



The consensus of the Task Force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for the treatment of acute myocardial infarction and heart failure: update 2016

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Introduction

In 2006, the Task Force of the European Society of Cardiology published its consensus document on the use of autologous cell therapy for repair of the heart.¹ Since then, there have been numerous clinical trials and analyses performed to establish the role of autologous cell therapy in the treatment of both acute and chronic cardiac disease. The majority of these studies have been Phase II clinical trials. Phase III clinical trials of autologous cell therapy have been launched (e.g. BAMI), which marks the successful progression of clinical investigation of autologous cell therapy in heart disease. The Task Force has reviewed its 2006 recommendations and the developments in this area of research and proposes updated recommendations for the future of autologous cell therapy in the heart. This article does not duplicate the many reviews on stem cells and the heart but gives considered recommendations based on the experience from the last 10 years (Table 1).

What has been achieved over the last 10 years

Autologous unfractionated bone marrow cells

In 2006, the Task Force noted that the evidence base for the use of cell therapy in cardiac disease came mostly from a series of small clinical trials

in acute myocardial infarction (AMI) that suggested a modest improvement in cardiac function. The largest Phase II study that has been performed² was published in 2006 after the consensus publication and demonstrated a 2.5% absolute increase in ejection fraction in patients treated with cell therapy vs. the control group. The authors concluded 'Large-scale studies are warranted to examine the potential effects of progenitor-cell administration on morbidity and mortality'. Unfortunately, no such study in the form of a randomized trial using unfractionated autologous cells in the treatment of AMI has been completed since then. The BAMI trial (effect of intracoronary reinfusion of bone marrow-derived mononuclear cells on all-cause-mortality in AMI—ClinicalTrials.gov NCT01569178) currently in recruitment throughout Europe is designed to measure efficacy regarding morbidity and mortality.

Autologous fractionated cells

Based on the modest results of unfractionated cell therapy, a large number of small trials have been conducted to test the potency of specific cell types or *ex vivo* modified cells in cardiac repair (mainly in heart failure patients). One of the most promising cell types appears to be the mesenchymal stem cell, although the results from studies using these processed cells seem no more efficacious than the result obtained with unfractionated (and thus potentially easier to produce and less costly) cell injection.^{3,4} Trials using skeletal myoblasts have all but ceased, whereas the concept of repairing cardiac damage with

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Table 1 Recommendations for the future direction of autologous cell therapy for heart disease**Clinical trials in acute myocardial infarction**

Await results of BAMI. BAMI data will help to decide if other studies are warranted to refine the technique.

Clinical Trials in facilitated/rescue angioplasty

Studies examining the role of cell therapy in rescue and facilitated angioplasty are not undertaken because of the change in practice and access to primary angioplasty across Europe.

Clinical Trials in heart failure

The 'heart muscle' target should be pursued using phenotypically relevant primary or engineered cells. The experimental approach should allow the rapid conversion of Phase I to Phase II clinical trials with meaningful intermediate end-points that are most likely to translate into clinical outcomes in larger studies.

Additionally, combining phenotypically more relevant cells with enhancement strategies for cell retention in the target tissue should be further explored in Phase II studies. Given the documented safety of cell therapy approaches to the heart, trials of repetitive treatment should be considered to improve long-term clinical outcome.

Small safety/mechanistic studies

More work is needed to develop 'translational mechanistic tools.' Without these, the prospects for translational research will remain compromised by an incomplete mechanistic understanding. Use of novel human experimental models to test mechanism, potency and efficacy of regenerative techniques should be pursued.

Clinical trials of paracrine factors alone or in combination

The paracrine theory is unlikely to yield clear candidate proteins given the complexity and likely interaction of many factors. Synergistic combinations of cytokine and autologous cell therapy should be explored based on promising early results. The paracrine hypothesis is likely to be superseded by new biological/small molecule strategies.

stem/progenitor cells of a muscle phenotype has continued with clinical trials of cardiac-derived progenitor cells showing promising initial results.^{5–7} The use of cardiac progenitor cells marks the transition from a mechanistic explanation based on cardiac repair/salvage in the trials using autologous unfractionated trials to genuine tissue regeneration trials. However, the magnitude of effect of this more relevant cell type on left ventricular ejection fraction as yet appears similar to the unfractionated bone marrow data.

