Stem cell therapy for heart diseases

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Background: Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Despite the advances in medical and catheter-based therapy for acute myocardial infarction the 1-year mortality remains as high as 13% and the 5-year prognosis for patients with heart failure remains as high as 50%. Left ventricular systolic dysfunction, a major determinant of prognosis, is associated with significant loss of cardiomyocytes which was previously thought to be irreversible as the heart was considered a post-mitotic organ.

Sources of data: Review of literature published in peer reviewed journals and ClinicalTrials.Gov website.

Areas of agreement: There is now growing evidence that the human heart is capable of undergoing repair and in recent years there has been an increase in basic and clinical research with the aim of harnessing the regenerative properties of stem cells in order to facilitate restoration of myocardial function.

Areas of controversy: The mechanisms of action of cell therapy with regards to cardiac repair remain unsatisfactorily understood and the magnitude of benefit demonstrated in animal models is yet to be fully translated in humans.

Growing points: The number of clinical trials continues to increase and include treating patients with acute myocardial infarction and chronic heart failure secondary to ischaemic heart disease or dilated cardiomyopathy.

Areas timely for developing research: The future of this field of research will require closer collaboration between scientists and clinicians to understand how cell therapy works and to define the ideal cell type and method of delivery to be able to derive maximum benefit.

Keywords: adult stem cell therapy/acute myocardial infarction/bone marrow stem/progenitor cells/dilated cardiomyopathy/heart failure

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Introduction

Ischaemic heart disease (IHD) is the most common cause of death in the world accounting for 7.2 million deaths per year (~12% of all reported deaths).\(^1\) Acute myocardial infarction (AMI) affects ~250,000 people each year in the UK\(^2\) and subsequent heart failure with left ventricular systolic dysfunction (LVSD) is common with an estimated prevalence of 3% of people aged over 45.\(^3\) Approximately 10% of patients with heart failure have dilated cardiomyopathy (DCM).\(^4\) Regardless of aetiology heart failure is associated with significant morbidity and mortality reflected by a 5-year mortality varying from 26 to 75%,\(^5\) a prognosis that is worse than most cancers. Patients with heart failure can be significantly limited in term of exercise capacity which can vary from being breathless on moderate exertion to being breathless at rest. This affects patients’ quality-of-life as well as having a major socioeconomic cost burden. The annual cost of heart failure to the UK National Health Service is just over £625 million and it has been estimated that IHD costs the economy £3.9 billion in lost productivity.\(^6\)

Myocardial infarction and heart failure are associated with significant loss of cardiomyocytes which was thought to be an irreversible process as the heart was considered a terminally differentiated organ. However, the discovery of tissue resident cardiac stem cells\(^7\) and the ability of bone marrow (BM)-derived stem cells to trans-differentiate into cardiomyocytes\(^8\) have challenged this long held belief. These findings have prompted intense basic and clinical research with the aim of harnessing the regenerative properties of stem cells in order to repair damaged myocardium, improve cardiac function and improve patient morbidity and mortality. Clinical trials have so far focused on three main situations: AMI (with the hope of preventing LVSD), chronic heart failure secondary to previous myocardial infarction and DCM. In this article we will review the cell types that have been explored as potential candidates for cardiac repair, the methods of cell delivery in clinical practice and the clinical trial evidence to date.

Cell types used for cardiac repair

A variety of cell types have been explored for the purposes of cardiac repair and these can be grouped as either allogeneic or autologous in origin. (see Table 1).
Allogeneic cell types

Embryonic stem cells
Embryonic stem (ES) cells have the broadest developmental potential (pluripotent) since they can give rise to cells of all three embryonic germ layers and functionally intact cardiomyocytes have been generated from human ES cells in vitro. In a mouse model ES cell-derived cardiomyocytes, when injected into infarcted myocardium, formed stable grafts and subsequently contracted in synchrony with adjacent cells. However, the use of ES cells is associated with teratoma formation in animal models which raises concerns regarding their malignant potential. This, together with the ethical and legal issues surrounding the use of human ES cells, has hampered further research efforts and current focus is on other sources of stem cells for cardiac repair.

