The Future of Pharmacological Therapy for Heart Failure

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Current pharmacological therapy for heart failure (HF) is based on improved understanding of the pathophysiological mechanisms of HF progression. In particular, inhibition of key activated neurohormonal systems (eg, the renin-angiotensin-aldosterone system) and the sympathetic nervous system has been the cornerstone of drug therapy for this condition. However, despite these major advances, many HF patients still only marginally respond to these therapies. Novel therapeutic approaches have been tested. Several recent phase III studies have failed, however, despite intriguing pathophysiological concepts and promising pilot data. In other studies, significant benefits have been observed in certain subgroups only, suggesting the need for a more tailored approach to individual risk and comorbidity. This review will focus on recent and potential future pharmacological HF therapies and where drug treatment may be in the next few years. In discussing future pharmacological therapy for HF, 3 key strategies will be considered: (1) optimization of conventional therapies, (2) a focus on new drug development within areas not yet adequately represented by major clinical data and (3) new drugs affecting novel therapeutic targets. \((\text{Circ J} 2010; 74: 809–817)\)

**Key Words:** Cardiac function; Heart failure; Pharmacology

Heart failure (HF) is a major public health problem in Western society, associated with high morbidity and mortality, frequent hospitalizations and a major cost burden on the community.

Strategies to impact therapeutically on this condition have been very successful over the past few decades, but mortality remains unacceptably high at around 8–12% annually, depending on symptom severity. Such strategies have primarily included nonpharmacological strategies (eg, salt restriction, alcohol reduction and exercise), as well as standard drug therapies. More recently, device-based interventions, including cardiac resynchronization therapy and implantable cardioverter defibrillators, have provided further morbidity and mortality benefits in addition to these background strategies. Cardiac transplantation remains an option for only a limited number of patients as does the use of ventricular assist devices as destination therapy.

Successful drug therapies in the setting of HF have focused on key neurohormonal systems activated as part of the pathophysiology of this disease process. In particular, the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) represent key neurohormonal targets. On this basis, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, aldosterone-receptor blockers and angiotensin-receptor blockers (ARB) have all been found in major trials to confer morbidity and mortality benefits and thus are the mainstays of current treatment as recommended by guideline authorities.

A key issue moving forward is whether additional benefit can be gained from either better use of existing drug therapies and/or the addition/substitution of novel therapies to the current agents. This review will evaluate the future role of pharmacological strategies in the management of the patient with HF.

**Recent Failed Pharmacological Trials in HF**

The recent past has revealed a number of failed therapeutic strategies in the setting of systolic chronic HF (CHF), HF with preserved ejection fraction (HFPEF) and acute decompensated HF (ADHF). It is of relevance to the consideration of future therapies to evaluate individual studies that have used these novel strategies, in order to determine why they may not have been successful.

The RENAISSANCE, RECOVER and RENEWAL studies were designed in 1996/1997, based on the “cytokine hypothesis” (ie, that inflammatory cytokines are produced in the failing heart and can contribute to cardiac dysfunction). However, when treated with a tumor-necrosis factor (TNF) α receptor antagonist, etanercept, systolic CHF patients showed no significant difference in rates of death or CHF hospitalization compared with placebo. Similar neutral (or even negative) observations were made with the anti-TNFα monoclonal antibody, infliximab.

The ENABLE (Endothelin Antagonist Bosentan for Low-
er Cardiac Events in Heart Failure) study evaluated the effects of low-dose bosentan, a nonspecific endothelin receptor antagonist, in systolic CHF patients with left ventricular ejection fraction (LVEF) <35%, New York Heart Association class (NYHA) IIIb–IV. In comparison with placebo, low-dose bosentan showed no significant difference in the incidence of all-cause mortality or CHF hospitalization.\(^6\)\(^-\)\(^8\)

The OVERTURE study was designed to compare omapatrilat, an inhibitor of both ACE and neutral endopeptidase, with enalapril in systolic CHF patients with LVEF <30% and NYHA II–IV. Omapatrilat did not achieve superiority over enalapril with regard to the primary endpoint of all-cause mortality or hospitalization with worsening HF.\(^6\)\(^-\)\(^8\)

EVEREST was a randomized, placebo-controlled study designed to evaluate the long-term efficacy of oral tolvaptan, a vasopressin (V2) antagonist. Tolvaptan was initiated for acute treatment of patients hospitalized with worsening HF (LVEF <40%, NYHA III–IV) then continued long term (vs placebo). However, with tolvaptan there was neither improvement nor reduction in the combined endpoint of cardiovascular mortality or HF hospitalization.\(^6\)\(^-\)\(^11\)

**Why Have Recent Studies Failed?**

It is unclear why these studies were unable to demonstrate additional clinical benefit to that of current standard therapies, but there are a number of potential explanations.