The question of autologous selected or unselected cell therapy is still unanswered, with selected cell types (e.g. adipose derived cells that could theoretically produce new cardiac muscle) currently showing similar efficacy to unselected cells in clinical trials.^{8,9} Combinations of selected cell types are currently under preclinical investigation¹⁰ and are being translated into clinical trials (e.g. CONCERT-HF, clinical trials.gov—NCT02501811).

Preconditioning of the cardiac target tissue

Cell retention in the heart is severely limited, regardless of the mode of administration (intracoronary vs. intramuscular injection), specifically in patients with chronic heart failure, where no cues or signals are emitted from the target tissue to facilitate cell homing. Therefore, clinically applicable strategies of preconditioning the cardiac target tissue to increase acute retention (and maybe long-term persistence) of administered cells have been developed and applied in first Phase II studies in recent years, see gene therapy using SDF-1¹¹ and shock wave application.¹² The question whether these may improve the efficacy of cell therapy in patients with chronic heart failure is still unanswered. Aside from these tissue-targeted approaches, the

adjunct of tissue engineering-derived biomimetic materials to stem cells has increasingly emerged as a potentially effective means of improving their viability and early engraftment and needs further testing in Phase II clinical studies.

Repetitive cell administration

Given the rather limited persistence of acutely retained cells in the heart, as well as paracrine mechanisms to be currently regarded as the prevailing mode of action, the potential effects of repetitive cell administration, have been clinically tested in patients with heart failure (REPEAT—clinicaltrials.gov NCT01693042) as well as patients with refractory angina.¹³ Although it is conceptually appealing to treat a chronic disease with repetitive treatments, clinical outcome data are not yet available.

Allogeneic vs. autologous cells

In order to minimize heterogeneity of the cellular product, circumvent potential functional impairments of the cellular product secondary to patient-specific factors, and provide for easier logistics with an off-the-shelf product, a variety of allogeneic cell types have entered early clinical testing. So far, allogeneic mesenchymal cells have at least proven to be as safe as their autologous counterparts in a small uncontrolled study of patients with ischaemic heart disease.¹⁴ One larger, placebo-controlled clinical trial is under way to test allogeneic mesenchymal cells in patients with chronic heart failure (DREAM-HF—clinical trials.gov NCT02032004) and a Phase II trial has reported a reduction in adverse events in heart failure patients treated with an allogeneic product.¹⁵ The results of the Phase II 'ALLSTAR' trial of allogeneic cardiosphere derived cells will also help address the role of allogeneic cells following myocardial infarction.¹⁶

Systematic reviews

In the absence of definitive large-scale clinical trials, a series of systematic reviews/meta-analyses have been published over the last 10 years, attempting to look for evidence of effect in the pooled analyses of the published small studies. Established methodologies (e.g. the Cochrane reviews) have consistently concluded that cell therapy has an overall beneficial effect on cardiac function and symptoms in patients with acute and chronic ischaemia.^{17–20} Recently, results from newly devised methodologies suggest that there are significant issues of reporting in the trials published previously²¹ and that novel pooled analysis of raw data, i.e. individual patient data (IPD)-based analyses, continue to show variable results with either confirmed Bone Marrow Cell (BMC)-mediated benefit²² or the absence of BMC-mediated effect in AMI.²³ Whilst these new and untested approaches to data analyses pose interesting questions and healthy debate, whether the new data collection and reporting techniques are more effective than accepted methodologies remains questionable. These controversies reflect the overall conclusions of the 2006 Task Force consensus paper that suggested large scale blinded clinical trials should be performed to answer specific questions with careful patient selection and rigorous study design. Few studies that meet this recommendation have been implemented with the exception of BAMI.

