The Hope and Hype of Cardiac Regeneration

Internal Medicine Grand Rounds
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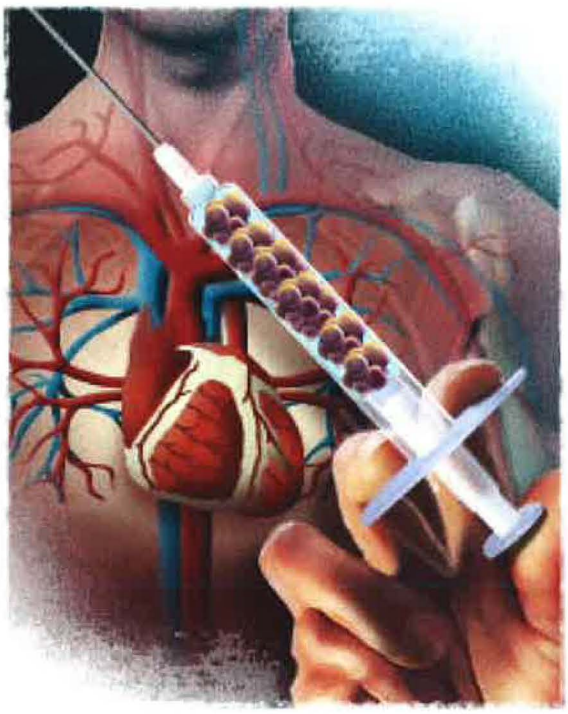
Hesham A. Sadek MD, PhD



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1) Heart Failure:

Definition:
Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood[2, 4].

Types of Heart Failure:

Diastolic heart failure (heart failure with preserved ejection fraction):
Due to increased stiffness of the left ventricle (LV) in the setting of normal systolic function, thereby resulting in increased the LV filling pressures. There is no role for myocardial regeneration in treatment of this type of heart failure, since the primary pathology is not associated with myocyte loss.

Systolic heart failure (heart failure with depressed EF):
HF with a depressed EF-commonly known as systolic heart failure (SHF)- accounts for 50-60% of all HF cases. Coronary artery disease (CAD) account for 70-80% of cases of systolic heart failure in industrialized countries (ischemic cardiomyopathy)[2, 4]. The remaining 20-30% are summed up under non-ischemic or dilated cardiomyopathy; etiology includes congenital heart defects, valvular heart disease, genetic defects, toxins, and most recently cardiac stem cell defects (resulting in failure of the normal turnover of cardiomyocytes).

Scope of the problem:
The overall prevalence of HF in the adult population in developed countries is 2%. HF prevalence follows an exponential pattern, rising with age, and affects 6–10% of people over the age of 65. In the United States, the lifetime risk of developing HF is approximately one in five for a 40-year-old. The majority of HF with depressed EF cases are progressive to end stage cardiomyopathy. Recovery of function occurs mostly when the underlying myocardium is still viable (stunned and hibernating myocardium in ischemic CM, and sometimes in early stages of

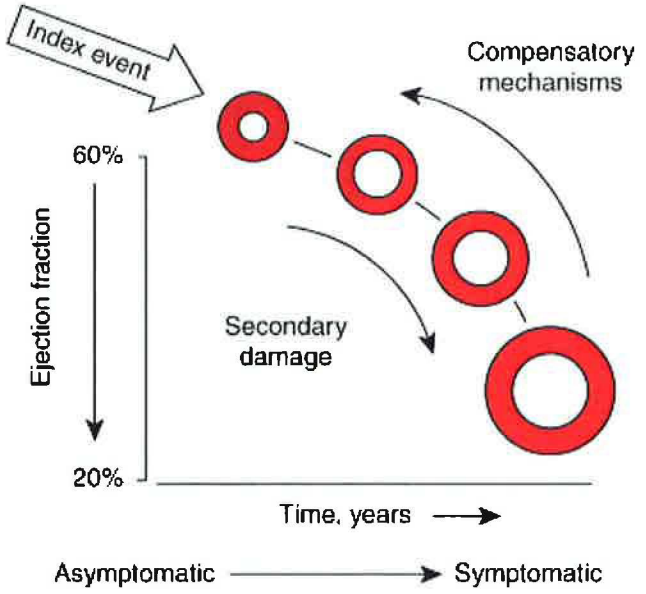

Figure 1. Progression of HF: Natural history of HF resulting in worsening pump function, and progression to terminal HF [5].

idiopathic CM). Once heart failure is established, in the absence of viable myocardium, about 50% of patients die within 5 years of diagnosis[8, 9].

