myocardial infarction is the principal cause of heart failure (Itescu *et al.* 2003). The most frequent cause of myocardial infarction is the narrowing of epicardial blood vessels as a result of atheromatous plaques. Plaque rupture with subsequent exposure of the basement membrane will result in platelet aggregation, thrombus formation, fibrin accumulation, hemorrhage into the plaque, and varying degrees of vasospasm. These can lead to partial or total occlusion of the vessel, causing imbalances between the oxygen supply and demand of the myocardium. A case of prolonged myocardial ischemia that leads to cell necrosis is referred to as acute myocardial infarction (AMI). Myocardial infarction can be categorized with the use of cardiac markers; categorization is considered part of a spectrum referred to as acute coronary syndromes that includes ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (Fenton *et al.* 2006). Myocardial contraction is severely diminished within a few minutes of the cessation of blood flow; however subsequent myocardial injury is fully reversible for up to 20 minutes following the onset of ischemia. If profound ischemia persists beyond an hour, isolated myocyte necrosis will progress to confluent sub-endocardial necrosis, which then spreads towards the epicardium (Rosengart *et al.* 2000). During the acute phase of myocardial infarction, the ultimate goal is reperfusion, essentially an effort to salvage as much myocardium as possible and to restore contractile function of the heart chambers by restoring blood flow. Pharmacological interventions for reperfusion would encompass the administration of thrombolytic drugs (e.g. streptokinase, urokinase) and aspirin. In addition to this, surgical interventions such as percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG) may be utilised as well (Fenton *et al.* 2006).

Heart failure after AMI occurs as a result of a process known as myocardial remodelling. This process is characterised by myocyte apoptosis, cardiomyocyte replacement by

fibrous tissue deposition in the ventricular wall, progressive expansion of the initial infarct area and dilation of the left ventricular lumen (Itescu *et al.* 2003). Current therapy for heart failure is limited to the treatment of an established disease and is predominantly pharmacological in nature, aiming primarily to suppress the neurohormonal axis that causes excessive cardiac activation through angiotensin or norepinephrine-dependent pathways (Itescu *et al.* 2003; Wollert and Drexler 2006). The substantial progress in understanding the pathophysiology of heart failure and the development of treatment strategies have succeeded in slowing the progression of the disease and have led to improved clinical outcomes (Wollert and Drexler 2006). Nevertheless current strategies do not address the underlying cause of the disease, which is the damage to cardiomyocytes and the vasculature sustained during AMI and the progressive loss of cardiomyocytes in the failing heart (Wollert and Drexler 2006). The only definitive therapy for heart failure is cardiac transplantation, an option that is limited to less than 3000 patients worldwide annually due to the severely limited supply of donor organs (Itescu *et al.* 2003; Ott *et al.* 2005). Despite the technological advances of implantable medical devices (left ventricular assist devices [LVAD] etc.) which have facilitated dramatic enhancement of organ perfusion, reduction in wall stress, improvement in functional capacity and enhanced quality of life; the implantation of these cardiac-assist/replacement devices is not an option for a vast majority of heart failure patients (e.g. patients over 65 years of age) (Ott *et al.* 2005) and carries inherent risks such as infectious, haemorrhagic and thromboembolic complications (Silva *et al.* 2004). In an effort to overcome the limited supply of donor hearts, clinicians and researchers have proposed utilising LVADs as destination therapy in patients where cardiac transplantation is not possible. Even so, LVADs do not encourage sufficient myocardial recovery to allow for the removal of the device at a later date and is unlikely to be capable of circumventing the need for cardiac transplantation indefinitely (Ott *et al.* 2005). Therefore it is clear that the development of approaches to prevent heart failure after myocardial infarction would be substantially more advantageous compared to techniques that ameliorate or treat a disease that has established itself.

Description of the Technology

Theoretically, replacement of the akinetic scar tissue (caused by AMI) with viable myocardium should improve cardiac function and inhibit cardiac remodelling. Lately, the prospect of tissue repair by transplantation of autologous adult progenitor cells has captured the attention of clinicians and researchers confronted with the limited treatment options for heart failure in acute or chronic ischemic heart disease. Various hypotheses with regards to the mechanism in which stem cell transplantation can reverse cardiac remodelling have been presented, one such hypothesis revolves around the ability of stem cells to differentiate into other cells (transdifferentiation). Traditionally, adult stem cells were thought to differentiate into progeny only within tissue lineage boundaries; however a relatively new concept of adult stem cell plasticity predicts that stem cells can transdifferentiate into cell types outside of their original lineage. Results from animal

studies have inferred that hematopoietic stem cells transdifferentiate into cardiomyocytes and vascular cells after transplantation into infarcted myocardium (Wollert and Drexler 2006). Furthermore, the accustomed thought of the heart as an organ composed of terminally differentiated myocytes incapable of regeneration has been challenged. Evidence from trials have indicated that a fraction of cardiomyocytes is able to re-enter the cell cycle (mitosis) and that limited regeneration can take place after tissue injury through the recruitment of resident cardiac stem and progenitor cells (Wollert and Drexler 2006; Ye *et al.* 2006). However, this regenerative capacity is by far too limited to compensate for the loss of myocardium during AMI (Ozbaran *et al.* 2004). Some researchers have postulated that the functional benefits observed after stem cell transfer in animal models of cardiac injury may relate to secretion of paracrine factors that can augment surviving cardiomyocyte function and confer a survival advantage on compromised or hypoxic tissue (Grigoropoulos and Mathur 2006; Wollert and Drexler 2006). To this date, the exact mechanism in which stem cell transfer can improve perfusion and contractile performance of the injured heart remains unknown, and the controversies surrounding the ability of these cells to undergo transdifferentiation continues to exist (Grigoropoulos and Mathur 2006). However, irrespective of the mechanism, there appears to be a general agreement that stem cells transplantation has considerable potential in reversing cardiac remodelling (Wollert and Drexler 2006).

At present, bone marrow is one of the most common sources of cells used for clinical cardiac repair. Bone marrow contains a complex assortment of progenitor cells, including hematopoietic stem cells (HSC); also known as side population (SP) cells, defined by their ability to expel a Hoechst dye, which account for most or possibly all long-term self-renewal and reconstitute the full panoply of hematopoietic lineages after single-cell grafting; mesenchymal stem cells (MSCs) or stromal cells; and multipotential adult progenitor cells (MAPCs), a subset of mesenchymal cells. Bone marrow is aspirated under local or general anaesthesia and the entire mononuclear cell fraction (a heterogenous mix of previously mentioned cells) is obtained, or if necessary, specific subpopulations can be purified and these isolated cells can be injected or infused into the heart without the need of ex-vivo expansion. However in certain cases, expansion in cell culture may prove to be desirable or advantageous if defined subpopulations of cells can lead to potentially better clinical outcomes (Dimmeler *et al.* 2005). Alternatively, peripheral-blood derived progenitor cells (circulating progenitor cells [CPCs]), which are derived from the bone marrow, can be used for clinical cardiac repair if desired. CPCs are isolated from mononuclear blood cells and are selected ex vivo by culturing in endothelium specific medium prior to injection or infusion into the heart. Current research has indicated that CPC levels can be elevated with hematopoietic stem cell-mobilising factors, granulocyte-colony stimulating factor (G-CSF) and SCF (stem cell factor), and therefore can be utilised to harvest CPCs for transplantation to the heart (Dimmeler *et al.* 2005).

The Procedures

The goal of a cell delivery strategy is to transplant sufficient numbers of cells into the myocardial region of interest and to achieve maximum retention[1] of cells within that area (Wollert and Drexler 2005; Wollert and Drexler 2006). There are three main modes of bone marrow cell (BMC) delivery documented within the literature; transvascular infusion, direct ventricular wall injection and progenitor cell mobilisation.

a) Transvascular approaches

If a transvascular approach is employed, cell adhesion, transmigration though the vascular wall and tissue invasion are important factors in determining the retention rate. Transvascular strategies appear to be more suited to the treatment of recently infarcted as opposed to chronically infarcted myocardium when chemoattractants are less abundantly expressed. In addition, selective application into a reperfused infarct-related coronary artery offers the advantage of delivering the maximum concentration of cells homogenously to the site of injury. A commonly utilised method of transvascular BMC delivery is via the central lumen of an over-the-wire balloon catheter. During BMC infusion, transient balloon inflations are applied to momentarily halt blood flow in order to maximise the contact time of the BMCs with the microcirculation of the infarct-related artery (Wollert and Drexler 2005).

b) Direct injections

An alternative transplantation method would involve direct myocardial injections, a technique which may be preferentially used in patients presenting late in the disease process where an occluded coronary artery precludes transvascular cell delivery (e.g. chronic myocardial ischemia) or when cell homing signals are expressed at low levels within the heart[2]. Direct intramyocardial injections appear to be especially suited for the application of large cells (myoblasts and mesenchymal stem cells) as transvascular infusion of these cells may cause microembolisation after delivery. Three routes for direct intramyocardial cell delivery has been described in the literature (Wollert and Drexler 2005):

1) Transepicardial cell injection: a technique which can be performed as an adjunct to coronary artery bypass grafting and allows for direct visualisation of the myocardium; however the invasive nature of this technique hinders its application as a stand-alone procedure.

2) Transendocardial injection: direct injection of cells into the left ventricular wall may be achieved by advancement of an injection needle catheter across the aortic valve and positioned against the endocardial surface. Electromechanical

[1] Retention is defined as the fraction of transplanted cells retained in the myocardium for a short period of time (hours).

[2] Depressed cell homing signals in the heart will result in less BMC retention; therefore the use of direct injections would be advantageous.

mapping of the endocardial surface can be used to delineate viable, ischemia, and scarred myocardium before cell injections.

3) Transcoronary vein injection: a catheter system incorporating an ultrasound tip for guidance and an extendable needle for myocardial access to deliver cells into the myocardium via the coronary veins.

c) Progenitor cell mobilisation

Mobilisation of bone marrow progenitor cells can be achieved with G-CSF administration, leading to increased concentrations in the circulation. Hence, administration of G-CSF can be utilised as an alternative to cell infusion or injection to circumvent the additional interventions required for stem cell delivery. Further understanding of this process should lead to an increase in the number of BMCs arriving at targeting ischemic myocardium, with the potential for increasing myocardial recovery in a dose-dependant process (Grigoropoulos and Mathur 2006).

Intended Purpose

For the treatment of patients recovering from myocardial infarction as a means of preventing necrosis of myocardial cells leading to heart failure.

Clinical Need and Burden of Disease

In 1999-2000, there were an estimated 48,313 coronary heart disease [3] (CHD) events in Australia among 40 to 90 year-olds (29,731 among men and 18,582 among women). This equates to an incidence rate[4] of 605 coronary events per 100,000 population aged 40 to 90 years. CHD is a major cause of morbidity and the most common cause of sudden death in Australia, accounting for 21% of all deaths among 40 to 90 year-olds in 2000; 23,012 deaths with 13,034 among men and 9,978 among women. This equates to a mortality rate of 285 deaths per 100,000 population aged 40 to 90 years. With regards to the prevalence of the disease, the 1995 National Health Survey revealed that 2.8% of respondents reported they had heart disease, translating to 506,461 Australians (Mathur 2002).

[3] It is important to note that mortality due MI is not accurately recorded within the Australian death certificate, therefore making it too unreliable for useful analysis (Dobson *et al.* 1983). In contrast, coronary heart disease (CHD) is coded accurately and reliably in Australian death certificates. Therefore the Australian Institute of Health and Welfare utilises CHD deaths as a measure of acute myocardial infarction (AMI) mortality rates due to the fact that there is a high likelihood that death coded as CHD are in fact deaths due to AMI. In view of this, CHD data will be utilised to represent AMI incidence and prevalence as well.

[4] CHD events are defined as CHD deaths plus non-fatal hospital admissions for AMI.

Hospital admissions for AMI are useful indicators for incidence as well, albeit it would undoubtedly be an underestimation of actual AMI incidences. In Australia, hospital admissions for AMI occurs predominantly in individuals aged 40 years and over (97%), with almost two thirds occurring among Australians aged 65 to 90 years. Data on hospital admissions revealed that in 1999-2000, there were 28,002 hospital admissions among 40 to 90 year-olds where AMI was the principal diagnosis and length of stay was greater than 2 days or the patient died within 2 days of admission (17,986 men and 10,016 women). This equates to an admission rate of 351 per 100,000 population aged 40 to 90 years. The age standardised rate of AMI admissions for Australians aged 40 to 90 years has been steadily decreasing since the early 1990s, which corresponds to a decrease in AMI incidents. However, it is important to note that despite falling admission rates, the absolute number of AMI admissions have remained virtually the same due to the increasing average age and overall growth of the population. As expected, men are more likely to be admitted for AMI (twice as likely), consistent with their greater risk of suffering a heart attack (Mathur 2002).

The number of public hospital separations[5] in Australia for patients with acute AMI in 2003 to 2004 was 46,885. Of these patients, there were 30,795 male and 16089 female separations, representing a total of 270,125 patient days. This equates to a rate of 519 separations per 100,000 population of Australians aged over 40 years (Mathur 2002).

In New Zealand, 51.1% of deaths in 2003 were due AMI, with male Maori death rates of 82 per 100,000 population and female Maori death rates of 43 per 100,000 population. Meanwhile, non-Maori male and female AMI death rates were 43 per 100,000 population and 22 per 100,000 population, respectively[6] (New Zealand Health Information Service 2006).

The number of public hospital separations in New Zealand for patients with AMI in 2002-2003 was 11,582 (7,272 male and 4,310 female). Provisional 2002 data reported 3,252 deaths with an underlying cause of AMI (New Zealand Health Information Service 2006).

Stage of Development

At the time of writing, one Australian case series study with five patients was identified (Boyle A *et al.* 2006). The study reported the results of intracoronary infusion of G-CSF mobilised CD34+ cells in patients suffering chronic ischemic heart disease. Unfortunately, the authors concluded safety could not be established and further studies

[5] The term 'separation' refers to the episode of care, which can be a total hospital stay (from admission to discharge, transfer or death), or a portion of a hospital stay beginning or ending in a change of type of care (for example, from acute to rehabilitation). A record is included for each separation, not for each patient. So patients who separate more than once have more than one record in the database (AIHW 2006)

[6] Reported New Zealand AMI death rates are approximations based on charts published by the New Zealand Health Information Service.

should be performed. However the study demonstrates that although autologous bone marrow cell transplantation for myocardial infarction or heart failure has not been conducted, bone marrow cell transplantation for the treatment of ischemic heart disease (a disease which may lead to myocardial infarction or heart failure) is being investigated in Australia.

International Utilisation

COUNTRY	LEVEL OF USE		
	Trials underway	**Limited use**	**Widely diffused**
Belgium	✓		
Brazil	✓		
China	✓		
Germany	✓		
Italy	✓		
Norway	✓		
South Korea	✓		
Spain	✓		
Switzerland	✓		
United States	✓		

Existing Comparators

At the time of writing, there are no alternative therapies that offer the potential to *regenerate myocardial tissue* after AMI. However, there are several alternative options in the realm of cell-based therapy for AMI.

Autologous skeletal myocyte transplantation has been investigated as a substitute for cardiomyocytes with varying success. Both skeletal myocytes and BMCs have comparable characteristics (autologous sources, ease of in vitro expansion), but skeletal myocytes appear to be more resistant to ischemia, and therefore may be more suitable for transplantation into ischemic myocardium. However, this technique is affected by the delay of more than three to four weeks before the harvest of skeletal muscle biopsy can be transplanted due to the processing required to achieve the required number of cells. Trials of skeletal myocyte transplantation for MI are currently ongoing (Ye *et al.* 2006).

Although heart failure can be a direct consequence of prior myocardial infarction, both are separate medical conditions. The safety and efficacy assessment of the use of bone marrow stem cells to treat patients with either of these conditions has been divided into two separate sub-sections to reflect this fact. The following diagram illustrates the presentation of the safety and efficacy studies based on condition and method of cell delivery (Figure 1).

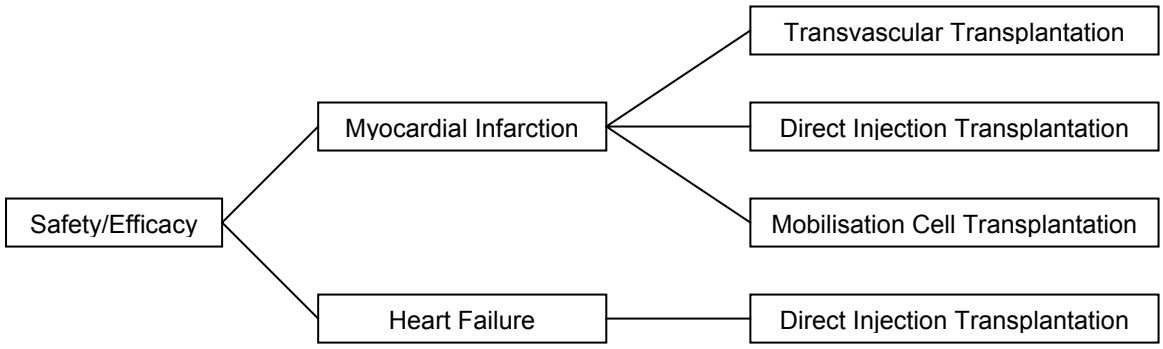


Figure 1: Presentation of the safety and efficacy studies based on condition.

Safety

Myocardial Infarction:

Transvascular Transplantation

Transvascular transplantation of bone marrow stem cells in the setting of myocardial infarction was on the whole a relatively safe procedure, taking into consideration the condition of the patients involved. Few deaths were reported in the studies included and no major recurrent adverse events were reported as a result of transvascular transplantation of cells. Table 1 summarises adverse events reported by the included studies.

Table 1: Adverse events following transvascular transplantation for Myocardial Infarction

Study	Study details	Cell type (number transplanted)	Adverse events summary
Assmus et al. (2006)	Level II intervention evidence *Follow-up* 3 months *Patients* 75	BMC ($205x10^6 \pm 110x10^6$) CPC ($22 x10^6 \pm 11x10^6$)	Local dissection of coronary arterial wall: 3/135 infusion procedures Defibrillation from implanted defibrillator during cell infusion: n=1 Infarct vessel revascularisation: n=2 (CPC group), n=4 (BMC group) Cumulative total in-hospital events: no significant difference between groups

Meyer et al. (2006)	Level II intervention evidence *Follow-up* 18 months *Patients* 60	BMC ($24.6\pm9.4 \times 10^8$ nucleated, $9.5\pm6.3 \times 10^6$ CD34+, $3.6\pm3.4 \times 10^6$ hemopoietic colony forming cells)	Infarct vessel repeat PCI: n=4 (control group), n=5 (BMC group) Heart failure: n=3 (control group),n=1 (BMC group) Death: n=1 (control group) AMI: n=1 (BMC group) No statistically significant difference between groups in clinical end points, composite clinical end point and incidence of syncope, documented sustained arrhythmias or NYHA functional class.
Schachinger et al. (2004)	Level II intervention evidence *Follow-up* 12 months *Patients* 59	Blood derived progenitor cells (no. not reported) BM derived progenitor cells ($5.5\pm3.9 \times 10^6$ CD34+/CD45+ cells)	Stented lesion restenosis: n=5 (reported by Assmus et al. 2002) Mild angina during balloon inflation: n=NR Reinfarction: n=1 (not related to treatment) Embolic occlusion: n=1 (group not stated) Death: n=1 (BM group, cardiogenic shock) No statistically significant difference between groups in adverse events (death, recurrence of AMI, hospitalisation for heart failure).
Schachinger et al. (2006)	Level II intervention evidence *Follow-up* 4 months *Patients* 204	BMC (no. not reported)	Death: n=6 (placebo group), n=2 (BMC group) No. of revascularisations: n=35 (placebo), n=21 (BMC), p=0.03 No statistically significant difference between groups in occurrence of individual adverse events (death, MI, rehospitalisation for heart failure, cerebral infarction and documented ventricular arrhythmia or syncope). Exception was no. of revascularisations at 1 year.
Janssens et al. (2006)	Level II intervention evidence *Follow-up* 4 months *Patients* 67	BMC ($304 \times 10^6 \pm 128 \times 10^6$ nucleated cells and $172 \times 10^6 \pm 72 \times 10^6$ mononuclear cells)	Recurrent angina: n=1 (control group), n=2 (treatment group) Acute in-stent thrombosis: n=1 (control group) Lung adenocarcinoma: n=1 (control group) Death: n=1 (BMC group, haemorrhagic shock) Squamous larynx carcinoma: n=1 (BMC group)
Strauer et al. (2005)	Level II-1 intervention evidence *Follow-up* 3 months *Patients* 36	BMC (4-6 fractional infusions of 15-22 $\times 10^6$ mononuclear cells)	Restenosis: n=1 (BMC group)
Fernandez Aviles et al. (2004)	Level II-1 intervention evidence *Follow-up* 6 months *Patients* 33	BMC ($78\pm41 \times 10^6$ cells)	Progression of non-significant stenosis in non infarct related artery: n=2 (BMC group)

Perhaps one of the most comprehensive studies conducted to date regarding the intracoronary transplantation of bone marrow progenitor cells was published recently by a German group (Assmus *et al.* 2006). The three phase study enrolled patients with stable ischaemic heart disease who had suffered AMI at least three months previously and randomised them to transvascularly receive balloon catheter mediated intracoronary infusion of progenitor BMCs, circulating progenitor cells (CPC) or no infusion at all (control). The study design included a randomised pilot trial with 17 patients (phase 1), a randomised controlled trial with 75 patients (phase 2) and a crossover (phase 3) (Figure 2). Initially, 35 patients received progenitor BMC infusions (phase 1 and 2), 34 received CPC infusions (phase 1 and 2) and 23 patients were allocated to the control group (phase 2). The median time since myocardial infarction was 24, 50 and 60 months in the control, CPC and progenitor BMC groups respectively.

