Current therapies targeting pathological ventricular remodeling manifest significant effectiveness in reducing morbidity and mortality in patients with systolic heart failure (HF). However, in many instances, disease progression continues unabated. Whereas novel disease targets are continually being discovered, most innovative therapies do not demonstrate consistent efficacy in patients; indeed, many prove to be ineffective, even deleterious, before reaching phase III clinical trials. Here, we review therapeutic strategies targeting cellular pathways governing left ventricular remodeling in the 2 major types of HF: HF with reduced systolic function (HFrEF) and HF with preserved systolic function (HFrEF). In an accompanying article, we highlight recent advances in our understanding of mechanisms underlying pathological ventricular remodeling.

Advances in this field are conditioned by the highly heterogeneous nature of HF. Notably, within the 2 broad categories of HFrEF and HFrEF, a wide variety of disease types dictate pathogenesis. In other words, HF, a syndrome defined on clinical terms, derives from numerous different diseases such as myocardial infarction, hypertension, cytokine or neuroendocrine dyscrasias, genetic disorders, and more. It seems likely that the therapies that have emerged with efficacy are those targeting features that are shared among these disorders. As a corollary, it is conceivable that some of the therapies that have failed in clinical trials target relevant elements of pathogenesis that are not common to all. As personalized medicine emerges in the discipline of HF, we envision therapies tailored to the specifics of molecular and cellular pathogenesis.

Antiremodeling Therapies

Pharmaceutical Agents

Over the last 3 decades, numerous randomized, clinical trials have demonstrated substantial efficacy of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and β-adrenergic blockers in reducing morbidity and mortality in patients with systolic HF. Currently, American College of Cardiology/American Heart Association guidelines for the diagnosis and treatment of HF in adults emphasize the use of these agents in patients with HFrEF (Figure).

Inhibitors of the Renin-Angiotensin-Aldosterone Axis

Originally, ACE inhibitors and ARBs were used to treat hypertension. However, it was subsequently found that these agents afforded substantial benefit in animal models of HF, including increased survival, by targeting adverse cardiac remodeling. Angiotensin receptor activation can induce cardiac remodeling independently of changes in blood pressure, and both ACE inhibitors and ARBs act to antagonize the effects of angiotensin II (Ang II), albeit at different points in the cascade. Numerous clinical trials have demonstrated that ACE inhibitors and ARBs reduce HF morbidity and mortality. More recently, antihypertensive agents targeting renin enzymatic activity, the rate-limiting step in Ang II production, have become available and are being studied for effects on adverse cardiac remodeling. For example, the renin inhibitor aliskiren blunts remodeling in experimentally infarcted mouse hearts and has been tested for efficacy in the Aliskiren Observation of Heart Failure Treatment (ALOFT) and the Assessment of Services Promoting Independence and Recovery in Elders (ASPITE) trials, but with disparate results in efficacy (favorable and unfavorable, respectively). Additional planned trials such as the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT; aliskiren versus placebo in addition to an ACE inhibitor or ARB) and Aliskiren Trial of Minimizing Outcomes for Patients With Heart Failure (ATMOSPHERE; aliskiren versus enalapril or combination) will evaluate the end points of death and rehospitalization resulting from HF.

Low-dose MRAs are recommended for treatment in select patients with moderately severe or severe HF symptoms (New York Heart Association class III–IV), recent decompensation, or left ventricular (LV) dysfunction early after myocardial infarction. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) revealed that eplerenone reduces mortality and hospitalization in patients with systolic dysfunction and mild symptoms, expanding the role of MRAs to include asymptomatic patients.

Aldosterone is a mineralocorticoid secreted by the adrenal gland in response to Ang II or cytokines; it can also signal directly within the myocardium via resident mineralocorticoid receptors and the requisite 11 β-hydroxysteroid...
dehydrogenase activity. Increases in cardiac aldosterone have been reported in experimental models of myocardial infarction, correlating with LV remodeling. The effects of aldosterone are similar to those observed with Ang II, including inhibition of nitric oxide synthase and promotion of inflammation, fibrosis, and cardiac myocyte apoptosis. However, the use of spironolactone is limited because of the metabolic and endocrine side effects and variations in patient response, which are largely absent with eplerenone. In addition, patients with chronic HF have increased aldosterone synthase activity, leading to non–mineralocorticoid receptor–mediated deleterious effects on cardiomyocytes. Blockade of mineralocorticoid receptors increases aldosterone synthase activity. Consequently, MRA therapy results in high levels of aldosterone. Aldosterone may also have non–mineralocorticoid receptor–mediated deleterious effects on cardiomyocytes.

