Introduction

Stem cells and their unique properties: Stem cells are special cells which not only have the ability of self-renewal but can also be a lifelong source of specialised functional cells of different human organs. Development of a human embryo into a healthy new-born child is possible because of the unique ability of embryonic stem cells to form different tissues and organs. Most adult human tissues and organs also have stem cells that can produce their functional specialised cells as and when required. The self-renewal ability of stem cells ensures that stem cells are not depleted and enough stem cells remain to produce sufficient number of specialized cells of that organ during the long human lifespan, until aging starts affecting stem cells.

Stem cells in Regenerative Medicine and human diseases: When a disease or injury causes severe depletion of the functional cells of a human organ or system, the function of that organ or organ system is lost. In the natural healing process, some organs such as skin, blood, liver etc. can often regenerate its form and function by producing sufficient numbers of new functional cells from the stem cells present in them. However, specialized cells of some organs like the nerve cells in the brain, spinal cord, eyes and muscles have limited or no capacity to regenerate and restore full function. In the last two decades, medical science has undertaken extensive research to explore the potential of stem cells from the same organ or tissue type (homologous use) or from a different organ or tissue type (non-homologous use) to restore some lost bodily function. These stem cells may be from the same person (autologous source) or from another person (allogeneic source). Research to regenerate the form and function of a human organ or organ system from stem cells or tissue engineering is called 'Regenerative Medicine'.

Status of Stem cells in Regenerative Medicine and human diseases: Unfortunately, the promise of Regenerative Medicine in general, and stem cells in particular, is yet to be realized due to several technical, biological, ethical and medical challenges. To produce sufficient number of specialised cells for restoring a lost body function with just a small number of stem cells or by using stem cells from one organ to restore cells and function of a different organ (such as mesenchymal stem cells in bone marrow or fat tissue to restore nerve or muscle function) has proven to be far more difficult in humans than what was thought based on animal experiments. As a result, the inherent appeal of stem cells has remained largely unfulfilled in human diseases. The exception is however the use of "Haematopoietic Stem Cells" for reconstituting or regenerating the bone marrow in order to start producing blood and immune cells. Transplantation of enough number of "Haematopoietic Stem Cell" in a procedure called

Bone Marrow Transplantation or Haematopoietic Stem Cell Transplantation from the same person (autologous) or from another human donor (allogenic) is a recognized medical indication of stem cell use for benign and malignant life threatening haemato-lymphoid diseases or few immune related diseases. Haematopoetic stem cells are also progenitors for other cells like osteoclasts and have successfully used in osteopetros is and some inborn errors of metabolism like Gaucher disease, mucopolysaccharidosis. Use of other types of stem cells and even the bone marrow derived stem cells to restore function of other organs remains experimental and is subject of ongoing controlled clinical trials. Not only the efficacy of these experimental stem cell use is uncertain, the process of taking out stem cells, culturing or growing them, storing them and putting them back can cause changes in these cells and sometimes serious side effects, including some reported cases of cancers.

Why Stem cells continue to be used for debilitating or incurable conditions outside controlled research studies: A large number of controlled prospective research studies (phase I, II and III clinical trials) investigating the safety and efficacy of stem cells for different diseases have been completed or are ongoing in Europe, USA, Korea and Japan. A small number of such research studies are also being conducted in other countries, including India. All developed countries have taken a very cautious and stringent regulatory approach regarding how different types of stem cells can be procured, processed, stored and used for preclinical or clinical research or as stem cell therapy outside research studies. Participants of regulated interventional research in any field, including stem cells, are made aware through a detailed written informed consent process about the experimental nature of the therapy, unproven efficacy and uncertainty regarding the benefits and risks of stem cells, the natural history of the disease, current standard therapy for that disease and any alternative treatments. It is the duty of the research sponsors to provide free of cost medical tests and treatments done as part of stem cell clinical trial and research, including the cost of procuring, storing and using stem cells. Circumventing the route of rigorous research studies to establish the safety and efficacy of a particular type of stem cells for a specific disease or aging condition, some unlicensed or even licenced and registered medical practitioners engage in unethical practices of selling unproven stem cell therapy as a magical remedy to desperate families with incurable and potentially fatal diseases with little or no hope of cure from other methods. Desperate patients from around the world including USA and Europe with stricter enforcement of regulations for stem cell use outside clinical trials get lured to stem cell clinics in South America, China, Russia and India. The US FDA and European Medical Agency has warned against this practice through several such advisories.

https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies

https://www.fda.gov/news-events/press-announcements/statement-stem-cell-clinic-permanent-injunction-and-fdas-ongoing-efforts-protect-patients-risks

https://www.fda.gov/news-events/press-announcements/federal-court-issues-decision-holding-us-stem-cell-clinics-and-owner-adulterated-and-misbranded-stem

Is Stem cell research permitted or encouraged by the governmental agencies?