Firstly, underlying hypotheses regarding the role of the particular target being explored as being critical to HF disease progression may have been incorrect. This potential explanation would, however, fly in the face of a large body of preclinical and early-phase clinical data supporting these development programs.

Next, the patient population studied may have been either too broad or not sufficiently targeted towards maximizing the benefits of the intervention being studied. It may be difficult to establish a specific hypothesis in a variety of clinical settings and patient populations with different etiologies and comorbidities. Significant benefits have been observed in certain subgroups only, suggesting an approach tailored for individual risk and comorbidity is needed to maximize therapeutic benefit.

In each trial, the determination of dose may have been inadequate, specifically because of a lack of appropriate pilot data on dose-response in these settings.

In addition, the therapeutic strategy may be inappropriate-ly specific for the broad cascade of derangements being addressed. For example, TNF is the only pro-inflammatory cytokine blocked by etanercept-like drugs, but HF is a disease of broad-based cytokine activation.

Finally, a threshold for therapeutic benefit with drug therapy may have been reached. This is supported by the finding that device trials have been able to demonstrate significant improvements in morbidity and mortality, in addition to background standard drug therapy.

**Future Pharmacological Therapy for HF: From Here to Where?**

Development of future pharmacological therapies for systolic CHF will still need to be based on well-supported hypotheses, adequate pilot data, clear dosing information and well-designed clinical trials. However, such trials will need to be much better targeted to the subgroup of patients most likely to benefit, rather than the broad brush stroke of HF patients in general. The role of pharmacogenomics and panels of biomarker data in guiding such treatments may be a key future development.

In discussing future pharmacological therapy for HF, 3 key strategies will be considered: (1) optimization of conventional therapies, (2) a focus on new drug development within areas not yet adequately represented by major clinical data and (3) new drugs affecting novel therapeutic targets.

**Optimize Proven Therapies**

Blockade of the RAAS and SNS is now well established as a no standard therapy in the treatment of systolic CHF. However, there are a number of factors that contribute to less than optimal use in real-world clinical practice. These 2 systems represent important targets for improving the overall wellbeing of HF patients and thus reducing the burden of HF on the community.

The first issue is why patients are not receiving these drugs in the first place. There are many reasons, including inadequate education, physician inertia, and concerns about adverse events. These concerns are particularly relevant to the elderly who of course comprise the majority of the HF population. Development of strategies to overcome these concerns is a major priority.

The other issue with regard to optimizing the use of established therapies is that of dose. The recent HEAAL study demonstrated that higher doses of the ARB losartan, were superior to lower (standard) doses, as used in earlier trials, which reinforces the importance of having patients not just on the appropriate drugs but also at the appropriate doses. In general, the doses used in clinical trials represent the optimal target doses for treatment. In this regard, it is of interest that there is wide biological variation in ACE inhibitors and \(\beta\)-blockers with regard to their efficacy. In the future, greater effort will be made to match the appropriate dose to the individual patient. A leading area in the development of these approaches is pharmacogenomics.

**Pharmacogenomics**

The DD genotype of the ACE gene has been associated with an increase in ACE activity with elevated levels of aldosterone, despite therapy with an ACE inhibitor.\(^12\) Thus the DD genotype has been associated with a variety of adverse cardiovascular effects related to diminished ACE inhibition, including higher mortality and a reduction in transplant-free survival in patients with CHF.\(^13\) This difference could be abolished with \(\beta\)-blocker therapy, as transplant-free survival was equivalent in patients with the DD, ID, and II genotypes.

In 2006, Liggett\(^14\) reported polymorphisms in the \(\beta\)1-adrenergic receptor. Activation of the SNS is an early response in HF and serves to support and stabilize myocardial performance. These effects are conferred via the \(\beta\)1- and \(\beta\)2-adrenergic receptors (B1-AR and B2-AR), which are expressed by cardiomyocytes. A series of single-nucleotide polymorphisms in the B1-AR and B2-AR have been described, with a significant impact on agonist-mediated contractility in non-failing and failing human hearts, as well as response to antagonists and partial agonists in the failing heart.