The aldosterone synthase inhibitor FAD286 reduced LV remodeling in a rat model of HF, and another, LCI699, demonstrated safety and tolerability in 14 patients with primary aldosteronism. Future studies will determine whether aldosterone synthase inhibitors are more effective than MRAs in treating HF.

A new class of therapeutics that target the renin-angiotensin-aldosterone axis comprises dual-acting agents for angiotensin receptor–neprilysin inhibition. Neprilysin activates the kinin and natriuretic peptide systems. One such inhibitor, LCZ696, combines a moiety of valsartan with an endopeptidase inhibitor. An initial safety study of this inhibitor has led to the ongoing Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial (NCT01035255) to compare LCZ696 with enalapril.

Selective ARBs are also currently in development. Ang II can act through 2 different receptors: Ang II receptor type 1 and type 2. Whereas the Ang II receptor type 1 is ubiquitously expressed in the cardiovascular system, the expression of Ang II receptor type 2 is low in the normal adult but elevated in the patient with HF. In many contexts, activation of Ang II receptor types 1 and 2 produces opposite effects, with the Ang II receptor type 2 promoting vasodilation and blunting of cardiac hypertrophy. A first-in-class Ang II receptor type 2 agonist, compound 21, has shown promising early results by decreasing infarct size in a rodent model.

β-Adrenergic Receptor Blockers

Inhibition of β-adrenergic signaling has long been used to treat hypertension and cardiac arrhythmias and more recently to treat patients with mild to severe HF. β-Blockers have been shown, both experimentally and clinically, to reduce adverse cardiac remodeling and to improve HF mortality. Specifically, cardiac myocytes express the β1-adrenergic receptor subtype and thus manifest responses to β1-selective inhibitors. However, the mechanisms underlying the full benefit of β-adrenergic receptor blockade in reducing LV remodeling remain elusive because fibroblasts express predominantly the β2-adrenergic receptor subtype.

Agonist-promoted β-receptor desensitization occurs via G-protein receptor kinases, which tag these receptors for cellular internalization and degradation. Specific to the heart, G-protein receptor kinase-2 (also known as β-ARK) has been engineered as a catalytically inactive fragment, β-ARKct, which interferes with G-protein receptor kinase-2 binding to the β-adrenergic receptor and subsequent receptor degradation, thus serving to block β-adrenergic uncoupling and desensitization. Experimentally, β-ARKct gene therapy in infarcted rabbit or rat hearts improved function and blunted HF. Although this gene therapy has not been tested in humans to date, it holds potential for diminishing β-receptor desensitization, thereby augmenting the efficacy of β-blockers in HF patients.
The role of β-blockers in the treatment of HF in patients with HFpEF remains unclear. For example, 6-month treatment with the β-blocker nebivolol did not improve 6-minute walk test performance in the Effect of Long-term Administration of Nebivolol on Clinical Symptoms, Exercise Capacity and LV Function in Patients With Diastolic Dysfunction (ELANND) trial. Some evidence suggests, however, that its negative chronotropic effects may have contributed to this result. There is a large ongoing trial evaluating a β-blocker in heart failure with normal left ventricular ejection fraction (β-PRESERVE) to test the efficacy of metoprolol succinate on mortality and hospitalization rates.

Of note, pharmacogenetic studies of both ACE inhibitor and β-blocker therapies have uncovered specific gene mutations that affect therapeutic efficacy. For example, a deletion variant in the gene coding for ACE is associated with greater survival benefit from ACE inhibitors and β-blockers. Ser49 (versus Gly49) in the β2 adrenergic receptor, a specific insertion in the α1C adrenergic receptor, and Gln41 (versus Leu41) in G-protein coupled receptor kinase 5 are associated with relatively greater survival benefit from β-blocker therapy.