An exciting alternative to ES cells is emerging in the form of inducible Pluripotent Stem Cells (iPSCs) adult stem cells that have been successfully reprogrammed back to an undifferentiated pluripotent state by inserting four genes, Oct3/4, Sox2, KL4 and c-Myc, into differentiated somatic cells. These cells have the morphological phenotype of ES cells and have been demonstrated in vivo and in vitro to have the same differentiation potential as ES cells (able to form all three germ layers). Functioning cardiomyocytes have already been produced from iPSCs demonstrating their potential use in cardiovascular regenerative medicine although there remain theoretical concerns regarding tumour genesis.

Foetal cardiomyocytes
Foetal cardiomyocytes were one of the first cell types to be investigated as potential candidates for cardiac repair. Animal studies have shown foetal cardiomyocyte transplantation improves the function of ischaemic and globally failing hearts. However, the use of foetal cardiomyocytes has similar concerns to ES cells including availability,

<table>
<thead>
<tr>
<th>Table 1: The different cell types that have been investigated for use in cardiac repair</th>
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<tbody>
<tr>
<td><strong>Allogeneic</strong></td>
</tr>
<tr>
<td>Embryonic stem cells</td>
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<tr>
<td>Foetal cardiomyocytes</td>
</tr>
<tr>
<td>Human umbilical cord-derived cells</td>
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<td></td>
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immunogenicity and ethics thus other cell types have surpassed this as likely candidates for use in cardiac repair.

**Human umbilical cord-derived stem cells**

Human cord blood mononuclear cells (hUCBCs) are currently used clinically for repopulating bone marrow (BM) in patients being treated for BM disorders, such as acute leukaemia. Cord blood contains a large number of non-haematopoietic stem cells which rarely express HLA class II antigens and appear to be immunologically naive thus reducing the risk of rejection and are therefore an attractive option for regenerative therapy. In animal models of AMI injection of hUCBCs is associated with significant reductions in infarct size particularly when given by the intramyocardial route. Phase I clinical studies are being planned/ performed with the use of hUCBCs for the treatment of patients with DCM and refractory angina.

**Autologous cell types**

Unlike ES cells, autologous adult stem cells are free from the risks of teratoma formation and immune rejection although display more limited differentiation potential. Adult stem cells that have been studied to date include circulating endothelial progenitor cells, tissue-resident cardiac stem cells, skeletal myoblasts and most commonly BM-derived stem cells.

**Resident cardiac stem cells**

The heart has been considered a terminally differentiated organ lacking self-renewal capabilities but this dogma has been challenged recently, particularly with the demonstration of continued cell division within the adult heart following injury, such as myocardial infarction. Several independent investigators have now isolated and identified resident cardiac stem cells which are capable of differentiating into multiple cardiac cell lineages, such as cardiomyocytes and vascular smooth muscle cells. These cells have been studied in animal models of myocardial infarction with beneficial outcomes in terms of reducing infarct size and improving LV function. Resident cardiac stem cells are clearly an attractive option for cardiac repair although a harvesting technique remains to be perfected and clinical trials of safety and efficacy are still awaited. The ongoing CArdiosphere-Derived aUtologous Stem CELls to Reverse ventricUlar dySfunction (CADUCEUS) study, which is a Phase 1 Study recruiting 30 patients to receive autologous cardiosphere-derived stem cells, will hopefully answer some of these questions (ClinicalTrials.gov Identifier: NCT00893360).
Adipose-derived stem cells
Adipose tissue has been investigated as a source of adult progenitor/stem cells for the purposes of cardiac repair as this tissue contains a heterogeneous mixture of endothelial, haematopoietic and mesenchymal progenitor cells which can be easily harvested by liposuction. Preclinical studies have shown that adipose-derived stem cells (ASCs) are associated with improvement in the ejection fraction in animal models of myocardial infarction and neoangiogenesis via paracrine factors has been postulated as a potential mechanism of action of ASCs. Clinical trials are currently ongoing and include the APOLLO Study (ClinicalTrials.gov Identifier: NCT00442806) and PRECISE Study (ClinicalTrials.gov Identifier: NCT00426868) which are assessing the safety and efficacy of ASCs in AMI and chronic myocardial ischaemia, respectively.