The unethical and unregulated use of stem cells as, often promoted as a magical remedy is not allowed by the government in the developed world and many Low and Middle Income Countries (LMIC) including India. However, considering the incurable nature of many diseases, and the acknowledged potential of stem cells, most countries, including India, encourage and fund scientific, ethical and regulated research in the field of stem cells. The purpose of such research is to obtain safety and efficacy data with the use of a particular type of stem cell in a particular condition. To provide guidance and to facilitate human research in stem cells, while curbing exploitation of vulnerable patients, the Indian government through the Indian Council of Medical Research (ICMR) has come out with successive National Guidelines in this field since 2007. The most recent National Guidelines for Stem Cell Research with inputs from all stakeholders including various government agencies and regulators, patients, medical and scientific experts and the industry, was released in 2017. These guidelines are revised at regular intervals to incorporate any new evidence for the safety or efficacy of stem cells.
https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf

Need for National Guidelines for evidence-based use of Stem cells as a routine or standard treatment option: In many countries including India, there is a lack of clarity among patients, and to some extent among the medical community, whether stem cell therapy can be considered as a standard treatment option for a specific medical condition or should remain as an unproven experimental approach. There are several reports of increasing use of stem cells therapy for a wide range of diseases, often with little or no scientific evidence of efficacy or cure. Unethical promotions with false claims and misleading advertisements have been widely used to promote unscientific stem cell therapy. Several instances of public exploitation and grievances from members of the public have been received by the ICMR and other government agencies from aggrieved patients describing how they were lured into unproven stem cell therapies. Often the complainants demanded actions to be taken by the regulatory agencies and professional bodies to curb such practices. With this background, the Govt. of India has entrusted the ICMR to frame guidelines on stem cell therapy.

In order to develop a scientific and unbiased guideline for evidence based use of stem cell as a routine or standard treatment option in India, the ICMR has solicited opinion from expert clinicians, professional medical societies and through its website from any clinician or member of public to submit level I or level II scientific evidence for clinical efficacy of stem cells in any

disease indications with reference for such evidence from peer reviewed Pubmed indexed medical and scientific journals.

https://icmr.nic.in/content/icmr-inviting-level-i-or-level-ii-scientific-evidence-and-grade-or-b-recommendation-use-stem

A critical review of the comments and evidence provided by medical experts and their professional societies or any member of the public and the scientific literature was done to draft guidelines and statements for evidence-based use of stem cell therapy.

Statements have been prepared for individual diseases or groups of diseases or conditions on the "EVIDENCE BASED STATUS FOR THE USE OF STEM CELLS IN (Disease condition)". In these statements the first section is for the public and patients using layman terms while the second section is for doctors, scientists and allied healthcare professionals providing major research studies in the scientific literature, scientific level of evidence and a summary recommendation based on the current scientific evidence.

International Society for Stem Cell Research (ISSCR)

The International Society for Stem Cell Research (https://www.isscr.org/) is the leading professional organization of stem cell scientists and represents over 4,000 members in 67 countries including India. Like ICMR in India, FDA in USA, EMA in Europe, this international society also felt the urgent need to address the growing public concern regarding the unscientific or unethical use of stem cell therapy. The ISSCR has also issued a statement on reporting false marketing claims and adverse events from clinics offering unapproved stem cell therapies.

https://www.closerlookatstemcells.org/patient-resources/how-to-report-false-marketing-claims-and-adverse-events-from-clinics-offering-unapproved-stem-cell-therapies/.

In parallel with the ICMR initiative and public advertisement inviting comments and evidence for stem cell use from public and medical professionals, the ISSCR has also come out with factsheets on current status of stem cell use. The ISSCR document highlights that other than Hematopoietic stem cell (also called Bone Marrow) transplant for certain haematological or immune system disorder, the "list of diseases for which stem cell treatments have been proven to be beneficial and/or have obtained regulatory approval for use is still very short" and that "some bone, skin and corneal (eye) injuries and diseases can be treated by grafting or implanting tissues in which stem cells are essential for the healing process". The ISSCR cautions that "However, clinics around the world continue to provide unproven stem cell treatments and often market them as cures for a variety of diseases and conditions without sound scientific

evidence or regulatory approval. These so-called treatments have, in some cases, caused patients great harm physically, and at great expense financially".
https://www.isscr.org/professional-resources/scientific-professional-resources/disease-fact-sheets
https://www.isscr.org/scientific-clinical-resources/disease-fact-sheetshttps://www.closerlookatstemcells.org/2020/01/14/truths-around-stem-cell-treatments/

The ISSCR concise factsheets provide the current state of stem cell science for specific diseases, including background on the disease, rationale for using cell-based therapies, evidence for specific approaches and current status of the field with respect to clinical trials. A total of 11 conditions have been covered so far.