Positive Inotropes

Positive inotropic agents play a critical role in controlling symptoms in decompensated or end-stage HF patients. However, long-term administration of these agents increases mortality, and long-term use of digoxin has no beneficial effect on mortality. Two new nonglycoside inotropic agents have entered the therapeutic arena recently. One is therapy to deliver the cDNA of the sarcoplasmic reticulum Ca2+ pump via an adeno-associated virus in an effort to replenish the downregulated sarcoplasmic reticulum Ca2+ levels, typical of failing myocardium. The second is a luso-inotropic compound, istaroxime, that inhibits Na+/K+ -ATPase, leading to accumulation of intracellular Na+, decreased activity of the Na+-Ca2+ exchanger to remove cytosolic Ca2+, and consequent activation of sarcomeric contraction (the same mechanism as digitalis glycosides). The Calcium Up-regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) study demonstrated safety and suggested benefit of adeno-associated virus type 1–delivered sarcoplasmic reticulum Ca2+-ATPase in advanced HF, prompting larger confirmatory trials. Istaroxime manifests a dual mode of action, combining inotropic (stimulation of myocardial contractility during systole) and lusitropic (improvement of diastolic relaxation) effects. A phase II trial to assess the hemodynamic effects of istaroxime in 120 HF patients (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: A Randomized Controlled Trial in Patients Hospitalized With Heart Failure [HORIZON-HF]) revealed lowered capillary wedge pressure and decreased heart rate.

Another novel and potentially exciting class of agents, cardiac myosin activators, includes omecamtiv mecarbil (CK-1827452). This compound binds the myosin catalytic domain, increasing the transition rate of myosin binding to actin into a more tightly bound state, thereby increasing force while simultaneously inhibiting ATP turnover, together leading to more myosin head–generating force per beat. This novel mechanism increases systolic ejection time, resulting in improved systolic function without increased myocardial oxygen demand and thus significant increases in cardiac efficiency. Preliminary evidence suggests that omecamtiv mecarbil is safe in patients with ischemic cardiomyopathy and angina, increasing stroke volume and fractional shortening and decreasing ventricular volumes.

Other Promising Therapeutic Agents

Lipid-Lowering Drugs

Inhibitors of HMG-CoA reductase are well established at lowering cholesterol, providing robust protection to patients with a variety of forms of ischemic heart disease. Beneficial anti-remodeling effects of these statins may occur in addition to those observed with traditional therapy (ACE inhibitors and β-blockers). However, in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial, rosuvastatin did not reduce the primary end point or the number of all-cause deaths in older patients with systolic HF, although it did reduce cardiovascular hospitalizations. In addition, in Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure (GISSI-HF), rosuvastatin 10 mg daily did not alter clinical outcomes in patients with chronic HF of any cause.

Vasopressin and Endothelin-1 Receptor Antagonists

Beyond the 2 major neurohormonal cascades, the sympathetic and renin-angiotensin-aldosterone axes, cascades elicited by endothelin and vasopressin are also activated during the pathogenesis of HF. Stimulation of the vasopressin V1A receptor increases intracellular Ca2+ levels and promotes myocyte hypertrophy and remodeling. Stimulation of V2 receptors increases the expression and membrane incorporation of aquaporin-2 water channels into the collecting duct cells in the kidney, resulting in free water absorption. Vasopressin receptor antagonists such as conivaptan, lixivaptan, mozavaptan, and tolvaptan block V1A and V2 receptors. In patients hospitalized with HF in the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan (EVEREST), the addition of oral tolvaptan to standard therapy improved many, but not all, HF signs and symptoms without serious adverse events. However, tolvaptan initiated for the acute treatment of patients hospitalized with HF had no effect on long-term mortality or HF-related morbidity.