Future therapeutic targets

The recommended target diseases for cell therapy remain (i) AMI, (ii) chronic myocardial ischaemia and (iii) dilated/ischaemic cardiomyopathy. The experience of the last 10 years and from the BAMI trial suggest, however, that the potential for a proven benefit in AMI of any new therapy, let alone cell therapy, is increasingly difficult to demonstrate because primary angioplasty is so effective on clinical outcome. Its spread across Europe means that in order to show an incremental therapeutic benefit of a new treatment large numbers of patients are needed or trials need to specifically target the subset of AMI patients with impaired clinical outcome (and unmet clinical need). Recent Randomized Control Trials in 'ST' Elevation Myocardial Infarction (STEMI) patients receiving guideline-recommended therapies report 1-year mortality rates of 6% and hospitalization rates for recurrent ischaemic events or heart failure ~14%.²⁴ These data clearly show that the problem of AMI is not solved given the ongoing mortality and morbidity and that the major challenge is to correctly identify in the STEMI population who would benefit from (cell-based) ancillary therapies. Moreover, with an increased number of survivors after a first STEMI and with an increasingly aging population, for it conceptual and pragmatic reasons, heart failure and dilated cardiomyopathy will become more important targets for cardiovascular research, given the limited availability of novel therapeutics and increasing burden of disease across Europe.

The ethics of proceeding with more clinical studies

The ethical debate addressed in the 2006 consensus document centred around whether clinical experimentation should proceed in

the absence of a full understanding of the mechanisms of cell-based therapies. The Task Force stated that, as long as patient safety is at the forefront of trial design, clinical studies should continue given the promising first results, the safety profile at the time and the paucity of new therapeutics for conditions such as heart failure. Review of the literature since reinforces this original recommendation. Although there have been advances in our understanding of the basic biology regarding the effector mechanisms involved in cell therapy these have not as yet lead to significant improvements in the results of clinical trials. Whilst preclinical experimentation would predict superiority of specific cell types such as cardiac progenitor cells or mesenchymal stem cells pretreated by cardiopoietic growth factors, clinical investigators have chosen a pragmatic approach to translating the use of existing cell types from animal models into human. Others have rather relied on stem cells driven towards a cardiac lineage, as recently illustrated by the first embryonic cell derived-cardiac progenitor cell transplant.²⁵

What studies are needed?

Below we present briefly the original Task Force recommendations with comments in light of today's knowledge and new recommendations for the field of autologous cell therapies for heart repair:

(i) **2006 comment: Further large, double-blind, randomized, controlled trials for the use of autologous bone marrow cells in the treatment of AMI. The patient population should be all those presenting within 12h of AMI and treated with immediate revascularization, be it primary angioplasty or fibrinolysis.**

2016 Comment

This is carried out in the ongoing BAMI trial (clinical trials.gov/NCT01569178)

New Recommendation

Await results of BAMI. BAMI data will help to decide if other studies are warranted to refine the technique.

(ii) **2006 comment: A double-blind, randomized, controlled trial for the use of autologous bone marrow cells in the treatment of myocardial infarction in those patients presenting late (> 12 h) or who fail to respond to therapy (candidates for 'rescue' angioplasty). Although these groups may represent a small proportion of all patients with AMI, their prognosis remains poor.**

2016 Comment

This has not occurred and is increasingly unlikely to occur given the change in practice and access to primary angioplasty across Europe. Although facilitated angioplasty for AMI still appears in guidelines, its use is relatively limited across Europe.

Future direction—unlikely that the logistics of this study design will allow such research to go ahead in a meaningful way. Ultimately, these patients may well develop heart failure, for which chronic cell therapy strategies are under development.

New Recommendation

Studies examining the role of cell therapy in rescue and facilitated angioplasty are not undertaken because of the change in practice and access to primary angioplasty across Europe.

(iii) **2006 comment: Double-blind, randomized, controlled trials for the use of autologous bone marrow cells or skeletal myoblasts in the treatment of heart failure secondary to ischaemic heart disease. At some stage, the role of autologous stem/progenitor cells in the treatment of cardiomyopathies (in particular, dilated cardiomyopathy) will need to be examined.**

2016 Comment

The skeletal myoblast no longer remains the focus of interest and has been superseded with cell types of a more cardiopoietic phenotype (e.g. 'cardiopoietic' mesenchymal stem cells and cardiac stem cells)

New Recommendation

The 'heart muscle' target should be pursued using phenotypically relevant primary or engineered cells. The experimental approach should allow the rapid conversion of Phase I to Phase II clinical trials with meaningful intermediate end-points that are most likely to translate into clinical outcomes in larger studies.