1. Age-related macular degeneration
2. Amyotrophic lateral sclerosis
3. Chronic obstructive pulmonary disease
4. Diabetes
5. Huntington's disease
6. Liver disease
7. Multiple sclerosis
8. Myocardial infarction / Heart failure
9. Osteoarthritis
10. Parkinson's disease
11. Paediatric leukodystrophies

Evidence Based Status of Use of Stem Cells in Heart Failure

A. Information for public and patients

What is Heart Failure?

Heart failure is a complex clinical syndrome that underlines the inability of the heart to perform its circulatory function with the desired efficiency due to structural and/or functional (systolic or diastolic) alterations. The prevalence of HF increases with age. Of the array of biomarkers available for the diagnosis of HF, BNP and NT-pro-BNP are the ones that are extensively used clinically.

What is the treatment of Heart Failure?

There are a number of therapies available for heart failure ranging from drugs like ACE inhibitors, beta blockers, angiotensin receptor- neprisyln inhibitors, ivabradine and left ventricular assist devices and when all else fails there is the option of a heart transplant. Advanced options like heart transplant are limited due to lack of donor hearts and LV assist devices are expensive and out of reach of many. There is, therefore, need for alternative forms of therapy and stem cell and gene therapy have been tried to repair the heart.

Have stem cells been used in Heart Failure?

The current status of research in stem cell therapy suggests that the therapy could reduce the risk of mortality in chronic ischemic heart disease with heart failure and that there are no major adverse events associated with it. This benefit has not been shown in acute myocardial infarction these studies still need to be confirmed in larger clinical trials before cell-based treatment for these patients can be developed as standard treatment. The next studies have to focus on better understanding, and improvement of the cell therapies used (eg, mononuclear cells, circulating progenitor cells, mesenchymal stem cells, embryonal or haematopoietic progenitor cells). Predictors of responders and outcomes need to be carefully assessed and perhaps therapy needs to be tailored to each patient.

Recommendations (2021):

Since the benefit of stem cells has not been shown consistently in all clinical trials, it is still recommended that all stem cell therapies be given within the framework of clinical trials and not as standard or routine therapy outside clinical trials.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to Heart Failure

patients outside the purview of regulated and approved clinical trials. Patients with Heart Failure from India and those coming from outside India should be aware that any type of stem cell therapy for Heart Failure should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the National Guidelines forStem Cell Research - 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the ICMR National Bioethics Guidelines 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf) clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

Stem cells are cells that have the ability to develop into different cell types. In some cases, they also have the ability to repair damaged tissues. The two broad types of stem cells are embryonic stem cells and adult stem cells. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells act as a repair system for the body. Stem cell therapy was first established in the treatment of blood malignancies in the form of a bone marrow transplant. Two decades ago this was extended to non-blood disorders in an attempt to repair non-blood disorders by using the pluripotent nature of stem cells to repair other organs.

Stem cell therapy and its types:

A. First Generation cell therapy

01. Skeletal Myoblasts

Skeletal myoblasts were the first cells tested in preclinical and clinical trials. The advantages include that they have minimum ethical concerns, their expansion in-vitro is quick, resistant to ischemic conditions, and there will be minimal risk of tumorigenicity. Contrarily disadvantages include there will be no transdifferentiation into functional cardiomyocytes, Due to lack of electrochemical coupling, risks of ventricular arrhythmias are high.

After the initial promising preclinical and clinical trials, the large MAGIC trial wasconducted and it showed no benefit and a high incidence of arrhythmias. Trials with myoblasts have since diminished.

02. Bone marrow-derived cells

The bone marrow contains a mix of mature and immature cells. Experiments have shown that an injury causes the recruitment of Bone marrow-derived cells to the injured/inflamed area and they can aid in repair. After the initial clinical experiments with bone marrow-derived cells, the interest shifted to Bone marrow-derived mononuclear cells [MNCs]. Trials with MNCs have shown mixed results showing a benefit of improvement in the ventricular function of about 2-5% in some trials while not showing a benefit in some.

