

# Suggested indications of clinical practice guideline for stem cell-therapy in cardiovascular diseases: A stepwise appropriate use criteria for regeneration therapy

**Mohaddeseh Behjati<sup>(1)</sup>**

## Short Communication

### Abstract

Despite astonishing progress concerning cardiovascular diseases, patients are still suffering from complications of acute insults. Due to reverse remodeling and improper myocyte rebuilding, heart failure has become a common problem these days which needs more powerful myocardial reconstructing strategies. Indeed, no option cases afflicted with non-healing peripheral vascular diseases; refractory stable and unstable angina is the other field with paucity of proper treatments. For these cases, stem cell-based therapies became optimistic treatment, but lack of guideline-based indications regarding stem-cell is still a major problem which limits application of these cells for such end-stage cases. Here, an outline of appropriateness criteria for stem cell-based therapy is suggested.

**Keywords:** Appropriate Use Criteria, Clinical Practice Guideline, Cardiovascular Diseases, Stem Cells

*Date of submission:* 15 Apr 2013, *Date of acceptance:* 29 Jun 2013

### Introduction

Despite the astonishing progress made in interventional cardiology, cases are still suffering from complications of acute events. Conflicted cases are most often survived from acute insults but deleterious effects of negative remodeling on future outcomes of patients are devastating. Unfortunately in some instances, the vicious cycle of progressive compensatory remodeling cannot be broken by reperfusion strategies and patients ultimately manifest signs and symptoms of poor ventricular function. Thus, myocyte rebuilding and vascular rebuilding seem to be necessarily adjoined.

The field of stem cell therapy for myocardial regeneration began to expand gradually. Since now, several clinical trials of cell transplantation in the setting of acute myocardial infarction (AMI) have been performed. Various stem-cell types and delivery routes have been examined for better efficacy with the goal of perseveration of left ventricular pump function and prevention of developing heart failure. In the case of neglected cell salvage in acute setting, recovery of the failing heart is essential. Much work is needed to be done by stem-cells to re-establish dead myocytes surrounded by fibrous tissue. Stem-cells opened new horizons in the treatment of patients with heart failure irrespective of the etiology. Cellular

therapeutic options are also applied for the treatment of refractory angina pectoris. As a matter of fact, stem-cells with high differentiation capacity have the potential to be used for different clinical scenarios, in which peripheral vascular diseases are not exclusion. Disorders related to vascular insufficiency as chronic non-healing wounds have been shown to be improved using cell-based approaches as well.

Despite proved efficacy and safety of cell-based interventions, lack of specific guidelines limit their broad applications especially in acute setting. Indeed, some might not be familiar with the concept of cell-based therapies for acute situations and keep this option just for chronic end-stage cases. Additionally, cellular approaches contain a broad category as pure or modified stem-cells or recruitment and mobilization of stem-cells using chemotactic agents.<sup>1,2</sup> The paucity of constructed guidelines for cell-based approaches in the field of cardiovascular diseases partly backs to ethical issues. Go with guideline (GWG) approaches are not yet paid attention for cell strategies as for other state-of-art medical managements. In any case, availability of guidelines makes both physician and patients confident about the accuracy of the decisions.<sup>3</sup>

Currently, appropriate use criteria (AUC) are generated and updated for various cardiovascular

1- Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran  
Correspondence to: Mohaddeseh Behjati, Email: behjati@med.mui.ac.ir

diagnostic and therapeutic tests under support of several professional organizations. AUC includes three categories as “appropriate” (acceptable and reasonable), “uncertain” (generally acceptable and may be reasonable) or “inappropriate” (acceptable and is not reasonable).<sup>4</sup> In order to shed more lights on cellular strategies, the need for development of a unified guideline is obvious.

To scheme such an outline published randomized clinical trials (RCTs), non-RCTs and case series articles have been selected and their inclusive, non-inclusive and exclusive criteria have been evaluated. All criteria have been collected and this scheme was approached.

### Discussion

An outline of AUC-based indications, uncertainties

and contraindications of cell-based interventions for cardiovascular diseases is presented in table 1. However, it is just a scheme and its development needs a technical panel of physicians to review and score vast of clinical scenarios as how likely it would improve outcomes or survival of a patient. This proposed scheme is based on current understanding of technical capabilities and potential benefits of this treatment. Proposed panelist team to give the rate of indications should include interventional cardiologists, non-interventional cardiologists, cardiovascular surgeons, health outcomes researchers, medical officers from a health plan, basic researchers expert in the field of stem cell-based therapies and members of data and safety monitoring board (DSMB). Certainly, these shared evidence-based tips are not intended to replace clinical experience and judgment.

