

World Journal of *Stem Cells*

World J Stem Cells 2017 December 26; 9(12): 203-240



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World Journal of Stem Cells is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, and BIOSIS Previews.

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NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

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E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
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PUBLICATION DATE
December 26, 2017

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<http://www.wjgnet.com/bpg/gerinfo/204>

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Pursuing meaningful end-points for stem cell therapy assessment in ischemic cardiac disease

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Author contributions: Popa-Fotea NM, Popa M and Rusu I contributed to this paper with literature review, analysis and drafting the paper; Dorobantu M and Micheu MM equally contributed to conception and design of the study, literature analysis, critical revision, editing and final approval of the final version.

Conflict-of-interest statement: Authors declare no conflict of interests for this article. No financial support.

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Manuscript source: Invited manuscript

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Received: August 10, 2017

Peer-review started: August 26, 2017

First decision: October 23, 2017

Revised: November 8, 2017

Accepted: November 27, 2017

Article in press: November 27, 2017

Published online: December 26, 2017

Abstract

Despite optimal interventional and medical therapy, ischemic heart disease is still an important cause of morbidity and mortality worldwide. Although not included in standard of care rehabilitation, stem cell therapy (SCT) could be a solution for prompting cardiac regeneration. Multiple studies have been published from the beginning of SCT until now, but overall no unanimous conclusion could be drawn in part due to the lack of appropriate end-points. In order to appreciate the impact of SCT, multiple markers from different categories should be considered: Structural, biological, functional, physiological, but also major adverse cardiac events or quality of life. Imaging end-points are among the most used - especially left ventricle ejection fraction (LVEF) measured through different methods. Other imaging parameters are infarct size, myocardial viability and perfusion. The impact of SCT on all of the aforementioned end-points is controversial and debatable. 2D-echocardiography is widely exploited, but new approaches such as tissue Doppler, strain/strain rate or 3D-echocardiography are more accurate, especially since the latter one is comparable with the MRI gold standard estimation of LVEF. Apart from the objective parameters, there are also patient-centered evaluations to reveal the benefits of SCT, such as quality of life and performance status, the most valuable from the patient point of view. Emerging parameters investigating molecular pathways such as non-coding RNAs or inflammation cytokines have a high potential as prognostic factors. Due to the disadvantages of current techniques, new imaging methods with labelled cells tracked along their lifetime seem promising, but until now only pre-clinical trials have been conducted in humans. Overall, SCT is characterized by high heterogeneity not only in preparation, administration and type of cells, but

also in quantification of therapy effects.

Key words: Stem cell therapy; Cardiac imaging techniques; Ischemic cardiac disease; Cardiac regeneration; End-points

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Core tip: Although multiple studies have been published on stem cell therapy (SCT) in ischemic cardiac disease, no universal conclusion regarding its clinical efficacy has been given in part due to the lack of appropriate end-points. A rightful appreciation of SCT impact should be made considering multiple parameters from diverse categories, either objective - evaluating structural and biological functions, or subjective - patient orientated impacting daily quality of life. Current end-points, but also novel parameters investigating molecular pathways and new imaging methods with labelled cells genetically modified are being analytically discussed in this review, disclosing high heterogeneity in SCT efficacy assessment.

Dorobantu M, Popa-Fotea NM, Popa M, Rusu I, Micheu MM. Pursuing meaningful end-points for stem cell therapy assessment in ischemic cardiac disease. *World J Stem Cells* 2017; 9(12): 203-218 Available from: URL: <http://www.wjgnet.com/1948-0210/full/v9/i12/203.htm> DOI: <http://dx.doi.org/10.4252/wjsc.v9.i12.203>

INTRODUCTION

Despite modern cardiac therapies mortality and morbidity caused by ischemic heart disease (IHD) are still high. Rapid blood flow restauration improves the late outcome of patients, but it does not completely hamper myocytes loss or cardiac remodeling. Even if it is not included in the current guidelines for IHD, stem cell therapy (SCT) is one of the latest disclosures in the field.

Since the ambitious beginnings of SCT more than fifteen years ago, numerous heterogeneous results have been published regarding its outcomes. The application of SCT in patients with IHD has been proved clinically feasible and safe by clinical trials aiming heart regeneration. However promising these results may seem, SCT has yet to demonstrate clinical benefit over standard of care^[1,2]. The incomplete profound understanding of cardiovascular regeneration process, inconsistency in study protocols, differences from study to study clinical and biological end-points and the inappropriate routes of delivery, type and dose of cells, patients selection and randomization are some aspects which have delayed its large-scale acceptance by practitioners^[1].

Conducted clinical trials have been comprehensively discussed and analyzed in previous reviews^[3] and meta-analyses (Tables 1 and 2). Analyses were concluded on different number of randomized controlled trials (5-43) including different number of patients (262-2732

patients). Subgroup analyses were centered on various parameters such as left ventricular ejection fraction (LVEF) at enrollment, timing of stem cells (SCs) injection, number of administrated SCs and also patients' age. Since a detailed discussion of utilized methodologies is beyond our topic of interest, we will briefly emphasize their main conclusions: SCT is safe when it is not combined with the administration of growth factors, such as granulocyte colony stimulating factor (G-CSF) that may induce stent restenosis^[4,5], thrombosis^[6] or other adverse events^[7].

Leaving aside the differences in study designs, the lack of a consistent answer to the dilemma concerning the efficacy of cell therapy is sustained by the shortage of adequate end-points and by the shortcomings in evaluating these end-points. Most studies used as evaluation marker LVEF, but it is not sufficient, taking into account that more than 50% of heart failures (HF) caused by IHD have a normal ejection fraction (EF). Other surrogate parameters investigated were: Left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV), infarct size, myocardial perfusion and viability.