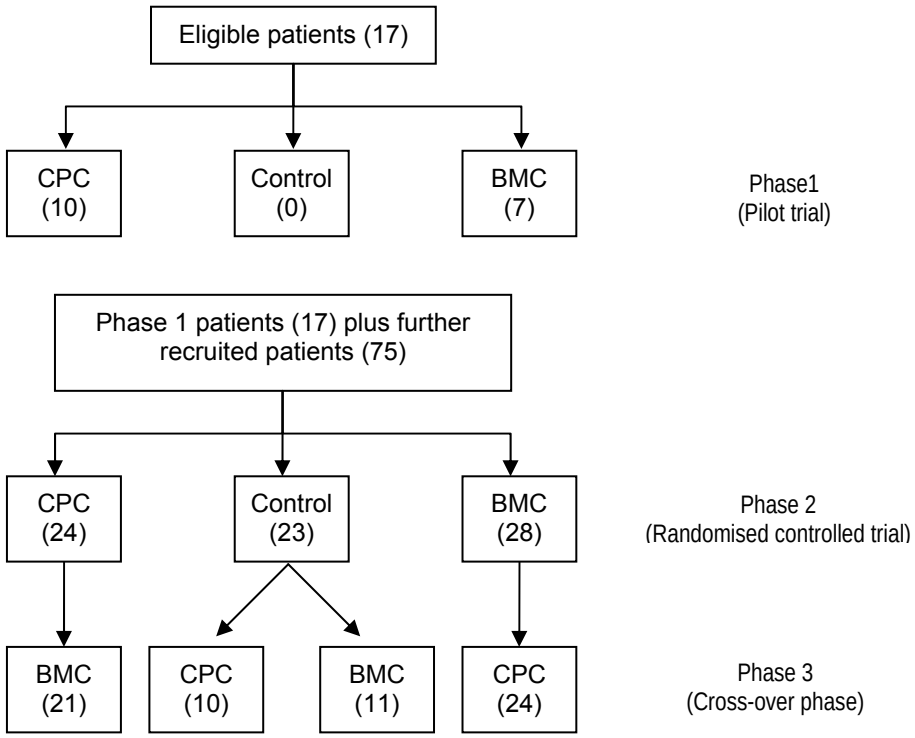


Figure 2: Assmus *et al.* (2006) study design.

A total of 135 cell infusions into the infarct-related artery were performed, in which three required stent implantation in order to correct a local dissection of the coronary arterial wall. Two of these patients developed subsequent increases in their level of creatine kinase indicating possible myocardial damage. All three patients went on to continue uneventfully for the remainder of the study. Post-procedurally (during the in-hospital period) there were no reports of death and the cumulative total of in-hospital events[7] did

[7] In-hospital events included death, MI, infarct-vessel stent thrombosis, stent thrombosis at site other than target vessel, cerebral infarction and ventricular arrhythmia.

not statistically differ between the groups. After discharge, one death occurred in the control group and infarct-vessel revascularisation was required twice in the CPC group and four times in the progenitor BMC group. The cumulative total of after discharge events[8] did not statistically differ between the groups (3 control, 5 CPC, 0 BMC). Although no major adverse events were reported in this study and the cell infusion procedure was in general uneventful, laboratory indicators of an inflammatory response were not reported in this study. Nonetheless, given the lack of significant occurrences of both in-hospital and after discharge events related to the procedure, this study suggests infarct-related artery infusion of progenitor BMCs (and CPCs) may be a safe procedure.

The randomised controlled BOOST (Bone marrow transfer to enhance ST-elevation infarct regeneration) trial examined the safety and efficacy of transvascular BMC infusion approximately five days after successful PCI for ST-elevated MI in 60 patients (30 control, 30 BMC) (Meyer *et al.* 2006). No complications were observed during BMC harvest or BMC infusion. Troponin T serum levels remained stable in all patients 24 hours after BMC infusion, indicating the procedure did not inflict additional ischemic damage to the myocardium. One control patient died from progressive heart failure nine months after randomization. During the 18 month follow-up, three patients (10%) from the control group and one patient (3.3%) from the BMC group were re-hospitalised for de-compensated heart failure. An additional BMC patient developed non-ST-segment elevation MI in the left circumflex territory four months after cell transfer; the patient subsequently underwent PCI and completed the study. Four control patients (13.3%) and five BMC patients (16.7%) required repeat PCI of the infarct-related vessel. There were no cases of sub-acute or late in-stent thrombosis or recurrent AMI in the infarct-related vessel reported in any of the BMC patients. Overall, the investigators found no significant differences between the two treatment groups in regards to clinical end-points, a composite clinical end-point (death, MI and re-hospitalisation due to heart failure), and the incidence of syncope or documented sustained arrhythmias or the New York Heart Association (NYHA) functional class at 18 months.

The preliminary report of the first 20 patients enrolled in the Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI) trial reported early results of patients randomised to receive blood-derived or bone marrow derived progenitor cells (Assmus *et al.* 2002). Patients were randomised to intracoronary infusion of blood-derived (n=11) or bone marrow-derived progenitor cells (n=9) via an over-the-wire balloon catheter 4.4 ± 1.5 days after AMI and were compared to a non-randomised reference group (n=11). The report documented that white blood cell count and C–reactive protein levels in both cell recipient groups remained stable before and 24 hours after cell therapy, indicating a lack of significant inflammatory response. Troponin T serum levels (elevated prior to cell transplantation)

[8] After discharge events included death, MI, rehospitalisation for HF, stent thrombosis after revascularisation, coronary bypass surgery, cerebral infarction, syncope and ventricular arrhythmia.

continued to decrease 24 hours after cell transplant, indicating the procedure did not cause further ischemic damage to myocardium. Restenosis of the stented lesion occurred in five patients while reinfarction (not related to treatment) occurred in another.
Schachinger and colleagues reported the one year results of the TOPCARE-AMI trial, which recruited 59 patients (Schachinger *et al.* 2004). Thirty patients were randomised to receive blood-derived progenitor cells while 29 received bone marrow-derived progenitor cells. In addition to evaluating procedural safety through troponin T levels, (which showed no signs of further myocardial damage as a result of cell infusion) and C-reactive protein levels (which showed a lack of a systemic pro-inflammatory response), other safety-related observations not presented in the Assmus *et al.* (2002) publication were reported. Procedure-related complications were limited to mild or no angina during balloon inflation during cell infusion. No complications during cardiac catheterisation such as ventricular arrhythmias, new thrombus formation or embolisation after cell infusion or dissection due to balloon inflations were reported. One patient with a small distal thrombus at the proximal stent edge did however experience embolic occlusion of the very distal vessel after balloon inflation, most likely owing to repeated intracoronary instrumentation required for cell infusion. None of the patients experienced an increase in Thrombolysis In Myocardial Infarction (TIMI) blood flow and following final angiography, embolisation as a result of cell infusion was ruled out. In patients who received bone marrow-derived cells, the bone marrow puncture did not lead to bleeding complications in patients receiving maximal anti-coagulant and anti-platelet therapy for cardiac catheterisation. Following the cell infusion procedure, 24 hour telemetric monitoring detected no ventricular arrhythmias. One patient died of cardiogenic shock in the bone marrow-derived group. The patient suffered a myocardial infarction and subsequent death at day five.
At the one year follow-up there were no further adverse events resulting from progenitor cell infusion. No syncope, ventricular arrhythmia or cerebral infarction was reported in any patient. Furthermore, 24 hour Holter monitoring in 47 patients showed no signs of ventricular tachycardia. No patient was re-hospitalised for the treatment of heart failure.

In a recent multi-centre, randomised sham-controlled trial the effects of intracoronary infusion of bone marrow-derived progenitor cells versus a placebo medium were investigated (Schachinger *et al.* 2006). Patients with acute ST-elevation myocardial infarction successfully reperfused with stent implantation and with residual left ventricular regional wall motion abnormality were randomised to a treatment group (bone marrow aspiration three to six days after reperfusion therapy and infusion of BMCs) or control group (bone marrow aspiration and infusion of medium containing patient's own serum). Patients received infusion of cells with the use of an over-the-wire balloon catheter. A total of 103 patients were randomised to the control group and 101 to the treatment group. No bleeding complications or hematoma formation at the bone marrow puncture site were reported. Following bone marrow aspiration, intracoronary infusion was attempted in 101 control patients (one withdrew consent and another experienced fever and elevated C-reactive protein levels) and 101 treatment patients.

Intracoronary infusion was successful in all of the treatment group patients while in three control group patients intracoronary infusion could not be performed (one had no guide-wire passage, one had air embolism and one had a thrombus in another vessel). At the one year follow-up, the occurrence of individual adverse events (including death, MI, rehospitalisation for heart failure, cerebral infarction and documented ventricular arrhythmia or syncope) was not significantly different between groups with the exception of the number of revascularisations which were significantly less in the treatment group ($p = 0.03$). At the one year follow-up six deaths in the placebo group and two deaths in the BMC group had occurred, however reasons were not stated.

Another recent study, a randomised, double-blind, placebo-controlled study was reported (Janssens *et al.* 2006). Patients with AMI and successful PCI with stent implantation and significant LV dysfunction were randomised to receive either BMC or placebo (sodium chloride and autologous serum solution) infusion. All patients underwent BMC harvest and cell or placebo solutions were injected using a perfusion catheter one day after PCI. Median time from symptom onset to PCI was less than five hours for both groups. One patient in the treatment group died from haemorrhagic shock at the two month period. One patient in the control group experienced an acute in-stent thrombosis after two months but was successfully treated with the implantation of a drug eluting stent. Another control group and two treatment group patients developed recurrent angina, which required dilatation of an in-stent stenosis. Finally, during the follow-up examination, one patient from the control group was diagnosed with lung adenocarcinoma and one from the treatment group was diagnosed with squamous larynx carcinoma. Both were heavy smokers.

In 2005, three years after an initial study on the intracoronary transplantation of mononuclear BMCs for MI, Strauer and colleagues published a second study investigating the use of BMCs in the treatment of old myocardial infarction (Strauer *et al.* 2005). Eighteen men, with chronic MI successfully treated with percutaneous transluminal coronary angioplasty (PTCA) and/or stent implantation received intracoronary infusions of 15-22 x 10^6 mononuclear cells via an angioplasty balloon catheter 27 $\pm$ 31 (mean $\pm$ SD) months after initial occurrence of myocardial infarction. These men were compared to a control group (n=18) who did not undergo bone marrow aspiration for a follow-up period of three months. No procedure-related or cell-induced complications were reported. White blood cell count, C-reactive protein serum levels and creatine phosphokinase serum levels were measured immediately prior to and immediately after treatment in order to show any inflammatory response as a result of cell infusion. No significant increases in white blood cell count, C-reactive protein and an expected increase (due to bone marrow puncture and/or cardiac catheterisation) in creatine phosphokinase levels indicated that no inflammatory response had taken place. Electrocardiography (ECG) at rest, 24 hour Holter ECG and echocardiography were also performed immediately after cell treatment and again at the three month follow-up. These results showed the absence of any rhythm disturbances at all time points. One

patient who had received cell infusion developed restenosis but was successfully treated with stent implantation.

In another safety and feasibility trial, patients who received intracoronary infusion of BMCs using an over-the-wire balloon catheter were investigated (Fernandez-Aviles *et al.* 2004). Twenty patients received BMC infusions while 13 control patients received standard therapy. All patients had received stent implantation within 24 hours of thrombolysis. Patients received an average of $78 \pm 41 \times 10^6$ cells in the culprit artery after a mean of 13 ± 5.5 days after symptom onset. No peri-procedural complications were reported in any of the patients who received BMC infusions. Levels of myocardial injury markers, troponin T and creatine kinase-MB (CK-MB; indicator of myocardial damage) did not significantly increase at 24 hours following cell infusion compared to before cell infusion levels. Infusion of the cells did not induce any statistically significant changes in the thermodilution coronary flow reserve or pressure fractional flow reserve values when compared to baseline values. Patients were followed up for a mean period of 11 ± 5 months. During this time no major cardiac events or symptoms, spontaneous or stress induced arrhythmias were reported. However, two cases of progression of non-significant stenosis in a non-infarct related artery requiring stent implantation were reported. Additionally, one patient experienced a transient stroke following cell infusion without sequelae.

One of the earliest clinical trials to investigate the therapeutic potential of BMCs for the treatment of AMI was published in 2002 (Strauer *et al.* 2002). This non-randomised, phase I study investigated the effects of intra-coronary transplantation of autologous mononuclear BMCs in 20 patients (10 BMC, 10 control). The time from symptom onset to invasive diagnostics and therapy (including re-canalisation of infarct-related artery and stent implantation) was 12 ± 10 hours. Between five and nine days following symptom onset 10 patients were allocated to receive an infusion of $2.8 \pm 2.2 \times 10^7$ (mean $\pm$ SD) mononuclear bone marrow cells via a balloon catheter. It is unclear how patients were allocated to the treatment groups and what bias such non-randomised allocation may have introduced. The remaining 10 patients received standard therapy only. No procedure related safety outcomes were reported. Additionally, although baseline values for creatine kinase and CK-MB were given, their post-procedure values were not measured. Indicators of an inflammatory response, such as white blood cell count were not reported either. Therefore although the authors did not report any procedural or post-procedural complications (up to the three month follow-up), the possibility of further myocardial damage or inflammatory response as a result of mononuclear bone marrow cell infusion cannot be discounted.

Direct Injection Transplantation

Only three studies were in which the direct injection transplantation method was used were included. As expected the largest of the three studies reported the largest number and variety of adverse events. Table 2 outlines the adverse events reported by the three studies.

Table 2: Adverse events following direct injection transplantation for Myocardial Infarction

Study	Study details	Cell type (number transplanted)	Adverse events summary
Lunde et al. (2006)	Level II intervention evidence *Follow-up* 6 months *Patients* 100	BMC (68 x10^6 cells)	Hospitalisations: n=6 (control group) n=4 (BMC group) Culprit lesion restenosis: n=9 (control group), n=8 (BMC group) CABG requirement: n=2 (control group), n=3 (BMC group) Progressive heart failure: n=1 (control group), n=1 (BMC group) Pulseless ventricular tachycardia: n=1 (control group) Contamination of cell suspension: n=1 (BMC group) Sustained ventricular tachycardia: n=1 (BMC group) Ventricular fibrillation: n=1 (BMC group) Lung cancer: n=1 (BMC group) Mild chest pain during balloon inflation: n=34 (group not stated) Ischemic ST elevation during balloon inflation: n=36 (group not stated) Acute stent thrombosis: n=2 (group not stated)
Ruan et al. (2005)	Level II intervention evidence *Follow-up* 16 months *Patients* 20	BMC (no. not reported)	TIMI flow grades of 3 for both groups following cell injections.
Hendrikx et al. (2006)	Level II intervention evidence *Follow-up* 4 months *Patients* 23	BMC (60.25 x10^6±31.35 x10^6 cells)	Death: n=1 (control group), n=1 (BMC group) Acute psychiatric illness: n=1

A recently completed study investigated the effects of intracoronary injection of mononuclear bone marrow cells in patients suffering AMI (Lunde *et al.* 2006). In this study patients with AMI of the anterior wall who had undergone PCI and stent implantation were randomised to a treatment group which included the intracoronary injection of 68 x 10^6 mononuclear cells six days after PCI (time from symptom onset to cell injection: six to seven days) or to a control group which did not receive aspiration or sham injection. Unlike the other studies presented so far, this study injected cells into the infarct-related myocardium rather than infusing them. Forty seven patients of the 50 randomised to treatment received successful intracoronary injections of mononuclear

BMCs. Acute stent thrombosis in two patients and low cell viability of 89% in another prevented successful injections. Aspiration of bone marrow had to be repeated in two patients due to low cell viability in one and contamination in another. During the procedure, 34 patients experienced mild chest pain and 36 experienced ischemic ST elevation during balloon inflation. No cases of re-infarction owing to the procedure were reported. Contamination of the cell suspension was found in one patient who was subsequently treated with intravenous vancomycin over three days. It was not clear if this was the same patient who required repeated aspiration of the bone marrow. One of the patients unable to receive intracoronary injections due to acute stent thrombosis went on to suffer re-infarction and was treated with PCI in the right coronary artery on day 27. At the six month follow-up one patient required PCI for culprit lesion restenosis in the control group and coronary artery bypass grafting (CABG) was required in one patient from each group. During the six month angiography, eight patients from each group required PCI for culprit lesion restenosis and further CABG were required in two patients in the treatment group and one in the control group. Re-hospitalisation in one patient from each group was required as a result of progressive heart failure. In the mononuclear BMC group one patient had sustained ventricular tachycardia before the intracoronary injection and one had ventricular fibrillation 24 hours after the injection. Both patients were resuscitated and recovered without sequelae and underwent implantation of defibrillators with no therapy delivered during follow-up. In the control group one patent had pulseless ventricular tachycardia which was converted to sinus rhythm with a precordial thump on day two. One patient in treatment group was diagnosed with lung cancer which retrospectively was evident at time of admission. Four patients in treatment group and six in the control group required re-hospitalisation for other reasons (reasons not stated).

One of the earliest randomised, sham controlled studies to be performed was reported by researchers from China and the United States (Chen *et al.* 2004). In this study AMI patients who had received PCI within 12 hours after symptom onset were randomised to receive intracoronary injection of autologous bone marrow mesenchymal stem cells (BMSC) or a sham injection of saline. Thirty four patients were randomised to receive BMSCs while 34 were randomised to receive saline (control group). All patients underwent bone marrow aspiration eight days after PCI and cells were cultured for 10 days prior to injection. Mean time from PCI to injection of cells or saline was 18.4 $\pm$ 0.5 days (treatment group) and 18.2 $\pm$ 0.3 days (control group). Six one millilitre injections of 8 to 10 x 10^9 cells/ml or 6 mL of saline were directly injected into the coronary artery using an over-the-wire balloon catheter. Patients were followed-up at baseline, three months and six moths after cell injections. No procedural complications, adverse events or deaths were reported by the authors. Electrocardiographic monitoring for 24 hours showed no arrhythmias at three months.

In 2005, a Chinese group of investigators published results from a small randomised controlled trial of the effects of autologous bone marrow cell transplantation in patients

with AMI (Ruan *et al.* 2005). What made this study different from the other studies is the use of Doppler tissue imaging (DTI), a relatively new echocardiograph technique for quantitative assessment of segmental myocardial function. Twenty patients with AMI were randomised to receive intracoronary injection of BMCs (n=9) or diluted serum (n=11) within two hours after successful PTCA (time from symptom onset to hospital admission 12.1 ± 12.6 hours). Unfortunately, very little safety data was provided in this study. The only safety related information presented were TIMI flow grades in both groups which following cell injections was grade 3.

The randomized controlled trial by (Hendrikx *et al.* 2006) of 12 control patients and 11 BMC patients examined the effect of BMC injection within the border zone of the infarct area in patients suffering from chronic MI admitted for elective CABG. One control patient died on the fifth postoperative day due to multi-organ failure secondary to low cardiac output syndrome while another patient was lost to follow-up as a result of acute psychiatric illness. Meanwhile in the BMC group, one patient died on the seventh postoperative day as a result of a perforated esophageal ulcer complicated by mediastinitis. Hendrikx and colleagues found no evidence of increased myocardial damage as a result of the injection of cells (peak CK-total, CK-MB and cardiac troponin I values did not differ significantly between treatment groups).

Mobilisation Cell Transplantation

An alternative method to obtain bone marrow stem cells for intracoronary transplantation involves the use of granulocyte-colony stimulating factor (G-CSF) to mobilise BMCs to the blood in a less invasive manner (Kang *et al.* 2004). Kang *et al.* (2004) investigated G-CSF mobilised peripheral blood stem cell transplantation in patients with acute and old myocardial infarction who had undergone PCI. The safety and improvements in cardiac function of G-CSF based peripheral blood stem cell (PBSC) transplantation (via an over-the-wire balloon catheter) were investigated in three randomised patient groups: G-CSF plus intracoronary PBSC infusion, G-CSF alone and patients who received a sham treatment (control) (Table 3).

Table 3: Adverse events following cell mobilization transplantation for Myocardial Infarction

Study	Study details	Cell type (number transplanted)	Adverse events summary
Kang et al. (2004)	Level II intervention evidence *Follow-up* 6 months *Patients* 28	PBSC ($1.5\pm0.5 \times 10^9$ leucocytes)	Headache complaints: n=3 in patients who received G-CSF High rate of in-stent restenosis at culprit lesion of patients treated with G-CSF led to enrolment for the study being stopped. Five out of seven G-CSF plus cell infusion and 2/3 G-CSF only group patients were affected.

For four days before PCI and stent implantation, patients in the G-CSF plus PBSC infusion and G-CSF alone groups received daily subcutaneous injections of G-CSF. Following the last G-CSF injection patients underwent PCI and stent implantation after which patients in the cell infusion group received intracoronary infusion of PBSCs.