Skeletal myoblasts
Skeletal myoblasts have been widely studied due to several favourable characteristics. They can be easily harvested (with a muscle biopsy) and cultured from the patients themselves, avoiding ethical considerations or immunological rejection. Preclinical animal studies have demonstrated the ability for skeletal myoblasts to engraft, form myotubules and enhance cardiac function after transplantation into infarcted myocardium. Human studies have shown that epicardial injection of these cells during coronary artery bypass (CABG) surgery is feasible with potential functional benefits. The main limitations regarding the use of skeletal myoblasts are that they remain committed to the skeletal muscle lineage and have been associated with arrhythmias, the mechanism of which is yet to be defined.

Bone marrow-derived progenitor/stem cells
The most widely studied of the adult stem cells has been bone marrow-derived mononuclear cells (BMSCs) in part due to the ease of obtaining cells via a BM aspirate. In a landmark animal study, myocardial infarction was induced in a mouse model by coronary artery ligation following which BMSCs were injected directly into the contracting wall bordering the infarct. The transplanted cells appeared to undergo trans-differentiation to cardiomyocytes with newly formed myocardium occupying a significant proportion of the infarcted area with significant improvement in the left ventricular ejection fraction (LVEF) just 9 days after cell transplantation. These results have been challenged by different groups, which have demonstrated that transplanted cells do not acquire a cardiomyocyte phenotype but rather develop into haematopoietic cell types after transplantation. It is therefore possible that adult stem cell plasticity (i.e. ability to transdifferentiate into
different cell types) has been overestimated particularly with regards to cardiomyogenic transdifferentiation. This has fuelled the ongoing debate regarding the mechanism of action by which stem cell therapy leads to cardiac repair and it is likely that the beneficial effects seen are multi-factorial in origin. Possible explanations include neovascularization by differentiation into an endothelial phenotype, paracrine effects of the cell infusate, cell fusion as well as myocardial regeneration.30

**Methods of stem cell delivery**

A variety of methods have been used to deliver cell therapy to the heart (Fig. 1).

**Peripheral infusion of cells**

Peripheral intravenous infusion has been extensively used in animal models but there has only been one human study to date.31 This technique is applicable only in patients with AMI as it is reliant on physiological homing signals which are not present in chronic heart failure. Another significant limitation is that only a few cells appear to reach the affected area due to trapping of the cells in the microvasculature of the lungs, liver and lymphoid tissues.32

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**Fig. 1** Potential delivery routes for stem cell therapy. Adapted by permission from Macmillan Publishers, Ltd., Nature,62 copyright 2002.
**Cell mobilization**

Prolonged pharmacological mobilization of BM stem cells with subcutaneous injection of granulocyte colony stimulating factor (G-CSF) is an attractive option because the treatment is non-invasive and is already widely used in clinical haematology with an excellent safety profile. Preclinical animal studies\(^{33}\) and phase 1 clinical trials\(^{34}\) after myocardial infarction have indicated that G-CSF treatment is safe and may improve left ventricular function. However, a recent meta-analysis on the effect of G-CSF in AMI showed no overall benefit although subset analysis showed that there may be benefit limited to patients with significant LVSD and if the infusion is started early.\(^{35}\) It remains to be determined if G-CSF treatment could be an effective part of a treatment strategy combining several cytokines and/or local stem cell delivery.

**Intracoronary infusion of cells**

Intracoronary infusion is the most popular mode of cell delivery in the clinical setting, especially after AMI. The technique is similar (hence the popularity) to that used for coronary angioplasty, which involves positioning of an angioplasty balloon in one of the coronary arteries. The coronary blood flow is then stopped, by balloon inflation, for \(\approx 2–4\) min while the stem cells are infused under pressure. A preclinical study in dogs raised concerns regarding the possibility of microinfarcts caused by intracoronary injection of mesenchymal stromal cells\(^{36}\) and there is likely to be a safety threshold with regards to the size and dose of cells delivered using the intracoronary route. Reassuringly, the safety of this technique has been confirmed in multiple clinical trials. A recent meta-analysis confirmed that the relative risks of mortality and morbidity, measured by incidence of re-infarction, arrhythmias, restenosis, hospital re-admission and target vessel revascularization, were not significantly increased in participants who received intracoronary BMSC treatment compared with controls.\(^{37}\)