Clinical use of the \(\beta\)1 partial agonist, bucindolol, is a good recent example of the potential utility of pharmacogenomics in drug therapy for HF. The BEST study\(^15\) was overall not beneficial in patients with systolic CHF; however, those with an arginine substitution at codon 389 (cyclic AMP gain-of-function) had better outcomes with bucindolol compared with the other groups, which is in keeping with the known pharmacology of that substitution. This approach has been put
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to regulatory authorities. However, the US Food and Drug Authority has recommended prospective trials rather than retrospective analyses before approving such pharmacoge- nomic approaches for routine use.

A further area for maximizing the benefits of established therapies is to consider their use in the prevention of the develop- ment of HF, not just in those with established disease. Although ACE inhibitors have been demonstrated to be of benefit in patients with asymptomatic LV dysfunction in ameliorating progression to overt disease, similar data have not been well established in such patients receiving β-blockers remote from an acute ischemic event. Furthermore, ACE inhibitors (eg, in HOPE) and ARBs to a lesser extent (eg, in ON-TARGET and TRANSCEND) have demonstrated reduced progression to HF in patients at high vascular risk but without overt LV dysfunction. Apart from the early anti- hypertensive literature on β-blockers, no such data exists for these agents.

Another interesting drug that may be of benefit in preventing progression from vascular disease to overt HF is the aldosterone blocker, spironolactone. Our group is currently studying spironolactone as a preventive strategy in patients at high risk of HF, with elevated B-type natriuretic peptide (BNP) levels but no known cardiac disease.

Figure 1. Rationale for development of renin-angiotensin-aldosterone system (RAAS) blockade in heart failure. ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; AT, angiotensin; ARB, angiotensin-receptor blocker.

Focus of New Drug Development in Areas That Have Not yet Been Adequately Represented by Major Clinical Trial Data

ADHF ADHF is a common and potentially fatal condition. ADHF most commonly occurs because of LV systolic or diastolic dysfunction, with or without additional cardiac pathology. The goals of initial management of ADHF are hemodynamic stabilization, support of oxygenation and venti- lation, and symptom relief.16

Inotropic agents, such as dobutamine and milrinone, vasodilators and natriuretic peptides, such as nitroglycerin and nesiritide, are frequently used for hemodynamic stabilization in ADHF patients. They provide benefits via a combination of neurohormonal, as well as hemodynamic and renal, effects.17–19 Several trials have revealed adverse outcomes with inotropic agents,20,21 however, mostly associated with an increase in myocardial oxygen consumption and risk of arrhythmias. In addition, stimulation of the β-adrenergic receptor has been implicated in HF disease progression, providing a rationale for β-adrenergic receptor blockade in the treatment of CHF.22–24 Vasodilators and natriuretic peptides lower ventricular filling pressures and systemic vascular resistance, thus improving cardiac performance indirectly. They do not stimulate atrial or ventricular tachycardia, and also do not increase heart rate (HR) or myocardial oxygen consumption. Despite concerns of risk in hypotension, it has been shown that the risk is low (4–5%).25

A therapeutic strategy to distinguish patients who could be best treated with vasodilators and natriuretic peptides instead of inotropic agents still remains to be established. Future studies will focus on expanding the application of vasodilators and natriuretic peptides for selected ADHF patients.

Overall, however, no ADHF therapy has yet been shown to reduce mortality in a placebo-controlled randomized controlled trial. New candidates are urgently required (see later).

HFPEF HFPEF or “diastolic” HF is associated with wors- ened long-term outcomes, exacerbated by poor tolerability to atrial and ventricular tachyarrhythmia, abrupt elevation of
systolic blood pressure, and ischemia. The treatment of HFPEF remains empiric because of limited trial data. Control of systolic and diastolic hypertension, the ventricular rate in patients with atrial fibrillation (AF), and ischemia related to diastolic dysfunction are the current standard therapeutic approaches.

Conventional therapies for systolic HF are not well established for HFPEF. Excessive preload reduction can cause sudden falls in output, especially in severe diastolic dysfunction with a small, stiff LV chamber.