Additionally, combining phenotypically more relevant cells with enhancement strategies for cell retention in the target tissue should be further explored in Phase II studies.

Given the documented safety of cell therapy approaches to the heart, trials of repetitive treatment should be considered to improve long-term clinical outcome.

(iv) **2006 Comment: A series of well-designed small studies to address safety or mechanism to test specific hypotheses (e.g. studies with labelled cells or to investigate paracrine or autocrine mechanisms). Such hypotheses would have arisen from basic science experiments.**

2016 Comment

There has been a lack of these mechanistic studies, probably due to the lack of translational tools that allow the assessment of such interventions. Questions concerning paracrine effects have been surpassed by miRNA and other biological therapeutics, including microparticles containing biologics such as exosomes. However, the goal of achieving a small molecule activator of a receptor-mediated mechanism of regeneration effected by stem cells remains an important option to consider.

New recommendation

More work is needed to develop 'translational mechanistic tools'. Without these, the prospects for translational research will remain compromised by an incomplete mechanistic understanding. Use of novel human experimental models to test mechanism, potency and efficacy of regenerative techniques should be pursued.

(v) **2006 Comment: Studies to confirm the risk/benefit ratio of the use of cytokines alone (e.g. granulocyte colony stimulating factor) or in conjunction with stem/progenitor cell therapy.**

2016 Comment

A number of studies have been conducted over the last 10 years to understand the benefits of cytokine therapy alone or in combination with cell therapy.^{26,27} It appears that cytokine therapy alone does not lead to sustained beneficial effects whilst combination therapy may well bring synergistic benefits.

New recommendation

The paracrine theory is unlikely to yield clear candidate proteins given the complexity and likely interaction of many factors. Synergistic combinations of cytokine and autologous cell therapy should be explored based on promising early results. The paracrine

hypothesis is likely to be superseded by new biological/small molecule strategies.

Biology and regulation of translation

Phase III clinical trials proceeded in line with the Task Force's views regarding standardization. All ongoing Phase III clinical trials are using standardized protocol in GLP compliant labs. The autologous unfractionated approach, however, can still utilize existing clinical stem cell processing units that meet regulatory requirements. If efficacy is proven, this would, therefore, be the easiest method for rolling out autologous stem cell treatments across Europe.

One of the biggest hurdles for clinical trial research in cell therapy over the last 10 years has been the change in regulations and the increasing complexity and costs of running large trials. The experience of the BAM1 consortium indicates that attempts to streamline regulatory processes across Europe have not delivered transparent, efficient systems that allow conducting these complex cell therapy studies in a timely fashion. Considerably more refinement in the regulatory processes is needed to safeguard the future role of academic consortia across Europe in the delivery of new therapies to the clinic.

BAMI

As a result of the original ESC Task Force consensus document, BAM1 was designed as the first Phase III controlled clinical trial with autologous bone-marrow-derived stem cell injection as part of standard treatment for AMI with the aim to finish recruitment by October 2017. The trial is led by academia, funded by the European Commission under FP7 and has a 2-year follow-up with a mortality endpoint that compares current best practice to best practice and autologous cell injection. As recommended by the Task Force, inclusion criteria are strict and limited to patients with an ejection fraction of <45% after successful primary angioplasty. For timely completion, a large patient population is needed and BAM1 is recruiting in 9 European countries. BAM1 complies with advanced therapy medicinal product regulation and trial conduct in accordance with EMA and voluntary harmonization procedure (VHP) conditions. BAM1 was the first successful application to the VHP by an academic consortium. The academic leadership was confronted with issues previously unaddressed as part of this process and relating to persisting differences in regulation between member states of the European Union.

Major delays to site initiation and patient recruitment arose from these regulatory conditions that require autologous cell therapy to follow the safety protocols for engineered cells. Access to ATMP laboratory sites for cell processing has been another major issue, where funding restrictions and competition with other approaches in the setting of acute coronary syndromes has impeded the work of academic leadership of autologous cell therapy trials across Europe. Moreover, harmonization of regulation of trial protocol and clinical ethics parameters has the side-effect that other cultural differences between BAM1 partner countries in practices such as the logistics of health care and reimbursement, insurance, and conventions of

patient information routine take time and money to align to comply with both EU regulations and local possibilities and expectations.