So, how can we properly assess the effects of SCT? The first to start with are hard clinical end-points (such as all-cause mortality or cause-specific mortality) employed to conclude whether functional improvement indeed translates into increased survival and reduced morbidity. At that point, other end-points including reinfarction, needed for revascularization and HF worsening can be taken into account. Because the hard primary end-points imply a large number of patients and a long surveillance, composite end-points are an option that overcomes the drawbacks of single end-points. Composite end-points increase the sensitivity of the study, but must be defined in the following manner: Each parameter has to be associated with the primary objective and quantified hierarchically based on its global importance. The foremost disadvantage of composite end-points is heterogeneity in the clinical relevance of the included markers. A solution to counterbalance this inconvenient is to assign a value to each end-point according to its importance, *e.g.*, reinfarction-1, hospitalization for heart failure 0.1, *etc.* This type of hierarchical evaluation proposed by Finkelstein and Schoenfeld^[8] - although controversial - reduces the needed number of included subjects to prove clinical efficiency. For example, a trial can have the following composite end-point with the outcomes ordered by relative severity: Cardiovascular mortality, hospitalization for HF decompensation, 6-min walk test and LVEF or LVESV. Another strategy that may be used for a better assessment is evaluation through multiple parameters from different categories^[9]: Structural measurements (the most frequently utilized group), include LVEF, LVEDV, LVESV, stroke volume, infarct size area, myocardial viability or myocardial perfusion; Biological markers: Brain natriuretic peptide, troponins, cytokines, short and long non-coding RNAs; Physiological determinants: Loading pressures, pressure-volume curves, diastolic function; Functional capacity or

Table 1 Meta-analysis evaluating left ventricle ejection fraction and other outcomes in acute myocardial infarction settings

Ref.	Included studies	Cell type	Pathology	Mean change in LVEF	Other outcomes
Hristov <i>et al</i> ^[104] (2007)	5 RCTs 482 subjects	BMMNCs	AMI	4.21% ($P < 0.00001$)	
Abdel Latif <i>et al</i> ^[105] (2007)	18 trials (RCTs/CSs) 999 subjects	BMMNCs MSCs BM-derived circulating progenitor cells	AMI	3.66% ($P < 0.01$)	Reduced infarct size Reduced LVESV
Lipinski <i>et al</i> ^[106] (2007)	10 trials (RCTs/CSs) 698 subjects	BMMNCs PMCs	AMI	3% ($P < 0.01$)	Reduced infarct size Reduced LVESV Reduced recurrent AMI
Martin Rendon <i>et al</i> ^[107,108] (2008)	13 RCTs 811 subjects	BMMNCs	AMI	2.99% ($P = 0.0007$)	Reduced LVESV Reduced LVEDV
Zhang <i>et al</i> ^[109] (2009)	7 RCTs 660 subjects	BMMNCs	AMI	4.63% ($P = 0.01$)	Reduced MACE
Bai <i>et al</i> ^[110] (2010)	10 RCTs 814 subjects	BMMNCs	AMI	3.79% ($P < 0.01$)	
Takagi <i>et al</i> ^[111] (2011)	15 RCTs 877 subjects	BMMNCs	AMI	2.87% ($P < 0.00001$)	Reduced LVEDV Reduced LVESV
Kuswardhani <i>et al</i> ^[110] (2011)	10 RCTs 906 subjects	BMMNCs Nucleated BMCs BMCs MSCs	AMI	2.07% ($P = 0.008$)	Reduced LVEDV No reduced mortality Reduced recurrent MI and rehospitalization for HF
Clifford <i>et al</i> ^[70] (2012)	33 RCTs 1765 subjects	BMMNCs BM-CD34+ BM-CD34+CXCR4+ MSCs BM-CD133+ BM-CD34+	AMI	2.87% maintained at 12-61 mo	Reduced LVESV Reduced LVEDV Reduced infarct size
Zimmet <i>et al</i> ^[111] (2012)	29 RCTs 1830 subjects	BMMNCs	AMI	2.70% ($P < 0.001$)	No reduced LVEDV No reduced LVESV
Chen <i>et al</i> ^[112] (2013)	5 RCTs 510 subjects	BMMNCs	AMI	4.18% ($P = 0.0002$)	No reduced LVEDV
Jeong <i>et al</i> ^[113] (2013)	17 RCTs 1072 patients	BMMNCs	AMI	2.51% ($P = 0.0002$)	Reduced LVESV Reduced LVEDV
Delewi <i>et al</i> ^[114] (2013)	24 RCTs 1624 subjects	BMMNCs BM-CD133+ BM-CD134+ BM-CD34+/CXCR4	AMI	2.23% ($P < 0.01$)	Reduced LVESV at 6 and 12 mo Reduced recurrent AMI Reduced readmission for HF, unstable angina/chest pain No reduction in infarct size No reduction in LVEDV
Jong <i>et al</i> ^[18] (2014)	30 RCTs 2037 subjects	BMMNCs MSCs BM progenitor cells	AMI	2.10% ($P = 0.004$)	Reduced LVESV Reduced infarct size No reduced LVEDV/LVESV (MRI) No reduced infarct size (MRI) No effect on MACE at 6 mo
Liu <i>et al</i> ^[115] (2014)	8 RCTs 262 subjects	MSCs BM-CD34+ BM-CD133+ BM-CD133+ CD34+	AMI	3.17% ($P = 0.02$)	A trend toward reduced LVESV Reduced MACEs
Delewi <i>et al</i> ^[116] (2014)	16 RCTs 1641 subjects	BMMNCs CD34+/CXCR4+ Nucleated BMCs	AMI	2.55% ($P < 0.001$)	Reduced LVEDV Reduced LVESV
Gyöngyösi <i>et al</i> ^[117] (2015)	12 RCTs 1252	BMMNCs BM-CD34/CXCR4	AMI	No improvement	No impact on MACE No reduction on LVESV/LVEDV
Fisher <i>et al</i> ^[17] (2015)	41 RCTs 2732 subjects	BMMNCs BM-CD34+ BM-CD133+ MSCs	AMI	No improvement in LVEF measured by MRI; 2%-5% increase by echo, PET CT and LV angiography	No reduced MACE No effect on morbidity, quality of life/performance
Cong <i>et al</i> ^[112] (2015)	17 RCTs 1393 subjects	BMMNCs BM-CD34+	AMI	2.74% ($P < 0.00001$, 3-6 mo) 5.1% ($P < 0.00001$, 12 mo)	Reduced LVESV at 3-6 mo Reduced WMSI at 3-6 mo