Endothelins, including endothelin-1, increase contractility and stimulate growth and myofibrillogenesis in cardiomyocytes, thereby promoting cardiac hypertrophy. Endothelin-1 binds to the endothelin-A receptor to elicit a wide range of responses, including increased expression of nuclear transcription factors and activation of protein kinases and ion channels responsible for cardiomyocyte contractility and growth. Disappointingly, multiple trials testing a variety of endothelin antagonists have yielded negative results, including the Enrasentan Clinical Outcomes Randomised (ENCOR), Efficacy and Safety of Irbesartan and Olmesartan in Patients With Hypertension (EARTH), and Randomised Intravenous Tezosentan 4 (RITZ-4) trials.
Anticytokine Agents
Proinflammatory cytokines promote hypertrophy, apoptosis, and extracellular matrix remodeling, thereby contributing to HF pathogenesis.59 Elevated levels of proinflammatory cytokines are also associated with poor clinical outcomes.50 However, clinical trials studying the tumor necrosis factor-α inhibitors etanercept and infliximab reported neutral or negative effects on all-cause mortality or hospitalization for HF.51 Some evidence suggests that suppression of inflammatory responses globally, as opposed to inhibition of a specific pathway, might hold promise.52 In addition, some inflammatory responses arise secondary to other cellular events, and inhibition of the inciting signaling pathways might prove more fruitful.52

Glucagon-Like Peptide-1
Metabolic derangements are significant elements of HF pathogenesis. Indeed, insulin resistance and lipotoxicity are recognized as hallmarks of dilated cardiomyopathy53 and diabetic cardiomyopathy.54,55 Glucagon-like peptide-1 stimulates myocardial glucose uptake in dilated cardiomyopathy through p38 mitogen-activated protein kinase,56 and long-term exposure to glucagon-like peptide-1 in a rat model of HF sustained LV systolic function and prolonged survival.57 These exciting preclinical findings have led to an ongoing clinical trial, the Functional Impact of Glucagon-like Peptide-1 for Heart Failure Treatment (FIGHT) trial (http://clinicaltrials.gov/ct2/show/NCT01800968).

Novel Vasodilators
Disorders in cGMP-dependent mechanisms contribute to myocardial dysfunction and remodeling. Specific phosphodiesterases govern the amplitude, duration, and compartmentalization of cyclic nucleotide signaling. An inhibitor of phosphodiesterase-5A, sildenafil, improved hemodynamics, LV diastolic function, and right ventricular systolic function in a small, single-center trial in HFpEF.58 These encouraging findings prompted the multicenter clinical trial Phosphodiesterase-5 Inhibition to Improve Quality of Life and Exercise Capacity in Diastolic Heart Failure (RELAX). The primary end point was change in peak oxygen consumption after 24 weeks of therapy; secondary end points included change in 6-minute walk distance and a hierarchical composite clinical status score.59 Unfortunately, sildenafil therapy did not result in a significant improvement in exercise capacity or clinical status.59 Another clinical trial, Phosphodiesterase Type 5 Inhibition With Tadalafil Changes Outcomes in Heart Failure (PITCH-HF), is underway in patients with HFrEF (http://neriresearch.net/overview.html).

Nitric oxide production by endothelial nitric oxide synthase limits cardiac hypertrophy, apoptosis, and fibrosis, thereby affecting adverse cardiac remodeling.60 In light of this, a novel approach to target and increase endothelial nitric oxide synthase activity has been developed. Preclinical studies of AVE9488, an oral agent targeting endothelial nitric oxide synthase, suggested an improvement in LV remodeling, including decreased hypertrophy, fibrosis, ventricular dilation, and enhanced contractility, but without effects on LV mass.61

Special Considerations in HFpEF
HFpEF is a clinical manifestation of many different pathophysilogies.5 These range from LV stiffness to impaired diastolic or systolic function to metabolic dyscrasias.5 In light of multiple failed clinical trials, efforts have focused on identifying biomarkers, risk factors, specific syndrome features, and appropriate study end points to parse these patients into defined subgroups and to test therapeutic efficacy.

The most widely used HFpEF biomarkers are brain natriuretic peptide (BNP) and N-terminal pro-BNP. Outcomes in RELAX were worse relative to prior HFpEF trials when the more sensitive N-terminal pro-BNP assay was required for diagnosis,59 possibly because this may indicate that the patient’s shortness of breath is more likely attributed to HF.62 Other circulating biomarkers have been used to diagnose HFpEF, including procollagen, inflammatory factors (interleukin-6 and –8 and tumor necrosis factor-α), matrix metalloproteinase, triiodothyronine, heart-type fatty acid binding proteins, troponin T, and carbohydrate antigen-125.5 However, these biomarkers remain to be validated in large cohorts.