Conclusions

The burden of proof for autologous cell therapy remains with the medical profession given the previous Task Force observations regarding the lack of intellectual property and the resulting reluctance of the pharmaceutical industry to pursue this clinical trajectory. The BAMI trial illustrates the difficulties faced by academic consortia in conducting Phase III studies and highlights both the need for novel funding streams and for technological provisions independent of industry in order to prevent bias of therapy development against approaches without ready commercial profits in the long-term interest of patients and public health care over business interests in cell therapy.

Finally, the unmet needs of the clinical targets identified in 2006 remain unchanged today. There have been advances in the understanding of the clinical utility of autologous bone marrow stem cells and thus far other types of stem cell products have not demonstrated clear clinical advantage over autologous cells.

Although harmonization of regulations concerning the preparation, transport, and use of cell preparations across the EU should have occurred, there remain barriers to clinical studies in this field due to significant differences in regulations that persist between and within member states. These differences can be inhibitory to pan-EU clinical trials. These disparities should be addressed urgently by the European Commission in order to support academically led research and clinical studies.

Since 2006 advance in the field has been small. This may be because for the new field of cell therapies pathways of clinical translation in Europe are only being developed whilst the research proceeds. Advances in the clinical understanding of autologous cells have been led by academics, whereas advances in understanding the role of non-autologous stem cells in the field have been undertaken primarily by companies (Small to Medium Enterprises).

The continuing BAMI trial remains the single clinical study which has the potential to give a definitive answer to whether autologous unfractionated bone marrow cells can play a role in the treatment of AMI. The Task Force recognizes the persistent need for similar definitive trials of autologous cell therapy in heart failure.

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References

- Bartunek J, Dimmeler S, Drexler H, Fernández-Avilés F, Galinanes M, Janssens S, Martin J, Mathur A, Menasche P, Priori S, Strauer B, Tendera M, Wijns W, Zeiher A, task force of the European Society of Cardiology. The consensus of the task force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for repair of the heart. *Eur Heart J* 2006;**27**:1338–1340.
- Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006;**355**:1210–1221.
- Heldman AW, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, Karantalis V, Mushtaq M, Williams AR, Suncion VY, McNiece IK, Ghersin E, Soto V, Lopera G, Miki R, Willens H, Hendel R, Mitrani R, Pattany P, Feigenbaum G, Oskoue B, Byrnes J, Lowery MH, Sierra J, Pujol M V, Delgado C, Gonzalez PJ, Rodriguez JE, Bagno LL, Rouy D, Altman P, Foo CW, da Silva J, Anderson E, Schwarz R, Mendizabal A, Hare JM. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. *JAMA* 2014;**311**:62–73.
- Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Fischer-Nielsen A, Kofoed KF, Haack-Sørensen M, Ekblond A, Kastrup J. Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial). *Eur Heart J* 2015;**36**:1744–1753.
- Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, Beache GM, Wagner SG, Leri A, Hosoda T, Sanada F, Elmore JB, Goichberg P, Cappetta D, Solankhi NK, Fahsah I, Rokosh DG, Slaughter MS, Kajstura J, Anversa P. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet* 2011;**378**:1847–1857.
- The Lancet Editors. Expression of concern: the SCIPIO trial. *Lancet (London, England)* 2014;**383**:1279.
- Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, Czer LS, Marban L, Mendizabal A, Johnston P V, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marban E. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet* 2012;**379**:895–904.
- Perin EC, Sanz-Ruiz R, Sánchez PL, Lasso J, Pérez-Cano R, Alonso-Farto JC, Pérez-David E, Fernández-Santos ME, Serruys PW, Duckers HJ, Kastrup J, Chamuleau S, Zheng Y, Silva G V, Willerson JT, Fernández-Avilés F. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE Trial. *Am Heart J* 2014;**168**:88–95.e2.
- Houtgraaf JH, den Dekker WK, van Dalen BM, Springeling T, de Jong R, van Geuns RJ, Geleijnse ML, Fernandez-Aviles F, Zijlstra F, Serruys PW, Duckers HJ. First experience in humans using adipose tissue-derived regenerative cells in the treatment of patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2012;**59**:539–540.
- Karantalis V, Suncion-Loescher VY, Bagno L, Golpanian S, Wolf A, Sanina C, Premer C, Kanelidis AJ, McCall F, Wang B, Balkan W, Rodriguez J, Rosado M, Morales A, Hatzistergos K, Natsumeda M, Margitich I, Schulman IH, Gomes SA, Mushtaq M, DiFede DL, Fishman JE, Pattany P, Zambrano JP, Heldman AW, Hare JM. Synergistic Effects of Combined Cell Therapy for Chronic Ischemic Cardiomyopathy. *J Am Coll Cardiol* 2015;**66**:1990–1999.
- Penn MS, Mendelsohn FO, Schaer GL, Sherman W, Farr M, Pastore J, Rouy D, Clemens R, Aras R, Losordo DW. An open-label dose escalation study to evaluate the safety of administration of nonviral stromal cell-derived factor-1 plasmid to treat symptomatic ischemic heart failure. *Circ Res* 2013;**112**:816–825.
- Assmus B, Walter DH, Seeger FH, Leistner DM, Steiner J, Ziegler I, Lutz A, Khaled W, Klotzsch J, Tonn T, Dimmeler S, Zeiher AM. Effect of shock wave-