**Table 1.** A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases

General cardiovascular conditions	AUC category
Age range (18-65 y)	A
Application of good manufacturing practice (GMP) and assessment of cell viability and product sterility	A
Lactating women, pregnant females, women planning to become pregnant or unwanted pregnancy to use appropriate birth control strategies [Intra uterine device (IUD), the pill and etc.] before and two months after cell based treatments	I
Uncorrected anemia (Hb < 8.5 mg/dl)	I
Thrombocytopenia (< 100,000/ $\mu$ l) or platelet counts < 10% above the upper limit of normal (ULN)	I
White blood cell (WBC) count < 2.5 /ul	I
Liver disease [liver enzymes > 2x norm or International normalized ratio (INR) > 1.5]	I
Active infection manifested by fever, WBC > 15000 or < 4000	I
Severe renal failure (serum Cr > 150-250 mmol/l) or hemodialysis	I
Severe chronic obstructive pulmonary disease under continuous use of bronchodilators or steroids	I
Serious co-morbidities with life expectancy < 1 year	I
Patients with poor compliance (unlikely follow-up)	I
Chronic inflammatory diseases	I
Known active or chronic infectious disease [Acquired immunodeficiency syndrome (AIDS), Hepatitis C virus (HCV), Hepatitis B virus (HBV), Treponema pallidum, Cytomegalovirus infection, etc.]	I
Primary bone marrow diseases	I
Patient is unwilling about the performance of cell-based strategies	I
Persistent cardiogenic shock after 72 hours	I
Significant valve disease [Aortic stenosis (AS) with Left ventricle/Aortic valve (LV/AO) gradient < 1.5 cm <sup>3</sup> , severe mitral or aortic stenosis and/or mitral regurgitation greater than moderate]	I
Any severe concurrent medical problem as sepsis	I
Acute myocarditis	I
Coagulopathy or bleeding disorders	I
Poorly controlled insulin-dependent diabetes (HbA1C > 7 or presence of proliferative retinopathy)	I
Alcohol consumption and substance abuse	I
Organ transplant recipient	I
Malignancy or use of immune suppressive medications	I
Current smoking unless cessation of smoking at least two weeks before enrollment	I
Left ventricular (LV) thickness of < 7 mm determined by echo in the target areas of cell injection	I
Presence of echocardiography confirmed intracardiac thrombus, left ventricular aneurysm and massive calcification of the aortic valve	I
Hematology disease	I
Multi-organ failure	I

**Table 1.** A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases (Continue)

<b>General cardiovascular conditions</b>	<b>AUC category</b>
Patients with cognitive or psychiatric problems unable to provide informed consent	I
Sensitivity to Penicillin, Streptomycin, Gentamicin, Amphotericin B, contrast agent or materials used for cell preparation	I
Allergy to Aspirin, Clopidogrel, Heparin	I
Active bleeding including blood on urine dipstick or fecal occult blood	I
Anticipated inability to aspirate patient's bone marrow or draw enough blood volume needed for stem cell isolation and preparation	I
Uncontrolled arrhythmia	I
Constant atrial fibrillation/flutter (unless paced in a regular rhythm)	I
Presence of mechanical aortic or mitral prosthetic valve	I
Stem cell tracking	U
Cardiac imaging after cell delivery in a timely manner	U
In-vitro and in-vivo assessment of cell potency [using cell invasion and migration assays and imaging protocols as Cardiovascular magnetic resonance (CMR), respectively]	U
5000-10,000 IU unfractionated heparin after sheath insertion for percutaneous cell delivery	U
<b>Specific conditions (Non-ischemic cardiomyopathies)</b>	<b>AUC category</b>
Ill children with cardiomyopathy due to anti-cancer agents	A
Ejection fraction (EF) less equal or less than 35% with evidence of congestive heart failure	A
Symptomatic patients for more than one year at New York Heart Association (NYHA III-IV) despite optimal pharmacologic therapy for more than 3 months	A
NYHA II have been hospitalized with a dilated cardiomyopathy related condition	A
At least 7% reversibility and viability showed by nuclear study	A
Confirmed diagnosis of non-ischemic cardiomyopathy with normal coronary angiography	A
Serum B-type Natriuretic Peptide (BNP) level > 100 pg/ml.	A
Heart transplantation is contraindicated	A
NYHA I	I
Acute left and/or right sided failure	I
Documented latest ejection fraction > 45%	I
Indication for surgical ventricular reconstruction or mitral valve repair	I
Coronary angiography with significant stenosis amenable to revascularization	I
Recurrent myocardial ischemia or recent acute coronary syndrome (ACS) within last 28 days	I
Known severe pre-existent left ventricular dysfunction (EF < 10%) prior to randomization	I
Cardiomyopathy due to a non-treated reversible cause as thyroid disease, alcohol abuse, etc.	I
Manifest ventricular asynchrony	I
Recent cerebrovascular disease within last 60 days	I
History of syncope during the last year	I
Evidence of life-threatening arrhythmia in the absence of a defibrillator (such as non-sustained ventricular tachycardia in $\geq 20$ consecutive beats, sustained ventricular tachycardia lasting 30 seconds or more, complete second or third degree heart block in the absence of a functioning pacemaker) or QTc interval > 550 ms	I
Previous myocardial infarction	I
Congenital heart disease and chromosomal abnormality	I
Weight >140kg	I
<b>Specific conditions (Ischemic cardiomyopathies)</b>	<b>AUC category</b>
Symptomatic patients with ischemic cardiomyopathy and HF II-IV NYHA class/stage D, for at least three months despite full medical treatments	A
Severe and persistent HF with EF < 35% and or limiting angina (classes II to IV)	A
Significant coronary heart disease not amenable to revascularization or ineffective coronary revascularization during last 6 months	A
Presence of a defect identified by nuclear imaging	A
History of Q-wave MI with a residual akinetic and nonviable scar	A
Scheduled for surgical revascularization within few days (< 2 weeks) of the initial screening	A
End-stage or uncontrollable congestive heart failure without continues infusion of catecholamine	I
Patient is scheduled for heart transplantation	I
Patients requiring surgical correction of LV aneurism	I