Compared with HFrEF, HFpEF patients are classically more likely to be older, hypertensive women.63 A retrospective study of new-onset HF in Framingham participants between 1981 and 2008 showed that ≈50% were classified as HFpEF. Older age, diabetes mellitus, and a history of valvular disease predicted both HFrEF and HFpEF.64 Higher body mass index, smoking, and atrial fibrillation predicted HFpEF only, whereas male sex, higher total cholesterol, higher heart rate, hypertension, cardiovascular disease, LV hypertrophy, and left bundle-branch block were predictive of HFrEF.65

To date, no therapeutic agents have been shown to reduce mortality and morbidity in HFpEF; negative trials include Digitalis Investigation Group–Preserved EF (DIG-PEF), Canesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Preserve (CHARM-Preserve), Irbesartan in Heart Failure With Preserved EF (I-PRESERVE), and RELAX.5 Substantial heterogeneity within this patient population is likely a significant contributor to these negative results. In addition, morbidity and mortality may not be optimal end points, given the age of these subjects and the presence of multiple comorbidities.5

Therapies Targeting Electrophysiological Remodeling

Medical Treatment
Agents that alter HF progression also affect disease-associated electrophysiological remodeling and may alter the risk of sudden cardiac death. For example, β-blockers reduce sudden death in both postinfarction patients and patients with HF regardless of origin.6 Aldosterone antagonists decrease sudden death and overall mortality in HF early after MI and in advanced HF;5 ACE inhibitors and ARBs decrease the risk of developing atrial fibrillation in HF patients.64

Device-Based Therapies
HF patients have elevated risk of life-threatening ventricular arrhythmia.6 Several clinical trials, including Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation
(DEFINITE), Multicenter Automatic Defibrillator Implantation Trial (MADIT) II, and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). demonstrated that implantable cardioverter-defibrillators reduced sudden cardiac death and overall mortality in HF patients. Accordingly, implantable cardioverter-defibrillators are a Class I recommendation in patients with LV ejection fraction (EF) <35%.

Intracardiac conduction delay in HF perturbs the coordinated mechanical contraction of the ventricle and worsens systolic performance. Therapy based on biventricular pacing ameliorates the resulting contractile dyssynchrony. Several clinical trials, including the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD), Cardiac Resynchronization in Heart Failure (CARE-HF), and Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) have demonstrated that cardiac resynchronization therapy can improve symptoms and reduce mortality. The improved outcomes derive largely from improvements in LV remodeling as assessed by enhanced systolic and diastolic function. In animal studies, cardiac resynchronization therapy can restore intracellular Ca²⁺ homeostasis, renormalize the ratio of β, adrenergic receptors, and alter the expression of genes involved in mitochondrial energetics, extracellular matrix remodeling, and myocardial stress responses.

Analysis of all studies assessing outcomes using cardiac resynchronization therapy reveals poor agreement between echocardiographic and clinical outcomes. For example, whereas MIRACLE reported beneficial effects of cardiac resynchronization therapy based on clinical indexes such as New York Heart Association symptom class and 6-minute walk test, reductions in LV volumes were found to be dependent on disease type, with greater reductions noted in nonischemic patients versus ischemic patients. On the contrary, reductions in mortality and improvements in cardiac function in CARE-HF were similar in nonischemic and ischemic patients. In an attempt to optimize patient selection, a multicenter trial (Predictors of Response to CRT [PROSPECT]) enrolling 498 patients was conducted, but no specific parameter emerged that conclusively improved patient selection criteria.

Mechanical Support Devices
Substantial evidence supports the notion that antagonism of neurohormonal stimulation improves survival in HF; nevertheless, HF progresses in the majority of patients. In response, a variety of mechanical devices, including physical restraints, have been developed to reshape the ventricle and to reverse pathological cardiac remodeling. These devices vary in terms of their design, material composition, ability to redistribute strain across the ventricle, and technique of implantation. Overall, a critical feature is the ability to decrease ventricular wall stress, ultimately counteracting the pathological remodeling process.