03. Mesenchymal stem cells

Mesenchymal cells are non-hematopoietic stem cells, which are multipotent, and immune privileged. A number of clinical trials have shown a benefit of mesenchymal cells on ventricular function. In the PROCHYMAL (EF improved 7.3%) and the POSEIDON (EF improved 5-8%), the improvement was significant.

B. Second Generation cell therapy

01. Cardiac stem/progenitor cells /Propagated cells.

Several cardiac stem cells (CSCs) and cardiac progenitor cells (CPCs), such as cardiosphere-derived cells (CDCs), stem cell antigen (Sca)-1+ cells and many other types of cardiac stem cells have been found. The clinical trials SCIPIO, CADUCEUS, All-Star and DYNAMIC used an intracoronary infusion of propagated cells or autologous c-Kit+ CSCs and CDCs grown from endomyocardial biopsy respectively and showed improvements in regional ventricular function.

02. Embryonic Stem Cells

ESCs are derived from the inner cell mass of the blastocyst and have the properties of self-renewal and differentiation into cell types of all 3 germ layers ie.: endoderm, mesoderm, ectoderm. There is a demonstrated risk of teratomas shown in animal experiments. They have the potential of forming cardiomyocytes. In phase one ESCORT trial human ESC derived cardiac progenitors embedded in a fibrin matrix were implanted in patients with severe

heart failure. In the first patient, there was an improvement in ventricular function with no tumor formation or arrhythmia.

Mechanism of Action:

A number of mechanisms have been proposed and these include direct cardiac differentiation of injected cells into cardiac muscle and the integration into the myocardium. However, this has been seen more in animal experiments and is probably a highly inefficient mechanism. However, data obtained from numerous *in vitro and in vivo* studies have shown paracrine signaling is the fundamental mechanism that mediates the beneficial effects of stem cell therapy. They can have immunomodulatory and effects. They can also recruit resident cardiac stem cells.

Improving Stem Cell therapy:

Attempts are being made to improve the homing ability of the stem cells and the proangiogenic properties by incubating the stem cells with growth factors and cytokines. Stem cells can also be modified to over express cytokines by transducing with a lentivirus construct. Using machine learning, responders to stem cell therapy can be picked up based on clinical and biochemical markers leading towards personalized stem cell therapy. Primarily to repair cardiocytes efficiently with the help of SCs, two considerable to formulate "next generation" is A) genetic engineering modifications and B) non genetic modification.

The interest in Stem Cell in India started with work at AIIMS, Delhi by Prof P Venugopal. This was a series of studies which was started in patients undergoing coronary artery bypass surgery who had a scar and had a non-viable myocardium which received a stem cell injection during the bypass surgery. This area showed improvement on subsequent evaluation on Echocardiograms and PET scan. This study was followed by a study in patients with dilated cardiomyopathy (The ABCD trial) in which patients with dilated cardiomyopathy were injected with bone marrow-derived stem cells injected into the coronary arteries. They showed an improvement in ventricular function and quality of life at 3 and 6 months, which was sustained at 3 years. The biopsies done in these patients showed that there was a trend towards increased vascularity but no new muscle seen. Subsequent studies done with labeling at AIIMS have shown interesting results with technetium-labeled stem cells showing inconsistent homing to the infarct area, which could be one reason why bone marrow-derived stem cells do not always result in an improvement in cardiac function after an intra-coronary injection.. An ICMR sponsored study was then done in patients with recent myocardial infarction where the infarct-related artery had not been opened up within 24 hours. The artery was opened between 24 hours and 30 days and then stem cells were injected. There was a significant improvement in ventricular function (article in press).

The ICMR also sponsored a multicentric study in India where stem cells were injected in patients who were successfully treated for myocardial infarction and were then injected with intracoronary stem cells. The study did not result in positive results.

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Current Status of Stem Cell Therapy

The current status of research in stem cell therapy suggests that the therapy could reduce the risk of mortality in chronic ischemic heart disease with heart failure and that there are no major adverse events associated with it. This benefit has not been shown in acute myocardial infarction these studies still need to be confirmed in larger clinical trials before cell-based treatment for these patients can be developed as standard treatment. The next studies have to focus on better understanding, and improvement of the cell therapies used (eg, mononuclear cells, circulating progenitor cells, mesenchymal stem cells, embryonal or haematopoietic progenitor cells). Predictors of responders, outcomes need to be carefully assessed and perhaps therapy needs to be tailored to each patient.