**Intramyocardial injection**

Intramyocardial injection has been performed in patients with chronic heart failure secondary to IHD. In contrast to the AMI setting, these patients are unlikely to release signals from chronically infarcted myocardium to induce stem cell homing and therefore it maybe more effective to use intramyocardial injection to deliver the cells to the target area. Intramyocardial injection can be performed via transendocardial
injections using catheter-based percutaneous techniques or via transepi-
ocardial injections during open heart surgery. Experimental data, using
radionucleotide-labelled BMSC, suggest that target area cell retention
may be higher with intramyocardial injection when compared with the
intracoronary delivery method although even then this is a small frac-
tion of the total cells injected. There is ongoing work to elucidate the
reasons for loss of cells following intramyocardial injection with a view
to hopefully making this technique more efficient.

Stem cell therapy in acute myocardial infarction

Primary angioplasty, optimal medical therapy and secondary preven-
tion measures have significantly decreased early mortality and
improved the long-term prognosis of patients with AMI. However, the
1-year mortality of patients with AMI and resultant LVSD is still as
high as 13%. A major reason for the high morbidity and mortality is
that the human heart has an inadequate regenerative response to the
myocardial damage following AMI; cell death from the ischaemic
damage can lead to progressive ventricular dilation and dysfunction
through the processes of adverse remodelling. It is therefore unsurpris-
ing that over recent years there has been an explosion in clinical trials
evaluating stem cell therapy following AMI, some with positive results
and some with neutral ones (see Table 2). The majority of the studies
have used intracoronary delivery of BMSCs following successful stent-
ing of the infarct-related artery. Improvements in the LVEF, reduction
in size of scar tissue and cardiac volume have been the surrogate
markers used to assess efficacy of cell therapy.

Four main randomized controlled trials (RCTs) have been published
with positive findings so far. The TOPCARE-AMI trial was the first
published RCT to demonstrate the potential beneficial effect of BSMC
therapy following AMI with improvement in the LVEF from 51.6 ±
9.6% to 60.1 ± 8.6% at 4 months. In the BOOST trial global
LVEF improved by 6% at 6 months although this improvement was
maintained only in patients with larger infarcts at long-term follow-up
(18 months). In the REPAIR-AMI trial, the largest trial to date, BMSC therapy was associated with an increase in the LVEF of 2.8% at
12 months and the FINCELL trial reported an improvement of 5%.
In contrast, three RCTs have produced neutral findings. Janssens
et al. from the LEUVEN-AMI study, reported no changes in global
LVEF after BMSC infusion, although sub-set analysis showed possible
benefits in reducing infarct size in patients who suffered the largest
infarcts. In the ASTAMI trial BMSC administration had no signifi-
cant effect on the LVEF, LV volumes, or infarct size. Finally, in the
recently published HEBE trial, no changes in global or regional LV systolic function were reported after BMSC therapy. The reasons for the inconsistent findings from these clinical trials are unclear but possibilities include variations in the number of cells delivered, timing of delivery after AMI and differences in the cell isolation protocol. A recent meta-analyses has been performed on the impact of BM-derived cells after AMI and comprises 811 patients. This confirmed the safety of this treatment option and overall stem cell therapy was associated with an improved LVEF of 2.99% and reduction in myocardial scar by 3.51% in comparison to controls. Although promising, these findings are much less than would have been anticipated from the earlier mouse models which showed up to a 40% improvement in the LVEF when BMSC were delivered to the peri-infarct zone within 3–5 h of AMI. There may be several reasons for the less impressive results in humans including suboptimal study designs which have been diverse particularly with regards to the timing of BMSC delivery and type of AMI treated. In an attempt to replicate the animal models as closely as possible the REGENERATE-AMI study has been designed to assess the safety, feasibility and efficacy of BMSC when delivered early in patients with AMI (ClinicalTrial.gov Identifier: NCT00765453). This study is ongoing and specifically aims to deliver BMSCs within 6 h of successful primary angioplasty and is limited to anterior wall AMI only.