Lee <i>et al</i> ^[118] (2016)	43 RCTs 2635 subjects	BMMNCs BM-CD133+ BM-CD34+	AMI	2.75% ($P < 0.001$) 6 mo 1.34 % ($P = 0.03$) at 1 yr	No reduced infarct size at 6 mo Reduced infarct size at 1 yr No reduced infarct size at 3 or 5 yr
		MSCs		No reduction at 3 and 5 yr	No reduced mortality at 6 mo and 1 yr Reduced all-cause mortality at 5 yr

AMI: Acute myocardial infarction; BM: Bone marrow; BMCs: Bone marrow cells; BMMNCs: Bone marrow mononuclear cells; CSs: Cohort studies; CXCR4: Chemokine receptor type 4; BM-EPC: Bone marrow endothelial progenitor cells; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; MACE: Major adverse cardiac events; MSCs: Mesenchymal stem cells; PMCs: Peripheral mononuclear cells; RCTs: Randomized control trials; WMSI: Wall motion score index.

Table 2 Meta-analysis evaluating left ventricular ejection fraction and other outcomes in chronic, or chronic and acute settings

Ref.	Included studies	Cell type	Pathology	Mean change in LVEF	Other outcomes
Wen <i>et al</i> ^[119] (2011)	8 RCTs 307 subjects	BMMNCs BM-CD34+	CIHD HF	8.40% ($P < 0.01$)	Reduced LVESV Reduced LVEDV
Zhao <i>et al</i> ^[120] (2011)	10 RCTs 422 subjects	BM-CD34+/ CD133+ BMMNCs CPCs	CIHD	4.02%	Reduced LVEDV Reduced LVESV
Donndorf <i>et al</i> ^[121] (2011)	6 trials (4 RCTs and 2 CSs) 179 subjects	BMMNCs BM-CD34+ BM-CD133+	CIHD	5.40% ($P = 0.09$)	No reduced LVESV No reduced MACEs
Jeevanantham <i>et al</i> ^[122] (2012)	50 trials (RCTs, CSs) 2625 subjects	BMMNCs BM-CD133+ and/or BM-CD34+ MSCs MSCs and EPCs	AMI CIHD	3.96% ($P < 0.00001$)	Reduced infarct size Reduced LVESV Reduced LVEDV
Jiang <i>et al</i> ^[123] (2010)	18 RCTs 980 subjects	BMCs BMMNCs MSCs	AMI or CIHD	2.93% ($P < 0.00001$)	Reduced LVESV Reduced LVEDV Reduced infarct area
Cheng <i>et al</i> ^[124] (2013)	5 RCTs 210 subjects	BMMNCs SM	Chronic ischemic HF	No significant increase	Increased 6-min walk distance Improved MLHF score Reduced NYHA class No reduce in all-cause mortality Reduced LVESV
Kandala <i>et al</i> ^[125] (2013)	10 RCTs	Unselected BMCs Enriched BMCs	CIHD	4.48% ($P < 0.0001$)	Reduced LVEDV Improved perfusion
Sadat <i>et al</i> ^[126] (2014)	32 trials (24 RCTs and 8 non-RCTs) 2306 subjects	BMMNCs BM-CD34+ BM-CD133+ CPCs HSCs MSCs	ACS and CAD/HF	4.6 ± 0.7 ($P < 0.05$)	
Xu <i>et al</i> ^[127] (2014)	19 RCTs 886 subjects	BMMNCs CD133+ CD34+ Circulating CPCs Peripheral blood SCs	CIHD	3.54% ($P < 0.001$)	Reduced LVESV No reduced LVEDV
Tian <i>et al</i> ^[128] (2014)	11 RCTs 492 subjects	BMMNCs CD34+ ALDH CD133+	CIHD	4.91% ($P < 0.00001$)	Reduced LVESV Reduced LVEDV
Fisher <i>et al</i> ^[129] (2014)	23 RCTs 1255 subjects	BMMNCs CPCs HSCs MSCs	CIHD HF	2.62% ($P = 0.02, \geq 12$ mo)	Reduced mortality Reduced hospitalization HF (≥ 12 mo) No effect on mortality, rehospitalization for HF at short term (< 12 mo)

Fisher <i>et al</i> ^[67] (2015)	31 RCTs 1521 subjects	BMMNCs BMMNCs/CPCs BM-CD34+ MSCs BMMNCs (enriched CD34+) CSCs BM-EPCs BM-CD133+ SM ALHDs ADRCs	HF	2.06% ($P < 0.0001$)	Reduced LVESV Reduced stroke volume index (≥ 12 mo) Reduced NYHA class Reduced CCS score Reduced mortality Reduced rehospitalization for HF Improved performance status Improved QOL Reduced BNP
Rendon <i>et al</i> ^[130] (2016)	6 systematic reviews	BMMNCs BM-CD133+ and/or BM-CD34+ MSCs BM-EPCs Peripheral blood- derived cells CPCs SM ALHDs ADRCs BMMNCs (enriched CD34+)	IHD AMI HF	No significant increase in LVEF in IHD/HF	Reduced mortality in IHD/HF No reduce mortality in AMI
Fisher <i>et al</i> ^[80] (2016)	38 RCTs 1907 subjects	BMMNCs MSCs BM-CD133+ BM-CD34+ CPC ALDH	CIHD HF Refractory angina	Improvement (MRI analysis) on short-term No improvement on long-term	Reduced mortality (≥ 12 mo) Reduced non-fatal AMI Reduced arrhythmias risk No reduced rehospitalization for HF No reduced MACE Reduced long-term
Fisher <i>et al</i> ^[81] (2017)	38 RCTs 1907 subjects	BMMNCs Progenitor cells	CIHD HF Refractory angina	Improvement (MRI analysis) on short-term No improvement on long-term	mortality Reduced refractory angina Reduced non-fatal MI Reduced arrhythmias Reduced rehospitalization for HF/MACE No impact on QOL Improved exercise capacity at long-term