Heart Failure	
S.No	**Review of Literature** **Critique / Applicability of the study results**
i.	Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LEJ, Berman D *et. al.* Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. The Lancet 2012; 379: 895-904 It showed that intracoronary infusion of autologous CDCs after myocardial infarction is safe, warranting the expansion of such therapy to phase 2 study. The unprecedented increases we noted in viable myocardium, which are consistent with therapeutic regeneration, merit further assessment of clinical outcomes.
ii.	Menasche P, vanneaux V, Fabreguettes JR, Bel A, Tosca L, Garcia S et. al. Towards a clinical use of human embryonic stem cell-derived cardiac progenitors: a translational experience.Eur Heart J 2015; 36 : 743-750 Although several facets of this manufacturing process still need to be improved, these data may yet provide a useful platform for the production ofhESC-derived cardiac progenitor cells under safe and cost-effective GMP conditions.
iii.	S.Seth, R. Narang, B. Bhargava, et. al. Percutaneous Intracoronary Cellular Cardiomyoplasty for Nonischemic Cardiomyopathy: Clinical and Histopathological Results: The First-in-Man ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) Trial. J Am Coll Cardiol,48 (2006),pp.2350-2351 In summary, 24 patients underwent intracoronary stem cell injection with coronary sinus blockage. Four patients died during the 6-month follow-up. Overall EF showed a small but

	significant improvement of 5.4%. There was a decrease in end-systolic volumes, but no change in end-diastolic volumes. Endomyocardial biopsy done at 3 months showed no significant change in the number of myocytes or capillaries, but the ratio of capillaries to myocytes showed an insignificant increase. There were soft data to suggest cell proliferation (binucleate cells and Ki 67 positivity)
iv.	Seth S, Bhargava B, Narang R, Ray R, Mohanty S, Gulati G, et.al The ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) Trial A Long-Term Follow-Up Study. J Am Coll Cardiol. 2010 Apr 13 ; 55(15) : 1643-4. Doi:10.1016/j.jacc.2009.11.070 Mortality was not significantly different between the treatment and control arms. The EF improved in the treatment arm by 5.9% with a reduction in end-systolic volumes and no change in end-diastolic volumes. Both NYHA functional class III and IV groups in the treatment arm showed improvement, although the effect on the NYHA functional class III patients (EF: 23.6 10.6.% to 30.1 11%) was greater than that on the NYHA functional class IV patients (EF: 20.1 9% to 24 13.8%). There was no significant improvement in the EF in the control patients. There was a significant improvement in quality of life as assessed by KCCQ and functional status on long-term follow-up in the treatment group. Endomyocardial biopsies showed a trend toward improvement in vascularity with no definite evidence of transdifferentiation. This was in the form of significantly increased capillary density with no increase in the supporting pericytes. No new myocardial cells or any immature cells were seen.
v.	Chetan D Patel, Agarwal S, Seth S, Mohanty S, Agarwal H, Gupta N. Detection of homing-in of stem cells labeled with technetium-99m hexamethylpropyleneamine oxime in infarcted myocardium after intracoronary injection. :2014 |29|4|276-277 Bone marrow stem cells having myogenic potential are promising candidates for various cell-based therapies for myocardial disease. We present here images showing homing of technetium-99m (Tc-99m) hexamethylpropyleneamine oxime (HMPAO) labeled stem cells in the infarcted myocardium from a pilot study conducted to radio-label part of the stem cells in patients enrolled in a stem cell clinical trial for recent myocardial infarction.
vi.	Nair, Velu; Madan, Hemant; Sofat, Sunil; Ganguli, Prosenjit; Jacob, M.J. ; data,et.al. Efficacy of stem cell in improvement of left ventricular function in acute myocardial infarction - MI3 Trial. The Indian Journal of medical research (2015). 142. 165-74.10.4103/0971-5916.164245 Infusion of stem cells was found to have no benefit in ST elevation AMI. However, the procedure was safe. A possible benefit was seen when the predefined cell dose was administered which was noted upto three weeks post AMI, but this was not significant and needs confirmation by larger trials
vii.	Menasche P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Triquart L, et.al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation.Circulation 2008;117: 1189-1200. Myoblast injections combined with coronary surgery in patients with depressed LV function failed to improve echocardiographic heart function. The increased number of early postoperative arrhythmic events after myoblast transplantation, as well as the capability of high-dose injections to revert LV remodeling, warrants further investigation.
viii.	Choudhury T, Mozid A, Hamshere S, yeo C, Pellaton C, Arnous S, Saunders N, et. al. An exploratory randomized control study of combination cytokine and adult autologous bone marrow progenitor cell administration in patients with ischaemic cardiomyopathy: the REGENERATE-IHD clinical trial. Eur J Heart Fail 2017;19:138-147