<table>
<thead>
<tr>
<th>Study name (ref)</th>
<th>Date published</th>
<th>n</th>
<th>Days after AMI</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPCARE-AMI41</td>
<td>2002</td>
<td>59</td>
<td>4.3 ± 1.5</td>
<td>Improvement in global LVEF from 51.6 ± 9.6% to 60.1 ± 8.6% (P = 0.003) at 4 months</td>
</tr>
<tr>
<td>BOOST42</td>
<td>2004</td>
<td>60</td>
<td>5.1 ± 1.3</td>
<td>Improvement in global LVEF at 6 months but effect was only maintained in large infarcts at long-term follow-up</td>
</tr>
<tr>
<td>REPAIR-AMI43</td>
<td>2006</td>
<td>187</td>
<td>3–6</td>
<td>Improvement in the LVEF at 4 months by 2.5% above baseline</td>
</tr>
<tr>
<td>ASTAMI46</td>
<td>2006</td>
<td>97</td>
<td>6 ± 1</td>
<td>No change in the LVEF at 6 months</td>
</tr>
<tr>
<td>LEUVEN-AMI45</td>
<td>2006</td>
<td>66</td>
<td>1</td>
<td>No change in global LVEF at 4 months but there was improvement in regional contractility and infarct size in patients with the largest infarcts</td>
</tr>
<tr>
<td>FINCELL44</td>
<td>2008</td>
<td>77</td>
<td>3</td>
<td>Improvement in the LVEF at 6 months by 5% above baseline</td>
</tr>
<tr>
<td>HEBE47</td>
<td>2010</td>
<td>200</td>
<td>3–8</td>
<td>No change in global LVEF at 4-month follow-up</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; BMSC, bone marrow stem cells; n, number of patients; LVEF, left ventricular ejection fraction.
Stem cell therapy in chronic ischaemic heart failure

Skeletal myoblasts and BMSCs are the two main cell types that have been investigated in patients with chronic heart failure and severely impaired left ventricular systolic function secondary to previous myocardial infarction (see Table 3). Skeletal myoblast transplantation was initially investigated in patients undergoing open heart surgery. The feasibility and safety of this approach was confirmed in a phase I, non-randomized, multi-centre pilot study published in 2005 where 30 patients with ischaemic heart failure undergoing CABG or left ventricular assist device surgery had autologous skeletal myoblasts (obtained from culture of a prior muscle biopsy) injected into the epicardium at the time of surgery. Skeletal myoblasts were successfully transplanted in all patients without any acute injection-related complications or significant adverse events.

<table>
<thead>
<tr>
<th>Study name (ref)</th>
<th>Date published</th>
<th>n</th>
<th>Cell type</th>
<th>Delivery method</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dib et al.26</td>
<td>2005</td>
<td>30</td>
<td>SM</td>
<td>Transepicardial</td>
<td>Improvement in viability and LVEF</td>
</tr>
<tr>
<td>MAGIC27</td>
<td>2008</td>
<td>97</td>
<td>SM</td>
<td>Transepicardial</td>
<td>No change in global LVEF with higher incidence of adverse arrhythmia events in the cell-treated group</td>
</tr>
<tr>
<td>SEISMIC</td>
<td>ACC 2008</td>
<td>40</td>
<td>SM</td>
<td>Transendocardial</td>
<td>No change in global LVEF but there was a trend towards improvement in patient symptoms</td>
</tr>
<tr>
<td>CAuSMIC48</td>
<td>2009</td>
<td>23</td>
<td>SM</td>
<td>Transendocardial</td>
<td>Improvement in heart failure symptoms, reduction in LV dimensions and evidence of improved viability in the cell-treated group at 1 year</td>
</tr>
<tr>
<td>Stamm et al.51</td>
<td>2007</td>
<td>40</td>
<td>BMSC</td>
<td>Transepicardial</td>
<td>Improvement in global LVEF with cell injection compared with CABG alone (47.1 ± 8% vs. 41.3 ± 9% at 6 months, ( P = 0.03 ))</td>
</tr>
<tr>
<td>Ang et al.50</td>
<td>2008</td>
<td>63</td>
<td>BMSC</td>
<td>Transepicardial</td>
<td>No beneficial effect in terms of regional or global LV function and no reduction in scar size</td>
</tr>
<tr>
<td>TOPCARE-CHD52</td>
<td>2006</td>
<td>75</td>
<td>BMSC</td>
<td>Intracoronary</td>
<td>Improvement in global LVEF by 2.9% in the BMSC-treated group at 3-month follow-up</td>
</tr>
<tr>
<td>STAR-Heart53</td>
<td>2010</td>
<td>391</td>
<td>BMSC</td>
<td>Intracoronary</td>
<td>Improvement in the LVEF and increased survival in the cell-treated group over 5-year follow-up</td>
</tr>
</tbody>
</table>