- facilitated intracoronary cell therapy on LVEF in patients with chronic heart failure: the CELLWAVE randomized clinical trial. *JAMA* 2013;**309**:1622–1631.
13. van Ramshorst J, Bax JJ, Beeres SL, Dibbets-Schneider P, Roes SD, Stokkel MP, de Roos A, Fibbe WE, Zwaginga JJ, Boersma E, Schalij MJ, Atsma DE. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. *JAMA* 2009;**301**:1997–2004.
 14. Perin EC, Borow KM, Silva G V, DeMaria AN, Marroquin OC, Huang PP, Traverse JH, Krum H, Skerrett D, Zheng Y, Willerson JT, Itescu S, Henry TD. A Phase II Dose-Escalation Study of Allogeneic Mesenchymal Precursor Cells in Patients With Ischemic or Nonischemic Heart Failure. *Circ Res* 2015;**117**:576–584.
 15. Patel AN, Henry TD, Quyyumi AA, Schaer GL, Anderson RD, Toma C, East C, Remmers AE, Goodrich J, Desai AS, Recker D, DeMaria A, Mozaffarian D, Benjamin E, Go A, McLaren D, Jones R, Plotnik R, Chen J, Normand S, Wang Y, Krumholz H, Chiong M, Wang Z, Pedrozo Z, Agnetti G, Piepoli M, Siniscalchi G, Nicolini F, Kilic A, Acker M, Atluri P, Patel A, Silva F, Winters A, Patel A, Mittal S, Turan G, Leistner D, Schmitt J, Palm S, Fisher S, Doree C, Taggart D, Schächinger V, Erbs S, Elsässer A, Assmus B, Fischer-Rasokat U, Honold J, Perin E, Willerson J, Pepine C, Ledford K, Murphy N, Zeigler F, Bartel R, Cramer C, Ledford K, Ledford K, Zeigler F, Bartel R, Henry T, Traverse J, Hamman B, Henry T, Schaer G, Demaria A, Pocock S, Ariti C, Collier T, Wang D, Finkelstein D, Schoenfeld D, Kissel C, Lehmann R, Assmus B, Heldman A, DiFede D, Fishman J, Perin E, Borow K, Silva G, Bolli R, Chugh A, D'Amario D, Makkar R, Smith R, Cheng K, Bartunek J, Behfar A, Dolatabadi D. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. *Lancet* 2016;**0**:e38–360.
 16. Chakravarty T, Makkar RR, Ascheim D, Traverse JH, Schatz R, DeMaria A, Francis GS, Povsic TJ, Smith R, Lima JA, Pogoda JM, Marbán L, Henry TD. ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration (ALLSTAR) trial: Rationale & Design. *Cell Transplant* 2016. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27543900>.
 17. Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Watt S, Martin-Rendon E, Brunskill SJ, Doree C, Hyde C, Watt S, Mathur A, Stanworth S. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev* 2007;**2**:CD006536.
 18. Martin-Rendon E, Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Clarke M, Watt SM. Long-term effect of stem cell treatment in acute myocardial infarction: what is new from 2008? *Cardiovasc Res* 2012;**55**:57–557.
 19. Fisher SA, Dorée C, Brunskill SJ, Mathur A, Martin-Rendon E, Doree C, Brunskill SJ, Mathur A, Martin-Rendon E. Bone Marrow Stem Cell Treatment for Ischemic Heart Disease in Patients with No Option of Revascularization: A Systematic Review and Meta-Analysis. Zheng Y, editor. *PLoS One* 2013;**8**:e64669.