Beta-blockers are theoretically promising in the setting of HFPEF, because of improved diastolic dysfunction, reduced filling pressures, increased diastolic filling time and indirect antifibrotic effects. The SENIORS study suggested the magnitude of the benefit in patients with relative preservation of EF (>35%) was similar to that observed in systolic LV dysfunction. ARBs have been disappointing in both the CHARM-Preserved and I-PRESERVE studies. Early benefits in PEP-CHF with the ACE inhibitor, perindopril, were offset by large drop-in and drop-out in an already under-powered study, leading to a neutral result. We are thus left with no proven therapies in HFPEF, but with a large number of potential candidate drugs in this area (see later).

**Development of New Drugs Acting on Novel Targets**

Progress in basic science has markedly expanded the repertoire of possible targets for HF therapy. The development of murine and other animal models of cardiomyopathy have provided new insights into the myocardial cellular and molecular basis of HF, generating a large number of potential targets for pharmacotherapy, and perhaps even gene therapy. Targeting of key intracellular signaling pathways has, in particular, become an important and promising new approach to drug development for HF.

The latest pharmacological therapies undergoing clinical evaluation for HF are reviewed.

**Novel Targets Within Existing Systems**

**Renin Inhibition** Direct renin inhibitors (DRIs) offer an additional, pharmacologically-distinct means of suppressing the RAAS, with the theoretical advantage of blocking an enzyme with only 1 known substrate (angiotensinogen), inhibiting the rate-limiting step in the RAAS cascade, and reducing synthesis of all subsequent components of the cascade.

The main drug development issue to be considered is whether renin blockade might offer therapeutic benefit over and above other downstream neurohormonal blocking strategies directed against the RAAS, such as ACE inhibitors, ARBs and aldosterone-receptor antagonists. DRIs might have additional benefits associated with blocking the system upstream rather than downstream. In particular, there is no reflex activation of angiotensin I and angiotensin II, with the potential for direct adverse effects of activation of these peptides (Figure 1).

Aliskiren, the first of a new class of non-peptide, orally
active DRIs, has been examined in CHF patients treated with ACE inhibitor and \( \beta \)-blockers. Plasma levels of NT-proBNP and urinary aldosterone showed significant reduction with aliskiren vs placebo.\(^{34,35} \) This study tested the effect of a DRI in patients who had experienced a compensatory rise in plasma renin activity caused by ACE inhibitor-induced (or ARB-induced) loss of negative feedback inhibition of renin secretion. This compensatory response may partially overcome the RAAS-blocking effect of ACE inhibitors. In this setting, aliskiren was generally well tolerated, which has led to a large-scale outcome study, ATMOSPHERE, in systolic CHF patients.

**Aldosterone Inhibition** The efficacy and safety of the aldosterone-receptor blocker, spironolactone, was assessed in the RALES trial for CHF with NYHA III and IV.\(^{36,37} \) Patients with less severe systolic HF (class II) have not been evaluated and that is the goal of the EMPHASIS-HF study.\(^{38} \)

Hyperaldosteronism in HF has been thought to reflect angiotensin II-mediated stimulation of the adrenal glands. However, there is also local production of aldosterone in the failing ventricle.\(^{39} \) This compensatory response may partially overcome the induced loss of negative feedback inhibition of renin secretion. An alternate approach to aldosterone blockade may therefore be aldosterone synthase inhibition. FAD286 has shown potential long-term therapeutic benefit. In a rat model of CHF, FAD286 improved cardiac hemodynamic parameters, as well as function, and prevented LV remodeling.\(^{40} \)

**New Drugs for Cardio-Renal-Anemia Syndrome** Chronic kidney disease and CHF share a number of common background factors (eg, hypertension, diabetes, and AF), clinical findings (eg, vasculopathy and malnutrition), and risk factors (eg, older age and anemia). These 2 pathologic situations coexist in a large number of patients and each could adversely affect the prognosis of the other (Figure 2).