Current HF management strategies:

Approach to HF therapy is based on the clinical stage (Figure 2). Generally, treatment focuses on prevention of progression of the disease in earlier stages, and pump replacement in later stages of HF.

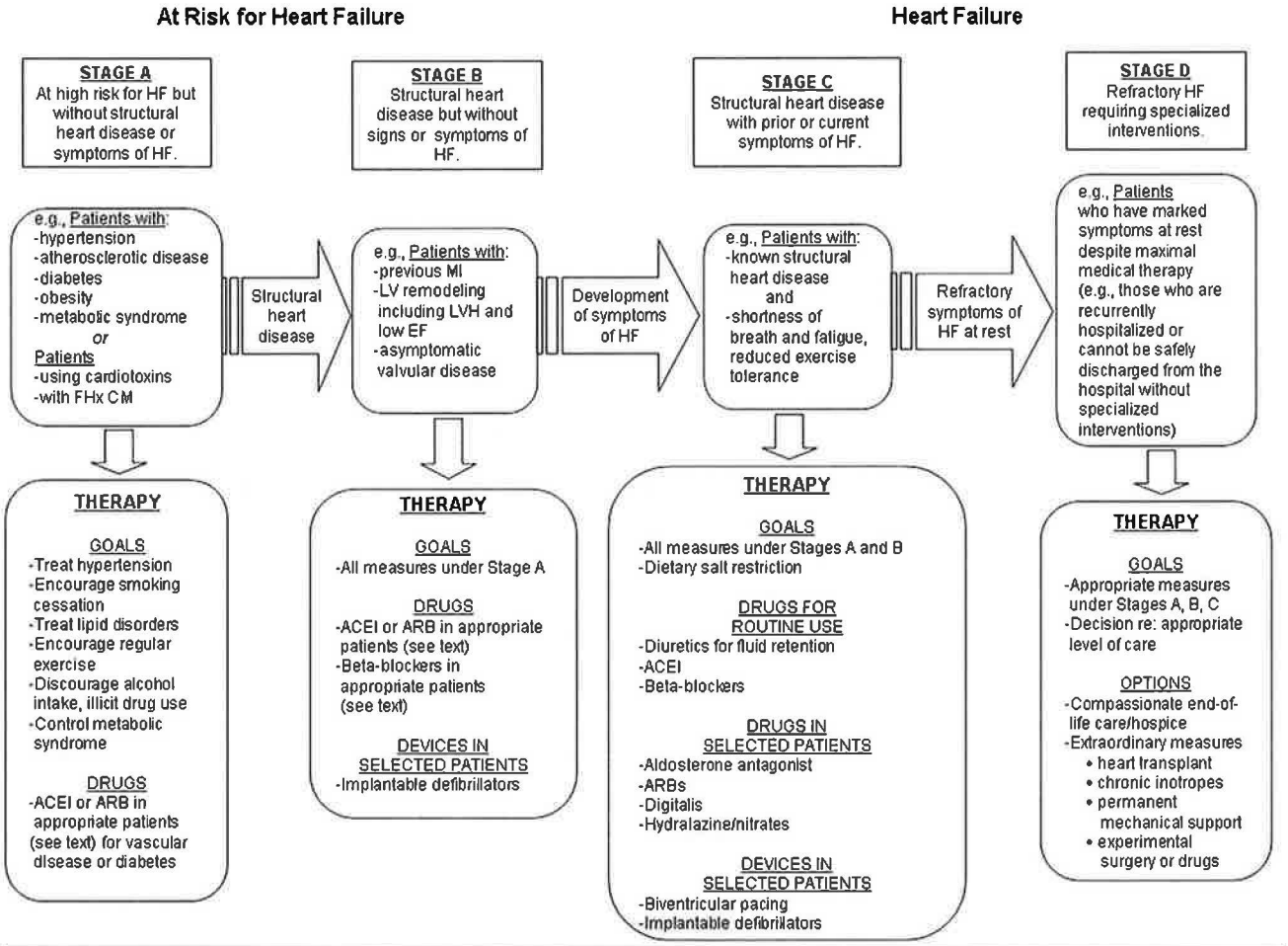

Figure 2. Current AHA/ACC Guidelines for management of HF: Therapy is aimed at myocardial salvage and prevention of progression in earlier stages (A,B and C). While in terminal HF (stage D), pump replacement is the only viable option[2].