 20. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. *Eur Heart J* 2008;**29**:1807–1818.
 21. Francis DP, Mielewicz M, Zargaran D, Cole GD. Autologous bone marrow-derived stem cell therapy in heart disease: discrepancies and contradictions. *Int J Cardiol* 2013;**168**:3381–3403.
 22. Delewi R, Hirsch A, Tijssen JG, Schachinger V, Wojakowski W, Roncalli J, Aakhus S, Erbs S, Assmus B, Tendera M, Goekmen Turan R, Corti R, Henry T, Lemarchand P, Lunde K, Cao F, Huikuri H V, Surder D, Simari RD, Janssens S, Wollert KC, Plewka M, Grajek S, Traverse JH, Zijlstra F, Piek JJ. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. *Eur Heart J* 2014;**35**:989–998.
 23. Gyöngyösi M, Wojakowski W, Lemarchand P, Lunde K, Tendera M, Bartunek J, Marban E, Assmus B, Henry TD, Traverse JH, Moyé LA, Sürder D, Corti R, Huikuri H, Miettinen J, Wöhrle J, Obradovic S, Roncalli J, Malliaras K, Pokushalov P, Romanov A, Kastrup J, Bergmann MW, Atsma DE, Diederichsen A, Edes I, Benedek I, Benedek I, Pejkov H, Nyolczas N, Pavo N, Bergler-Klein J, Pavo IJ, Sylven C, Berti S, Navarese EP, Maurer G, ACCRUE Investigators. Meta-Analysis of Cell-based Cardiac stem Cells (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circ Res* 2015;**116**:1346–1360.
 24. Cung T-T, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guérin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit J-F, Jouve B, Motreff P, Tron C, Labeque J-N, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De Poli F, Morice M-C, Ider O, Dubois-Randé J-L, Unterseech T, Le Breton H, Béard T, Blanchard D, Grollier G, Malquarti V, Staat P, Sudre A, Elmer E, Hansson MJ, Bergerot C, Boussaha I, Jossan C, Derumeaux G, Mewton N, Ovize M. Cyclosporine before PCI in Patients with Acute Myocardial Infarction. *N Engl J Med* 2015;**373**:1021–1031.
 25. Menasché P, Vanneaux V, Haggège A, Bel A, Cholley B, Cacciapuoti I, Parouchev A, Benhamouda N, Tachdjian G, Tosca L, Trouvin J-H, Fabreguettes J-R, Bellamy V, Guillemain R, Suberbielle Boissel C, Tartour E, Desnos M, Larghero J. Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report. *Eur Heart J* 2015;**36**:2011–2017.
 26. Hamshere S, Arnous S, Choudhury T, Choudry F, Mozid A, Yeo C, Barrett C, Saunders N, Gulati A, Knight C, Locca D, Davies C, Cowie MR, Prasad S, Parmar M, Agrawal S, Jones D, Martin J, McKenna W, Mathur A. Randomized trial of combination cytokine and adult autologous bone marrow progenitor cell administration in patients with non-ischaemic dilated cardiomyopathy: the REGENERATE-DCM clinical trial. *Eur Heart J* 2015;**36**:3061–3069.
 27. Yeo C, Mathur A. Autologous bone marrow-derived stem cells for ischemic heart failure: REGENERATE-IHD trial. *Regen Med* 2009;**4**:119–27.