Patients in the control group did not receive a placebo treatment. The study planned to recruit 16 patients in each treatment group, but the study was stopped early due to safety concerns in the G-CSF group. At the time of stopping, 11 patients had completed six months follow-up (seven from cell infusion group, three from G-CSF only group and one from the control group). Patients in the cell infusion group received $1.5 \pm 0.5 \times 10^9$ leucocytes. Enrolment of further patients was cancelled due to an unexpected high rate of in-stent restenosis at the culprit lesion in patients treated with G-CSF. Peri-procedurally there were no serious adverse reactions in the 10 patients (seven in cell infusion and three in G-CSF only) who received G-CSF administration. However, three patients complained of headaches, which were successfully treated with the use of analgesics and termination of G-CSF administration. There were no signs of aggravated angina or ECG changes indicative of ischemia or substantial arrhythmia. Mobilisation of BMCs with G-CSF did not elicit a pro-inflammatory response as indicated by stable levels of C-reactive protein before and directly after G-CSF administration. Furthermore, there were no thrombotic complications during injection of the G-CSF or the peri-procedural period. Patients in the cell infusion group experienced a statistically significant increase in the levels of CK-MB from 3.4 ± 3.0 IU/L prior to PCI to 5.6 ± 4.4 IU/L 12 hours after cell infusion ($p = 0.012$), although no symptoms or signs of significant ischemia or arrhythmia during and after cell infusion were evident. Angiography revealed infusion of cells did not affect microcirculation and coronary flow reserve. During follow-up there were no reports of any deaths, aggravation of heart failure or angina or substantial arrhythmias.

An unexpectedly high rate of in-stent restenosis at the culprit lesion was observed in five of the seven patients in the cell infusion group and 2 of the three patients in the G-CSF only group. Additionally, a close correlation between increase in neo-intimal volume and improvements of systolic function in the cell infusion group suggested that cell transplantation accelerated neo-intimal growth in proportion to the improvement of systolic function. Due to the high rate of restenosis experienced, enrolment in the study was stopped.

The high rate of in-stent restenosis highlights potential complications and risks in using G-CSF mobilised cells. While G-CSF mobilisation is a less invasive method of harvesting BMCs, bone marrow puncture has not presented evidence of serious complications in the previous studies presented. Therefore at present bone marrow puncture appears to be the safest method of harvesting BMCs for intracoronary transplantation. Future studies investigating the use of G-CSF mobilised BMCs should adopt an aggressive anti-restenosis protocol in order to minimise a repeat of the high rates of in-stent restenosis seen in this study.

Heart failure:

Despite the significant numbers of studies investigating the use of BMCs to treat AMI, there are relatively small numbers of clinical studies investigating the therapeutic potential of these cells in the setting of heart failure.

Direct Injection Transplantation

In one of the earliest examples of BMC therapy for the treatment of heart failure, Perin and colleagues transendocardially injected a suspension of mononuclear BMCs into 14 patients with severe ischemic heart failure and compared the effects with nine patients receiving standard therapy (Perin *et al.* 2004). Patients in both groups were considered to be high risk with mean baseline ejection fractions of 26 ± 5.9% and 24 ± 7.4% for the treatment and control group respectively. Patients received injections of cells comprising of a heterogenous cell mixture (mesenchymal stem cells, hematopoietic progenitor cells, endothelial progenitor cells, natural killer lymphocytes, T lymphocytes and B lymphocytes). Few adverse events were reported by the authors resulting from the direct injection of mononuclear BMCs (Table 4).

Table 4: Adverse events following direct injection transplantation for heart failure

Study	Study details	Cell type (number transplanted)	Adverse events summary
Perin et al. (2004)	Level II-1 intervention evidence *Follow-up* 12 months *Patients* 23	BMC ($2X10^6$ cells)	Death: n=2 (BMC group, presumed sudden cardiac death in one and presumed neurological cause in the other) Transient episode of pulmonary oedema (n=1)

No peri-procedural complications were reported. Post-procedurally, one patient suffered a transient episode of pulmonary oedema, which was successfully resolved. At 14 weeks post-procedure one patient (treatment group) died from what was presumed to be sudden cardiac death while at 11 months another patient (treatment group) died presumably from a neurological cause. Despite the injection of several subpopulations of bone marrow mononuclear cells, two, six and 12 month white blood cell count, serum C-reactive protein and brain natriuretic peptide levels did not significantly differ between the two groups, indicating no significant inflammatory response was induced. Further support for the short term safety of the technique was obtained through the absence of any malignant arrhythmias on any of the 24 hour Holter monitoring studies at two and six months following the procedure. No statistically significant changes in the number of premature ventricular contractions or any of the signal averaged electrocardiography parameters of any patient were reported.

Effectiveness

Myocardial Infarction:

Transvascular Transplantation

The effectiveness of transvascular transplantation of bone marrow cells for the treatment of myocardial infarction was reported using a variety of outcome measures. These measures ranged from measurement of left ventricular function (e.g. ejection fraction, end diastolic volume and end systolic volume) which was reported by the majority of studies to measurement of the size of the infarct size. Table 5 presents a summary of the main outcomes reported by studies in which transvascular transplantation of bone marrow cells for the treatment of myocardial infarction was performed.

Table 5: Summary of main outcomes following transvascular transplantation for myocardial infarction

Study	Patient allocation	Main outcomes
Assmus et al. (2006)	*Phase 2/3* BMC (n=35) CPC (n=34) Control (n=23)	*LVEF (mean difference at 3 months, %)* BMC: +2.9 ± 3.6 CPC: -0.4 ± 2.2 (BMC versus CPC p=0.003) Control: -1.2 ± 3.0 (BMC versus Control p<0.001) *Regional contractility (central target area)* BMC: -1.63 ± 0.40 (baseline), -1.38 ± 0.42 (3 months) (p = 0.006) CPC/Control: No statistically significant improvement at 3 months Between groups: No statistically significant difference *Regional dysfunction, LVEDV, LVESV, stroke volume, LV end diastolic pressure (3 months)* No statistically significant improvement in any group **Subgroup analysis:** *No. hypocontractile segments* BMC: 10.1±3.6 (baseline), 8.7±3.6 (3 months) (p=0.02) CPC/Control: No statistically significant improvement at 3 months *No. of normocontractile segments* BMC group: 3.8 ± 4.5 (baseline), 5.4 ± 4.6 (3 months) (p = 0.01) CPC/Control group: No statistically significant improvement at 3 months *Infarct size* No statistically significant improvement at 3 months in any group
Meyer et al. (2006)	BMC (n=30) Control (n=30)	*Mean global LVEF increase* Control: 0.7±8.1% (6 months);3.1±9.6 (18 months) BMC: 6.7±6.5% (6 months, p=0.0026); 5.9±8.9% (18 months, p=NS) Between groups: No statistically significant differences *LVEDV, LVESV, LVEF, LV mass index, wall thickening, wall motion, late contrast enhancement volume* No statistically significant difference between groups *LV mass index* Entire cohort: statistically significant decrease (p=0.0002) at 18 months *Late contrast enhancement* Entire cohort: statistically significant decrease (p<0.0001) at 18 months. *Regional wall thickening of border zone/infarct area* Entire cohort: statistically significant improvement at 18 months (border zone, p=0.0009; infarct area, p=0.01) *Wall motion of infarcted region/border zone* No statistically significant improvement

Assmus et al. (2002)	BM derived group (n=9) Circulating blood derived group (n=11) Reference group (n=11)	*LVEF* Blood and BM derived groups combined: Statistically significant improvement at 4 months (p=0.003) Blood derived group: 51.3±11% (baseline), 59.5±9% (4 month) (p=NR) BM derived group: 51.9±9% (baseline), 60.7±9% (4 months) (p=NR) Between group comparison: Not statistically significant difference Reference group: No statistically significant improvement *LVESV* Blood and BM derived groups combined: Statistically significant improvement at 4 months (p=0.011) Blood derived group: 56.9±17.6 ml (baseline), 48.9±14.2 ml (4 months) (p=NR) BM derived: 55.2±24 ml (baseline), 34.9±13 ml (4 months) (P=NR) Between group comparison: Not statistically significant difference Reference group: No statistically significant improvement *LVEDV* Blood and BM derived groups combined: No statistically significant improvement Between group comparison: Not statistically significant difference Reference group: No statistically significant improvement *Regional wall motion (infarct zone, infarct centre, infarct border zone)* Blood and BM derived groups combined: Statistically significant improvement at 4 months (p<0.001) Blood derived group (infarct zone): -1.5±0.3 (baseline), -0.6±0.6 SD/chord (4 month) (p=NR) BM derived group (for infarct zone): -1.6±0.2 (baseline), -0.4±0.8 SD/chord (4 month) (p=NR) Between group comparison: Not statistically significant **Regional LV function (as assessed by echocardiography)** *Presence of hypo/akinetic segments* Blood and BM derived groups combined: 86 (baseline, resting echocardiography), 75 (baseline, dobutamine stress echocardiography), 44 (4 months, resting echocardiography, p<0.05 compared to baseline stress and p<0.001 compared to baseline resting echocardiography). *Wall motion score* No statistically significant difference between groups *Coronary flow reserve of infarct artery* Blood and BM derived groups combined: Baseline, coronary flow reserve compared to reference vessel significantly reduced. Blood derived group: Statistically significant increase at 4 months (infarct artery p=0.001, reference vessel p=0.004) BM derived group: Statistically significant increase at 4 months (infarct artery p=0.0017, reference vessel p=NS) Between groups: Significantly greater increase in infarct artery than reference vessel at 4 months (p<0.05). *Myocardial viability(Mean tracer uptake in infarct territory)* Blood and BM derived groups combined: 54.1±12.5% (baseline), 62.9±11.0% (4 month; p<0.05) No significant changes in reference vessel
Schachinger et al. (2004)	BM derived group (n=29) Circulating blood derived group (n=30)	*LVEF (determined by angiography)* Two groups combined: Statistically significant improvement at 4 months (p<0.001) *LVEDV (determined by angiography)* Two groups combined: No statistically significant improvement at 4 months *LVESV (determined by angiography)* Two groups combined: Statistically significant improvement at 4 months (p<0.001) *Regional wall motion for infarct, infarct centre and infarct border (determined by angiography)* Two groups combined: Statistically significant improvement at 4 months (p<0.001) Subgroup analysis *LVEF (as determined by contrast enhanced MRI)* Two groups combined: Statistically significant improvement from baseline to 4 months (p<0.001), 4 months to 12 months (p=0.003) and baseline to 12 months (p<0.001) *Late enhancement volume (as determined by contrast enhanced MRI)* Two groups combined: Statistically significant improvement from baseline to 4 months (p=0.003), 4 months to 12 months (p=0.007) and baseline to 12 months (p<0.001)

Schachinger et al. (2006)	Placebo (n=103) BMC (n=101)	*LVEF* Placebo: 46.9±10.4% (baseline), 49.9±13.0% (4 months, p<0.001) BMC: 48.3±9.2% (baseline), 53.8±10.2% (4 months, p<0.001) Between groups: Statistically significant better improvement in BMC at 4 months (p<0.01) *LVEDV* Placebo: 139±46ml (baseline), 153±57ml (4 months, p<0.001) BMC: 128±38ml (baseline), 141±43 (4 months, p<0.001) Between groups: No statistically significant difference *LVESV* Placebo: 75±32 ml (baseline), 80±45 ml (4 months, p=0.02) BMC: 67±26 ml (baseline), 67±30ml (4 month, p=NS) Between groups: Placebo group had significantly higher mean LVESV at 4 months (p=0.01) *Regional wall motion (infarcted zone contractility)* Placebo: -1.54±0.42 (baseline), 1.27±0.60 (4 months, p<0.001) BMC: -1.54±0.42 (baseline), -1.17±0.60 (4 months, p<0.001) Between groups: Statistically significant better improvement in treatment group (p<0.001)
Janssens et al. (2006)	Placebo (n=34) BMSC (n=33)	*LVEF* Placebo: 46.9±8.2% (baseline), 49.1±10.7% (4 months, p=NR) Treatment: 48.5±7.2% (baseline), 51.8±8.8% (4 months, p=NR) Between groups: No statistically significant difference between groups *LVESV index* Placebo: 44.4±12.3ml/m^2 (baseline), 45.0±17.9 ml/m^2 (4 months, p=NR) Treatment: 42.2±10.5 ml/m^2 (baseline), 41.0±15.5 ml/m^2 (4 months, p=NR) Between groups: No statistically significant difference between groups *LVEDV index* Placebo: 83.1±14.7 ml/m^2 (baseline), 85.9±19.5 ml/m^2 (4 months, p=NR) Treatment: 81.2±14.0 ml/m^2 (baseline), 84.1±20.8 ml/m^2 (4 months, p=NR) Between groups: No statistically significant difference between groups *LV mass index* Placebo: 64.5±15.8g/m^2 (baseline), 58.7±11.1 g/m^2 (4 month, p=NR) Treatment: 57.0±11.0 g/m^2 (baseline), 50.9±9.6 g/m^2 (4 month, p=NR) Between groups: No statistically significant difference between groups *Systolic wall thickening (infarct area)* Placebo: 21.8±19.2% (baseline), 23.7±18.9% (4 month, p=NR) Treatment: 23.6±17.9% (baseline), 29.3±21.7 (4 month, p=NR) Between groups: No statistically significant difference between groups *Systolic wall thickening (border zone)* Placebo: 32.7±15.4% (baseline), 38.4±21.1% (4 months, p=NR) Treatment: 36.6±18.9% (baseline), 40.8±17.2% (4 months, p=NR) Between groups: No statistically significant difference between groups *Infarct size (late contrast enhancement)* Placebo: 22.3±16.1g (baseline), 14.7±9.3g (4 months, p=NR) Treatment: 20.6±14.3g (baseline), 10.3±8.0g (4 month, p=NR) Between groups: Statistically significant better reduction in treatment group (p=0.036)
Strauer et al. (2005)	BMC (n=18) Control (n=18)	*Infarct size* Treatment: 27±8% (baseline), 19±9% (3 months) Control: 27±9% (baseline), 26±9% (3 months) Between group: Statistically significant better improvement in treatment group (p=0.02) *LVEF* Treatment: 52±9% (baseline), 60±7% (3 months) Control: 51±10% (baseline), 51±10% (3 months) Between group: Statistically significant better improvement in treatment group (p=0.02) *Infarct wall movement velocity* Treatment: 1.9±0.7cm/s (baseline), 2.9±0.9cm/s (3 months) Control: 1.9±0.8cm/s (baseline), 1.9±0.8cm/s (3 months) Between group: Statistically significant better improvement in treatment group (p=0.001)
Fernandez Aviles et al. (2004)	BMC (n=20) Control (n=13)	*LVEDV* BMC: 163.9±39.7ml (baseline), 160.9±43.3ml (6 months, p=NS) Control: No statistically significant improvement *LVESV*

		BMC: 81.3±29.2ml (baseline), 71.7±31.8ml (6 months, p=0.007) Control: No statistically significant improvement *LVEF* BMC: 51.3±6.6% (baseline), 57.1±10.4% (6 months, p=0.002) Control: No statistically significant improvement *LV stroke volume* BMC: 82.6±13.2ml (baseline), 89.2±19.9% (6 months, p=NS) Control: No statistically significant improvement *Regional contractility (segments with asynergy per patient)* BMC: 3.7±2.1 (baseline), 2.3±1.6 (6 month, p=0.017) Control: No statistically significant improvement *Wall motion score index* BMC: 1.4±1.5 (baseline), 1.2±0.2 (6 month, p<0.001) Control: No statistically significant improvement *Infarct wall thickening* Treatment: 2.0±1.0 mm (baseline), 3.2±1.5 (6 months, p=0.01) Control: No statistically significant improvement
Strauer et al. (2002)	Cell therapy (n=10) Control (n=10)	*Infarct region (as percentage of hypokinetic, akinetic or dyskinetic segments of the circumference of left ventricle)* Cell therapy: 30±13% (baseline), 12±7% (3 months, p=0.005) Control: 25±8% (baseline), 20±11% (3 months, p=NS) Between groups: Statistically significant smaller infarct region at 3 months in cell therapy group (p=0.04) *Wall movement velocity* Cell therapy: 2.0±1.1cm/s (baseline), 4.0±2.6cm/s (3 months, p=0.028) Control: 1.8±1.3cm/s (baseline), 2.3±1.6cm/s (3 months, p=NS) Between groups: No statistically significant difference *LVEF* Cell therapy: 57±8% (baseline), 62±10% (3 months, p=NS) Control: 60±7% (baseline), 64±7% (3 months, p=NS) Between groups: No statistically significant difference

The randomised, controlled crossover trial by Assmus *et al.* (2006) employed a three phase design, with randomised pilot and main phases followed by a crossover phase (see Figure 2). In phases two and three, patients were randomised to initial intracoronary infusions of bone marrow progenitor cells (n = 35), circulating progenitor cells (CPCs, n = 34) or a control group which received no infusion of cells (n = 23). Analyses focussed appropriately on the 75 patients in the main randomised phase. Global left ventricular ejection fraction (LVEF) improvement over three months was significantly different between the three groups. Patients who received bone marrow progenitor cells experienced a significantly better improvement in LVEF than CPC group patients (absolute change: +2.9 ± 3.6% versus -0.4 ± 2.2%, p = 0.003) and control patients (absolute change: +2.9 ± 3.6% versus -1.2 ± 3.0%, p < 0.001) with an improvement from 41 ± 11% to 43 ± 10% (p = 0.001). Similar results were also obtained when patients without evidence of viable myocardium were analysed separately. Regional contractility in the central target area improved significantly over the three months in the bone marrow progenitor cell group from -1.63 ± 0.40 at baseline to -1.38 ± 0.42 (p = 0.006) but not in the CPC or control groups. However, the difference among groups was not significant. Left ventricular angiography did not reveal any further significant improvements in the extent of regional dysfunction, LVEDV, LVESV, stroke volume or LV end diastolic pressure in any of the three groups.

A subgroup of 35 patients (11 in progenitor BMC, 20 in CPC and 4 in control) underwent MRI analysis of left ventricular function. Although fewer patients were analysed via MRI than angiography, support for the angiographic results was obtained. Additionally, MRI regional analysis showed a significant decrease in the number of hypocontractile segments from 10.1 ± 3.6 at baseline to 8.7 ± 3.6 at three months ($p = 0.02$) and an accompanying increase in the number of normocontractile segments from 3.8 ± 4.5 to 5.4 ± 4.6 ($p = 0.01$) in the progenitor BMC group only. In terms of infarct size, MRI-measured late enhancement volume did not significantly improve in either the progenitor BMC or CPC groups. However it must be noted that this analysis only included nine patients from the progenitor BMC group and 13 patients from the CPC group. Raw data for late enhancement volume were not reported.

Taken together, the three month data suggest an association of intracoronary BMC infusion with significant improvements in both global and regional contractile function. In order to shed some light into this possible association, the authors conducted multivariate regression analysis of various factors to identify any potential predictors of improved global LVEF. Analysis revealed that the treatment group (i.e. type of cell infused) and baseline stroke volume were the only statistically significant independent predictors of global LVEF recovery ($p = 0.003$ for treatment group and $p = 0.002$ for baseline stroke volume).

To add further weight to their results and to rule out the possibility that the beneficial effects seen were a phenomenon of the patient population, the crossover phase began at the three month time point. Twenty-one out of the 24 patients originally assigned to CPC infusion received bone marrow progenitor cells and 24 out of the 28 patients who originally received bone marrow progenitor cell infusion received CPCs. Patients in the control group were also crossed over, with 10 patients receiving CPCs and 11 receiving bone marrow progenitor cells. Results from the crossover phase supported phase 2 results with the observation that infusion of bone marrow progenitor cells regardless of time of previous infusion (i.e. whether as an initial treatment or after CPC infusion or after no infusion) led to a significant increase in the global LVEF (CPC to progenitor BMC transition improvement $p = 0.01$, control to bone marrow progenitor cell transition improvement $p = 0.03$). In comparison, infusion of CPCs after either progenitor BMC infusion or no infusion did not lead to a significant improvement in the global LVEF. Furthermore, although six month raw data was not provided, the authors note a preserved improvement in cardiac function at six months in patients who originally received progenitor BMCs and later crossed over to CPCs, demonstrating the persistence of the beneficial progenitor BMC effect despite CPC infusion.

This study, demonstrated beneficial effects of intracoronary infusion of bone marrow progenitor cells for both regional and global cardiac function. However, longer follow-up periods with larger numbers of patients as well as reporting of laboratory indicators of myocardial damage an inflammatory response would not only support the results presented but also help answer questions regarding the long term safety and efficacy effects in these patients. Additionally, it would be both interesting and beneficial to

conduct similar experiments in patients suffering heart failure in order to determine whether these beneficial effects could be transferred into another patient population.