n, number of patients; SM, skeletal myoblasts; BMSC, bone marrow stem/progenitor cells; LVEF, left ventricular ejection.
long-term, unexpected adverse events. Follow-up positron emission tomography (PET) scans showed new areas of glucose uptake within the infarct scar suggestive of improved myocardial viability. Echocardiography measured an average improvement in the LVEF from 28% at baseline to 35% at 1 year and of 36% at 2 years. The MAGIC trial was the first randomized placebo-controlled study of myoblast transplantation in patients with LVSD secondary to previous myocardial infarction and who required coronary surgery. Cells were injected into the epicardium within scarred areas during open heart surgery. This study was prematurely stopped for reasons of futility as cell injection did not improve regional or global left ventricular function but led to a higher number of arrhythmic events.

More recently, percutaneous transcatheter intramyocardial injection of skeletal myoblasts (CAUSMIC study) into areas of viable myocardium in patients with severe ischaemic heart failure \((n=12)\) has shown promise with improvement in NYHA functional class, quality-of-life and evidence of reverse ventricular remodelling when compared with controls after 1-year follow-up. In a similar study design the SEISMIC trial (presented at the 2008 American College of Cardiology Meeting) confirmed the safety and feasibility of catheter-based intramyocardial injection of skeletal myoblasts \((n=26)\). There appeared to be some improvement in patient symptoms but the study failed to show any significant improvement in the LVEF. The results of these small studies have prompted the design of larger RCTS including the MARVEL Trial (ClinicalTrials.gov Identifier: NCT00526253) which is an ongoing randomized, double-blind, placebo-controlled, multi-centre Phase II/III Trial involving 330 patients in North America and Europe. Enrolment in the MARVEL Trial began in October 2007, targeting patients who fall into Class II or III heart failure. The MARVEL Trial will further study the safety and efficacy of intramyocardial injection skeletal myoblasts in patients with chronic ischaemic heart failure.

BMSC transplantation has also been assessed in patients with chronic ischaemic heart failure and has been delivered either directly (transepicardial injection) during CABG surgery or by percutaneous intracoronary injection. One of the initial surgical studies injected unmanipulated BM, obtained from a sternal aspirate, directly into areas of scarred myocardium in 14 patients undergoing CABG. There appeared to be an improvement in regional contractility in those segments treated with revascularization and cell injection. However, a follow-up randomized controlled trial, with 63 patients undergoing elective CABG, by the same group failed to show any benefit of BMSC injection. In contrast to this, another randomized study with a similar study design (40 patients undergoing CABG) showed additional cell injection was associated with better global left ventricular function than CABG alone.
(LVEF = 47.1 ± 8% vs. 41.3 ± 9% at 6 months). The limitations of this study included no sham-injection of placebo material in the control group and standard 2D echocardiography served as the only measurement of global LV contractility. Hence there is now an ongoing double blind, randomized and placebo-controlled multi-centre trial in Germany (NCT00950274) aiming to recruit 142 patients and will be assessing the efficacy of BMSC injection during CABG with cardiac MRI.

There have so far been relatively few studies assessing intracoronary delivery of BMSCs in chronic ischaemic heart failure. In the TOPCARE-CHD trial, intracoronary delivery of BMSCs showed an improvement in the LVEF of 2.9% with no major adverse cardiac events (MACEs). The STAR-Heart Study is the largest study to date of BMSC therapy in chronic ischaemic heart failure. Of the eligible patients screened 191 patients underwent intracoronary BMSC therapy, and the control group consisted of 200 patients who declined to have the active intervention. Over a 5-year follow-up period intracoronary BMSC therapy was associated with significant improvement in the LVEF as well as patients’ exercise capacity. Interestingly, there was a significant decrease in long-term mortality in the BMSC-treated patients compared with the control group. This is the first stem cell study with long-term follow-up to show a survival benefit in patients receiving cell therapy. A criticism of this study has been the use of patients who declined the intervention in the control arm as this introduces an element of selection bias since these patients may be less likely to be compliant with medications and follow-up.