Limitations of available treatment options:

The majority of patients with stage C heart failure eventually progress to stage D or refractory heart failure, which has frustratingly limited treatment options. The only definitive treatment for stage D heart failure is pump replacement, either by orthotopic heart transplant, or by destination therapy using mechanical support. And although heart transplant is the only option that offers a real chance at disease free survival for refractory heart failure, its use is markedly limited by donor availability [10]. Recently, with

the advent of newer left ventricular assist devices (LVAD), mechanical support as a destination therapy for refractory heart failure became a viable alternative, however the long-term outcome of these devices remains to be determined [10]. These realities have fueled intense interest in cardiac regeneration research as a means of restoring pump function and curing heart failure.

2) Cardiac Regeneration:

A Historical Perspective:

The textbook description of the heart is that it is a terminally differentiated organ, incapable of any degree of regeneration [11]. This is perhaps a logical conclusion given what we know about the natural history of heart failure, and the lack of any true functional recovery following significant myocardial necrosis. However, over the past decade, there has been mounting evidence demonstrating that the heart is certainly not a terminally differentiated organ, and that there is constant cardiomyocyte turnover within the mammalian, and the human heart throughout life [11-14]. The mechanism of cardiomyocyte turnover, and the role of cardiomyocyte division, or contribution of an extracardiac, or a resident stem cell population remains to be determined.

Evidence of Spontaneous Cardiac Regeneration:

The past decade has witnessed a paradigm shift in cardiac regeneration biology. There is now concrete evidence that the heart of some species is capable of complete regeneration of cardiomyocytes and vasculature following partial amputation of the ventricular apex. In addition, while the mammalian heart is seemingly incapable of complete regeneration, there is now clear evidence that the mammalian heart has a measurable regenerative capacity.

A) Regeneration of the Zebra Fish Heart:

So far, only a few organisms are known to be capable of complete regeneration of the heart following significant myocardial damage. These organisms include zebrafish[1] and newt [15, 16]. The zebra fish is a small (2-4 grams) tropical fish that is capable of complete regeneration of virtually any organ or tissue. Most of the recent cardiac regeneration studies utilized zebra fish due to the feasibility of generating genetic models to dissect regenerative mechanisms. In 2001, Ken Poss and colleagues showed that the zebrafish is heart completely regenerates following resection of the entire apex[1]. Since then, numerous genetic models have been developed to examine

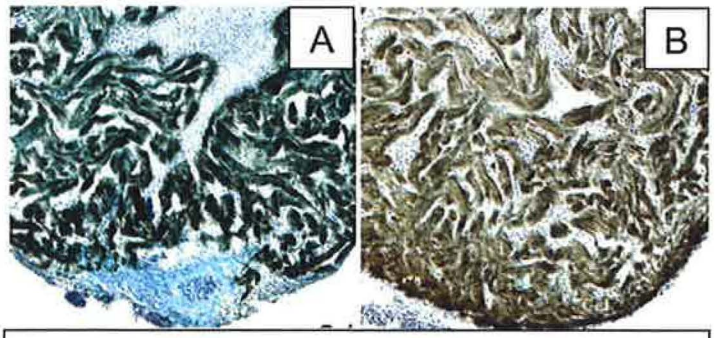

Figure 3. Regeneration of the Zebrafish Heart Following Resection: A) Ventricular apex 9 days following resection demonstrating tissue loss and B) Ventricular apex 60 days after resection demonstrating complete regeneration[1].

the mechanism of cardiac regeneration in zebra fish. In their most recent report, the same group demonstrated that regeneration of the ventricular apex in zebrafish occurs through proliferation and differentiation of an immature population of cardiomyocytes[17].

B) Regeneration of the Mouse Heart:

Recent evidence has unequivocally demonstrated that mammalian heart is capable of limited regeneration following injury. Although this regenerative response appears to be limited to the formation of few new cardiomyocytes, with no measurable functional recovery, these findings still represented a significant advancement to our understanding of cardiomyocyte biology. The strongest evidence of regeneration in the mouse heart to date comes from a report by Hsieh et al in 2007 [6], where they used a fate mapping technique to show that there is significant turnover of cardiomyocytes following cardiac injury. Their finding also demonstrated that these new cardiomyocytes are derived from an unidentified stem or progenitor cell population.