ACS: Acute coronary syndrome; ADRCs: Adult adipose-derived regenerative cells; ALHDs: Aldehyde dehydrogenase positive stem cells; AMI: Acute myocardial infarction; BM: Bone marrow; BMCs: Bone-marrow derived cells; BM-EPCs: Bone marrow endothelial progenitor cells; BMMNCs: Bone marrow mononuclear cells; CAD: Coronary artery disease; CCS: Canadian Cardiovascular Society grading of angina pectoris; CIHD: Chronic ischemic heart disease; CPCs: Cardiac progenitor cells; CSs: Cohort study; CSCs: Cardiac stem cells; HSCs: Hematopoietic stem cells; HF: Heart failure; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiac events; MLHF: Minnesota living with heart failure questionnaire; MSCs: Mesenchymal stem cells; QOL: Quality of life; RCTs: Randomized control trials; SM: Skeletal myoblasts.

performance status: 6-min walk test, maximal oxygen consumption ($VO_{2\max}$) - the evaluation category with the most important impact from the patient point of view.

Quality of life

Major Adverse Cardiac Event (MACE) composite end-point with no strictly delimited parameters.

STRUCTURAL END-POINTS

While being the most currently used, imaging techniques

are extremely useful for assessing mainly the structural effects of SCT. The majority of studies concentrated on the following outcomes: LVEF, infarct size, myocardial perfusion and viability.

LVEF and left ventricular volumes

The generally measured end-point for assessing SCT outcomes is LVEF. The first clinical studies utilized unselected mononuclear bone marrow or peripheral SCs injected intracoronary. Meta-analyses dealing with these type of cells in acute myocardial infarction (AMI)

settings showed a modest increase in LVEF evaluated by various methods, between 2%^[10,11] and 5%^[12]. One of the arguments against SCT was that the observed differences, albeit being statistically significant, had no clinical benefits. Although the LVEF recovery was small in the early period and not every time sustained, it may induce long-term positive outcomes. In this regard, it is mandatory to assess the effect of SCT on long-term, but few trials extended the follow-up after the period of one year^[13-15]. An additional key aspect depicted by REPAIR-AMI was the importance of timing from AMI until cell injection. It seems that later infusion of SCs has a better outcome (*i.e.*, LVEF) compared with the treatment administered within 4 d. This may be explained by the hostile environment which hampers cell viability due to the presence of inflammatory cells recruited in the injured area; on the other hand, a prolonged interval after AMI is inappropriate for cell transplant as a scar tissue forms and the lack of a proper vascularization also impairs SCs survival. Different imaging techniques were used to determine LVEF: Left ventricular (LV) angiography, radionuclide ventriculography, echocardiography, gated Single-Photon Emission Computed Tomography (gated-SPECT) or magnetic resonance imaging (MRI). The most accurate method to quantify LV volumes and EF is MRI and more recently, 3D-echography^[16]. In Fisher's meta-analysis it can be seen that LVEF improved in the studies that employed echography, gated SPECT or ventriculography, but not in the trials that used MRI imaging^[17]. LVEF increase is a time-dependent process; some meta-analyses investigating SCT in AMI exposed an enhancement in LVEF on short-term, but not on the long-term, explained at least in part by the increase in LV volumes over time^[18].

One aspect being imputed to cell based therapy and an important drawback is the targeted population, the included subjects being not very sick, with baseline LVEF around 50%. The largest trial in AMI settings (BAMI, NCT01569178) is planning to shed light and answer the question if SCT reduces all-cause mortality in patients with impaired systolic function (LVEF < 45%) when compared to a control group of patients undergoing best medical care. According to the Task Force of the European Society of Cardiology, it is the only clinical study able to answer the question if autologous unfractionated bone-marrow offers supplemental advantages on top of AMI standard of care^[19]. Unfortunately, there are no such studies on HF or chronic myocardial ischemia.

Myocardial deformation

The standardization of other modern techniques such as strain/strain rate or tissue Doppler echocardiography are mandatory requests to find a more sensitive and specific marker for SCT outcomes. There are already small clinical trials indicating that tissue^[20] and strain Doppler^[21] assessment of regional systolic function might be more sensitive than global LVEF for the evaluation of SCT after AMI. The concept of myocardial

strain was extended from echocardiography also to MRI detecting subtle improvements in myocardial function earlier than commonly used methods for myocardial function assessment. Myocardial MRI strain imaging has been evaluated only in one study, but when assessed showed significant increment in circumferential strain in the myocardial segments adjacent to the infarction area^[22].

Infarct size

There are several techniques that allow the quantification of the infarction area, either directly, such as nuclear imaging with Positron Emission Tomography-PET or SPECT, contrast-enhanced MRI, or indirectly, appreciating the extent of LV impairment (cine MRI, 2D-3D echocardiography, LV angiography). From the aforementioned approaches the most accurate is contrast-enhanced MRI and the only one capable to distinguish the transmural from the subendocardial infarction. Although the majority of studies using MRI assessment proved no decrease of infarct size compared with placebo^[23,24], there was one trial that interestingly showed a greater reduction in the infarction area in patients having a higher percentage of CD45⁺CD31⁺ cells in the bone marrow. These findings endorse the conclusion that cells' phenotype, as well as their functional capacity are key determinants of individual responses to SCT^[25].