The BOOST trial randomised patients into a control group (n = 30) or BMC transplantation group (n = 30) (Meyer *et al.* 2006). Mean global LVEF for control patients increased by 0.7 ± 8.1 and 3.1 ± 9.6 percentage points at six and 18 months respectively. Meanwhile, BMC patients achieved global LVEF improvement of 6.7 ± 6.5 and 5.9 ± 8.9 percentage points at six and 18 months respectively, a significantly greater improvement in LVEF at six months compared to control ($p = 0.0026$) but not at 18 months ($p = 0.27$). Overall, no significant differences were observed between BMC and control patients for LVEDV, LVESV, LVEF and LV mass index. Similarly, BMC transplantation did not result in significant improvements compared to controls for wall thickening, wall motion and late contrast enhancement volume. Meanwhile LV mass index and late contrast enhancement volume decreased significantly ($p = 0.0002$ and $p < 0.0001$, respectively) for the entire cohort. Regional wall thickening of the infarcted area and border zone improved significantly for the entire cohort ($p = 0.0009$ and $p = 0.01$, respectively) but wall motion of the infarcted region did not exhibit any significant improvement ($p = 0.07$), as with wall motion at the infarct border zone ($p = 0.89$). From a regression analysis, greater LVEDV indices and greater later contrast enhancement volumes appear to predict poorer LVEF improvement for this study cohort ($p = 0.02$ and $p = 0.045$ after Bonferroni correction, respectively).

In addition to the data presented on Table 5, detailed echocardiographic analysis of diastolic function reported by (Schaefer *et al.* 2006) revealed that E/A[9] and Ea/Aa[10] ratios decreased significantly in control patients compared to BMC patients at 18 months ($p = 0.008$ and $p = 0.02$, respectively). Meanwhile, BMC transplantation had no significant effects on DT and IVRT[11]. However, IVRT was prolonged (> 100ms) and DT was within the upper normal range for both groups. Prolongation of IVRT is indicative of the earliest stage of diastolic dysfunction and therefore infers an impairment of the energy-dependant process of LV relaxation. The E/Ea[12] ratio is an indicator of elevated filling pressures and decreased survival after AMI, this ratio was not elevated in both groups over the course of the trial. These data indicate that control patients developed stage 1 diastolic dysfunction after AMI (decreased E/A ratio, prolongation of IVRT, no change in E/Ea ratio); meanwhile the outstanding feature of BMC patients was the prolongation of IVRT, indicating development of a very mild form of early diastolic dysfunction.
Subgroup analysis of patients with hypertension at baseline revealed a persisting improvement of E/A ratio after BMC transfer (0.43 ± 0.16; 95% CI: 0.08 to 0.77; p =

[9] E/A ratio: Transmitral peak early velocity / Peak late velocity; measure of transmitral flow pattern.
[10] Ea/Aa ratio: Early diastolic mitral velocity / Late diastolic mitral velocity; measure of diastolic myocardial velocities.
[11] IVRT: Isovolumic relaxation time

0.01), suggesting that these patients benefit less from BMC therapy. As stated previously, MRI assessment of BMC transfer in this trial revealed significant LVEF improvement at six months compared to controls ($p = 0.0026$) (Meyer *et al.* 2006), surprisingly echocardiographic assessment did not report any significant difference between the two groups. This discrepancy was attributed to investigator variabilities and the intrinsic limitations of echocardiography to detect LVEF changes in patients with regional wall motion abnormalities. Echocardiographic measures of LVEDV, LVESV and LVEF were not different between groups throughout the study period (baseline, 6 months and 18 months) while IVSD (diastolic interventricular septal thickness) and PWD (diastolic posterior wall thickness) decreased in both groups. For the entire cohort, there was a correlation of LVEF according to echocardiographic analyses ($r = 0.6$, $p < 0.001$), a result in line with the MRI results of this trial (Wollert *et al.* 2004). This correlation was also detected in patients with large anterior MI and involvement of the apical segments and in patients with inferior/lateral MI ($r = 0.6$, $p < 0.001$; $r = 0.5$, $p < 0.001$).

The initial publication arising from the TOPCARE-AMI study reported data for the first 20 patients four months after transplantation of blood-derived or bone marrow-derived progenitor cells (Assmus *et al.* 2002). The study assessed LV function in patients who had received cell therapy versus patients from a non-randomised reference group. At four months following cell transplantation, combined data for patients who had received cell therapy showed a statistically significant improvement in LVEF ($p = 0.003$) and LVESV ($p = 0.011$). No statistically significant change in LVEDV was reported in these patients. Regional wall motion in the infarct zone, infarct centre and infarct border zones were also analysed, with a significant improvement reported at four months ($p < 0.001$). When groups were analysed individually, patients who received blood-derived cells experienced an improvement in ejection fraction, a decrease in LVESV and an increase in regional wall motion in the infarct zone at four months (p values not reported). Similarly, patients who received bone marrow-derived cells demonstrated an improvement in LVEF, LVESV and regional wall motion in the infarct zone at four months (p values not reported). Corresponding values between the two cell therapy groups were statistically non significant. In contrast, patients in the reference group did not experience significant improvements in LVEF, LVESV or LVEDV.
Regional LV function assessed by low-dose dobutamine stress echocardiography before cell infusion revealed the presence of viable but dysfunctional myocardium in 12 of 19 cell recipient patients. Resting baseline echocardiography showed 86 hypo/akinetic segments while baseline dobutamine stress echocardiography showed 75 segments. At the four month follow-up, 44 segments were revealed using resting echocardiography, a significant improvement compared to baseline stress and resting echocardiography ($p < 0.05$ and $p < 0.001$ respectively). The four month resting echocardiography also revealed an improvement in regional wall motion in 12 of 19 patients when compared to the low-dose dobutamine stress echocardiography at baseline. Furthermore, five of the seven

[12] E/Ea: Transmitral peak early velocity / early diastolic velocity

patients deemed to have irreversibly damaged myocardium at baseline improved regional wall motion at the four month follow-up. No cases of deteriorating regional wall motion were reported. No statistically significant differences in wall motion scores between blood-derived and bone marrow-derived patients were reported.
In comparison to a reference vessel, coronary flow reserve in the infarct artery was significantly reduced at baseline. At the four month follow-up, coronary flow reserve had significantly increased in patients who had received blood-derived cells (infarct artery $p = 0.001$, reference vessel $p = 0.004$) and bone marrow-derived cells (infarct artery $p = 0.017$, reference vessel $p = 0.153$). Further analysis showed the increase in coronary flow reserve in the infarct artery to be significantly larger than the reference vessel ($p < 0.05$). Myocardial viability was also assessed in 14 patients via fluorodeoxyglucose PET (FDG-PET). Combined data for the blood-derived and bone marrow-derived cell groups showed significant mean tracer uptake improvement at the four month follow-up ($p < 0.01$) in the infarct territory, indicating improved myocardial viability. No significant changes in the reference vessel territory were reported. Out of 14 patients, 11 experienced an increase in FDG-PET tracer uptake in the infarct territory suggesting preferential improvement in myocardial viability in the infarct area. Of the three patients who did not improve, two had restenosis in the stented lesion. No significant differences between both cell therapy groups were reported.

Schachinger *et al.* (2004) reported the final four month and 12 month results of the TOPCARE-AMI trial. A total of 54 patients were available for analysis at four months follow-up of the same variables reported by Assmus *et al.* (2002) and although combined data for both cell groups supported data previously reported by Assmus *et al.* (2002), (i.e. statistically significant improvement for LVEF, LVESV and regional wall motion), data for the individual groups was not backed up with corresponding p values. Thirty seven patients were assessed by contrast enhanced MRI at 10 ± 5.9 days following AMI, four months and 12 months follow-up. Again, only combined data for both cell groups was provided. In these patients, global ejection fraction significantly improved from baseline to four months ($p < 0.001$) and 12 months ($p < 0.001$). Similarly, a reduction in late enhancement volume from baseline to four and 12 months ($p = 0.003$ and $p < 0.001$ respectively) was observed. Although these results represent positive benefits from cell therapy and suggest sustained improvement, they must be taken with caution as they are combined data for both cell groups. Taken together the data presented by both the initial and final TOPCARE-AMI study results point to a positive effect of bone marrow cells in the LV remodelling process as seen by improvements in myocardial viability, infarct size, LVEF and coronary flow reserve.

The multi-centre, randomised, controlled trial by Schachinger *et al.* (2006) evaluated variables of LV function using LV angiography. Paired LV angiograms were available for 95 treatment patients 92 placebo group patients at the four month follow-up. Global LVEF significantly improved in both the placebo ($p<0.001$) and treatment group ($p<0.001$) at four months. Similarly, LVEDV also significantly increased in both groups

between baseline and the four months ($p < 0.001$ for both groups). Four month results for LVEF and LVEDV comparisons between groups showed a statistically significant better improvement in LVEF ($p<0.001$) but not for LVEDV.
End-systolic volume at four months saw a statistically significant increase in volume from baseline in placebo group patients ($p = 0.02$) while no such changes were observed in the treatment group ($p = NS$). Between group comparisons demonstrated that placebo group patients had significantly higher four month recordings ($p = 0.01$).
Regional wall motion in the infarcted zone showed that contractility was significantly more improved in the treatment group ($p < 0.001$) despite both groups significantly improving from baseline to the four month follow-up ($p < 0.001$ for both groups).
Pre-specified subgroup analyses investigated the interaction between the change in LVEF and baseline LVEF and time to cell infusion. A significant inverse relationship between baseline LVEF and the absolute change in LVEF at four months was discovered ($r = -0.21$, $p = 0.04$) in the treatment group only. It was found that treatment group patients with baseline LVEF at or below the median (48.9%) experienced an absolute increase in LVEF three times that of patients in the placebo group ($7.5 \pm 7.1\%$ versus $2.5 \pm 7.7\%$, absolute difference, 5.0%; 95%CI: 2.0 to 8.1) where as those above the median had an absolute difference between groups of only 0.3% (95%CI: -2.2 to 2.8). In terms of time from reperfusion therapy to cell infusion, it was noted that as time from reperfusion therapy to BMC infusion increased, a progressive increase in BMC-associated recovery of contractile function was also noted (p for interaction = 0.01). More specifically, beneficial effects of cell therapy were confined to patients who were treated more than four days after infarct reperfusion. Infusion of BMCs on day five or later was significantly associated with an absolute increase in LVEF of 5.1% (95%CI 1.7 to 8.5) ($p = 0.004$). The interaction between the treatment effect of the BMC infusion and timing of the infusion was significant ($p = 0.03$) and remained significant when baseline LVEF entered into model as covariate ($p = 0.04$). The results from this study support the previously presented studies in terms of the effect of BMC infusion on global LVEF, LVEDV, LVESV as well as regional contractility indicating a beneficial effect. In addition, this study was able to add that the treatment effect of BMC infusion may be at least in part determined by the timing of the infusion. Those patients who appeared to have the greatest LVEF impairment (i.e. equal to or below the median) had a much greater beneficial effect than patients whose baseline LVEF has higher than the median. These results, although derived through exploratory analysis and univariate in nature, may play a role in determining which patients are most likely to benefit from this type of therapy thus helping optimise treatment for future patients.

Patients from the randomised double-blind controlled trial by Janssens *et al.* (2006) were assessed for improvements in LVEF, infarct size and regional LV function at four months follow-up by MRI analysis. At the four month follow-up paired MRI results were available for 30 patients from each group. Although both groups saw an improvement in global LVEF over the four months, no significant beneficial effect over the control was observed in patients receiving cell infusion. Similar results were obtained for both end-

systolic and end-diastolic volume indexes. Additionally, LV mass index and systolic wall thickening in the infarct area and border zone also did not significantly improve at four months in patients receiving cell infusion compared to patients in the control.
Over half of patients (19 control group and 17 treatment group) demonstrated prevalent microvascular obstruction and according to the authors precluded LV function recovery. Infarct size was the only parameter to significantly ($p = 0.036$) improve more in the treatment group than in the control group.
Preliminary longitudinal shortening analysis at two months follow-up revealed significantly greater shortening in patients in the treatment group compared to those in the control group ($p = 0.0014$). Additionally, treatment group patients had significantly greater end-systolic strain in both infarcted ($p = 0.047$) and remote ($p = 0.017$) zones compared to control patients, suggesting a transient beneficial effect of cell therapy.
In this study, cell infusion was performed prior to the fourth day after AMI in most patients. Unlike previous studies which infused cells after the fourth day, this study did not detect a clear benefit of cell infusion over the control group. Additionally, over half of patients presented with prevalent microvascular obstruction. It is unclear whether the time to infusion or presence of microvascular obstruction prevented beneficial effects from occurring. Similar experiments using patients without microvascular obstruction would help answer this question.

A study published by Strauer and colleagues investigated the effects of mononuclear bone marrow cell infusion in patients with chronic MI (Strauer *et al.* 2005). In order to ensure that any effects seen were a result of cell infusion, stable ventricular dynamics for infarct size, LVEF and wall movement velocity for at least 9 ± 6 months before cell infusion were confirmed in the 36 participants (18 treatment and 18 control patients). Patients were not randomised into groups but were consecutively recruited. Those who did not consent to receive BMC harvest and infusion were allocated to the control group.
Three months after cell infusion, patients in the treatment group experienced an improvement in infarct size from $27 \pm 8\%$ immediately after cell infusion to $19 \pm 9\%$, whereas control group patients showed no such improvement.
Similarly, LVEF of treatment group patients improved from $52 \pm 9\%$ immediately after cell infusion to $60 \pm 7\%$ at three months. Control patients saw an increase of 1% during the same period. In both cases, the three month improvements in the treatment group were significantly better than the control group ($p = 0.02$).
Infarct wall movement velocity improved in both groups at three months, however treatment patients achieved a significantly better improvement ($p = 0.001$).
The exercise capacity of patients was assessed by maximum load levels and maximum peak oxygen uptake (Vo_{2max}). An 11% increase in Vo_{2max} was reported at three months and this was statistically significant ($p = 0.0001$). Unfortunately results for maximum load levels were not reported. PET examination of glucose uptake in the infarcted zone of patients who had received cell infusion showed significantly increased glucose uptake ($p = 0.012$) suggesting regeneration of previously chronically infarcted myocardium.

The results from this study add weight to previous studies presented, evidenced by the better improvement in the cell infusion group in infarct size, LVEF and infarct wall movement over the control group. This study also shows potential beneficial effects of cell infusion in exercise capacity, although maximum load level results were not reported.

The safety and feasibility trial by Fernandez-Aviles *et al.* (2004) utilised MRI and low dose dobutamine stress echocardiography to assess any beneficial effects provided by the intracoronary transplantation of BMCs. In a similar fashion to previous studies, although no significant increase in LVEDV was observed; LVESV and LVEF significantly improved in the BMC group at six months ($p = 0.007$ and $p = 0.002$ respectively). Further improvements in regional contractility also emerged as evidenced by a significant ($p = 0.017$) reduction in the number of segments with asynergy per patient and better wall motion score index ($p < 0.001$). Significant improvements in the left ventricular contractile reserve were also demonstrated. Both the end-diastolic thickness and the end-systolic thickness in the cell therapy patients significantly increased from 6.3 ± 1.7 mm at baseline to 7.7 ± 2.2 mm at six months ($p < 0.01$) and 8.3 ± 2.2 mm at baseline to 10.9 ± 3.1 mm at six months ($p < 0.01$) respectively. Similarly, significant thickening of the infarcted wall was also observed ($p = 0.01$). Given that baseline low dose dobutamine stress echocardiography revealed an absence of cell viability, the authors propose that it is unlikely that wall thickening is a result of compensatory hypertrophy or improvement in stunned myocardium, giving rise to possibility of myocardial regeneration.
Coronary angiography at six months showed no statistically significant differences between control and treatment groups in post-stenting late loss and binary significant restenosis. As with other studies, results from this small trial indicate that transplantation of BMCs has potential to reduce LV remodelling and improve cardiac outcomes.
Although the mechanism by which cells may confer beneficial effects is beyond the scope of this report, a parallel in vitro experiment using the same population of BMCs showed that these cells had the ability to graft onto injured mouse myocardium and acquire characteristics of cardiac myocytes, giving light to the possibility that regeneration of myocardial tissue may be involved in the recovery of cardiac function in humans.
Another important characteristic of this trial is the time of cell transplantation. Unlike other studies which have transplanted cells at approximately four to seven days after infarction, this study performed cell transplantation 13.5 ± 5.5 days following infarction and still observed many of the beneficial effects as seen by previously presented studies.

Although the non-randomised study by Strauer *et al.* (2002) only followed 20 patients (10 treatment and 10 control) for three months, a large number of parameters for functional assessment of hemodynamics were assessed via left and right heart catheterisation, left and radionucleotide ventriculography, echocardiography, coronary angiography and ^{201}Thallium scintigraphy.
Left ventriculography results demonstrate that cell therapy but not control patients experienced a statistically significant ($p = 0.005$) reduction in the infarct region as a percentage of hypokinetic, akinetic or dyskinetic segments of the circumference of the

left ventricle. Additionally, when compared to control patients, the size of the infarct region at three months was significantly smaller in patients who had received cell therapy ($p = 0.04$). There were no significant differences between the groups in terms of the wall movement velocity at the three month examination.
Both groups experienced similar increases in LVEF, neither however was statistically significant nor was three months LVEF values significantly different between the groups. Further indicators of cardiac function including perfusion defect, stroke volume index, ejection fraction, LVEDV, LVESV, velocity of circumferential fibre shortening and ratio of systolic pressure to end-systolic volume were also measured in the cell therapy group only. The size of the infarct region as perfusion defect significantly decreased from $174 \pm 99 cm^2$ at baseline to $128 \pm 71\ cm^2$ at three months ($p = 0.016$). The stroke volume index but also significantly improved from baseline ($49 \pm 7\ ml/m^2$) to three months ($56 \pm 7\ ml/m^2$, $p = 0.010$) indicating potential improvement in hemodynamic characteristics of the cell therapy patients. Decreases in the end-diastolic ($p = NS$) and end-systolic volumes ($p = 0.011$) by radio nucleotide ventriculography, suggested an improvement in cardiac geometry. Finally, an indication of improved contractility as demonstrated by a slight increase in the velocity of circumferential fibre shortening ($p = NS$) and a significant increase in the ratio of systolic pressure to end-systolic volume ($p = 0.005$) was reported.
Although the results suggest that repair of infarcted myocardium may be possible with mononuclear BMC transplantation, the lack of comparative data available for many of the measured parameters, small patient sample and short follow-up period does not allow for a conclusive statement on the efficacy of this type of therapy. However it must be considered that this was one of the earliest trial conducted on the infusion of BMCs for the treatment of AMI and despite its shortcomings demonstrates similar positive results as the larger more recent studies.

By far the largest number of studies investigating the use of autologous BMCs for the treatment of AMI has been using transvascular transplantation as the method of delivery. Although many of these studies are constructed in a similar fashion, obvious inconsistencies, particularly in terms of improvements in LVEF and other efficacy indicators have been reported. A possible explanation may lie in the patient characteristics. Studies such as the BOOST and TOPCARE-AMI trials have included patients who have suffered limited myocardial damage. These patients tend to achieve more favourable outcomes as they generally have better preserved ejection fractions following reperfusion therapy than patients who have suffered more extensive myocardial damage. As a result, benefits seen with these patients may not be as obvious or as large as may otherwise be in patients with more extensive myocardial damage.

Direct Injection Transplantation

Four studies documented the use of direct injection transplantation in the treatment of myocardial infarction. Each of the four studies included appropriately reported the effects of bone marrow cell transplantation on left ventricular function as well as other important outcome measures. A summary of the main outcomes reported by these studies is presented in Table 6.