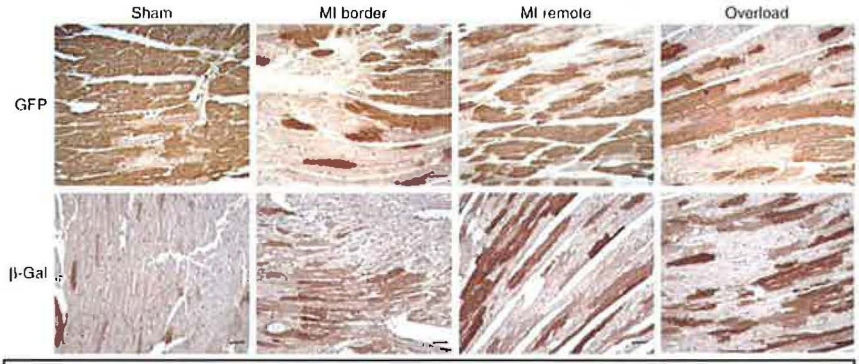

Figure 4. Formation of new cardiomyocytes in the mouse heart following injury: Decreased percentage of old cardiomyocytes (GFP brown staining-in upper row), and increased percentage of newly formed cardiomyocyte (β-Gal brown staining-in lower row). The highest percentage of newly formed cardiomyocytes was in the MI border zone[6].

C) Regeneration of the Human Heart:

Two back-to-back reports in 2002 clearly documented the formation of new cardiomyocytes in the human heart [13, 14]. Using fluorescence in situ hybridization, the authors studied patients who received sex mismatched heart transplants, and identified a small percentage (0.016-0.04%[13]) of newly formed, host derived, cardiomyocytes and vascular cells in the transplanted hearts. These studies not only proved unequivocally that the formation of new cardiomycytes in the human heart is a reality, but also showed that new cardiomyocytes develop as a result of differentiation of an adult stem cell population. These findings, along with coinciding reports of contribution of bone marrow cells to regeneration of the rodent heart[18], served as proof-of-principle for a barrage of cardiac regeneration animal studies, and clinical trials, that are still ongoing to date.

While these studies were ground breaking in that they challenged the "heart is a terminally differentiated organ" dogma, they did not provide a quantitative assessment of the regenerative capacity of the human heart (partly due of their short time course). In 2009, a landmark study by Bergmann et al[12] used carbon dating to quantify turnover in the human heart. They showed that about 50% of all cardiomyocytes that were present

at birth are replaced by newly formed ones in a human lifespan. This study provided hope that perhaps this slow regenerative capacity of the heart can be exploited for cardiac repair. However, it also raised more questions. For example, if the heart can spontaneously turnover half its contractile cells, why is there no evidence of any meaningful recovery following cardiac injury?

3) Cardiac Regeneration Therapy:

Despite years of research, hundreds of completed, and thousands of ongoing clinical trials, cell therapy for myocardial regeneration has yet to demonstrate palpable and consistent recovery of left ventricular function. One of the biggest challenges facing the cardiac regeneration field is choosing the correct stem or progenitor cell type. Due to a seemingly favorable safety profile of a number of cell populations, hundreds of centers around the world rushed to clinical trials where everything from autologous fibroblasts, to off the shelf single-donor mesenchymal cells were tested, with huge variations in outcomes. It is therefore important to closely examine the different types of cells, and the current status of cell therapy trials, to differentiate between the true potential, and the false hope of regenerating the human heart.

Stem Cells:

Stem cells have a hierarchy in terms of their ability to differentiate into other cell types. This ability is termed their differentiation 'potential'. In nature, the stem cell with the greatest ability to differentiate into various different cell types is the zygote, which is termed 'totipotent' as it can give rise to all cell types of the body. An embryonic stem cell, which arises from subsequent division of a zygote, is termed 'pluripotent' as it is capable of differentiating into any cell type from all three germ layers (endoderm, mesoderm, and ectoderm). Adult stem cells are termed 'multipotent' given their ability to differentiate into different tissue types. Finally, a committed progenitor cell is termed 'unipotent' as it is can only differentiate into one cell type.

Types of cells used for myocardial regeneration:

Embryonic stem cells (ESCs):

ESCs that develop as the inner cell mass in the blastocyst are the prototypical stem cell. They fulfill all of the criteria of stemness including clonality, self-renewal, and multipotency. In vitro, human ESCs proliferate and form spontaneously beating embryo-like cell aggregates (called embryoid bodies). The beating embryoid bodies contain a mixed population of newly differentiated cell types including