Studies using SPECT disclosed a significantly reduced number of myocardial scar segments per patient in case of intracoronary infusion of an autologous population of culture expanded mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs)^[26], while transplantation of unselected bone marrow mononuclear cells had no impact on the above cited parameter^[27].

Myocardial viability

The current imaging techniques for appraising myocardial viability are: Nuclear imaging (PET or SPECT), low-dose dobutamine echocardiography and MRI. From the practical point of view, an ideal device is the one that provides real-time information as regards myocardial viability and allows targeted cell delivery. Cardiac electromechanical mapping solved this problem and significantly correlates with PET, because in the same time it can be seen if electrical activation translates into mechanical contraction; studies relying on this method showed that SCT increases the local shortening in the infarcted area^[28,29]. Nuclear perfusion imaging, mainly PET-CT has been considered a gold standard for the detection of viable myocardium. Other techniques such as SPECT reported no change compared with control groups^[30-32]. On the other hand, studies using ¹⁸F-FDG PET indicated a gain in myocardial viability^[29,33-36] which was not every time confirmed in trials with low-dose dobutamine echocardiography, possibly due to the fact that severe damaged myocardium can still preserve glucose uptake whilst the contractility is lost^[37]. Low-dose dobutamine echocardiography showed no improvement in the contractile reserve of patients with AMI and mononuclear bone marrow SCT compared

with the non-treated^[34,38], however when MSCs and EPCs were used an increased number of viable segments was observed^[26].

Myocardial perfusion

The available tools for myocardial perfusion evaluation are: MRI (rest first-pass perfusion and late gadolinium enhancement imaging), nuclear imaging (SPECT, PET) and contrast echocardiography. The majority of studies that used SPECT showed a slight increase in myocardial perfusion^[39,40], although more specific and sensitive methods such as PET^[41,42] failed to prove significant difference between SCT and control groups. MRI studies also revealed no improve in perfusion after SCT^[43,44]. PET has the additional benefit of quantifying myocardial blood flow (MBF) using ¹³N-ammonia, ¹⁵O water or ⁸²Rb. MBF quantification is a useful tool to identify patients with balanced triple vessel disease and to diagnose endothelial dysfunction^[45]. One study successfully assessed cardiac perfusion, metabolism, and function in patients treated with intracoronary injection of endothelial progenitors using ¹³N-ammonia and ¹⁸F-FDG PET^[42], showing that selected bone marrow-derived CD133⁺ cells significantly reduced the number of scarred segments and infarct size along with an increase in MBF. Larger studies are required in order to certify the diagnostic and prognostic value of quantitative MBF in relation to SCT.

BIOLOGICAL END-POINTS

N-terminal pro-brain type natriuretic peptide (NT-proBNP) is an important biomarker in IHD. However, when it comes to compare patients treated with SCT to those without treatment, it does not significantly differ. On a short-term follow-up intracoronary bone marrow mononuclear cells (BMMNCs) therapy does not have any impact on NT-proBNP or inflammatory markers such as IL-6, high-sensitivity CRP (C reactive protein) and TNF- α in ST elevation myocardial infarction (STEMI) patients^[46]. Furthermore, on long-term, it was shown that patients with chronic ischemic HF treated with intramyocardial BMMNCs therapy during coronary artery bypass grafting had not had different levels of NT-proBNP from control patients^[47]. In addition, in a 5-year follow-up study, NT-proBNP used as an objective marker for cardiac function remained significantly low in patients treated with circulating or bone marrow-derived progenitor cells^[24]. Even though it was believed that troponin elevation during SCs harvesting and intramyocardial delivery has no meaningful impact on clinical outcome^[48], latest published data support the hypothesis that high-sensitive troponin T serum levels inversely correlate with cell retention and may regulate the response to SCT in patients with post-infarction HF^[49].

Recent data revealed the implication of several cytokines in the progenitor cell evolution and cardiac function in experimental models, but there is only one study which analyzed it in humans. Shahrivari *et al.*^[50] demonstrated that increased platelet-derived growth

factor BB (PDGF-BB) glycoprotein in the peripheral blood is related to increased bone-marrow function, while high levels of IL-6 is related with bone-marrow impairment. In the same vision, supporting the hypothesis that SCT has a role in maintaining the balance of inflammatory markers, Alestalo *et al.*^[51] investigated the implication of cytokines in STEMI patients undergoing SCT by evaluating the levels of IL-4, IL-10, IL-13, IL-1 β , IL-6, TNF- α and IFN- γ ; obtained results pointed to the conclusion that SCT reduces inflammatory cytokines and promotes anti-inflammatory markers.

PHYSIOLOGICAL END-POINTS

Diastolic dysfunction was associated with neurohormonal activation and also with the severity of coronary disease evaluated by angiography, being in consequence an independent predictor of post-AMI prognosis^[52]. Although the majority of studies with SCT in AMI focused their attention on LVEF and LV remodeling evaluation, few of them investigated diastolic function with heterogeneous findings. In the BOOST study, E/A ratio, deceleration time, diastolic tissue velocities and isovolumic relaxation time were determined; among these, the only parameter positively influenced was E/A ratio, which is not satisfactory taking into account that LV filling patterns have a U-shaped relation with LV diastolic function^[53]. This favorable result was maintained only in the first 18 mo^[54], but not at 5 years^[55].