Table 6: Summary of main outcomes following direct injection transplantation for myocardial infarction

Study	Patient allocation	Main outcomes
Lunde et al. (2006)	BMC (n=50) Control (n=50)	*LVEF (SPECT recordings)* BMC: 41.3±10.4% (baseline), 49.3±13% (6 months, p=NS) Control: 42.6±11.7% (baseline), 49.3±11.0% (6 months, p=NS) Between groups: No statistically significant difference *LVEDV (SPECT recordings)* BMC: 162.3±59.1ml (baseline), 151.1±52.9ml (6 months, p=NS) Control: 148.0±46.3ml (baseline), 146.0±50.0ml (6 months, p=NS) Between groups: No statistically significant difference *Infarct size (SPECT recordings)* BMC: 43.8±17.4% (baseline), 32.8±20.4% (6 months, p=NS) Control: 38.3±21.1% (baseline), 30.5±20.9% (6 months, p=NS) Between groups: No statistically significant difference *Echocardiography results (LVEF and LVDV)* BMC/Control: No statistically significant improvement at 6 months Between groups: No statistically significant difference *MRI results (LVEF, LVEDV and infarct size)* BMC/Control: No statistically significant improvement at 6 months Between groups: No statistically significant difference
Chen et al. (2004)	BMSC (n=34) Control (n=35)	*Functional defect percentage* BMSC: 32±11% (baseline), 13±5% (3 months, p=NR) Control: 33±10% (baseline), 28±10% (3 months, p=NR) Between groups: Statistically significant better improvement in BMSC group (p=0.001) *Infarcted area movement velocity* BMSC: 2.17±1.3cm/s (baseline), 4.2±2.5cm/s (3 months, p=NR) Control: 2.19±1.5cm/s (baseline), 2.7±1.7cm/s (3 months, p=NR) Between groups: Statistically significant better improvement in BMSC group (p=0.01) *LVEF* BMSC: 49±9% (baseline), 67±11% (3 month, p=NR), 67±3% (6 month, p=NR) Control: 48±10%(baseline), 53±18% (3 month, p=NR), 54±5% (6 month, p=NR) Between groups: 3 and 6 month BMSC group values statistically significant better (p=0.01) *Cardiac functional index(LVEDV index, LVESV index, circumferential shortening, ratio of end-systolic pressure to end-systolic volume and perfusion defect)* Statistically significant better results in BMSC group over control at 3 months in all except circumferential shortening (p≤0.01) *Cardiac functional index (line local shortening, unipolar voltage, perfusion defect, stroke volume index, LVEDV index and LVESV index, n=15)* BMSC group only: Statistically significant improvement at 3 months (p=0.01)
Ruan et al. (2005)	BMC (n=9) Control (n=11)	*Peak systolic displacement (Infarcted area)* BMC: 4.49±2.71mm (baseline), 7.56±2.95mm (3 month, p<0.01), 7.37±3.58mm (6 months, p<0.01) Control: 4.74±2.67mm (baseline), 5.01±3.23mm (3 months, p=NS), 5.03±2.87mm (6 months, p=NS) Between groups: Statistically significant better improvement in BMC group at 3 and 6 months (p<0.01) *Peak systolic displacement (Non infarcted area)* BMC: 7.28±3.04mm (baseline), 9.94±2.90mm (3 months, p<0.01), 10.12±2.67mm (6 months, p<0.01)

		Control: 6.70±2.35mm (baseline), 7.77±2.42mm (3 months, p<0.05), 7.86±2.86mm (6 months, p<0.01) Between groups: Statistically significant better improvement in BMC group at 3 and 6 months (p<0.01) *Peak systolic strain (Infarcted area)* BMC: -13.40±6.00% (baseline), -17.06±6.05% (3 month, p<0.01), -18.98±6.29% (6 months, p<0.01) Control: -13.84±6.05% (baseline), -15.04±6.75% (3 month, p=NS), -15.35±6.66% (6 months, p=NS) Between groups: Statistically significant better improvement in BMC group at 6 months (p<0.01) *Peak systolic strain (Non infarcted area)* BMC: -14.70±7.45% (baseline), -16.69±8.18% (3 months, p=NS), -17.70±7.09% (6 months, p=NS) Control: -14.79±7.38% (baseline), -16.79±8.22% (3 months, p=NS), -15.40±7.62% (6 months, p=NS) Between groups: No statistically significant difference *LVEF* BMC: 53.37±8.92% (baseline), 56.04±10.93% (3 month), 59.33±12.91% (6 month) Control: 53.51±5.84% (baseline), 50.28±7.28% (3 month), 50.30±8.30% (6month) Between groups: Statistically significant better improvement at 6 months in BMC group (p<0.05) *LVEDV* BMC: 113.74±23.24ml (baseline), 107.85±33.21ml (3 month), 117.71±28.20ml (6 month) Control: 129.92±32.72ml (baseline), 154.89±46.34ml (3 month), 159.20±49.84ml (6 month) Between groups: Statistically significant lower at 3 and 6 months in BMC group (p<0.05) *LVESV* BMC: 57.12±18.66ml (baseline), 49.54±23.32ml (3 month), 52.43±24.69ml (6 month) Control: 62.09±17.68ml (baseline), 82.91±35.79ml (3 month), 81.18±32.98ml (6 month) Between groups: Statistically significant lower at 3 and 6 months in treatment group (p<0.05)
Hendrikx et al. (2006)	BMC (n=11) Control (n=12)	*LVEF* BMC group: 42.9±10.3% (baseline), 45.8±13.2% (post operative), 48.9±9.5% (4 months) Control group: 39.5±5.5 (baseline), 41.2±10.1% (post operative), 43.1±10.9% (4 months) Between groups: No statistically significant difference *LVEDV index (ml/m^2)* BMC group: 86.9±28.4 (baseline), 87.0±28.5 (post operative), 87.1±20.4 (4 months) Control group: 89.4±28.4 (baseline), 87.6±22.4 (post operative), 92.8±25.6 (4 months) Between groups: No statistically significant difference *LVESV index (ml/m^2)* BMC group: 49.6±19.2 (baseline), 47.1±17.0 (post operative), 44.5±30.1 (4 month) Control group: 54.1±18.3 (baseline), 51.5±14.9 (post operative), 52.8±15.5 (4 month) Between groups: No statistically significant difference *Wall thickening (mm)* BMC group: -0.6±1.3 (baseline), 0.3±1.6 (post operative), 1.8±2.6 (4 months) Control group: -0.5±2.0 (baseline), 0.4±1.6 (post operative), 0.4±1.7 (4 months) Between groups: Statistically significant better improvement at 4 months in BMC group (p=0.007)

The randomised control trial by Lunde *et al.* (2006), in which 50 patients were randomised into intracoronary injection of mononuclear BMCs or a control group (no sham aspiration or injection) investigated the effects of cell transplantation on LV function. To date this is one of the most comprehensive studies investigating the effects of BMC transplant via intracoronary injection. The investigators utilised SPECT analysis and echocardiography at baseline and MRI techniques at two to three weeks after infarction for initial values and again at six months for follow-up evaluations. SPECT analysis showed that although at the six month follow-up both groups had improved LVEF, this was not statistically significant. Additionally, the difference

between groups at six months was also not significant. Similar results were obtained for the other two SPECT measured variables, LVEDV and infarct size.
The echocardiography results for LVEF and end-diastolic volume demonstrated similar results with no significant improvements or differences at six months between groups. MRI results also confirmed the results for changes in LVEF, LVEDV and infarct size. In the cell injection group, no significant correlations between the improvement in LVEF and the number of mononuclear cells injected ($r = 0.03$, $p = 0.82$), time from PCI to cell injection ($r = -0.01$, $p = 0.97$) or recipient's age ($r = -0.02$, $p = 0.88$) were found. Unlike similar studies where cell infusion was used, the beneficial effects of BMC transplantation were not evident in this good quality study. This study did contain less infused cells per patient than the BOOST or TOPCARE-AMI trials however similar amounts of cells to the Fernandez-Aviles *et al.* (2004) trial were delivered. Although these studies were of poorer quality it is still unlikely that cell number may have been the main factor in the contrasting results.

Chen *et al.* (2004) also investigated intracoronary injection of mesenchymal BMCs in a randomised controlled study. Left ventriculogram results of LV dynamics demonstrated a significant improvement in the functional defect percentage in both groups of patients at three months follow-up, with patients in the treatment group experiencing significantly better improvements at the three month period than patients in the control group ($p = 0.001$). Similarly, three month improvements in the infarcted area movement velocity were significantly better in the treatment group than in the control group ($p = 0.01$). The only parameter of LV hemodynamics followed up for a period longer than three months was LVEF, which was followed up to six months. Baseline values for LVEF were $49 \pm 9\%$ and $48 \pm 10\%$ for the treatment and control groups respectively and these improved to $67 \pm 3\%$ and $54 \pm 5\%$ respectively at six months. For both the three and six month recordings, values in the treatment group were significantly better ($p = 0.01$) indicating a sustained improvement in LVEF.
Positron emission tomography analyses at three months demonstrated significantly better results in the treatment group over control group in various parameters. Both LVEDV and LVESV indices were significantly lower in the treatment group ($p = 0.001$ for LVEDV and $p = 0.01$ for LVESV). Similar results were obtained for the ratio of end-systolic pressure to end-systolic volume ($p = 0.01$) and perfusion defect ($p = 0.001$).
Real time cardiac electromechanical mapping results at three months supported previous data demonstrating significant improvements in LVEDV and LVESV indices, stroke volume index and perfusion defect in the treatment group. Furthermore, these analyses demonstrated a significant improvement in cardiac mechanical capability by improved left line local shortening and electrical property (LV endocardial unipolar voltage) at three months ($p = 0.01$).
Although promising, caution in interpreting these results should be taken. It must be highlighted that in this study the period between myocardial infarct occurrence and cell transplantation was substantially longer than in other studies reported. Therefore such a large positive effect is somewhat surprising considering that at the time of cell

transplantation the infarcted area and culprit coronary artery were no longer inflamed and expression of homing signals were longer at their peak.

Using the two refinements of Doppler tissue imaging echocardiography (a more objective and precise form of echocardiography than traditional echocardiographic methods), tissue tracking (TT) and strain (**ε**) imaging, Ruan *et al.* (2005) measured the longitudinal myocardial motion amplitude in each region during systole (TT) and the extent of myocardial fibre shortening (**ε**) in patients who had received intracoronary injections of BMCs. End-diastolic and end-systolic volumes and the LVEF were determined via traditional echocardiographic methods. Quantitative analysis of the wall motion using DTI was performed by measuring peak systolic displacement (Ds, reflects myocardial contractility) and peak systolic strain (**ε** peak, reflects contractile function) on 12 segments of the LV wall. Peak systolic displacement and peak systolic strain measurements were taken in infarcted and non-infarcted areas at 1 week (baseline), three and 6 month time points. In the infarcted areas, patients in the treatment group experienced significant increases at three and six months in Ds values ($p < 0.01$ for three and six months). Control group patients experienced slight increases in Ds at three and six months, however these were non significant. Corresponding three and six month recordings were significantly better ($p < 0.01$) in the treatment group.
In the non-infarcted area, Ds improvement in the treatment group was not as strong as in the infarcted area, however three and six month improvements were statistically significant ($p < 0.01$). Despite the fact that patients in the control group also experienced significant improvements at three ($p < 0.05$) and six months ($p < 0.01$), three and six month treatment group recordings were again significantly better ($p < 0.01$).
In terms of the peak systolic strain, in the infarcted area, patients in the treatment group experienced significant increases at three and six months ($p < 0.01$). As for the Ds recordings, patients in the control group did not experience any significant changes in peak systolic strain. Only the six month treatment group recording was significantly better ($p < 0.01$) than the corresponding control group recording.
In the non-infarcted area, peak systolic strain improvements were not as strong and in this case were not statistically significant at either the three or six month follow-up. Similarly there were no significant improvements in peak systolic strain in the control group in the non-infarcted area.
Analysis of global LV function and volume were also conducted in this study by way of measurement of LVEF, LVEDV and LVESV. Treatment group patients experienced an improvement in LVEF at both the three and six month follow-up. However only at six months was LVEF in the treatment group significantly better than in the control group ($p < 0.05$). Improvements in the LVEDV and LVESV were also evident. At three and six month follow-up both LVEDV and LVESV were significantly lower in the treatment group than in the control group ($p < 0.05$). These LVESV and LVEDV results support the possibility that transplantation of BMCs in the treatment group was responsible for a slowing down in the ventricular remodelling process.

The study by Hendrickx *et al.* (2006) excluded three randomized patients in the efficacy analyses because they died or were lost to follow-up early in the study. At four months follow-up, there was no significant improvement in LVEF for both control and BMC groups. Additionally, no significant difference in LVEF was noted between groups. Similarly, the LVEDV and LVESV indices did not differ between groups.
Thallium scintigraphy was performed before surgery and repeated at discharge and the four month follow-up assessment as a measure of myocardial metabolic activity. Segments in the area with intention to treat and a TI uptake of four at 10 minutes and four hours post-injection were analysed. Defect score for BMC and control patients did not decrease significantly throughout the study period, and the difference between groups at four months were not statistically significant.
Furthermore, MRI assessment revealed that wall thickening did not differ at discharge compared to baseline for both treatment groups. However, BMC patients experienced significant wall thickening ($p = 0.007$) compared to control patients at four months. Hendrickx *et al* (2006) proceeded to conduct subgroup analysis by dividing BMC patients to responders (patients with significant wall thickening at four months and a decrease in thallium defect score, five patients) and non-responders (four patients). In the responder BMC patient subset, improvements for wall thickening and thallium defect scores did not correlate with the number of transplanted cells. However, the number and percentage of CD34+ cells was significantly higher compared to non-responder patients ($3.10 \pm 1.97\%$ vs $0.90 \pm 0.38\%$, $p = 0.03$), indicating that CD34+ cells may have an important role in successful BMC treatment. When LVEF was plotted as a function of absolute CD34+ cells transplanted, Hendrikx *et al.* (2006) noted that greatest improvements in LVEF was observed in patients with higher numbers of engrafted CD34+ cells ($r = 0.49$).

Mobilisation Cell Transplantation

Kang *et al.* (2004) investigated the use of G-CSF mobilised progenitor cell infusion to treat patients with acute and old myocardial infarction. Patients in the G-CSF plus PBSC cell infusion group received a mean of $1.5 \pm 0.5 \times 10^9$ leucocytes. At the six month follow-up seven patients from the G-CSF plus PBSC infusion group, three from the G-CSF only group and one patient from the control group were available for analysis. Following a high rate of in-stent restenosis (described in the safety section) this study was stopped early. Therefore, no efficacy analysis is appropriate and has not been reported.

Heart failure:

Direct Injection Transplantation

In the comparative study of patients with severe ischemic heart failure by Perin *et al.* (2004), efficacy of the transendocardial injection of bone marrow mononuclear cells was evaluated through exercise testing, functional status, 2D Doppler echocardiography and SPECT (Table 7). The first 14 patients were assigned to treatment and the next nine to control, evaluations were performed at two, six and 12 months of follow-up.

Patients in the treatment group began to experience statistically significant better improvements in functional status as early as two months after the procedure. SPECT studies revealed a significant ($p = 0.01$) total reversible defect reduction compared to the control group at two, six and 12 months. However, the percent of rest defect with 50% activity (scar) did not experience such improvements.

The maximum oxygen uptake ($Vo_{2\ max}$) and metabolic equivalents (METS) were used to asses exercise capacity between groups. At baseline both $Vo_{2\ max}$ and METS were similar between the groups. By the two month follow-up a statistically significant improvement in the treatment group compared to the control group was evident in Vo_{2max} ($p = 0.03$). This significant improvement was maintained at six and 12 month follow-ups. METS values also experienced a statistically significant improvement in the treatment group compared to the control group starting at two months ($p = 0.02$). Taken together, the $Vo_{2\ max}$ and METS data point to a significant improvement in exercise capacity in patients who received transendocardial injection of bone marrow mononuclear cells.

Left ventricular ejection fraction, unlike in many of the AMI studies presented, did not significantly differ from the control group at any of the time points.

In an attempt to elucidate the subpopulation(s) of cells responsible for the improvement in total reversible defect, Pearson correlation coefficients were calculated for various bone marrow mononuclear cell subpopulations. The results indicate that several cell subpopulations correlate with improvements in reversible perfusion defects at six months. These cells include monocyte ($r = 0.8$, $p = 0.03$), B-cell ($r = 0.7$, $p = 0.02$), hematopoietic progenitor cells ($r = 0.6$, $p = 0.04$) and early hematopoietic progenitor cells ($r = 0.6$, $p = 0.04$). Therefore at least in the setting of this clinical study it appears as if these four cell types may contribute to improved perfusion in patients.

Table 7: Summary of main outcomes following direct injection transplantation heart failure

Study	Patient allocation	Main outcomes
Perin et al. (2004)	BMC (n=14) Control (n=9)	*Total reversible defect (%)* BMC: 14.8±14.5 (baseline), 4.45±11.5 (2 months), 8.8±9 (6 months), 11.3±12.8 (12 months) Control: 20±25.4 (baseline), 37±38.4 (2 months), 32.7±37 (6 months), 34.3±30.8 (12 months) Between groups: Statistically significant better reduction in treatment group at 2, 6 and 12 months (p=0.01) *Total fixed defect with 50% activity (%)* BMC: 42.6±10.3 (baseline), 39.8±6.9 (2 months), 38±6.7 (6 months), 38.2±8.5 (12 months) Control: 38±12 (baseline), 39.1±11.2 (2 months), 36.4±12 (6 months), 35.2±9.3 (12 months) Between groups: No statistically significant difference *Maximum oxygen uptake (ml/kg per min)* BMC: 17.3±8 (baseline), 23.2±8 (2 month), 24.15±7 (6 months), 25.1±8.7 (12 months) Control: 17.5±6.7 (baseline), 18.3±9.6 (2 month), 17.3±6 (6 months), 18.2±6.7 (12 months) Between groups: Statistically significant better improvement in BMC group at 2, 6 and 12 months (p=0.03) *Metabolic equivalents* BMC: 5.0±2.3 (baseline), 6.6±2.3 (2 months), 7.19±2.4 (6 months), 7.2±2.5 (12 months) Control: 5..0±1.91 (baseline), 5.2±2.7 (2 months), 4.92±1.7 (6 months), 5.1±1.9 (12 months) Between groups: Statistically significant better improvement in BMC group at 2, 6 and 12 months (p=0.02) *LVEF (NYHA score)* BMC: 30±6 (baseline), 37±6 (2 months), 30±10 (6 months), 35.1±6.9 (12 months) Control: 37±14 (baseline), 27±6 (2 months), 28±4 (6 months), 34±3 (12 months) Between groups: No statistically significant difference

Potential Cost Impact

Cost Analysis

In Australia, CHD creates enormous costs for the healthcare system, with the associated direct healthcare costs exceeding those of any other disease. The Australian Institute of Health and Welfare reported direct healthcare expenditure on CHD in 1993-1994 of $894 million, or 2.8% of total recurrent health expenditure. Heart failure accounts for 11% of the $3,719 million utilised for the treatment of cardiovascular disease in Australia (Australian Institute of Health and Welfare 2006).

Length of stay in hospital has a large impact on the health system costs for AMI due to the fact that a large proportion of health expenditure for AMI is related to hospital costs, and the majority of these hospital costs relate to ongoing staff costs and hospital overheads rather than diagnostic tests and procedures. Since 1993-1994, the average length of stay for AMI patients has declined from 8.6 days in 1993-1994 to 7.5 days in 1999-2000. The average length of stay declined faster for AMI patients treated with cardiac catheterisation, PCI or CABG compared to the overall AMI population (18% decline compared to 13% decline); however the average length of stay in1999-2000 for patients who underwent cardiac catheterisation (8.7 days), PCI (7.0 days) and CABG (15.3 days) was longer than AMI patients overall despite the greater decline in hospital stays in the last few years. Overall, patients admitted to hospital for AMI tend to stay longer compared to other patients (7.5 days compared to 3.5 days for all conditions) (Australian Institute of Health and Welfare 2006).

The average total expenditure per admission for AMI was $5,898 in 1998-1999; this includes overhead and administrative costs, which account for 22% of the average total expenditure per admission. For complicated AMI with PTCA, the average total expenditure increased to $9,575 per admission. Meanwhile AMI patients who underwent CABG had substantially higher expenditure at $17,596 per admission, presumably due to the longer length of stay for this procedure (Australian Institute of Health and Welfare 2006).

There are currently no cost-effectiveness data available on the use of autologous BMC transplantation for MI. The procedure is expected to add about USD$1,500 to the cost of standard PCI (Peck 2003). It is presumed that if this technique is proven effective, savings could be realised as recovery of the myocardium would presumably result is decreased hospital readmissions and length of stay.

Despite the fact that exact costings of autologous BMC transplantation for MI are not available, several items listed within the Medicare Benefits Schedule may provide some insight for the total costs of BMC transplantation for MI (Medicare Australia 2006):

Category	Item number	Benefit (AUD)
Harvesting of homologous (including allogenic) or autologous bone marrow for the purpose of transplantation.	13700	$288.45
Administration of blood or bone marrow already collected.	13706	$72.20
In vitro processing (and cryopreservation) of bone marrow or peripheral blood for autologous stem cell transplantation as an adjunct to high dose chemotherapy.	13760	$660.05
Initiation of management of anaesthesia for percutaneous bone marrow harvesting from the pelvis.	21116	$102.90
Initiation of management of anaesthesia for harvesting of bone marrow for the purpose of transplantation.	21949	$85.75
Administration of blood or bone marrow already collected when performed in association with the administration of anaesthesia.	22002	$68.60

Table 1: Year 2006 Medical Benefits Schedule of fees for procedures related to bone marrow transplantation.

Ethical Considerations

Informed Consent

Patients undergoing autologous bone marrow cell transplantation for myocardial infarction will need to be made aware of the potential risks associated with the use of this experimental technique. In addition to this, patients have to be informed of the possibility that this treatment may not result in substantial improvements of myocardial performance and is currently undergoing trials in various countries.

Access Issues

Autologous transplantation of BMCs is a complex procedure, requiring a trained cardiologist or cardiac surgeon (depending on delivery method) to conduct the infusion or injection of cells as well as a specialised laboratory for purification and expansion of specific cells lines (if required). At the time of writing, BMC transplantation for MI is being extensively trialled in various countries and this technology is still preliminary and experimental. Therefore this procedure is not available to all AMI patients and is only utilised in strictly controlled clinical trials. If this technology is proven safe and efficacious, it is unlikely to be offered in rural areas as the expertise required to conduct this treatment will be limited to major medical centres in cities.

No religious or cultural issues were identified from the retrieved material.

Training and Accreditation

Training

There were no specific statements from the retrieved information that suggests that cardiologists or cardiac surgeons are required to undergo specific training before utilising this procedure. Overall, it appears that autologous BMC transplantation for MI is an amalgamation of various established surgical techniques (e.g. bone marrow aspiration, transvascular infusion etc).

Clinical Guidelines

No clinical practice guidelines have been developed in Australia or New Zealand for autologous BMC transplantation for MI. Clinical guidelines will need to be developed prior to its adoption into the healthcare system if autologous BMC transplantation for MI achieves consistent success upon its application and has a reasonable safety profile. It is essential that these guidelines (if developed) clarify how autologous BMC transplantation will fit into the plethora of treatment strategies for MI and heart failure.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of autologous BMC transplantation for MI and its potential use in the Australian health system.