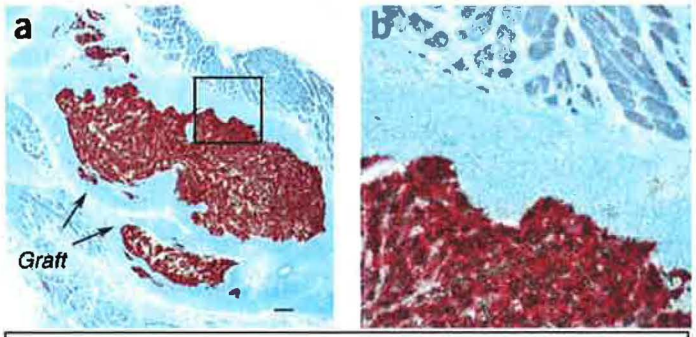

Figure 5. Engraftment of Human ESC derived Cardiomyocytes into Rat Myocardium: A) Combined human pan-centromeric in situ hybridization (brown) and beta-myosin heavy-chain (red) immunostain showing that the implanted ESC derived cardiomyocytes cells formed a large graft within the infarct scar tissue. **B)** High magnification of outlined zone in panel A [3].

cardiomyocytes [19]. ESCs can also differentiate into all cell lines necessary for formation of new blood vessels [20]. Ethical issues aside, no clinical studies using embryonic stem cells for myocardial regeneration have been initiated because of the possibility of immunologic rejection and teratoma formation [21]. Nevertheless, limiting tumorogensis and immunogenicity of ES cells remain active avenues of cardiac regeneration research.

Induced pluripotent Stem Cells (iPS cells)

Takahashi and Yamanaka challenged the entire stem cell field in 2007 when they demonstrated that normal skin fibroblasts can be re-programmed to become ES cells in vitro [22]. These cells showed all characteristics of ES cells including morphology, cell surface markers and gene expression profile. More importantly, these cells displayed the ability to differentiate into all three embryonic germ layers both in vivo and vitro [22]. This seminal work launched a new field aimed at discovering methods of re-programming of differentiated adult cells into ESCs, followed by subsequent induction of differentiation into a desired cell type, or even organ. Since the original report utilized viral genetic integration, subsequent studies demonstrated that similar results can be obtained without stable integration. Moreover, several groups have been able to re-program human skin fibroblasts into iPS cells [13], and derive fully functional cardiomyocytes from these iPS cells [7, 23, 24]. Although there are no clinical trials using iPS cells for myocardial regeneration yet, intense research is currently focused on discovering new methods for safe cellular reprogramming, and for induction of lineage specific differentiation of iPS cells to prevent teratoma formation.

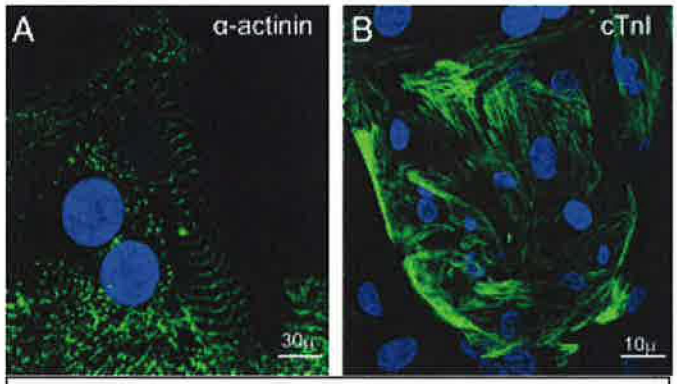

Figure 6. Differentiation of human iPS cells into cardiomyocytes: Immunostaining for sarcomeric α-actinin (A) and cardiac troponin-I (cTnI; (B). Nuclei were counterstained with DAPI (blue). C, Costaining with anti–sarcomeric α-actinin (green) [7].

Adult skeletal myoblasts:

Skeletal myoblasts (satellite cells) are progenitor cells resident within skeletal muscle that can be isolated by skeletal muscle biopsies and expanded in culture, therefore facilitating their use for autologous transplantation, and minimizing the likelihood of rejection. Skeletal myoblasts are relatively ischaemia-resistant as they can withstand several hours of severe ischaemia without becoming irreversibly injured. As a result, they were the first cells to be used for cardiac regeneration[25]. These stem cells home and engraft into the damaged myocardium, preventing progressive ventricular dilatation and improving cardiac function[26, 27]. Myoblasts can be delivered into the myocardium by

either intramural implantation or arterial delivery [28] [29]. Moreover, in animal models of dilated cardiomyopathy the use of skeletal myoblasts restored left ventricular function, demonstrating that the use of skeletal myoblasts can be extended to nonischaemic cardiomyopathy[30]. However, despite clear evidence that engrafted skeletal myoblasts are electrically insulated form the neighboring myocardium [31, 32], clinical trials proceeded to test the regenerative potential of skeletal myoblasts in humans.

Clinical Trials using adult skeletal myoblasts:

Initial case reports and a few small, nonrandomized trials using skeletal myoblasts in patients with ischaemia cardiomyopathy showed safety and efficacy. However, more recent randomized controlled trial failed to show any significant beneficial effects in global or regional LV function (Table 1).