E/e' has a more linear relation to LV filling pressure and therefore is recommended for the evaluation of LV diastolic function. Four months after cell transplant, Herbots *et al.*^[21] did not identify a statistically significant difference between groups with reference to E/e', but another trial proved an improvement, despite the fact that no comparison with the placebo group was completed^[39]. On the other hand, Beitnes *et al.*^[58] reported a constant decrease in E/A and E/e' ratio along with an increase in deceleration time in both groups, independently of SCT. A meta-analysis that included 6 trials with a total of 365 patients revealed a superior improvement in E/e' ratio at 1 year in the treated group compared with control^[56]. In the study conducted by Yao including patients with chronic myocardial disease it was disclosed that even though there were no significant differences between groups in LV volumes, infarct size or myocardial perfusion, there was an overall effect of SCT on E/A, E'/A' ratio and isovolumic relaxation time at 6 mo follow-up^[57].

There are also a series of negative studies, as ASTAMI, where reduced E/A ratio, increased deceleration time and reduced E/e' were observed in both groups, probably reflecting a decrease in filling pressure^[58].

FUNCTIONAL CAPACITY

Apart from the classic parameters, a small number of trials also included patient-centered end-points evaluating the impact of SCT on status performance and quality of

life.

An indicator of functional improvement after myocardial infarction is the performance status which has been assessed in certain studies by means of the New York Heart Association (NYHA) Functional Classification. The published results did not show improvements in NYHA class between the group receiving cell therapy and the control group^[59-63], but the heterogeneity index of the studies was high ($I^2 = 80\%$) making interpretation questionable^[17].

Other manners to address performance are exercise tests: Treadmill test^[40], 6-min walk test^[64], bicycle ergometer^[59] and symptom-limited maximal exercise test^[65]. A meta-analysis including the previous types of tests exposed no improved exercise tolerance. From the analyzed trials only one displayed higher O₂ consumption and better ventilatory response to exercise^[66]. Meta-analysis conducted by Fisher *et al.*^[67] explored, among other parameters, the effect of SCT on exercise capacity; the authors concluded that patients undergoing SCT had greater performance status, but the measurement scales were different impeding correct interpretation.

However, the relationship between SCT and exercise is bidirectional: It is not only that cell transplant can produce changes in performance status, also exercise influences cells' behavior and clinical outcome. Preclinical studies demonstrated that exercise could increase exogenously infused bone marrow cell retention in mouse myocardium, suggesting that exercise may support SCT^[64]. Hence, we should display more interest in addressing this issue.

QUALITY OF LIFE

Whereas 5 trials have examined the quality of life (QOL) after SCs transplantation in AMI on short term, there is still lack of information on the long-term, just one study reporting end-points at 12 mo^[68]. In this small study with only 26 participants, QOL was significantly improved at one year follow-up. From the 5 trials mentioned above, 3 evaluated QOL with Minnesota Living with Heart Failure Questionnaire (MLHFQ)^[64,68,69] and 2 trials with the Short Form 36 Health Survey^[59,62]. A meta-analysis including only 3 of the 5 trials - due to missing data - did not show a significant improvement on short term in the life quality of treated patients compared with the control^[70]. There were also a few studies in chronic IHD or HF, but due to the fact that the results have not been presented quantitatively but only descriptively, no conclusions can be drawn^[71,72].

Angina frequency is one of the disease-specific health-related QOL (HRQOL) items measured using dedicated instruments^[73], therefore there is no wonder that it has been widely assessed in relation to SCT.

Concerning the frequency of angina, all published trials in unanimity showed a reduction in the number of episodes, reported either by a reduction in the frequency of angina episodes per week^[74] or as the frequency of angina at short-term follow-up^[71,75].

A valuable parameter in evaluating the clinical

assessments of SCT would be the psychological dimension, proved to be an essential factor in cardiac rehabilitation^[76]. A pilot study evaluated the impact of psychological and behavioral factors in patients with AMI undergoing SCT indicated that psychological factors should be taken into consideration in evaluation of the response to SCT^[77].

MACE

One commonly evaluated composite end-point in cardiology research is MACE. Although created to evaluate effectiveness and safety, it is study variable as the outcomes differ from trial to trial and there is no universal definition. Meta-analyses proved that MACE creates high heterogeneity in conclusions between studies according to the parameters taken into account^[78].

There is some evidence indicating that even small improvement in LVEF in AMI patients treated with SCT reduces cardiovascular mortality in the long term. REPAIR-AMI trial at 2 and 5 years follow-up showed beneficial clinical effects in cardiovascular mortality and rehospitalization for HF (4 deaths/100 patients in treated group compared with 14 deaths/100 in the placebo group)^[79]. One important limitation of the mentioned study is related to the small number of events (15 deaths in the placebo group and 7 in BMMNCs group during the 5-year follow-up interval). Of note, enrolled patients had a mean baseline LVEF above 45%, meaning that patients with severe impaired systolic function have not been included, namely the cohort at the highest risk for future adverse cardiovascular events.

Unlike the majority of trials where SCT was applied in AMI settings, most recent meta-analyses conducted in chronic IHD and HF pointed out beneficial clinical effects in long term mortality, without losing sight that the quality of evidence is low^[80,81]. In refractory angina patients candidates for revascularization SCT improved the scores for angina, myocardial perfusion and a composite end-point MACE (myocardial infarction, cardiac-related hospitalization and mortality)^[82].

EMERGING PARAMETRES

In recent studies, it was shown a great interest toward microRNAs (miRNAs) as clinical biomarkers in cardiovascular disease^[83]. MiRNAs are small non-coding RNA molecules implicated in gene expression regulation by suppressing the translation of their target messenger RNAs (mRNAs); they can be released in circulation, easily detected in the plasma and quantified by real-time PCR or microarrays, therefore not hard to obtain and analyzed^[84]. Lately, miRNAs have proved their implication in cardiogenesis and regeneration of cardiac tissue, so it is likely to have a possible impact in patients undergoing SCT.