The pathophysiology of the cardiorenal syndrome involves impaired intrarenal hemodynamics, reduced transrenal perfusion pressure and systemic neurohormonal and cytokine activation. Clinical management of the patient with cardiorenal syndrome includes the challenge of diuretic resistance, which may involve correcting the underlying cause, and use of combination diuretics or diuretic infusions. Nesiritide, or recombinant BNP, has courted controversy regarding its exact role in cardiorenal syndrome and is being evaluated in a large-scale outcome study, ASCENID.\(^{35,36} \)

**Agents Augmenting Renal Function in HF** Adenosine antagonists are novel agents that inhibit adenosine (A1) receptors and promote diuresis. In the setting of impaired tubular glomerular filtration, adenosine is released and binds to A1 receptors to induce constriction of the afferent arterioles. This decrease in renal blood flow enhances sodium resorption by the proximal tubules. Adenosine antagonists therefore have the potential to improve renal blood flow and simultaneously increase sodium excretion. The net effect is diuresis with maintained or even enhanced glomerular filtration, which is an attractive pharmacological profile in congestive HF.

The effect of the A1 antagonist (BG9719) added to furosemide was studied in patients with HF because of volume overload. BG9719 showed a significant increase in the volume of diuresis. Although furosemide alone caused a decline in renal function, the addition of BG9719 prevented that decline. Thus, adenosine antagonists may enhance diuresis with loop diuretics, while preserving renal function.\(^{37} \)

Rolofylline, also an intravenous adenosine A1 receptor antagonist, facilitated diuresis and preserved renal function in patients with acute HF (AHF) with renal impairment. Early phase II studies with rolofylline suggested it may prevent renal impairment in patients with ADHF, positively affect acute symptoms, and improve 60-day outcomes. A 2,000-patient trial of this agent was, however, recently found to be neutral in its key findings.\(^{38} \)

Relaxin is a naturally occurring peptide hormone that plays a central role in the hemodynamic and renovascular adaptive changes of HF. Effects of relaxin include the production of nitric oxide, inhibition of endothelin, inhibition of angiotensin II, production of vascular endothelial growth factor, and production of matrix metalloproteinases (MMPs). These multiple mechanisms cause systemic and renal vasodilation, increased arterial compliance and other vascular changes that may prove beneficial in HF patients. Relaxin showed marked improvement in the hemodynamic parameters in stable CHF.\(^{39} \) This naturally occurring peptide hormone therefore appears to hold promise as a novel pleiotropic vasodilator for the treatment of patients with AHF.

RELAX-AHF was undertaken to evaluate the effects of relaxin on the symptoms and outcomes in AHF. When given to patients with normal-to-increased blood pressure, relaxin was associated with favorable relief of dyspnea. Cardiac death or readmission because of heart or renal failure at day 60 was reduced, with acceptable safety.\(^{40} \)

The roles of the particulate and soluble guanylate cyclase (pGC and sGC, respectively) pathways have been developed for application in HF. Nesiritide and urodilatrin are natriuretic peptides with vasodilating, natriuretic and diuretic effects, acting via pGC, and cinaciguat is a novel sGC activator.

Urodilatrin is an endogenous peptide synthesized in the kidney and regulates renal sodium and water excretion. After synthesis in the distal tubular cells, urodilatin increases intracellular cyclic guanosine monophosphate (cGMP) levels, and regulates renal sodium and water excretion. The SIRIUS I and II studies in the management of ADHF demonstrated a lowering of elevated pulmonary pressures, diuresis and natriuresis without untoward neurohormonal activation or excessive hypotension.\(^{41} \)

Cinaciguat has a promising and novel mode of action because it can stimulate cyclic guanosine-3,5-monophosphate synthesis by targeting sGC in its nitric oxide-insensitive, oxidized ferric (Fe\(^{3+} \)) or haem-free state. Because of different mechanisms of spatial compartmentalization of cGMP within cardiac cells, therapeutic agents that target sGC (eg, cinaciguat) may offer complementary pharmacodynamic effects to that of uraluretic or nesiritide, which target pGC. A phase II, non-randomized, unblinded, uncontrolled multicenter study of patients with ADHF investigated the effect of different doses of cinaciguat. After dose titration, cinaciguat reduced preload and afterload, as well as improving the cardiac index. Despite the limited clinical data for cinaciguat in ADHF, these results imply that a pool of oxidized or haem-free sGC is present in patients with ADHF, and that these forms may be preferentially activated by cinaciguat.\(^{42} \)

Adrenomedullin, a 52-amino-acid peptide, is a member of the calcitonin gene-related peptide family that is thought to play an important regulatory role in circulatory homeostasis under normal physiological conditions. This peptide may therefore be a potential therapy for ADHF and cardiorenal syndrome, based on its known vasodilatory, natriuretic, neurohormonal modulatory and antifibrotic actions.
Several investigators reported hemodynamic benefits of intravenous adenomedullin in vivo, as well as in vitro. As with the natriuretic peptides, a combination of vasoconstrictor inhibitor and vasodilator augmentative approaches might be optimal. Nishikimi et al showed significant improvements in the hemodynamic, renal, hormonal and oxidative stress responses with adenomedullin combined with human atrial natriuretic peptide in a pilot study of patients with ADHF.  