	It showed that G-CSF combined with autologous i.m. BMCs has a beneficial effect on cardiac function and symptoms. However, this result should be considered preliminary in support of a clinical benefit of i.m. stem cell infusion in 'no option' patients and needs further exploration in a larger study.
ix.	Wollert KC, Meyer GP, Lotz J, Ringes Lichtenburg S, Lippolt P, Breidenbach C et. al: Intracoronary Autologous bone- marrow cell transfer after myocardial infarction: The BOOST randomized controlled clinical trial. The Lancet 2004;364:141-148 Intracoronary transfer of autologous bone-marrow cells promotes improvement of left ventricular systolic functions after acute myocardial infarction.
x.	Lee JW, Lee SH, Youn YJ, Ahn MS, Kim JY, Yoo BS, et.al: A randomized, open-label, multicenter trial for the safety and efficacy of adult mesenchymal stem cells after acute myocardial infarction. K Korean Med Sci 2014; 29: 23-31 The main finding is that the intracoronary administration of autologous purified BM-derived MSCs at 1 Month after STEMI is tolerable without serious complications and provides modest improvement in LVEF at 6-month follow-up by SPECT.
xi.	Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, et.al. :Effect on Left Ventricular Function of Intracoronary Transplantation of Autologous Bone Marrow Mesenchymal Stem Cell in Patients With Acute Myocardial Infarction. Am J Cardiol 2004; 94: 92-95 The results showed that BMSCs 3 months after transplantation were viable, with high left line local shortening and unipolar voltage in the infarcted area and increased cardiac functional indexes as demonstrated by cardiac echocardiography, which encouraged our further study. The results clinically resolved the assessment of viability of implanted BMSCs and confirmed that BMSCs function with host cardiomyocytes.Serial cardiac echocardiographic monitoring demonstrated improvement of cardiac function 1 to 3 months after implantation of BMSCs, and improvement was maintained nearly 6 months after the procedure
xii.	Chugh AR, Beache GM, Loughran JH, Mewton N, Elmore JB, Kajstura J et. al. Administration of cardiac stem cells in patients with ischemic cardiomyopathy: The SCIPIO trial : surgical aspects and interim analysis of myocardial function and viability by magnetic resonance. Circulation 2012; 126:S 54-64 Isolation of CSCs from cardiac tissue obtained in the operating room is feasible and doesnot alter practices during CABG surgery. CMR shows that CSC infusion produces a striking improvement in both global and regional LV functiona, a reduction in infarct size, and an increase in viable tissue that persist atleast 1 year and are consistent with cardiac regeneration.
xiii.	Mathiasen AB, Qayyum AA, Jorgensen E, Helqvist S, Fischer – Nielsen A, kofoedKF,etal.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 Intra-myocardial injections of autologous culture expanded MSCs were safe and improved myocardial function in patients with severe ischaemic heart failure.
xiv.	Balram A, Talwar S, Choudhary S.K, Bisoi A, Chowdhury UK, Hote M.K, et.al. Application of stem cell technology for coronary artery disease at the All India Institute of Medical Sciences, The Heart Surgery Forum # 2007-0701 10(2), 2007,1-4,doi:10.1532/HSF98 CABG along with Intramyocardial infection of bone marrow stem cells showed improvement in contraction of infracted segments of the heart.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Heart Failure.

The current status of research in stem cell therapy suggests that the therapy could reduce the risk of mortality in chronic ischemic heart disease with heart failure and that there are no major adverse events associated with it. This benefit has not been shown in acute myocardial infarction these studies still need to be confirmed in larger clinical trials before cell-based treatment for these patients can be developed as standard treatment. The next studies have to focus on better understanding, and improvement of the cell therapies used (e.g. mononuclear cells, circulating progenitor cells, mesenchymal stem cells, embryonal or haematopoietic progenitor cells). Predictors of responders, outcomes need to be carefully assessed and perhaps therapy needs to be tailored to each patient. Since the benefit of stem cells has not been shown consistently in all clinical trials, it is still recommended that all stem cell therapies be given within the framework of clinical trials and not as standard or routine therapy outside clinical trials.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Heart Failure.