Schulte *et al.*^[85] outlined the perspective use of miRNAs as biomarkers for diagnosis and prognosis of

HF patients. In a recent published study, Karakas *et al.*^[86] evaluated the prognostic value of circulating miRNAs in a cohort of 1112 patients with acute coronary syndrome or stable angina pectoris and pointed out the potential of miRNAs to predict cardiovascular death in these patients. There has been only one study which performed profiling and validation of circulating miRNAs related to MACE in patients with STEMI, demonstrating that specific miRNAs reflect the clinical outcome after STEMI^[87].

Long non-coding RNAs (lncRNAs) were less studied than miRNAs in cardiac pathology^[88]. Still, it was demonstrated that lncRNAs can predict the prognosis in patients with AMI and HF^[89,90]. One of the advantages of lncRNAs is their ability to differentiate between ischemic and non-ischemic HF compared with miRNA. Also, lncRNAs expression differs with hemodynamic conditions, suggesting that it could be a potential biomarker in evaluating myocardial recovery under mechanical circulatory support^[89,90].

Another parameter to consider could be the impact of SCT on endothelial function. There is robust evidence showing that MSCs restore endothelial progenitor cell function and vasculogenesis, thus improving flow mediated dilatation, decreasing vascular endothelial growth-factor (VEGF) while concomitantly increasing EPC-CFU_{sm} (endothelial progenitor cell colony-forming units smooth muscle)^[91].

IMAGING MODALITIES TO BE TRANSLATED FROM BENCH TO BEDSIDE

Different from the presented imaging techniques that assess only marginally and indirectly the fate of transplanted cells, the ideal imaging modality should be able to provide information about their engraftment, survival, proliferation, differentiation, maturation and integration. Labelling strategies for adequate *in vivo* surveillance and cell tracking is the key to solve some unanswered questions about SCT in cardiovascular diseases and it includes superparamagnetic-iron oxide (SPIO) MRI, direct labelling and reporter genes.

Direct imaging implies cells incubation with various probes that enter the cell by endocytosis (SPIOs), transporter uptake (¹⁸FDG) or passive diffusion (¹¹¹In-ox). Direct labelling of cells using magnetic resonance agents tracks cells and gives details about their biology. SPIO persists in the cells and along with the high resolution and good tissue contrasts make MRI a suitable tool for cell tracking^[92]. A drawback of MRI-SPIO worth considering in long-term imaging is the uptake of the contrast agent in the resident macrophages that can show a false-positive increase of the signal as if there would be high engraftment and survival. This inconvenient of SPIOs accumulation in macrophages is of interest in studies investigating inflammation sites^[93]. What is more, even if there is little or no impact of SPIO as regards cells viability and proliferation capacity, some evidence indicate that

SPIO labeling of MSCs impedes cellular differentiation down a specific pathway (*i.e.*, chondrogenesis but not adipogenesis or osteogenesis)^[94]. Nevertheless, this effect must be product dependent because there are other iron-based products approved that do not illicit harmful effects neither on the hematopoietic, nor on the BM MCSs^[95].

Direct radionuclide labelling is widely spread, has high sensitivity, but poor spatial resolution. SPECT and PET are the most frequently employed to describe bio distribution. When cells are injected into the coronary artery or vein by using the stop-flow technique, the retention of BMMNCs is 10.3% and 3.1%, respectively^[96]. When CD34⁺ cells are labelled with ^{99m}Tc-HMPAO retention rises at 19% at 18 h post-injection^[97]. But an important disadvantage is the short half-lives of the used radiotracers that does not allow long-term follow-up.^[11] In-oxine having a T_{1/2} = 2.8 days lengthens the total tracking duration to 3-4 d, pointing a level of 2% cell retain^[98].

Reporter gene imaging needs transfection or transduction with reporter gene constructs. After transcription and translation of the reporter gene under the control of a promoter, reporter proteins cumulate into the cell. Upon insertion of a probe specifically to the reporter gene (optical, radio-labelled), the signal starts to be generated and the cells are detected with different imaging modalities (PET, MRI, SPECT, CT, bioluminescence or fluorescence imaging). Reporter genes for cardiovascular SCT seem to be an ideal approach, but apart from one study^[99] that applied it to cytolytic CD8⁺T_s in a patient with glioblastoma, all other trials were preclinical^[100,101]. Not only distribution and proliferation can be assessed with reporter genes, but also differentiation and maturation of cells using a promoter for a differentiation-specific locus, such as sodium-iodide symporter^[102]. On the other hand, reporter gene technique implies genetic modification that seriously increases the risk for mutagenesis. In order to impede inappropriate insertion and prompt targeted insertion, novel gene editing methods can be used such as transcription activator-like effector nuclease (TALEN) or clustered regularly interspaced short palindromic repeats (CRISPR).

All the aforesaid imaging modalities are valuable tools for *in vivo* surveillance and cell tracking waiting to be refined and translated in clinical practice.

CURRENT RECOMMENDATIONS REGARDING SCT

Recommendations in the field of SCT target preclinical and clinical research and are of great value in the perpetual quest to overcome the above mentioned hurdles. In accordance with the requirements for good clinical practice and clinical research established by the regulatory bodies in the United States and Europe, phase II clinical trials should not only consider a variety of efficacy domains, but also should assess the potential benefits of SCT while not focusing on the statistical significance of *P* value^[1]. Furthermore, they should