Study	Number of Pts	Study Design	Mode of Delivery	Timing	Number of Cells	F/U in months	Change in EF
Menasche[31]	10	NR	Tep	CABG/3-228 month after MI	8.7+/- 1.9 x 108	52	4% ↑
Smits[33]	5	NR	Ten	24-132 months after MI	1.9+/- 1.1 x 108	6	9% ↑
Chachques[34]	20	NR	Tep	CABG/NA	3.0+/-0.2 x 108	14	24% ↑
Siminiak[35]	10	NR	Tep	CABG/4-108 months after MI	4-5 x 106	12	6.8% ↑
Gavira[36]	12	NR	Tep	CABG/24-132 months after MI	1.9+/- 1.2 x 108	12	20% ↑
Dib[37]	30	NR	Tep	GABG or LVAD/ NA	3 x 108	24	8% ↑
CAuSMIC[38]	23	RCT	Ten	24-132 months after MI	3-60 x 107	12	NS
MAGIC[39]	120	RCT	Tep	CABG/ > 4 weeks after MI	4-8 x 108	6	NS

Table 1. Clinical Trials Using Skeletal Myoblasts for Myocardial Regeneration: The table summarizes the design and major clinical endpoint for studies utilizing skeletal myoblasts for myocardial regeneration. While initial studies showed promising results, later randomized trials failed to show an appreciable benefit of skeletal myoblast therapy. RCT: Ranodmized control trial. NR: Non randomized. Tep: Transepicardial. Ten: Transendocardial

One clinical trial worth discussing is **The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial [39]:** This is the largest clinical trial examining the use of skeletal myoblasts in cardiac regeneration to date. It is a multicenter, randomized, placebo-controlled, double-blind study which included patients with left ventricular (LV) dysfunction (ejection fraction ≤35%), myocardial infarction, and indication for coronary surgery. Out of 300 patients planned, 120 patients enrolled, and 97 actually got CABG and cells. Each patient received either cells grown from a skeletal muscle biopsy or a placebo solution injected in and around the scar. All patients received an implantable cardioverter-defibrillator. The primary efficacy end points were the 6-month changes in global and regional LV function assessed by echocardiography. The safety end points comprised a composite index of major cardiac adverse events and ventricular arrhythmias. Ninety-seven patients received myoblasts (400 or 800 million; n=33 and n=34, respectively) or the placebo (n=30). At 6 months myoblast injection did not

improve regional or global LV function compared to control, however the high-dose cell group demonstrated a significant decrease in LV volumes compared with the placebo group. Moreover, the myoblast group had a higher number of arrhythmic events, without a significant change in the overall 6-month rates of major cardiac adverse events. The conclusion of this study was that myoblast injections combined with coronary surgery in patients with depressed LV function failed to improve echocardiographic heart function. Moreover, the increased number of early postoperative arrhythmic events after myoblast transplantation, supports earlier reports of increased arrhythmogenic potential of skeletal myoblasts, perhaps due to lack of proper electrical coupling.

The disappointing results of the MAGIC trial [39], as well as the lack of unequivocal proof of transdifferentiation of skeletal myoblasts to cardiomyocytes [40], and the inability of myoblasts to electrically couple to resident cardiomyocytes [31], has significantly hampered enthusiasm for their use for myocardial regeneration. However, due to an observed decrease in LV volumes in the MAGIC trial, studies are currently underway to improve the safety of skeletal myoblasts.

Bone-marrow stem cells:

The first animal study by Orlic et al in 2001[18] marked the beginning of hundreds of animal and human studies to test the role of bone marrow cells in cardiac regeneration. In this study, the authors demonstrated that bone marrow derived stem cells can acquire a cardiomyocyte-like phenotype and improve functional recovery following myocardial infarction. Since then, a large number of clinical trials using bone marrow derived cells have been completed, and many more are ongoing. The bone marrow houses a highly heterogenous population of cells that carry out various functions. A small percentage of these cells are true hematopoietic stem cells (0.01% of total BM cells). These hematopoietic stem cells (HSCs) are capable of giving rise to all blood lineages, and in some reports, to any cardiac lineage as well, although this later statement is heavily contested[41-43]. Clinical trials have used primarily 3 types of bone marrow derived cells; namely mononuclear cells (MNC), $CD34^+$ cells (hematopoietic progenitor cells), and mesenchymal stem cells (MSC). MNC are essentially all single nucleated cells in the bone marrow, which are primarily differentiated cells, but contain a small percentage of stem and progenitor cells. $CD34^+$ cells are a hematopoietic progenitor population that express cardiomyocyte and vascular markers, and are mobilized to the heart following injury. MSCs are bone marrow cells, that do not directly contribute to hematopietic lineages, but have a multilineage differentiation capacity[44, 45], in addition to having the advantage of being easily expandable in vitro[45]. Recent reports indicate that MSC can stimulate proliferation and differentiation of resident cardiac stem cells[46].