Search Strategy Used for Report

A systematic search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted up to October 2006. The search terms were: 'autologous bone marrow transplant$', 'autologous bone marrow stem cell transplant$', 'bone marrow stem cell transplant$', 'bone marrow mononuclear cell transplant$', 'BMMC', 'myocardial infarction', 'heart failure', 'myocardial regeneration', 'cell transplant$ for heart failure', 'cell transplant$ for myocardial infarction'.

Articles were obtained if the abstract contained safety and efficacy data on autologous bone marrow cell transplantation for myocardial infarction or heart failure in the form of randomised controlled trials, other controlled or comparative studies, case series and case reports.

Availability and Level of Evidence

List of studies found:

Total Studies	**14**
Randomised Controlled Trials	**10**
Non-Randomised Comparative Studies	**4**

Fourteen studies were identified from the literature, ten randomised controlled trials, and four non-randomised comparative studies.

Sources of Further Information

The BOOST II (Bone marrow transfer to enhance ST-elevation infarct regeneration-2) randomised controlled, double blin, multi-centre trial is underway in Germany to investigate intracoronary nucleated BMC transfer in patients after AMI. BOOST-II will investigate whether intracoronary BMC transfer has an effect on LV function and structural regeneration. In addition, BOOST-II will attempt to address a number of biological and procedural issues. An additional arm of this trial will involve irradiation of BMCs in two groups of patients prior to intracoronary transfer. This will reveal whether replication competent cells (non-irradiated cells) are required for regeneration after AMI. BOOST-II will also attempt to determine whether cell dosage plays an important role in BMC therapy for AMI. This trial is expected to be completed by the end of 2009.

The PRIMATIVE (Percutaneous Randomised Infusion of Marrow Aspirate to Improve Ventricular Efficiency) study currently underway in the United Kingdom attempts to determine if percutaneous delivery of autologous BMCs significantly improves ventricular function without significant adverse events. A total of 150 patients will be enrolled into this trial and results are expected by the end of 2009.

A randomised double blinded trial in Brazil (Cell therapy in myocardial infarction) is currently recruiting patients with the purpose of evaluating the effect of autologous bone marrow stem cell implantation with ST segment elevation acute myocardial infarction. A total of 300 patients will be recruited.

The REGENT (Myocardial REGeneration by Intracoronary Infusion of Selected Population of stEm Cells in Acute Myocardial iNfarcTion. Randomized Multicenter Trial) trial is currently recruiting up to 200 patients to compare the efficiency of sorted subpopulation of CD34+/CXCR4+ cells and unselected bone-marrow-derived progenitor cells in treatment of patients with acute myocardial infarction and low LVEF. Completion of the REGENT trial is expected in September 2007.

The MYSTAR (Myocardial Stem Cell Administration After Acute Myocardial Infarction) study in Austria is recruiting up to 360 patients to compare early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of BM derived stem cells to patients after AMI with re-opened infarct-related artery. This trial is expected to be completed by December 2008.

Table 2 lists clinical trials of autologous BM derived cells for the treatment of MI or heart failure. At the time of writing all of the studies listed were in the recruitment stage.

Cell Type	Phase	Condition	Expected Enrolment	Sponsor	Location
BM mononuclear cells	I	Congestive heart failure undergoing CABG	75	University of Pittsburgh	Pittsburgh, United States
BM mononuclear cells	I	Congestive heart failure	10	University of Pittsburgh	Pittsburgh, United States
BM mononuclear cells	I	Acute myocardial infarction	60	Minneapolis Heart Institute Foundation	Minneapolis, United States
BM mononuclear cells	II	Acute myocardial infarction	100	Nantes University Hospital	Nantes, France
BM mononuclear cells	I/II	Acute myocardial infarction	50	Azienda Unita Sanitaria Locale di Piacenza	Piacenza, Italy
BM mononuclear cells	III	Acute myocardial infarction	300	Ministry of Health	Brazil
BM derived stem cells	I	Acute myocardial infarction	10	Odense University Hospital	Odense, Denmark
BM derived stem cells	II	Myocardial infarction	200	Silesian School of Medicine	Katowice, Poland
BM derived stem cells	II	Myocardial infarction	360	Medical University of Vienna	Vienna, Austria
BM derived stem cells	II/III	Acute myocardial infarction	100	University of Oulu	Oulu, Finland
BM derived stem cells	II	Acute myocardial infarction	60	University of Zurich	Zurich, Switzerland
BM derived mesenchymal cells	II	Heart failure, myocardial infarction, coronary artery disease undergoing CABG	60	Helsinki University	Helsinki, Finland
BM derived CD34+ cells	I	Myocardial infarction, coronary artery disease	40	Emory University	Atlanta, United States

Table 2: Clinical trials of BM derived stem cell therapy for MI or heart failure recruiting patients at the time of writing.

Conclusion

Cardiac remodelling as a result of AMI continues to be a debilitating process that leads to heart failure. Current medical treatments are inadequate and are only capable of slowing progression without addressing the underlying cause of the disease, which is the damage to cardiomyocytes and the vasculature sustained during MI and the progressive loss of cardiomyocytes in the failing heart. Stem cell therapy offers the potential to regenerate the myocardium and therefore reverse cardiac remodelling.

The studies included for assessment in this report investigated the impact of bone marrow cell transplantation on recovery of myocardial infarction and heart failure resulting from myocardial infarction. Additionally the results were separated into those studies in which cells were transplanted via intracoronary infusion or intracoronary injection.

In general, the studies which investigated the effect of bone marrow cell transplant via intracoronary infusion demonstrated positive effects in a variety of cardiac function indicators. Although not all studies demonstrated the same beneficial effects across all measured variables in general both global and regional cardiac function improved. The studies included did however present some shortcomings; most obvious is the short periods to which patients were followed up. Most studies only conducted follow-ups up until the three, four or six month follow-up. Additionally even during these follow-up periods high attrition rates were observed. Larger studies with longer follow-up periods and greater patient numbers (preferably multicentric randomised controlled trials) are required to establish the long term effects of this potentially revolutionary treatment.

Studies which investigated intracoronary injection of bone marrow cells did not present as clear an indication of efficacy as did studies which infused cells. Much less evidence was available in terms of numbers of studies for intracoronary injection of these cells. Conflicting results from two studies were observed where the most notable difference appears to be the time at which patients were injected. Again further larger long term studies are required to reveal the true extent of benefit from the intracoronary injection delivery method.

Therefore it appears as if the method of cell delivery may be associated with different levels of efficacy. The current evidence suggests intracoronary infusion of cells may be the best method for cell delivery. However this will need to be verified by further studies.

In terms of safety, the procedure of harvesting and transplanting bone marrow cells (whether it is infusion or injection) tended to be safe in the vast majority of patients. Reports of death or serious adverse events were rare, indicating that at least for the short term this type of therapy is relatively safe. However, serious long term adverse events cannot be excluded and studies with long follow-up periods should be conducted to determine any unforseen long term effects of this therapy. In particular the possibility of tumour formation from possible chromosomal mutation, deregulated angiogenesis or

myogenesis should be investigated. In saying this however, one must consider that for patients who have suffered MI development of heart failure can have serious if not fatal consequences.

Although not covered in substantial detail in any of the studies retrieved, the composition of the cell suspension infused or injected, as well as their numbers may well impact on the extent of benefit conferred by bone marrow cells. While most studies mentioned the total numbers of cells transplanted and others also reported the composition, there is a need for investigation into whether the composition and quantity of the bone marrow cells transplanted plays a significant role in determining any benefits to the patient. More specifically, the question of whether a particular cell type or a specific combination of cell types confers the optimal benefit to the patient should be investigated. Currently, neither the optimal cell dosage nor the optimal cell type combination is known.

While clinical improvements have been observed in the studies presented, autologous bone marrow cell transplantation must overcome the hurdle of showing long term clinical improvement. Should long term safety and efficacy be demonstrated, potential impacts include reduced hospitalisation (which may lead to reduced costs) and longer survival times (which could potentially lead to increased costs) for patients.

Glossary of Terms

AMI	Acute myocardial infarction
BMC	Bone marrow cell
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CPC	Circulating progenitor cell
CVD	Cardiovascular disease
ECG	Electrocardiography
G-CSF	Granulocyte-colony stimulating factor
HSC	Hematopoietic stem cell
IVSD	Intraventricular septal wall thickness at end diastole
LV	Left ventricular
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESF	Left ventricular end-systolic volume
LVAD	Left ventricular assist device
MAPC	Multipotential adult progenitor cell
MI	Myocardial infarction
MSC	Mesenchymal stem cell
NSTEMI	Non ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
PWD	Posterior wall thickness, diastolic
SCF	Stem cell factor
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§among non-consecutive patients with a defined clinical presentation††	A prospective cohort study ***	A prospective cohort study ***	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§among non-consecutive patients with a defined clinical presentation††	All or none§§§	All or none§§§	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial† Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognosis factors amongst unrelated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study with concurrent controls: Historical control study Two or more single arm study‡ Interrupted time series without a parallel control group	Diagnostic case-control study††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ‡‡	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

[*] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[§] Definitions of these study designs are provided on pages 7 – 8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[†] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C).

[‡] Comparing single arm studies i.e. case series from two studies.

[**] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies.* Available at: www.msac.gov.au

[§§] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews, *BMC Medical Research Methodology*, 2003, 3: 25.

[††] Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-controlled studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

[‡‡] Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

[***] At study inception the cohort is either non-diseased or all at the same stage of the disease.

[§§§] All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come deom the disappearance of small-pox after large-scale vaccination.

[†††] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot be feasibly captures within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and dales reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; (Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

Appendix B: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCOHTA) http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- Finnish Office for Health Technology Assessment (FINOHTA)
  http://finohta.stakes.fi/FI/index.htm

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)
  http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA
  http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
  http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)
  http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment
  http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland
  http://www.nhshealthquality.org

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)
  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.your.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

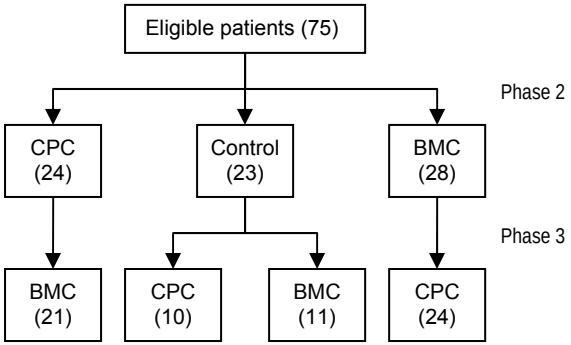
UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)
  http://www.bcbs.com/tec/index.html

Appendix C: Table of Key Efficacy and Safety Findings

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised Controlled Trial			
Assmus *et al.* (2006) TOPCARE-AMI study *3 phase study:* Phase 1: 10 CPC, 7 BMC patients Phase 2: 23 control, 24 CPC, 28 BMC Phase 3 (crossover phase): 34 CPC, 32 BMC *Allocation of patients from Phase 2 to Phase 3 (crossover):*  Follow-up: 3 months Randomisation: technique not stated	Pooled data from all study phases reported that 3/135 of the intracoronary progenitor-cell-infusion procedures had local dissection of the coronary arterial wall (due to balloon inflation during cell infusion). Resolved with immediate stent implantation. One patient required defibrillation from his implanted defibrillator during induction of myocardial ischemia by transient balloon occlusion for cell infusion. 4/35 BMC patients experienced infarct-vessel revascularisation compared to 2/34 patients in the CPC group. No BMC patients experienced death, MI, rehospitalisation or ventricular tachycardia before or after discharge.	Baseline characteristics for all groups of patients were well matched. *LV function* Patients receiving BMC had a significantly larger change in LVEF than patients receiving CPC ($p = 0.003$) and those in the control group ($p < 0.001$). Similar results were obtained when patients from Phase 1 and Phase 2 were pooled. Results did not differ when patients without evidence of viable myocardium before inclusion were analysed separately. The LVEF was -0.3 ± 3.4 percentage points in the control group ($n = 9$), $+0.4 \pm 3.0$ percentage points in the CPC group ($n = 18$), and $+3.7 \pm 4.0$ percentage points in the BMC group ($n = 18$) ($p = 0.02$ compared to control group and $p = 0.02$ compared to CPC group).	*Potential for bias:* Method of randomisation was not stated. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* All patients had full conventional pharmacologic treatment throughout the course of this study. Therefore all improvements occurred in the presence of pharmacological treatment.

Intervention

Control: Full conventional pharmacological treatment

BMC: Mean of 205 x 10^6 ± 11 x 10^6 BMC was infused into the vessel supplying the most dyskinetic LV area by means of balloon catheter with a stop-flow technique.

CMC: Mean of 22 x 10^6 ± 11 x 10^6 CPC infused.

Inclusion criteria

Patients between 18 and 80 years old, documented myocardial infarction at least 3 months before inclusion, a well-demarcated region of LV dysfunction and a patent infarct related artery.

Exclusion criteria

Presence of acutely decompensated heart failure with a NYHA class of IV, a history of other severe chronic diseases or cancer, or unwillingness to participate.

Subgroup of 35 patients underwent serial assessment of LV function by MRI. MRI-derived global LVEF increased significantly by 4.8 ± 6.0% (p = 0.03) in BMC patients (n = 11) and by 2.8 ± 5.2% (p = 0.02) in CPC patients (n = 20). No change was noted in the control patients (n = 4, p = 0.14).

Regional left ventricular contractility increased significantly for BMC patients at the central target area (-1.63 ± 0.40 to -1.38 ± 0.42, p = 0.006). Regional MRI analysis supports this result with the number of hypercontractile segments significantly reduced from 10.2 ± 3.6 to 8.7 ± 3.6 segments (p = 0.02), while the number of normocontractile segments significantly increased from 3.8 ± 4.5 to 5.4 ± 4.6 segments (p = 0.01) in the BMC group. No significant changes were noted in the CPC group.

Infarct size (MRI-derived) remained constant in both CPC (25 ± 18% to

23 ± 14% at 3 months, n = 13) and BMC (20 ± 10% at both time points, n = 9) groups.

Functional status
NYHA classification improved significantly from 2.23 ± 0.6 to 1.97 ± 0.7 (p = 0.005) for the BMC patients while no improvements were noted in CPC (p = 0.13) and control patients (p = 0.27).

Crossover phase
Regardless of whether patients received patients received BMC as initial treatment, as crossover treatment after CPC infusion, or as crossover treatment after no cell infusion (control), global LVEF increased significantly after infusion of BMC *(refer to Figure 2 of article)*.

CMC infusion did not significantly alter LVEF when given either before or after BMC.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Schächinger *et al.* (2004) TOPCARE-AMI study CPC group: 30 patients BMC group: 29 patients Randomisation: Method not stated. *Intervention* **CPC group:** 250ml of venous blood collected. Cell suspension of contains a heterogenous population of progenitor cells. Cells were infused via over-the-wire balloon catheter advanced into the stent previously implanted. A total of 10ml progenitor cell suspension was infused. **BMC group:** 50ml of bone marrow aspirated. Mean of 5.5 ± 3.9 x 10^6 CD34+/CD45+ cells infused per patient. *Inclusion criteria* 18 to 75 years old, first ST-segment elevation AMI treated by coronary stenting using bare metal stents with glycoprotein IIb/IIIa blockade in the acute phase of MI.	*Procedural safety* No or mild angina experienced during the 3 minutes of balloon inflation for cell infusion, no procedural complications during cardiac recatheterisation related to intracoronary progenitor cell injections such as ventricular arrhythmias, new thrombus formation, embolisation after cell infusion, or dissections due to balloon inflations. One patient suffered from embolic occlusion due to a small residual thrombus at the proximal stent edge after balloon dilation. This occurred prior to cell infusion. Thrombolysis in myocardial infarction blood flow did not worsen in all patients. There was no evidence of myocardial damage induced by cell infusion. No evidence for a systemic proinflammatory response to cell therapy or bleeding complications associated with bone marrow puncture. *In-hospital course* One BMC patient experienced MI and subsequent death (day 5) due to additional stent thrombosis which led to cardiogenic shock.	*LV angiography (4 months)* Global LVEF for both groups increased significantly from 50 ± 10% to 58 ± 10% ($p < 0.001$). LVEDV did not differ significantly from baseline for both groups. LVESV decreased significantly from 54 ± 19 ml to 44 ± 20 ml ($p < 0.001$). Analysis of regional wall motion revealed that the most prominent improvement was noted in the border zone adjacent to the central infarct area (Table 4). Baseline LVEF ($r = 0.42$, $p = 0.002$) was the only significant univariate predictor of improvement in ejection fraction during the 4 months follow-up. Patients with the most severe impairment of LV function demonstrated the largest absolute improvements in LVEF irrespective of treatment group ($r = -0.42$, $p = 0.002$). *MRI assessment* Subset of 37 patients underwent MRI	*Potential for bias:* Randomisation method not stated. No apparent blinding. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* N/A.

Exclusion criteria Presence of cardiogenic shock (defined as systolic blood pressure < 88 mmHg requiring intravenous pressors or intra-aortic balloon counterpulsation), major bleeding requiring blood transfusion after acute reperfusion treatment, a histpry of leukopenia, thrombocytopenia, hepatic or renal dysfunction, evidence for malignant diseases and unwillingness to participate.	*Clinical follow-up (4 and 12 months)* 7 CPC patients (23%) and 5 BMC patients (18%) required vessel revascularisation. No further stent thrombosis, MI or death occurred beyond the initial hospitalisation period. No delayed adverse events related to progenitor cell therapy.	assessment (10 ± 5.9 days after AMI, 4 months and 12 months follow-up). MRI revealed that global LVEF improved significantly at 4 months ($p < 0.001$) and continued to improve from 4 months to 12 months ($p = 0.003$), total increase of 9.3 ± 8.0%. Late enhancement volume (a measure of infarct size) significantly decreased from baseline to 4 months and further improvement up to 12 months, resulting in overall reduction of -34 ± 34% ($p < 0.001$). LV mass decreased from 86 ± 15ml/m^2 to 79 ± 15 ml/m^2 at 4 months and remained at 77 ± 15 ml/m^2 at 12 months.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised Controlled Trial			
Lunde *et al.* (2006) Acute Myocardial Infarction (ASTAMI) study BMC group: 50 patients Control group: 50 patients Follow-up: up to 6 months post-MI. Randomisation: permuted-block randomisation stratified according to center. Consecutively numbered, sealed envelopes. *Intervention* Control: Acute PCI BMC group: Acute PCI and autologous mononuclear BMC injections (median: 6 days post-PCI). Median number of mononuclear cells injected was 68 x 10^6 *Inclusion criteria* Age of 40 to 75 years, the presence of ST-elevation myocardial infarction of the anterior wall and treatment with PCI 2 to 12 hours after the onset of symptoms, successful PCI with stent	*Control group* During the 6 month follow-up period, PCI was performed for culprit-lesion stenosis in eight patients. One patient underwent coronary artery bypass grafting. Another patient was rehospitalised due to progressive heart failure. One patient experienced pulseless ventricular tachycardia, which was converted to sinus rhythm by means of a precordial thump on day 2. Six other patients were rehospitalised (reasons not stated). *BMC group* Of the 47 patients who received intracoronary cell injections, 34 had mild chest pain and 36 had transient ischemic ST deviation during balloon inflation. There was one case of cell suspension contamination by coagulase-negative staphylococci. Patient was treated with intravenous vancomysin (500mg, 4 times daily) for 3 days. Eight patients underwent PCI for culprit-lesion restenosis. Coronary artery bypass grafting was performed in 2 BMC patients. Two patients experienced stent thrombosis in the acute phase and required a new PCI instead of	*Patients* Initially, 51 patients were assigned to the control group; however one patient was excluded later due to reinfarction and cardiogenic shock on day 11, followed by heart transplantation at day 30. Three patients from the BMC group did not receive intracoronary injection due to acute stent thrombsis in two patients and low cell viability (89%) in one patient. Baseline measurements were obtained for SPECT at 4.0 ± 1.4 days, echocardiography at 4.5 ± 1.1 days and MRI at 18.8 ± 4.3 days after MI. LVEF, EDV and infarct size was comparable between groups. *SPECT* At 6 months, LVEF increased for both patient groups (mean change 7.6 ± 10.4 percentage points). No significant differences were noted between the two groups in LVEF, EDV or infarct size. For the BMC group, no significant correlation between the increase in	*Potential for bias:* No aspiration or sham injection was performed in the control group. It is unclear if assessors were blinded to the patient's treatment group. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* Study did not find any substantial advantage in LVEF improvement, EDV and infarct size for BMC injection compared to controls.

implantation performed on the culprit lesion in the left anterior descending coronary artery proximal to the second diagonal branch, three or more hypokinetic left-ventricle segments observed on echocardiography and a creatine kinase MB level more than three times the upper reference value. *Exclusion criteria* Previous Q-wave <I, cardiogenic shock, severe coexisting condition that interfered with the ability of the patient to comply with the protocol.	BMC injection. One patient was hospitalised due to progressive heart failure. Another patient had sustained ventricular tachycardia before intracoronary injection of mononuclear BMC while another had ventricular defibrillation at day 6, 24 hours after injection. One patient was diagnosed with lung cancer. Four patients were rehospitalised (reasons not stated). Lung cancer was diagnosed in one BMC patient.	LVEF and the number of mononuclear cells injected ($r = 0.03$, $p = 0.82$), the time from PCI to BMC injection ($r = -0.01$, $p = 0.97$, or the patient's age ($r = 0.02$, $p = 0.88$). *Echocardiography* Echocardiographic results at 6 months revealed that changes in values of LVEF and EDV did not differ significantly between the two groups. *MRI* No significant differences between the two groups in changes in LVEF, EDV or infarct size.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised Controlled Trial			
Lunde *et al.* (2005) Acute Myocardial Infarction (ASTAMI) study Control group: 25 patients BMC group: 24 patients Follow-up: 30 days. Randomisation: permuted-block randomisation stratified on 2 centres. *Intervention* Control: standard medical therapy BMC group: Intracoronary transplantation of autologous mononuclear BMC in the left anterior descending artery (LAD) 5 to 8 days after successful acute PCI with stent for anterior wall AMI. *Inclusion criteria* Age 40-75 years, anterior wall Ami with 120 to 720 min from onset of symptoms to PCI, ST-elevation on ECG according to WHO criteria,	*Control patients* One control patient experienced ventricular tachycardia 3 days after AMI and was cardioverted. One patient received elective PCI on circumflex coronary artery. One patient was admitted to the hospital twice and was diagnosed with non-coronary chest pain while another patient was admitted with suspected stent thrombosis and non-coronary chest pain. *BMC group* During the cell transplantation procedure, 20 patients experienced chest pain while 16 had reversible ischemic ECG changes after inflation of the balloon. During follow-up, one patient experienced reinfarction due to stent thrombosis one day before BMC transplantation, after bone marrow aspiration, SPECT and stress echocardiography were performed. This patient was treated with new PCI and was not treated according to randomisation due to safety concerns. One patient had ventricular fibrillation 24 hours after transplantation, he was resuscitated and had ICD implantation. One patient was admitted twice due to worsening	N/A	*Potential for bias:* N/A *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* The full results of the ASTAMI study are described in the paper by Lunde *et al.* (2006).

angiographically significant stenosis on LAD proximal to the second diagonal branch, successful PCI with stenting of culprit lesion, ≥ 3 hypokinetic/akinetic/dyskinetic segments assessed by echocardiography in a standard 16 segment model, creatine kinase MB above three times upper reference value. *Exclusion criteria* Previous MI with established significant Q-waves on ECG, cardiogenic shock, permanent pacemaker or other contraindication to MRI, stroke with significant sequela, short life expectancy due to cardiac reason, uncontrolled endocrinological disturbance, HIV and/or HBV/HCV positive serology, mental disorder or other condition that interferes with patient possibility to comply with the protocol.	heart failure, One patient was admitted twice to hospitals not taking part in this study and was diagnosed with non-coronary chest pain and vasovagal syncope.	