Ventricular Assist Devices
In the setting of end-stage HF, cardiac transplantation is one of the options for patients resistant to medical therapy. However, as a result of an enduring shortage of donors, LV assist device therapies have emerged as an important therapeutic option, both as a bridge to transplantation and more recently as destination therapy. Initially, pulsatile volume-displacement pumps were engineered, providing critical circulatory support to improve survival until transplantation becomes an option. Each of the first-generation ventricular assist devices proved capable of improving survival, end-organ dysfunction, and quality of life; that said, they are not without drawbacks. Adverse events such as bleeding, infection, thrombosis, and mechanical failure limit their utility to <1 year, and in the long term, they do not replace cardiac transplantation. The Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial revealed a 35% 2-year failure rate for the HeartMate XVE device with mortality in excess of 10%. These shortcomings, coupled with chronically inadequate availability of organ donations and excessive waiting times, have prompted attempts to develop new, more reliable, smaller devices, including those with nonpulsatile dynamics.

The HeartMate 2 (Thoratec Inc) is the most successfully used nonpulsatile device to date with >6000 implants worldwide. It is compact with fewer moving parts compared with first-generation devices. Other second- and third-generation ventricular assist devices (the centrifugal pumps) lack bearings and are driven by a magnetically levitated impeller. Patients implanted with these second-generation devices have a 65% to 69% first-year survival rate with rare mechanical failure and few fatal events. However, infection remains an important problem, even though it rarely leads to increased mortality.

Myocardial Regeneration
A major mechanism of pathological cardiac remodeling involves myocyte death. Given that cardiac myocytes have only limited capacity for regeneration, there is great interest in developing progenitor cells—resident to the myocardium or otherwise—to enhance the regenerative capacity of the injured heart. Embryonic stem (ES) cells hold great promise because they are by definition capable of differentiating into any cell type in the body. However, there are several disadvantages of using this cell type, including the possibility that they would differentiate into unwanted cell phenotypes to form teratomas. Their manipulation typically involves growth on a layer of feeder cells containing animal products, necessitating immunosuppressive therapy and predisposing to rejection. In some circles, the use of ES cells has ignited ethical concerns that have led to legal restrictions. Although there are no current clinical trials underway using ES cells to treat heart disease, a first phase I application to treat spinal cord injury with human ES cells was approved by the US Food and Drug Administration in January 2009.

One of the earliest cell types to be considered for cardiac regenerative therapy was skeletal myoblasts. These so-called satellite cells were attractive candidates because they could be harvested from the host, expanded in vitro, followed by autologous transplantation into the heart. Furthermore, these cells are relatively resistant to ischemia. However, the Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial demonstrated no significant benefit from the
use of these cells.\textsuperscript{80} Worse, patients receiving the skeletal myoblasts were at a significantly increased risk of malignant ventricular arrhythmias.\textsuperscript{80}

It has been demonstrated that the cardiac stem cell pool diminishes with aging.\textsuperscript{81,82} In addition, several populations of cardiac stem cells have been described; however, it is still not clear whether these cells are truly endogenous to the heart or derive from bone marrow or circulating cellular elements. Furthermore, cell surface markers used to define stem cell populations are subject to molecular regulation and may be increased or decreased, depending on context. Therefore, rather than the existence of numerous different cardiac stem cell populations/infiltrating cells, it is possible that these cells derive from 1 population and represent a continuum of cellular phenotypes.

Stem cells being considered for myocardial regeneration derive from bone marrow, circulating pools of progenitor cells, and tissue-resident stem cells derived from adipose tissue, skeletal muscle, umbilical cord blood, myocardium, and epicardium. To date, the majority of the clinical trials using stem/progenitor cells to treat patients after an ischemic event have used adult stem cells derived from bone marrow. Recent meta-analyses of the completed clinical trials using bone marrow--derived stem cells to treat ischemic heart disease suggested that the transplantation of these cells is safe and affords benefits beyond those achieved using standard therapy.\textsuperscript{83-85} These studies went on to document decreases in infarct size, improvements in EF, and decreased LV end-systolic volumes, suggesting improvement in overall global function. However, not all clinical trials using autologous stem cells have demonstrated efficacy because most patients receiving autologous adult stem cells are at an advanced age and are more likely to suffer from comorbidities such as hypertension, diabetes mellitus, and ischemic disease, which lead to decreased stem cell viability and function.\textsuperscript{86-89} In addition, whether the transplanted cells actually replace dead or dying cardiac myocytes is hotly debated. In fact, a number of other mechanisms have been proposed to underlie the benefit, including elicitation of paracrine factors that mediate endogenous repair, angiogenesis, or differentiation of native progenitors. Whether these stem cells actually differentiate into cardiac myocytes remains controversial. Furthermore, low rates of engraftment decrease the likelihood that a sufficient number of dead myocytes can be replaced, which can approach 1 billion cells lost during a myocardial infarction. Therefore, strategies to reprogram cells native to the heart may hold significant promise.