**Table 1.** A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases (Continue)

<b>General cardiovascular conditions</b>	<b>AUC category</b>
Aortic aneurysm > 5.5 cm (including dissecting aneurysm)	I
Inability to walk on a treadmill except class IV angina patients, who will be evaluated separately	I
Implantable cardioverter-defibrillator shock within 30 days	I
Revascularization within 30 days of consent	I
<b>Specific conditions (Unstable angina)</b>	<b>AUC category</b>
Severe refractory chest pain and non-revascularizable coronary disease in diagnosed unstable angina	A
<b>Specific conditions (Chronic stable angina)</b>	<b>AUC category</b>
Minimum 7 episodes of chest pain/WK despite of optimal medical therapy for at least 4 weeks, Canadian cardiovascular class (CCS) class II or IV chronic refractory CP with exercise limitation (3-10 min on Bruce) III/IV FC, no candidacy for revascularization, presence of $\geq 1$ myocardial segment with ischemia features determined by nuclear imaging, evidence of inducible myocardial ischemia	A
History of successful or partially successful coronary artery bypass surgery (CABG) within 6 months or coronary intervention within last 60 day	I
<b>Specific conditions acute myocardial infarction (AMI)</b>	<b>AUC category</b>
AMI with a fixed perfusion defect more than 10% of LV mass on single photon emission computed tomography (SPECT) after 72 hours	A
Still symptomatic patient with extensive AMI after successful reperfusion and culprit artery repair as well as repair of other significant lesions in non-culprit arteries	A
AMI with successful recanalization [Thrombolysis in myocardial infarction (TIMI) 2-3] and impaired reperfusion [myocardial blush 0 or 1 at the end of the procedure and ST segment recovery less than 50% 1 hour after percutaneous coronary intervention (PCI)]	A
Lack of resolution of ST-segment elevations after thrombolysis	A
Still symptomatic patients with AMI after treatment by primary PCI (PPCI) within 6-12 hours of chest pain (CP) or initial treatment with thrombolysis within 2 hours followed by PCI within 24 hours of CP onset	A
Still symptomatic AMI cases with EF < 45-50% and significant regional wall motion abnormality in the territory of infarct related artery (IRA) within 24 hours after PCI of IRA, treated by PPCI within 24 hours of the onset of CP or initial treatment with thrombolysis within 12 hours followed by PCI within 24 hours of the onset of CP, NYHA $\geq 2$ and no need for immediate CABG	A
Ungraftable non-viable fibrotic area during mitral valve replacement (MVR) or CABG	A
Verification of coronary blood flow thrombolysis in myocardial infarction (TIMI) 3 before application of cell-based therapies	U
Final coronary angiography in order to ascertain vessel patency, absence of embolization and unimpeded flow and TIMI count	U
Evaluation of periprocedural safety measures by checking cardiac enzymes at the day after cell-based therapies	U
AMI with successful reperfusion within 24 hours after symptom	I
Indication for immediate CABG after AMI	I
Mechanical complications of AMI (myocardial rupture of interventricular septum and LV free wall, papillary muscle rupture)	I
IRA with TIMI flow < 3 by the time of cell injection	I
<b>Specific conditions peripheral vascular disease (PVD)</b>	<b>AUC category</b>
Ischemic and refractory peripheral vascular disease (PVD) or with rest pain of the index limb (Rutherford category 4) defined as pain requiring analgesia (> two weeks) that occurs at night or at rest or dry gangrene as signs of end stage vascular disease	A
Refractory ambulatory critical limb ischemia (Rutherford score 4/5), ischemic lower extremity non-healing ulcers (Grade II of Wagner's classification) due to infra-inguinal disease present for > 4 weeks	A
Claudication at 100 meters or peak walking time of 1 to 6 minutes on two exercise tests apart by 2 weeks on graded treadmill with Ankle brachial index (ABI) < 1.0, monophasic Doppler waveforms at posterior tibial artery and dorsalis pedis artery with toe pressure < 30 mmHg, ankle pressure < 60 mmHg or toe pressure < 40 mmHg, flat or barely pulsatile pulse on volume recording, toe brachial index $\leq 0.35$ or III, TcPO <sub>2</sub> /TcO <sub>2</sub> of $\leq 40$ mmHg, reduced TCpO <sub>2</sub> (< 30-45 mmHg) at calf muscle	A
Moderate or severe limb-threatening peripheral arterial disease (PAD), defined as ABI < 0.7 in two consecutive examinations at least 1 week apart, peripheral arterial obstructive disease (PAOD) at Fontaine class [IIb, III or IV], distal arterial occlusion of two of the following lower extremity arteries: anterior tibial, posterior tibial, and peroneal	A