Bone marrow MNC:
BM derived MNCs are by far the most widely used stem cell in cardiac regeneration clinical trials. They can be easily harvested from patients immediately before coronary angiography, and require very simple cell separation techniques. They have been used

both in the acute MI setting, as well as in chronic cardiomyopathy (CM). Tables 2 and 3 outline major clinical trials using MNCs. Unfortunately, the collective outcome of these trials does not provide a solid conclusion for the utility of MNCs in cardiac regeneration. As is often the case, early, small, non randomized trials showed promise, but later trials showed conflicting results. At this point, it is unclear if MNC confer any benefit either acutely following MI, or in chronic CM.

Study	# of Pts/Ctrl	Study Design	Type/ Mode of Delivery	Timing	Number of Cells	F/U	Endpoint
BOOST[47]	30/30	RCT	MNC/IC	6 days post AMI	2.5×10^9	61m	↑ EF short term. No long-term benefit.
TOPCARE -AMI[48]	59	NR/NC	MNC/IC	3-7 days post AMI	2.4×10^8	4-12m	↑ EF (8%)
REPAIR-AMI[49]	102/102	Placebo Controlled	MNC/IC	4 days post MI	2.4×10^8	4&12m	↑ EF (3-5%) ↓ death/MI/revasc
Janssens et al[50]	33/34	RCT	MNC/IC	1 day post MI	3×10^8	4m	↓ infarct size (28%)
ASTAMI	50/50	RCT	MNC/IC	5-8 days post MI	8.7×10^7	6m	No effect
First-In-Man[51]	20	NR/NC	MNC/TE	10 days post MI	2×10^8	6&12m	↑ EF (7%)

Table 2. Bone Marrow MNC for following in the setting of acute myocardial infarction (AMI): While several studies showed improved LV function and outcomes, others failed to show any benefit. NR: Non-Randomized. NC: Non-Controlled. RTC: Randomized Controlled Trial. IC: Intracoronary. TE: Transendocardial

Study	# of Pts/Ctrl	Study Design	Mode of Delivery	Number of Cells	F/U	Change in EF	Other Endpoints
Perin[52]	14/7	NR	Ten	$3\text{-}4 \times 10^7$	4m	↑ (5%)	↑ Regional WM
IACT[53]	18	NR	IC	9×10^7	3m	↑ (7%)	↑ Viability
TOPCRE-CHD[54]	51/16	RCT	IC	$2\text{-}17 \times 10^7$	3m	↑ (3%)	Improved RWM
TABMMI[55]	10	NR	Ten	3×10^8	12m	↑ (7%)	
Beeres[56]	15	NR	Ten	8.7×10^7	3m	↑ (4%)	Improved RWM
Ang[57]	63	RCT	Ten or IC		6m	No change	No change

Table 3. Bone Marrow MNC in Chronic CM: These trials represent the real hope for treatment of established cardiomyocpathy. Unfortunately, only initial small trials showed promise, while randomized trials showed conflicting results, with no clear improvement. NR: Non-Randomized. NC: Non-Controlled. RTC: Randomized Controlled Trial. IC: Intra-coronary. Ten: Trans-endocardial. RWM: Regional wall motion

Bone marrow $CD34^+$ cells:

Isolation of $CD34^+$ cells requires magnetic sorting following antibody selection, and therefore is more expensive, and labor intensive, compared to other less fractionated cell populations. These progenitor cells showed promise in preclinical studies and in early clinical trials, however the largest randomized clinical trial failed to show any benefit in the post MI setting (Table 4).