Three recent phase I clinical trials using autologous cardiac stem cells yielded promising results in terms of myocardial repair. The Bolli and Anversa groups conducted a phase 1 trial called Stem Cell Infusion in Patients With Ischemic Cardiomyopathy (SCIPiO) of autologous cardiac stem cells (c-kit positive and lineage negative) for the treatment of HF resulting from ischemic heart disease. In 14 patients receiving cell therapy, LVEF increased from 30.3% to 38.5% at 4 months after infusion. Importantly, the beneficial effects of stem cell therapy were even more pronounced at 1 year in 8 patients whose LVEF increased by 12.3%. Magnetic resonance imaging measurements of infarct size demonstrated 24% and 30% decreases at 4 and 12 months, respectively.\textsuperscript{90}

The recently reported Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS) trial tested the effects of autologous stem cells cultured as cardiospheres as a mechanism of myocardial regeneration. These investigators reported significant reductions in scar, increases in viable heart mass, and improvements in regional contractility and regional systolic wall thickening based on magnetic resonance imaging at 6 months. However, changes in end-diastolic volume, end-systolic volume, and LVEF did not differ between groups.\textsuperscript{91}

The Pilot Study of the Comparative Safety and Efficacy of Transendocardial Injection of Autologous Mesenchymal Stem Cells Versus Allogeneic Mesenchymal Stem Cells in Patients With Chronic Ischemic Left Ventricular Dysfunction Secondary to Myocardial Infarction (POSEIDON) compared autologous and allogeneic mesenchymal stem cells (MSCs) in ischemic cardiomyopathy.\textsuperscript{92} Injection of either autologous or allogeneic stem cells was associated with a low occurrence of major adverse effects, and allogeneic MSCs did not stimulate significant donor-specific immune reactions. Relative to baseline, autologous, but not allogeneic, MSC therapy was associated with an improvement in the 6-minute walk test and the Minnesota Living With Heart Failure Questionnaire score; however, neither approach improved exercise VO\textsubscript{2}\text{max}. Allogeneic and autologous MSCs reduced mean infarct size and sphericity index but did not increase EF. Overall, allogeneic MSCs reduced LV end-diastolic volumes. Interestingly, in a subgroup analysis, low-dose MSCs (20 million cells) produced the greatest reductions in LV volumes and increased EF.\textsuperscript{92}

### Cellular Reprogramming

As a result of technical and ethical issues surrounding the use of human ES cells for regenerative medicine, scientists have explored alternative strategies to generate cells with the capability of differentiating into cardiomyocytes. Scientists have successfully reprogrammed adult fibroblasts to dedifferentiate into a ES cell–like state.\textsuperscript{93,94} These cells, called induced pluripotent stem (iPS) cells, are viewed as a major scientific breakthrough in the field of regenerative medicine. These cells offer the advantage of being taken directly from the patient and reprogrammed into a dedifferentiated state with subsequent manipulation into the desired cell type. These cells overcome obstacles associated with human ES cells in that they may escape immune rejection, and there are no ethical concerns associated with the use of human embryos. However, the study of iPS cells is currently in its infancy, and several barriers must be overcome before the cells can be used to regenerate the human heart. For example, iPS cells appear to be less efficient than ES cells in their capacity to differentiate into all cell types, and it is not known for each iPS cell clone whether reprogramming is complete. Even if a small number of cells are incompletely reprogrammed within the recipient tissue, the risk of teratoma formation remains present. Furthermore, to date, most iPS cells have been generated with viruses carrying transgenes, which are integrated into the host genome; reactivation could lead to tumorigenesis. However, this concern may be overcome by the engineering of tiny nonviral DNA vectors (rings of DNA about half the size of those usually used to reprogram cells).\textsuperscript{95} Other challenges...
include disease-related mutations and polymorphisms harbored within iPSC cells derived from diseased patients and the fact that many diseases are attributable to >1 cell type.