There is yet to be a comparative RCT study of different BMSC delivery methods in ischaemic heart failure and the REGENERATE-IHD study has been designed to answer this question (ClinicalTrials.gov Identifier: NCT00747708). This is an ongoing study comparing the efficacy and safety of delivering BMSCs using three different methods: indirect cell delivery by mobilization using peripheral infusion of G-CSF versus direct injection of cells using the intracoronary or intramyocardial route. This is the largest trial of its kind in the UK and will hopefully provide some answers as to the best delivery method.

**Stem cell therapy in dilated cardiomyopathy**

A proportion of patients (~10% in one series) with LVSD do not have a history of prior myocardial infarction and no evidence of coronary artery disease on angiography. Most of these patients have DCM which can be due to either a primary genetic abnormality or previous episode of myocarditis in genetically susceptible patients. There is considerable genetic heterogeneity in the molecular defects that lead to
hereditary DCM including defects in genes encoding contractile, cytoskeletal or nuclear proteins as well as those that regulate cardiac ion homeostasis. Current management includes the same medical and device therapy utilized in chronic ischaemic heart failure although a higher proportion of patients go on to have cardiac transplantation given the typically younger age at presentation. This has a significant impact on mortality with a survival rate following heart transplantation of 83% at 1 year and 72% at 5 years. However, due to stringent selection criteria and chronic shortage of donor hearts, the vast majority of patients do not receive a transplant. Therefore, preventing the progression of myocardial dysfunction is a major challenge requiring novel therapeutic strategies, such as stem cell transplantation, to improve the prognosis and quality-of-life for these patients. Preclinical studies have shown that intramyocardial injection of ES cells and mesenchymal stem cells in genetic knockout models of DCM can lead to improvement in LV function and survival.

The first pilot study of intracoronary BMSC infusion in patients with DCM \( n = 24 \) showed a significant improvement in the LVEF by 5.4% and an improvement in NYHA functional class in the treatment group at 6-month follow-up. The largest study to date (TOPCARE-DCM, \( n = 33 \)) again showed that intracoronary administration of BMSCs was associated with regional and global improvement in the LVEF at 3-month follow-up. These pilot studies have prompted the design of large RCTs to confirm these findings including the REGENERATE-DCM study which recently began recruiting patients. This is the first randomized, double blind, placebo-controlled trial worldwide investigating the role of G-CSF and BMSCs to improve cardiac function in patients with DCM.

**Summary and future directions**

The past decade has seen an explosion in clinical studies investigating the safety and efficacy of stem cell therapy for heart diseases. The safety of this therapy has been demonstrated uniformly in the vast majority of the studies despite heterogeneity in study design. In terms of efficacy there does seem to be some beneficial effects of cell therapy in the settings of AMI, chronic ischaemic heart failure and DCM. However, the magnitude of benefit is less impressive than was seen in the previous animal models. The future of this area of research will rely on elucidating the reasons for this difference which will require closer collaboration between basic scientists and clinical researchers. There is also a need for larger randomized controlled trials with longer term follow-up assessing morbidity and mortality as primary outcome.
measures as well as mechanistic studies to determine the ideal cell type(s) and delivery method(s). The recently established European Society of Cardiology\textsuperscript{61} task force group on stem cell therapy will be valuable in guiding development of universal protocols to produce standardized procedures for the safe and effective delivery of cell therapy for heart diseases.

**Key points**

- Stem cell therapy is an exciting novel treatment strategy for the management of patients with impaired cardiac function.
- The efficacy of cell therapy in improving cardiac function has been proved in animal models although the mechanisms of action need to be clearly defined.
- Clinical trials of cell therapy have and continue to be performed in the settings of acute myocardial infarction, chronic ischaemic heart failure and dilated cardiomyopathy. These trials have uniformly shown the safety of this treatment regardless of study design.
- The clinical efficacy of cell therapy remains to be fully translated from the animal models although with closer collaboration between scientists and clinical researchers this remains a realistic goal.

**Conflict of interest:** none declared.

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