Study	# of Pts/Ctrl	Study Design	Type/ Mode of Delivery	Timing	Number of Cells	F/U	Endpoint
REGENT [58]	160/40	RCT	MNC and $CD34^+$ IC	3-12 days post AMI	1.8×10^8 MNC or 1.9×10^6 $CD34^+$	6m	No effect
Pasquest el at[59]	7	NR/NC	$CD34^+$ IC	Post MI		49m	↑ EF and improved HF class
Losordo et al[60]	24 Phase 1	RCT	$CD34^+$ IM	Chronic angina	$5x10^4$,$1x10^5$,$5x10^5$	4&12 m	↓ angina
Manginas et al[61]	24 Phase 1	NR/NC	$CD34^+$ or $CD133^+$ IC	1 day post MI	3×10^8	28	↑ EF and improved perfusion
ABCD	24/20	NR	IC	Chronic CM	1.6×10^6	12	↑ EF (5%)

Table 4. Bone marrow $CD34^+$ cells for myocardial regeneration: The vast majority of these trials are small and non randomized. REGENT,the largest trial to date, failed to show any benefit following myocardial infarction. RCT: Randomized controlled trial. NR: Non-Randomized. NC: Non-Controlled. RTC: Randomized Controlled Trial. IC: Intra-coronary.

G-CSF Mobilization:

Another approach that was used to induce cardiac regeneration is stem cell mobilization using granulocyte-colony stimulating factor (G-CSF). Enthusiasm for this approach has been blunted after published 7 trials showed markedly conflicting results[62-64], and even a tendency towards myocardial damage in some cases[65].

Bone marrow derived MSCs:

Only a few clinical trials examined the use of MSC in cardiac regeneration. The initial study by Chen et al[66] was a small randomized controlled trial (69 patients) where patients were randomized to either autologous MSC, or placebo. At 6 months followup, there was a significant increase in LVEF (14%), with increased viability. In a recent phase I study, Hare et al[67] randomized 53 patients to allogeneic intravenous injection of MSCs or placebo. After 6 months, the MSC group had improved LVEF, and improved HF symptoms.

It is perhaps surprising, given the barrage of clinical trials that's used BMCs for cardiac regeneration, that one of the most controversial issues to date is whether BMCs actually differentiate into functional cardiomyocytes[43]. While expression of cardiac markers by various bone marrow populations has been clearly demonstrated, the functional significance of this phenomenon is unclear. Several alternative theories have been proposed both for the expression of cardiac markers by bone marrow cells[68], and for their seemingly modest beneficial effect[46, 69]. Nevertheless, there are numerous ongoing clinical trials using each of the cell types discussed above.

Discussion:

Recent landmark studies have established that cardiomyocyte turnover in the adult human heart is a reality, and that stem cell populations may contribute to this endogenous reparative mechanism. However, numerous clinical trials, using a variety of cell types, have failed to demonstrate significant, and consistent recovery of left ventricular function. There are several important questions that need to be answered before a firm conclusion can be drawn. For example, it is still unclear which cell type can actually contribute to cardiac regeneration, and how. Similarly, it is not even clear if the cells remain within the myocardium following delivery.

Another crucial and obvious issue is the dose of cells used for therapy. Systolic heart failure generally ensues after loss of at least 25% of the 4 billion cardiomyoctes in the human heart. This means that complete regeneration of the human heart requires delivery of cells that will produce at least 1 billion functional cardiomyocytes[42]. Therefore, it should not come as a surprise that using heterogenous populations of mostly differentiated cells, at concentrations that are orders of magnitude lower than what is needed to regenerate the heart, does not result functional recovery.

In conclusion, it is important to draw a distinction between the endogenous regenerative capacity of the heart, which was only recently established, and the prospect of cell therapy as a treatment for systolic dysfunction. The excitement created by the realization that the heart is not a terminally differentiated organ, has undoubtedly created a gold rush approach to cardiac regeneration therapy, not surprisingly with mostly discouraging results. It remains to be seen whether the endogenous regenerative capacity of the heart can be exploited to realize the hope of cardiac regeneration.

Cardiac regeneration research at UTSouthwestern:

Identifying new stem cell populations:
We recently outlined the metabolic footprint of hematopoietic[70] and resident cardiac stem cells. We demonstrated that these cells are characterized by low levels of oxygen consumption, and preferential utilization of glycolytic metabolism. Moreover, we showed that separation of cells solely based on their metabolic footprint enriches for both hematopoietic, and resident cardiac stem cells. These metabolic profiling techniques allowed us to identify a novel type of resident cardiac stem cells, that we named glycolytic cardiac stem cells (GCSCs). These cells are clonagenic, self renewing, and are capable of differentiating into all cardiac lineages. Current studies are underway to identify unique surface markers of GCSCs, and to characterize their regenerative capacity.

NIH NHLBI Progenitor Cell Biology Consortium:
UTSouthwestern-Harvard Stem Cell Institute-MGH Hub (Olson/Schneider/Scadden/Kim co-PIs).

American Heart Association/John Holden DeHaan Foundation:
UTSouthwestern Myogenic Research Cetnter (Olson/Hill/Schneider co-PIs)

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