Adult stem cells typically maintain epigenetic memory of their tissue or origin. Thus, full cardiac myocyte differentiation may be insufficient without nuclear reprogramming. This is one reason why manipulation of cells from within the heart offers significant advantages, potentially eliminating the need for exogenous stem cell transplantation. Recently, it was demonstrated that cardiac fibroblasts could be reprogrammed into functional cardiac myocytes,96–98 raising the possibility that fibroblasts within the heart might be redirected from contributing to scar formation to muscle regeneration.

Potentially important work is presently underway to discover means of reprogramming the heart using small-molecule therapies.99,100 By activating resident progenitor cells, coaxing myocytes to reenter the cell cycle, or transforming other cell types into a myocyte lineage, these strategies hold promise as novel ways to rebuild injured myocardium.

Tailored HF Therapies

Despite the widely recognized fact that the syndrome of HF derives from a broad range of disease origins with vastly different molecular mechanisms of pathogenesis, current treatment strategies are largely uniform. Several hurdles must be overcome before type-specific therapy can be applied to defined patient subgroups. First, it is difficult to parse etiologic subgroups based on clinical presentation. Biomarkers may prove useful, as is emerging with NT-pro-BNP, procollagen, and inflammatory factors in HFP EF patients.5,39 In 2011, the United Kingdom–based National Institute for Health and Clinical Excellence issued clinical practice guidelines in HF based on serum NT-pro-BNP levels, echocardiography, and specialist assessment.101 Second, innovative approaches may overcome deficiencies in conventional clinical trial design and deficient subgroup analysis. For example, bayesian adaptive trial design uses information existing at the time of trial initiation, combined with data accumulated during the trial, to identify treatments most beneficial for specific patient subgroups.102 Another approach uses multivariate prediction tools for risk stratification.103 In the end, these approaches may prove superior to conventional 1-variable-at-a-time subgroup analysis to minimize false positives and false negatives.104

The ultimate goal of targeted HF therapy is individualized treatment based on each patient’s clinical and genetic signatures. This, however, requires knowledge of each patient’s genetic composition and a meaningful interpretation of genetic variations in disease and their interactions with therapies. For example, sexual dimorphism has been reported in the transcriptional responses to HF. In women, genes involved in cyclic nucleotide metabolism, glucose transport, and neurohumoral pathways are upregulated, whereas in men, genes involved in arrhythmia, self-immunity, and cellular homeostasis are altered.105 In addition, pharmacogenetic studies have uncovered genetic variants contributing to variable responses to ACE inhibitor and β-blocker therapies.32 Ultimately, therapeutic modalities, duration of treatment, and medication doses will need to be customized for each patient.

Conclusions and Perspectives

In recent years, significant strides have been made in our understanding and therapeutic targeting of pathological ventricular remodeling. ACE inhibitors, ARBs, aldosterone antagonists, MRAs, and β-blockers have become standard of care; in patients with advanced HF, device-based therapy is important. Yet, HF continues to expand rapidly in incidence and prevalence, exacting enormous individual and societal tolls. Furthermore, efforts to translate preclinical discoveries into the clinical arena have disappointed in most instances. Undoubtedly, much of this failure derives from an incomplete understanding of the underlying complex biology and the currently accepted practice of aggregating all forms of HF together regardless of underlying etiology. The extent and proportionate contributions of multiple events, including myocyte loss, hypertrophy, hyperplasia, extracellular matrix changes, metabolic derangements, and immunologic events, differ by disease type and affect the response to therapy in a meaningful way.

Because of redundancy in cellular and molecular pathways involved in LV remodeling, it is unlikely that future therapies will target just 1 cell type or signaling pathway. In addition, it is likely that blockade of neurohormones (eg, catecholamines, angiotensin, aldosterone) or loading (vasodilators or diuretics) may have overlapping cellular targets (cardiac myocytes, fibroblasts, etc). Furthermore, targeting 1 signaling pathway or an individual molecule may be inefficient because of the existence of intricate, interlacing cellular signaling networks and regulatory loops; a multidisciplinary experimental/systems biology may be key. In the end, elucidation of the complex and fascinating biology of LV remodeling is likely to yield significant benefit to the growing number of patients with HF.

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Disclosures

None.

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