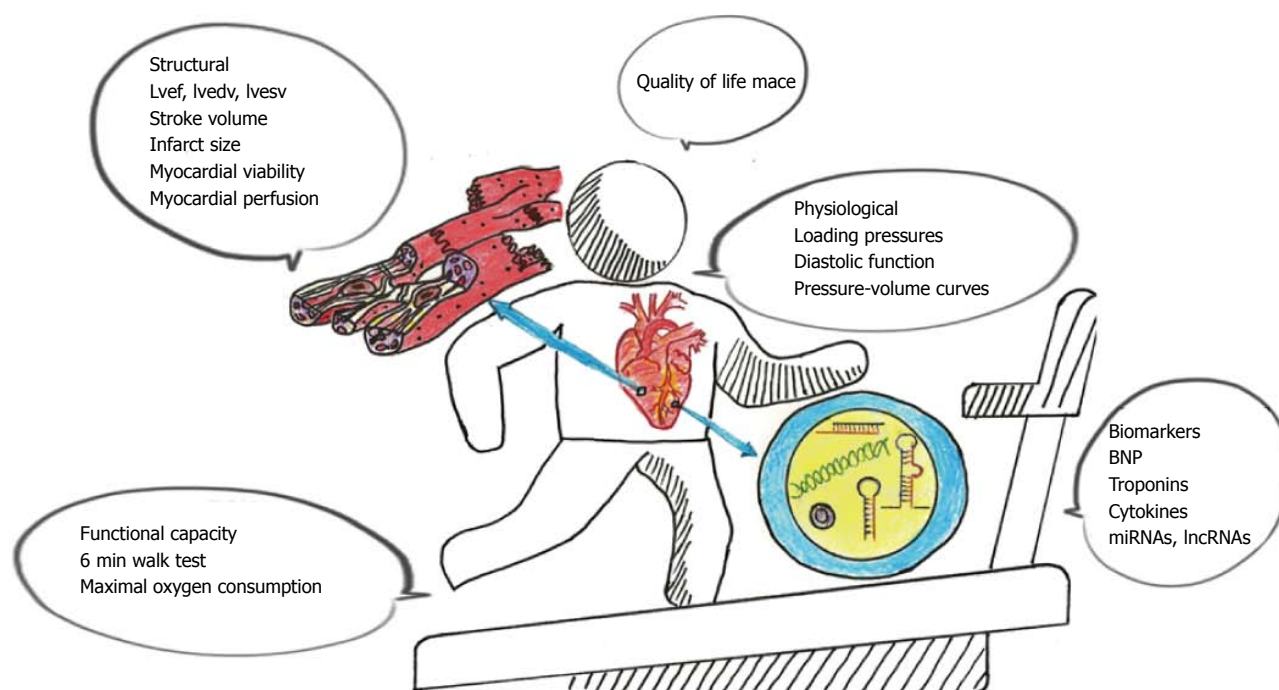


Figure 1 Schematic representation of primary surrogate endpoints grouped by categories. LVEF: Left ventricle ejection fraction; LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; MACE: Major adverse cardiac events; BNP: Brain natriuretic peptide; miRNAs: MicroRNAs; lncRNAs: Long non-coding RNAs.

include many primary surrogate end-points such as functional and structural measures, biomarkers, quality of life and functional capacity (Figure 1). More precisely, phase II clinical trials have the purpose of generating hypotheses to be used in the appropriate design of pivotal confirmatory phase III clinical trials^[1,2]. Finally, the utilization of hard clinically meaningful end-points is compulsory for the assessment of whether functional improvement positively translates into heightened survival and reduced morbidity^[103]. In this regard, phase III trials should test hard clinical end-points such as all-cause mortality or cause specific mortality, improved survival, reduced clinical events/number of hospitalizations which have applicability in the daily clinical practice. Also, well-designed phase III trials should evaluate subjective clinically relevant end-points as symptom score and HRQOL^[1,2].

Another recommendation is related to the techniques that should be used for surrogate end-points measurements; accordingly, the most reproducible techniques are endorsed (e.g., MRI, PET), while centralized analysis should be settled by core laboratories^[1]. Nonetheless, patient selection is of the essence. When designing a new clinical trial, confounders such as gender, age, comorbidities, concomitant medications, disease vulnerability and severity should always be taken into consideration, if possible by means of predictive scores of outcomes^[1,103]. The focus for inclusion/exclusion criteria in the trial should be on subpopulations with poor prognosis, as they are the target patient that could benefit the most from SCT^[1].

New "mechanistic" end-points are required in order

to better understand the regeneration capacity of the adult mammalian heart and to validate hypothesis on SCs mechanisms of action; these novel end-points should be integrated in traditional safety and efficacy end-points - either surrogate or clinical, only after proper validation in the preclinical research field and in agreement with regulatory recommendations^[1].

With regard to the aforementioned recommendations, in their position paper issued on May 2017, TACTICS highlights the challenges in the field of cardiovascular regenerative medicine for the next decade. Among their global aims are achieving uniformity and, consequently, meeting the required norms for clinical research of animal models for cardiovascular research; using collective achievement of phase III multicenter clinical trials that are optimally designed to improve standard of care in cardiovascular medicine and demonstrate the clinical efficiency of SCT. The last but not the least goal is to certify implementation of accepted SCT *via* transnational standardization of regulatory requirements.

Regarding initiation of future autologous bone marrow cells clinical trials in AMI, the recommendation is to await results from on-going BAMI trial (NCT01569178)- multicenter, randomized, controlled, phase III study- designed to assess efficacy of SCT with concern to morbidity and mortality in patients with reduced LVEF after successful reperfusion when compared to a control group of patients undergoing best medical care.

As for clinical trials in HF, cardiopoietic cells-either primary or engineered - should be used. Taking into consideration the documented safety of SCT approaches, trials evaluating repeated administration should be

studied in order to enhance long term clinical outcome^[19].

CONCLUSION

SCT in ischemic cardiac disease is characterized by high heterogeneity in the assessment of therapeutic benefits due in part to the imprecise end-points. Apart from the classic structural parameters, new emerging imaging or biological markers promise to enlighten the field of cardiac regeneration offering less debatable results.

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P- Reviewer: Kiselev SL, Liu L, Liu SH **S- Editor:** Ji FF
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