**Table 1.** A suggested scheme for appropriate use criteria (AUC)-based indications; uncertainties and contraindications of cell-based interventions for cardiovascular diseases (Continue)

General cardiovascular conditions	AUC category
No option patients as cases amenable for each kind of vascular reconstruction, defined as cases with prior vascular reconstruction, diffuse multi-segment disease, inability to locate a suitable vein for grafting, or extensive infra-popliteal disease	A
Gangrene (Rutherford 6) or pre-existing major tissue loss	I
Unstable angina, Myocardial infarction (MI), stroke, Congestive heart failure (CHF) (class III or IV) within 6 months of study or presence of conditions that preclude general anesthesia	I
Active infection in the affected leg	I
Eligible patients for traditional endovascular or surgical treatments for PVD	I
Popliteal vascular entrapment syndrome	I
Trans-metatarsal or higher amputations in the affected limb or amputation required within 30 days	I
Gastrointestinal bleeding within last 3 months	I
Surgery or trauma within the last 2 months	I
Successful bypass operation or intervention within the last 3 months	I
Subjects not likely to be benefited with maximal tolerated medical therapy for PVD including stop smoking, control of blood sugar, blood lipids, blood pressure and treatment with aspirin and / or cilostazol (unless medically contraindicated)	I
Stem cell treatment within the past 6 months	I
Patient is unwilling to receive Aspirin and clopidogrel	I
Ischemic ulcers with infectious symptoms ( $\geq$ Grade 3 of Wagner classification)	I
Coronary angioplasty within the past 1 year	I
Requiring major amputation (at or above the ankle) within 4 weeks of starting the treatment	I

### Conflict of Interests

Authors have no conflict of interests.

### References

- Musialek P, Tekieli L, Kostkiewicz M, Miszalski-Jamka T, Klimeczek P, Mazur W, et al. Infarct size determines myocardial uptake of CD34+ cells in the peri-infarct zone: results from a study of (99m)Tc-extametazime-labeled cell visualization integrated with cardiac magnetic resonance infarct imaging. *Circ Cardiovasc Imaging* 2013; 6(2): 320-8.
- Arefieva TI, Krasnikova TL, Potekhina AV, Ruleva NU, Nikitin PI, Ksenevich TI, et al. Synthetic peptide fragment (65-76) of monocyte chemotactic protein-1 (MCP-1) inhibits MCP-1 binding to heparin and possesses anti-inflammatory activity in stable angina patients after coronary stenting. *Inflamm Res* 2011; 60(10): 955-64.
- Yu T, Vollenweider D, Varadhan R, Li T, Boyd C, Puhon MA. Support of personalized medicine through risk-stratified treatment recommendations-an environmental scan of clinical practice guidelines. *BMC Med* 2013; 11: 7.
- Chan PS, Brindis RG, Cohen DJ, Jones PG, Gialde E, Bach RG, et al. Concordance of physician ratings with the appropriate use criteria for coronary revascularization. *J Am Coll Cardiol* 2011; 57(14): 1546-53.

**How to cite this article:** Behjati M. Suggested indications of clinical practice guideline for stem cell-therapy in cardiovascular diseases: A stepwise appropriate use criteria for regeneration therapy. *ARYA Atheroscler* 2013; 9(5): 306-10.