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Schachinger *et al.* (2006) REPAIR-AMI trial 204 patients (103 placebo, 101 BMC) Follow-up: 4 months Randomisation: Randomisation technique not stated. *Intervention* **Control/Placebo:** Bone marrow aspiration, administration of placebo medium. **BMC group:** Bone marrow aspiration and BMC infusion. Cell numbers not stated. *Inclusion criteria* Patients 18 to 80 years, acute ST-elevation MI that has been successfully reperfused by means of stent implantation and has a substantial residual left ventricular regional wall-motion abnormality (as defined by ejection fraction ≤ 45% according to visual estimate).	One patient withdrew after bone marrow aspiration while another was excluded due to fever and increased C-reactive protein levels. Bleeding complications or hematoma formation at the bone marrow puncture site did not occur. Intracoronary infusion was successful in all BMC patients. Intracoronary infusion could not be performed in three control patients; in one patient the guidewire could not be advanced into the infarct-related artery, the other patient had air embolism during initial angiography and the final patient had angiographic evidence of thrombus in a non-infarct-related artery. Adverse events such as death, recurrence of MI, and rehospitalisation for heart failure did not differ between groups. The incidence of the prespecified combined clinical end point of death, recurrence of myocardial infarction, and coronary revascularisation was significantly lower in the BMC group ($p = 0.01$). The combined clinical end point of death, recurrence of myocardial infarction, and rehospitalisation for heart failure was significantly lower in the BMC group as well ($p = 0.006$).	*LV function* At 4 months, results were available from 92 placebo and 95 BMC patients. Global LVEF of placebo patients increased from (mean ± SD) 46.9 ± 10.4% at baseline to 49.9 ± 13.0% at 4 months. In BMC patients, global LVEF increased from 48.3 ± 9.2% to 53.8 ± 10.2%. LVEF was significantly higher in the BMC group compared to the placebo group ($p = 0.02$). Absolute increase in LVEF was significantly greater in the BMC group compared to the placebo group (2.5%; 95% CI, 0.5 to 4.5; $p = 0.01$). Selective analysis of the infarct zone showed significant improvement in regional contractility for BMC patients compared to placebo patients ($p < 0.001$). Placebo group; baseline: – 1.54 ± 0.42, 4 mth: 1.27 ± 0.60, absolute difference: 0.28 ± 0.52. BMC group; baseline: -1.54 ± 0.42, 4 mth: -1.17 ± 0.60, absolute difference: 0.37 ± 0.53.	*Potential for bias:* No explanations of how randomisation was performed. No statement if evaluators/researchers were blinded to patient treatment. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* Patients with most severely depressed LV contractile function had greater improvement in contractile function after administration of BMC. Intracoronary infusion of BMC within 4 days after reperfusion had only marginal effects on recovery of LV contractile function.

Exclusion criteria N/A		LVESV remained constant in the BMC group but increased significantly from 75 ± 32ml to 80 ± 45ml (p = 0.02) for the placebo group. The absolute change in LVESV differed significantly between groups as well (p = 0.04) but this significance was negated when nonparametric testing was conducted (p = 0.06). LVEDV increased significantly for both groups (p < 0.001 for both) but did not differ significantly between groups. *Interaction between change in LVEF and both baseline LVEF and time to infusion* A significant inverse relation between baseline LVEF and the absolute change in LVEF at 4 months was noted in the BMC group (r = -0.21, p = 0.04) but not in the placebo group (r = +0.11, p = 0.31). Significant interaction (p = 0.02) between treatment effect of BMC infusion and baseline LVEF was obtained when the patient population was dichotomised according to median baseline LVEF. BMC patients with baseline LVEF ≤ median (48.9%) had an absolute LVEF increase that was 3 times greater than the placebo

			patients (7.5 ± 7.1% vs 2.5 ± 7.7%; absolute difference = 5.0%, 95% CI, 2.0 to 8.1). Patients with baseline LVEF > median had absolute difference between groups of 0.3% (95% CI, -2.2 to 2.8), with absolute improvement in LVEF of 3.7 ± 4.6% for placebo patients and 4.0 ± 7.1% for BMC patients. Progressive increase in BMC-associated recovery of contractile function was noted in patients treated more than 4 days after reperfusion as the interval between reperfusion therapy and BMC infusion increased (p = 0.01). BMC infusion ≥ 5 days was associated with an absolute increase in LVEF of 5.1%, no benefit was noted in patients treated for < 4 days after reperfusion.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Meyer *et al.* 2006 BOOST randomised controlled trial Control group: 30 patients BMC group: 30 patients Randomisation: Method not stated. *Intervention* **Control:** Optimum post-infarction medical treatment. This includes aspirin, ACE inhibitor or angiotensin-receptor blocker, a beta-blocker and a statin. **BMC group:** Optimum post-infarction medical treatment and infusion of autologous bone marrow cells into infarct related artery via the central lumen of an over-the-wire balloon catheter. The balloon was inflated to temporarily block antegrade blood flow during cell infusion. The final BMC preparation (26 ± 4 ml) contained 24.6 ± 9.4 x 10^8 nucleated cells, 9.5 ± 6.3 x 10^6 CD34+ and 3.6 ± 3.4 x 10^6 hematopoietic colony-forming cells. *Inclusion criteria*	BMC harvest was well tolerated and there were no bleeding complications at the harvest site. No increases of troponin T serum levels, indicating that the procedure did not inflict additional ischemic damage to the myocardium. *Control group* One patient died of progressive heart failure at 9 months. 3 patients were hospitalised with decompensated heart failure at 18 months. 4 patients had to undergo repeat PCI of infarct related vessel. *BMC group* 1 patient hospitalised with decompensated heart failure at 18 months. 1 patient developed non-ST-segment elevation MI in the left circumflex territory 4 months after cell transfer. Patient underwent PCI and completed the study. 5 patients underwent repeat PCI of the infarct-related vessel.	*MRI assessment* Mean global LVEF in the control group increased by 0.7 and 3.1 percentage points after 6 and 18 months, respectively. Mean global LVEF in the BMC transfer group increased by 6.7 and 5.9 percentage points after 6 and 18 months, respectively. The increase in global LVEF at 6 months was significantly greater in the BMC group compared to controls (p = 0.0026). However, the global LVEF change at 18 months was not significantly enhanced in the BMC group compared to controls (p = 0.27). LVEF recovery speed (over 18 months) was greater in BMC patients compared to controls (p = 0.001). LVEDV index tended to increase over the course of the study for the entire cohort (p = 0.06) while LVESV did not change significantly. LV mass index decreased significantly for both groups over 18 months (p = 0.0002).	*Potential for bias:* Randomisation method not stated. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* Results of this study appears to indicate that BMC transfer has limited effect on LV remodelling after AMI.

Admitted to Hannover medical school within 5 days after symptom onset of a first ST-segment elevation myocardial infarction, underwent successful PCI with stent implantation of the infarct-related artery, demonstrated hypokinesia or akinesia that involved more than two thirds of the LV anteroseptal, lateral, or inferior wall. *Exclusion criteria* Presence of multivessel coronary artery disease, pulmonary oedema, cardiogenic shock, advanced renal or hepatic dysfunction, and documented terminal illness or cancer.	Late contrast enhancement decreased significantly for the entire cohort as well ($p < 0.0001$). Wall thickening at the infarct region and the border zone improved significantly over 18 months for the entire cohort ($p = 0.0009$ and $p = 0.01$, respectively). However no significant improvement was noted for wall motion at the infarct region ($p = 0.07$) and border zone ($p = 0.89$). There were no significant differences between the two treatment groups for these parameters. Overall recovery of regional LV function was not significantly different between both groups. *Baseline predictors of sustained LVEF improvement after BMC transfer.* Greater LVEDV indices and greater volumes of late contrast enhancement at baseline predicted poor improvement in LVEF over 18 months for the entire cohort. Patients with an infarct transmurality at baseline greater than the median tended to benefit from BMC transfer with regard to

		global LVEF improvement throughout the 18 month study period.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Schaefer *et al.* 2006 BOOST randomised controlled trial Control group: 30 patients BMC group: 30 patients Randomisation: Method not stated. *Intervention* **Control:** Optimum post-infarction medical treatment. This includes aspirin, ACE inhibitor or angiotensin-receptor blocker, a beta-blocker and a statin. **BMC group:** Optimum post-infarction medical treatment and infusion of autologous bone marrow cells into infarct related artery via the central lumen of an over-the-wire balloon catheter. The balloon was inflated to temporarily block antegrade blood flow during cell infusion. The final BMC preparation (26 ± 4 ml) contained 24.6 ± 9.4 x 10^8 nucleated cells, 9.5 ± 6.3 x 10^6 CD34+ and 3.6 ± 3.4 x 10^6 hematopoietic colony-forming cells. *(Obtained from Wollert et al. 2004)*	One patient from the control group died from progressive heart failure 9 months after randomisation.	*Parameters of diastolic function* BMC transfer had an overall effect on E/A (Transmitral peak early velocity / Transmitral peak late velocity)(p = 0.008) and Ea/Aa ratios (ratio of early diastolic [Ea] and late diastolic [Aa] velocities) (p = 0.04). The control group had significantly lower E/A and Ea/Aa compared to BMC patients over time. In addition to this, control patients had prolongation of IVRT and no change in E/Ea ratio. This indicates that patients from the control group developed stage I diastolic dysfunction after AMI. BMC transfer had no effect on DT (E-wave deceleration time), IVRT and E/Ea ratio. Comparison between groups at 6 and 18 months showed no differences for DT, IVRT and E/Ez ratio. In a subgroup BMC of patients without hypertension, a persisting improvement of the E/A ratio was noted (0.43 ± 0.16;	*Potential for bias:* Randomisation method not stated. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* BMC therapy appears to improve echocardiographic parameters of diastolic function after AMI.

Inclusion criteria
Admitted within 5 days of the onset of symptoms of a first ST-segment elevation myocardial infarction, had undergone successful PCI with stent implantation in the infarct-related artery, and had hypokinesia or akinesia involving more than two thirds of the LV anteroseptal, lateral, and/or inferior wall, as shown by angiography done immediately after PCI.

Exclusion criteria
Patients with multivessel coronary artery disease, pulmonary oedema, cardiogenic shock, advanced renal or hepatic dysfunction, or documented terminal illness or cancer.

(Obtained from Wollert et al. 2004)

95% CI: 0.08 to 0.77; p = 0.01).

Cardiac dimensions, systolic LV function, LVEDP and MRI comparison
Echocardiographic measures of LVEDV, LVESV and LVEF were not different between groups at baseline, 6 months and 18 months.

IVSD and PVD decreased in both groups. For the entire study population, there was a correlation of LVEF as determined by MRI and echocardiography (r = 0.6, p < 0.001). This correlation was detectable in patients with large anterior MI and involvement of the apical segments and in patients with inferior/lateral MI (r = 0.6, p < 0.001; r = 0.5, p < 0.001).

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Wollert *et al.* (2004) BOOST (Bone marrow transfer to enhance ST-elevation infarct regeneration) randomised controlled trial. 30 control patients 30 BMC patients Follow-up: 6 months Randomisation: Patients were randomly allocated in a 1:1 ratio to either the control or bone-marrow-cell groups with the use of sequentially numbered, sealed envelopes provided by IST (DM). *Intervention* **Control:** Optimum post-infarction medical treatment. This includes aspirin, ACE inhibitor or angiotensin-receptor blocker, a beta-blocker and a statin. **BMC group:** Optimum post-infarction medical treatment and	No bleeding complications were noted at the bone marrow cell harvest site. There were no deaths or loss to follow-up. No increases in troponin T concentrations in serum in any of the patients 24h after intracoronary transfer of BMCs indicates that no additional ischemic damage occurred to the myocardium. 3 controls and 1 BMC patient required at least one hospital admission for worsening heart failure. One BMC patient had non ST-segment elevation MI In the left circumflex territory 4 months after BMC infusion, PCI was required and the patient completed the study. There were no differences between the controls and the BMC patients in number of premature ventricular complexes per hour and the occurrence of non-sustained or sustained ventricular tachycardias at 6 wks, 3 mths and 6 mths. *Electrophysiological results (28 controls and 27 BMC patients*) Non-sustainable ventricular tachycardia was inducible in one control and one BMC patient. Ventricular fibrillation was inducible in one control patient. *Coronary angiography (29 controls, 28 BMC patients)* Mean in-stent restenosis in the infarct-related artery (expressed as % of luminal diameter) was 32 ± 20%	Mean time from PCI to baseline cardiac MRI was 3.5 ± 1.5 (mean ± SD) days. Mean time from PCI to bone-marrow harvest was 4.8 ± 1.3 days. Time from symptom onset to harvest of bone-marrow cells was 5.7 ± 1.2 days. *LV results* 6 months after treatment, global LVEF increased significantly in the BMC group compared to controls ($p = 0.026$). The effects of bone-marrow-cell transfer on global LVEF change at 6 months follow-up were consistent in all investigated subgroups. Compared with the control group, patients in the BMC group had increased regional LVEF ($p = 0.04$) and systolic wall motion in the border zone ($p = 0.03$) at 6 months. Systolic wall motion in the infarct region was not significantly enhanced by transfer of BMCs. Changes of LVEDV index, LVESV index, left-ventricular-mass index and late-contrast enhancement from baseline to 6 months did not differ significantly in the	*Potential for bias:* No aspiration or sham injection was performed in the control group due to ethical considerations. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* N/A

infusion of autologous bone marrow cells into infarct related artery via the central lumen of an over-the-wire balloon catheter. The balloon was inflated to temporarily block antegrade blood flow during cell infusion. *Inclusion criteria* Admitted within 5 days of the onset of symptoms of a first ST-segment elevation myocardial infarction, had undergone successful PCI with stent implantation in the infarct-related artery, and had hypokinesia or akinesia involving more than two thirds of the LV anteroseptal, lateral, and/or inferior wall, as shown by angiography done immediately after PCI. *Exclusion criteria* Patients with multivessel coronary artery disease, pulmonary oedema, cardiogenic shock, advanced renal or hepatic dysfunction, or documented terminal illness or cancer.	and 33 ± 23% for controls and BMC patients respectively (p = 0.88). Four control and seven BMC patients had at least 50% in-stent restenosis (p = 0.28). One control patient had complete in-stent occlusion.	BMC group compared to the control group.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised Controlled Trial			
Kang *et al.* (2004) 28 patients enrolled. 1 control patient excluded due to elective coronary artery bypass graft surgery due to unsuccessful PCI. Results for 11 patients presented (7 cell infusion, 3 GM-CSF, 1 control). Follow-up: 6 months Randomisation: First 3 patients were not randomised and were assigned to the cell infusion group (to verify safety of procedure). Randomisation was done by a blinded independent coordinator (technique not stated). Study processes were not blinded. *Intervention* **Control:** PCI only **Cell infusion group:** Intracoronary infusion of PBSC (which was collected before PCI) was done utilising the over-the-wire angioplasty balloon catheter after PCI. Minimum target cell dose was 7 x 10^6 CD34+ cells. The infusion cell dose was 1 x 10^9	No serious adverse reactions related to G-CSF administration was noted during the periprocedural period. Three patients complained of headache which was managed with analgesics; this was completely relieved with discontinuation of G-CSF. There were no incidences of aggravation of angina or any ECG changes which suggests ischaemia or substantial arrhythmia. No thrombotic complications were noted during G-CSF infusion and the periprocedural period. Intracoronary cell infusion led to mild elevation of cardiac enzyme, creatine kinase, from 3.4 ± 3.0 IU/L before PCI to 5.6 ± 4.4 IU/L 12 hours after infusion (p = 0.012). No symptoms of ischemia or arrhythmia were noted during and after cell infusion. An unexpectedly high rate of in-stent restenosis at the culprit lesion of patients treated with G-CSF was observed (5/7 patients in the cell infusion group, 2/3 patients in the G-CSF group), which led the investigators to stop further enrolment into the study.	*Functional capacity and cardiac function* The duration of symptom-limited treadmill exercise increased from 450 ± 178s to 578 ± 168s (p = 0.004) at 6 months follow-up. At baseline, 3/7 patients had asymptomatic significant ST depression during the treadmill test after successful revascularisation of the lesion. At follow-up, patients had no chest pain, significant ST changes or substantial arrhythmias during the treadmill test. At 6 months, the cell-infusion group had significant improvements of LVEF (p = 0.005) and reductions of LV end systolic volume (p = 0.05) as measured by SPECT. The G-CSF group did not have any improvements in LVEF (45.4 ± 14.4% to 44.0 ± 16.0%, p = 0.707). These observations were validated with echocardiography, and measurements from both methods were well correlated (r = 0.933, p = 0.002). No significant improvements of wall motion score index was noted during	*Potential for bias:* No aspiration or sham injection was performed in the control group. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* The study revealed that G-CSF administration resulted in high rates of in-stent restenosis (as indicated by the close correlation between gain of neointimal volume and improvements of systolic function in the cell-infusion group). This warrants further investigation to assess and manage this potential risk of this therapy is to be utilised effectively.

mononuclear cells for all patients except for the first 3 patients.

G-CSF group: PBSC mobilised with daily subcutaneous injections of G-CSF at 10μg/kg body weight for 4 days prior to PCI. After G-CSF injection, all patients underwent PCI and implantation of stents for culprit lesion.

Inclusion criteria
Acute and old MI who underwent elective PCI for the culprit lesion of infarction. Free from chest pain and showed stable vital signs for at least 24 hours

Exclusion criteria
Persistent severe heart failure (greater than Killip class II or LVEF < 25%), uncontrolled myocardial ischaemia or ventricular tachycardia, culprit lesion of infarct related artery not feasible for PCI, age older than 75 years, malignant disease, serious current infection or haematological disease, and life expectancy less than 1 year.

low-dose dobutamine infusion from resting values in the cell infusion group ($p = 0.356$), which suggests that there were no substantial portions of hibernating myocardium.

The cell-infusion group had reduced regions of hypoperfused myocardium at 6 months follow-up (as measured by SPECT), from a baseline of $11.6 \pm 9.6\%$ to $5.3 \pm 5.0\%$ ($p = 0.02$). Coronary flow reserve showed some improvement as well but was not significant (1.5 ± 0.2 to 2.6 ± 1.0, $p = 0.072$).

Improvements in perfusion were not observed in the G-CSF group.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised Controlled Trial			
Janssens *et al.* (2006) 67 patients (34 placebo, 33 BMC) Follow-up: 4 months Randomisation: Patients were assigned according to a computer-generated randomisation list in a 1:1 ratio, using sequentially numbered sealed envelopes provided by the Leuven Coordinating Centre for Clinical Trials to BMC or placebo infusion. Study was double blinded. *Intervention* **Placebo group:** Bone marrow cells aspirated and stored in the Bone Marrow Transplantation Laboratory's cell bank. Patients received placebo preparation in three fractions over 2 to 3 minutes using a perfusion catheter during three low-pressure stop-flow inflations in the stent. **BMC group:** Bone marrow cells aspirated. Injected in three fractions (24 hours after PCI) over 2 to 3 minutes using a perfusion catheter	*Placebo group* One patient developed acute in-stent thrombosis after 2 months and was treated with a drug-eluting stent. One patient developed recurrent angina which required dilatation of in-stent stenosis while another patient (heavy smoker) was diagnosed with lung adenocarcinoma. *BMC group* One BMC patient died from haemorrhagic shock and was excluded. 2 patients developed recurrent angina and required dilatation of in-stent stenosis. One patient was diagnosed with squamous larynx carcinoma (heavy smoker).	66 patients completed the 4 month follow-up. Paired MRI (39 controls, 30 BMC) revealed that global LVEF increased over time on both groups (or for treatment effect 1.036, 95% CI 0.961 to 1.118, p = 0.36). Changes in LVEDV and LVESV did not differ significantly over time. BMC infusion did not have an additional effect on LVEF across all clinically relevant subgroups (time to PCI, infarct location, infarct size) compared to placebo. Microvascular obstruction precluded LV function recovery at 4 months and was associated with adverse remodelling (LVEDV was 162 ± 33 ml at day 4 compared to 175 ± 43 ml at follow-up, p = 0.014). Significant correlation was noted between microvascular obstruction and changes in LVEDV (r = 0/41, p = 0.02) and in LVESV (r = 0.49, p = 0.004), and was not affected	*Potential for bias:* N/A *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* Intracoronary BMC transfer did not further enhance global LV functional recovery beyond improvements obtained by contemporary reperfusion therapy in this study.

during three low-pressure stop-flow inflations in the stent. Mean of 304 x 10^6 ± 128 x 10^6 nucleated cells and 172 x 10^6 ± 72 x 10^6 mononuclear cells were injected.

Inclusion criteria
Aged 18 to 75 year, acute myocardial infarction with cumulative ST-segment elevation of 6mm or more, successful epicardial reperfusion after percutaneous coronary intervention with stent replacement, and significant LV dysfunction (hypokinesia or akinesia, involving more than half of the enterior, septal or inferior wall, using angiography, or involving three contiguous segments or more out of 17, using echocardiography).

Exclusion criteria
Patients who presented within 2 hours of symptom onset, previous coronary artery bypass graft, pulmonary oedema, cardiogenic shock or major co-morbidities.

by treatment assignment.

Infarct size decreased over time from 22 ± 16g to 15 ± 9 g in placebo patients but BMC patients achieved significantly greater reduction in infarct area from 21 ± 14 g to 10 ± 8 g (28% treatment effect, 95% CI 3 to 47, p = 0.036).

Systolic wall thickening at the infarct area and systolic wall thickening in the border zone was similar between groups at 4 months.

The greater the infarct transmurality, the smaller the improvement in contractility, but this was significantly less so in BMC patients compared to placebo (p = 0.038).

At 2 months, longitudinal shortening was significantly greater in BMC patients compared to the placebo group. Average mitral ring displacement was enhanced (treatment effect 1.1121, 95% CI 1.049 to 1.199, p = 0.0014). End-systolic strain in the infracted (p = 0.047) and remote (p = 0.017) zones were significantly greater after BMC infusion.

	Paired PET analysis revealed that myocardial flow and metabolism of infracted segments were similar between groups at follow-up.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Chen *et al.* (2004) 69 patients (35 control, 34 BMSC) Follow-up: 6 months. Randomisation: Technique not stated. *Intervention* **Control group:** Autologous bone marrow was aspirated from the ilia 8 days after PCI. Saline (6 ml) was injected instead of BMSC (Bone marrow mesenchymal stem cells). **BMSC group:** Autologous bone marrow was aspirated from the ilia 8 days after PCI. BMSC (6 ml, 8 to 10 x 10^9 cells/ml) was directly injected into the target coronary artery through an inflated over-the-wire balloon catheter in the central lumen with high pressure (10 atm). *Inclusion criteria* Acute myocardial infarction within 12 hours of the onset of continuous chest pain, underwent emergency angiography or angioplasty, formal consent from patient's relatives, age <	No deaths occurred during the 6 month follow-up. Electrocardiographic monitoring for 24 hours demonstrated no arrhythmias at 3-month follow-up.	The percentage of hypokinetic, akinetic and dyskinetic segments decreased significantly in BMSC patients after 3 months (from 32 ± 11% to 13 ± 5%) as indicated in the functional defect percentage. The improvement in functional defect for the control group was lesser (from 33 ± 10% to 28 ± 10%). Statistical analysis revealed that the difference between groups was significant (p = 0.001). At 3 months, wall movement velocity over the infarct region increased significantly in the BMSC group (2.17 ± 1.3 cm/s to 4.2 ± 2.5 cm/s) but not in the control group (2.19 ± 1.5 cm/s to 2.7 ± 1.7 cm/s). LVEF increased significantly in the BMC group compared to baseline (49 ± 9% to 67 ± 11% at 3 months and 67 ± 3% at 6 months), this improvement was significantly greater than the control group as well (p = 0.01 at 3 months and 6 months). Perfusion defects as detected by positron	*Potential for bias:* Randomisation method not stated *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* N/A

70 years old, no cardiac shock or cardiac block. Stable haemodynamics and no severe co-morbidities. *Exclusion criteria* Not stated.	emission tomography was significantly lower in BMSC patients compared to controls (134 ± 66 cm2 vs 185 ± 87 cm2). LVEDV was significantly lower in the BMSC group compared to controls (136 ± 31ml vs 162 ± 27 ml, p = 0.001). In addition to this, LVESV was significantly lower in BMSC patients as well (63 ± 20 ml vs 88 ± 19 ml, p = 0.01). The ratio of end-diastolic pressure to end-diastolic volume was significantly lower in the BMSC group compared to the controls (1.72 ± 1.23 mm Hg/ml vs 2.84 ± 1.3 mm Hg/ml). Real-time cardiac electromechanical mapping of BMSC patients revealed significant improvement at 3 months compared to preimplantation in cardiac mechanical capability measured as left line local shortening (7.32 ± 1.86% to 11.29 ± 1.64%, p = 0.01), and electrical property measured as left ventricular endocardial unipolar voltage increased significantly as well (7.61 ± 1.09 mV to 10.38 ± 1.12 mV, p = 0.01). Perfusion

		defects decreased significantly from 36.2 ± 6.2% to 20.3 ± 5.31% (p = 0.01) while cardiac functional indices all improved significantly as well (stroke volume, LVEDV, LVESV; all p = 0.01).

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised Controlled Trial			
Hendrikx *et al.* 2006 Control group: 12 patients BMC group: 11 patients Randomisation: Patients were randomly allocated in a 1:1 ratio to either the control, or BMC group by means of sequentially numbered sealed envelopes. *Intervention* **Control group:** Conventional CABG and sham injection. Bone marrow aspirated from the iliac crest one day before surgery. Heparinised saline injected at the border zone of the infarct scar as sham treatment. **BMC group:** Conventional CABG with BMC injection. Bone marrow aspirated from the iliac crest one day before surgery. Mononuclear cells were isolated and injected at the border zone of the infarct scar (total volume 10 ml). Total amount of recovered BMCs used for transplant was 60.25 x 10^6 ± 31.35 x 10^6 nucleated cells; viability was 95.05 ± 2.54%, recovery was 73.0 ± 14.6%.	Direct myocardial injection of cells did not cause additional damage to the myocardium. *Control group* One patient died on the 5th postoperative day due to multiorgan failure secondary to low cardiac output syndrome. Another patient was lost to follow-up due to acute psychiatric illness. *BMC group* One patient died on postoperative day 7 due to perforated oesophageal ulcer complicated by mediastinitis.	Final cohort consisted of 10 control and 10 BMC patients. Global ejection fraction increased in both groups, but not significantly. There was no significant difference in improvement between the control and the BMC treated group at 4-months follow-up (p = 0.41). Changes in LVEDV and LVESV index did not differ significantly between groups. Metabolic activity was measured with thallium scintigraphy (before surgery, at discharge and at 4 months follow-up). Thallium uptake scores for BMC patients recorded a decreased from 4 to 3.5 ± 0.9 at discharge and 3.3 ± 1.0 at 4 months. Control patients recorded a decrease from 4 to 3.7 ± 0.4 at discharge but no further decrease was noted at 4 months. The difference in thallium uptake scores was not statistically significant at discharge (p = 0.51) or 4 months follow-up (p = 0.63).	*Potential for bias:* N/A *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* This study suggests that the amount of CD23+ cells that are integrated into the infarct area results in better patient outcomes.

Inclusion criteria Admitted for elective CABG surgery, had a transmural myocardial infarction on ECG and akinesia or dyskinesia in part of the left ventricle as shown by angiography. *Exclusion criteria* Patients needing urgent surgery, advanced renal or hepatic failure or with documented malignancy, patients with pacemakers.	MRI analysis revealed that wall thickening values did not differ significantly at discharge from baseline in both groups ($p = 0.18$). A significant improvement was noted at 4 months for the BMC group while no improvement was noted in the control group ($p = 0.007$ for BMC patients vs controls). BMC patients were divided into subgroups of responders ($n = 5$), non-responders ($n = 4$) and discordant findings ($n = 1$). The improvement noted in responders were nor correlated to the number of transplanted mononuclear cells ($p = 0.82$). However the number and percentage of CD34+ cells was significantly higher in the responders compared to the non-responders ($p = 0.03$). A greater improvement in LVEF was observed in patients with higher numbers of engrafted CD34+ cells ($r = 0.49$, Figure 3).

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Randomised controlled trial			
Ruan *et al.* (2005) Control group: 11 patients BMC group: 9 patients Randomisation: Method not stated. Double blind trial. *Intervention* Control group: Intracoronary injection of diluted serum. BMC group: Intracoronary injection of BMCs. *Inclusion criteria* Chest pain of 12.1 ± 12.6 hours prior, angiography indicating > 90% coronary stenosis or occlusion in left anterior descending artery. *Exclusion criteria* N/A	N/A	*Peak systolic displacement* No significant improvements were noted in the control group for peak systolic displacement in the infarct-related region and the non-infarct-related region. BMC patients achieved significant improvement in peak systolic displacement (Ds): a) infarct-related region (baseline 4.49 ± 2.71 mm, 3 months 7.56 ± 2.95 mm, 6 months 7.37 ± 3.58 mm, $p < 0.01$ compared to baseline and control group at 3 months and 6 months). b) non-infarct related region (baseline 7.28 ± 3.04 mm, 3 months 9.94 ± 2.9, 6 months 7.86 ± 2.86, $p < 0.01$ compared to baseline and control group at 3 months and 6 months). *Peak systolic strain* Peak systolic strain (ε peak) did not improve significantly in controls. BMC patients experienced significant improvement in ε peak: a) infarct-related region (baseline -13.4 ± 6%, 3 months -17.56 ± 6.05%, 6	*Potential for bias:* Randomisation method not stated. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* No safety data presented.

		months -18.98 ± 6.29). $p < 0.01$ at 3 months vs baseline, $p < 0.01$ at 6 months vs baseline and controls. b) Non-infarct related region (baseline -14.7 ± 7.45%, 3 months -16.69 ± 8.18%, 6 months -17.7 ± 7.09%). $p < 0.05$ at 6 months vs baseline. *LV global function and volume* At 6 months, LVEF of BMC patients was significantly higher compared to controls ($p < 0.05$). At 3 months, LVEDV and LVESV was significantly higher in the control patients (both $p < 0.05$) indicating that BMC transplantation is attenuatinf LV remodelling processes. LVEDV and LVESV did not change much from 3 months to 6 months in either group ($p > 0.05$).

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Non-randomised comparative study			
Fernandez-Aviles *et al.* (2004) 20 BMC patients 13 controls Follow-up: 6 months *Intervention* **Control group:** Patients received the same acute treatment as BMC group, no sham transplantation treatment. **BMC group:** acute reperfusion of MI and infusion/transplantation of BMC. Bone marrow was aspirated from the posterior iliac crest. An over-the-wire balloon catheter was positioned at the site of stent implantation and inflated to block blood flow. BMC suspension was infused with a pump at 1-2 ml/min in periods of 3 min inflation and cell infusion alternating with 1 minute deinflation and reperfusion until total dose of BMC was given (10 to 25ml). Average of 78 ± 41 x 10^6 cells per patient, 13 ± 5.5 days post-infarction. *Inclusion criteria* Age between 18 and 75 years,	Mean follow-up after transplantation was 11± 5 months. No patient experienced periprocedural complications or increase in myocardial injury markers at 24 hours. Intracoronary cell infusion did not induce any changes in the fractional flow reserve or the coronary flow reserve. No major cardiac events or spontaneous/stress-induced arrhythmias were observed during follow-up. 2 patients (BMC group) required stenting at 5 months due to progression of previous nonsignificant stenosis in a noninfarct-related artery.	*LV outcome* **Baseline** / **6 mths** / **p-value** LVEDV (ml): 163.9 ± 39.7 / 160.9 ± 43.3 / 0.541 LVESV (ml): 81.3 ± 29.2 / 71.7 ± 31.8 / 0.007 LVSV (ml): 82.6 ± 13.2 / 89.2 ± 19.9 / 0.088 LVEF (%): 51.3 ± 6.6 / 57.1 ± 10.4 / 0.002 Segments with asynergy per patient: 3.7 ± 2.1 / 2.3 ± 1.6 / 0.017 WMSI: 1.44 ± 1.47 / 1.20 ± 0.18 / <0.001 *LV contractile reserve* The end-diastolic and end-systolic thickness of the infracted wall measured by MRI increased significantly at 6 months (both $p < 0.01$). Infarcted wall thickening rose from 2.0 ± 1.0mm up to 3.2 ± 1.5mm.	*Potential for bias:* No aspiration or sham injection was performed in the control group. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* N/A

extensive ST-elevated MI (baseline total ST elevation ≥ 6mm) treated with primary or post-thrombolysis stent-angioplasty, , successful reperfusion and culprit-artery repair (thrombolysis-in-myocardiac-infarction grade 3 flow plus residual restenosis <30%), no significant lesions in the remaining coronary segments and baseline low-dose dobutamine stress echocardiography negative for viability in the infracted area. *Exclusion criteria* Women of child-bearing age, Killip class ≥ II or LV ejection fraction <30%, cardiogenic shock, mechanical complication, automatic defibrillator bearers or candidates, history of any cancer in the last 5 years, major bleeding, haematological disease and life expectancy < 1 year.	Dobutamine-induced increment in ejection fraction tended to be significantly larger after 6 months then in the baseline study (9.61 to 4.78, p = 0.07). *Coronary angiography* At 6 months, poststenting late loss in BMC patients was 0.67 ± 0.34 mm, and significant restenosis was observed in 2 patients (10%). Two additional patients (10%) had initial nonsignificant stenosis in the culprit artery which became severe during follow-up. 6 month angiographic results revealed a late loss of 0.66 ± 0.78mm in the control group (p > 0.05 compared to BMC patients), and 2 patients (15%) developed binary significant restenosis (p > 0.05 compared to BMC patients).

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Non-randomised comparative study			
Perin *et al.* (2004) 23 patients (9 control, 11 BMC) Follow-up: 12 months *Intervention* **Control group:** Details of treatment not stated. **BMC group:** Injection of autologous BMC (mononuclear) suspension into the LV wall with a NOGA Myostar injection catheter into areas of hibernating myocardium (transendocardial injection). *Inclusion criteria* Chronic coronary artery disease with reversible perfusion defect detectable by SPECT, LVEF < 40%, ineligibility for percutaneous or surgical revascularisation as assessed by coronary arteriography, signed informed consent. *Exclusion criteria* Difficulty in obtaining vascular access for percutaneous procedures, previous	No major periprocedural complications. One patient had transient pulmonary oedema that was resolved with loop diuretics after the procedure. No sustained arrhythmias were associated with the procedure and there were no incidences of significant arrhythmias during hospitalisation. One BMC patient died at 14 weeks, presumable due to sudden cardiac death. One control patient died at 11 months, presumable due to neurological complications.	One patient was lost to follow-up, treatment group not stated. White blood cell count, CRP, and BNP levels were similar for both groups at baseline, 2 months, 6 months and 12 months. Serum creatinine levels were significantly higher in the control group compared to the BMC group ($p = 0.04$). *Functional status* NYHA class did not improve significantly in the control group. However, NYHA improved significantly from 2.2 ± 0.9 (baseline) to 1.5 ± 0.5 (2 months), 1.3 ± 0.6 (6 months), and 1.4 ± 0.7 (12 months) ($p = 0.01$ for BMC vs control). Significant improvement was noted since the 2 months follow-up evaluation. CCSAS did not improve significantly in the control. For the BMC group, CCSAS improved from a baseline of 2.6 ± 0.8 to 1.5 ± 0.5 (2 months), 1.4 ± 0.5 (6 months) and 1.2 ± 0.4 (12 months) ($p = 0.002$ for BMC vs control). Significant improvement was noted since the 2	*Potential for bias:* Treatment details for control patients were not stated. *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* N/A

or current history of neoplasia or other comorbidity that could impact the patient's short-term survival, significant LV dysrhythmias (sustained ventricular tachycardia), LV aneurysm, unexplained baseline laboratory abnormalities, bone tissue with abnormal radiological aspect, primary haematologic disease, acute MI within 3 months of enrolment in study, presence of intravascular thrombus as shown by 2D Doppler echocardiography, haemodynamic instability at the time of procedure, atrial fibrillation and any condition that the investigator feels would place the patient at undue risk.	months follow-up evaluation. *SPECT* At 2 months, there was significant reduction in myocardial ischemia in the BMC group compared to the control group ($p = 0.01$). This was inferred by the difference in total reversible defect, significant difference was noted from the 2 months follow-up evaluation. Percent of rest defect with 50% activity (scar) was similar between both groups. *Exercise* At 2 months follow-up, there was a significant increase in exercise capacity as measured by VO2 max and metabolic equivalents (METs) for the treatment group. VO2 max for BMC patients increased from 17.3 ± 8 to 23.2 ± 8 (2 months), 24.15 ± 7 (6 months) and 25.1 ± 8.7 (12 months) ($p = 0.03$ for BMC vs control). METS improved from 5 ± 2.3 to 6.6 ± 2.3 (2 months), 7.19 ± 2.4 (6 months) and 7.2 ± 2.5 (12 months) for BMC patients ($p = 0.02$ for BMC vs control).

		There was no significant difference between groups for LVEF, 24 hour Holter monitoring (ventricular arrhythmias), number of PVCs or SAECG parameters. Monocyte, B-cell, naematopoietic progenitor cell, ad early haematopoietic progenitor cell subpopulations correlated with improvement in reversible perfusion defects at 6 months.

Study Details	Key Safety Findings	Key Efficacy Findings	Appraisal/Comments
Non-randomised comparative study			
Strauer *et al.* (2005) Control group: 18 patients BMC group: 18 patients *Intervention* **Control group:** Intervention not stated **BMC group** Cell transplantation via intracoronary administration route. Infusion was performed directly into the infracted zone through the infarct related artery via an angioplasty balloon catheter. Four to six fractional infusions were performed over 2 to 4 minutes of 3 to 5 ml of cell suspension, each containing 15 to 22 x 10^6 mononuclear cells. *Inclusion criteria* Transmural myocardial infarction 27 ± 31 months before, all infarcts had been treated acutely by PTCA and/or stent implantation, age < 70 years, one vessel disease with an open infarct-related artery at the time of stem cell therapy, sinus rhythm, a clear-cut demarcation of the ventriculographic infarct area and no coronary bypass surgery.	No impairment of LV function occurred in any patient. Electrocardiogram at rest and during exercise and 24 hour Holter ECH revealed no rhythm disturbances at any time point. One BMC patient (6%) developed relevant restenosis and was treated with stent implantation. No inflammatory response or myocardial reaction (white blood cell count, C-reactive protein and creatine phosphokinase) was noted after cell therapy despite an increase in CRP (0.58 ± 0.48 mg/dl to 1.07 ± 0.73 U/l after treatment, p = 0.002). This is commonplace after bone marrow puncture and/or cardiac transplantation.	At 9 ± 6 months and <10 days before treatment, both groups had similar baseline values for area of infarction, LCEF and infarction wall movement velocity. At 3 months, control patients did not exhibit any significant improvement in infarct size, LVEF or wall movement velocity of the infracted area. Meanwhile BMC patients experienced significantly greater improvement in infarct area (p = 0.02), LVEF (p = 0.02) and infarction wall movement velocity (p = 0.001) compared to controls. Clinical performance improved as indicated by the 11% increase in Vo2max (p = 0.0001). SPECT investigation revealed 5% improvement in tetrofosmin uptake in the infracted zone, indicating regeneration of formerly avital, chronically infracted heart muscle. PET analysis revealed that myocardial metabolism increased by 15% (p =	*Potential for bias:* N/A *Outcome measurements and their validity:* The outcome measurements used in this study are validated. *Other comments:* N/A.

Exclusion criteria Severe comorbidity and alcohol or drug dependency.	0.012) in BMC patients (FDG uptake).

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