**Anemia Correction** Anemia is a frequent finding in patients with HF, especially those with complex comorbidities and cardiorenal syndrome. Whether it may be incidental or directly related to HF itself, the prevalence of anemia increases with the severity of HF, and consequently it is tempting to suggest (although still unproven) that treatment of anemia positively influences survival in HF patients. Moreover, the degree of anemia is strongly correlated to the severity of the underlying HF.  

The etiology of anemia in patients with CHF is complex and multifactorial: renal failure, pro-inflammatory cytokine activation, hemodilution, and anemia of chronic disease. Even though there is a relative deficiency of erythropoietin (EPO) in CHF, EPO levels are generally increased in these patients, which might relate to reductions in EPO synthesis and ineffective iron supply for erythropoiesis, as well as a reduced bone marrow response to endogenous EPO.  

One of the most intriguing aspects of EPO and the treatment of HF is that it may contribute to improvements in ventricular function independent of improvements in peripheral hemodynamic status and/or the delivery of oxygen to the peripheral musculature. There has been considerable work in the area of direct effects of EPO on the heart.  

The final verdict on the efficacy of EPO and thus its future clinical use in HF patients with anemia should be defined by the results of the RED-HF study. In RED-HF, 2,600 patients are being randomized to treatment with darbopoetin or placebo, with a primary combined endpoint of death or first hospital admission for worsening HF. The estimated completion of the study is December 2011.  

On the other hand, iron deficiency is also commonly observed in patients with CHF and may be related to malnutrition, malabsorption, and cardiac cachexia. Furthermore, the use of aspirin and oral anticoagulation may lead to microscopic amounts of gastrointestinal blood loss, which further contributes to the iron deficiency. The FAIR-HF trial investigated the role of intravenous iron in CHF. Weekly ferric carboxymaltose therapy rapidly increased iron levels; a modest increase in hemoglobin levels was observed in the subgroup of patients with anemia, but not in patients without anemia. Compared with placebo, the administration of iron significantly improved symptoms, NYHA class, quality-of-life, and exercise capacity not only in the anemic but also in the nonanemic groups.

More larger-scale studies are needed to definitively establish the safety and efficacy profile of intravenous iron in HF patients. As with EPO, there remain concerns regarding allergic reactions, increased oxidative stress, and worsened endothelial function. Thus, further studies designed to reveal the pathophysiology of anemia are vitally important.

### Myocardial Targets

The myocyte is the major cardiac cell involved in the ventricular remodeling process. At the level of the myocyte, the initial response is an increase in cell width, followed by an increase in length that leads to an unfavorable length-to-width ratio, and at the cellular level multiple signaling pathways interact to drive hypertrophy. Other components in the remodeling process include the interstitium, cardiac fibroblasts, collagen, and the coronary vasculature.  

Consistent with the hypothesis that remodeling is pathogenically important in HF is the observation that ACE inhibitors and some β-blockers, which can slow or even reverse, parameters of cardiac remodeling, also provide clinical outcome benefit. Based on the concept of the LV remodeling process, we review the following novel pharmacological approaches targeting myocardial contractility and LV remodeling.

#### Myocardial Contractility

Reduced myocardial contractility is a central feature of the failing myocardium, and the cellular and molecular processes that account for this have been well described. Recently, cardiac myosin activators have been developed, which increase cardiac contractility without changing intracellular calcium concentrations. CK-1827452 (CK-452) increases systolic function by directly activating cardiac myosin. Importantly, these effects on cardiac function do not appear to result in an increase in coronary blood flow or myocardial oxygen demand. As opposed to β-adrenergic receptor agonists and phosphodiesterase inhibitors, which increase the rate of pressure development (dP/dt) and shorten the LV systolic ejection time, CK-452 increases systolic function by increasing the systolic ejection time without changing dP/dt. A potential side-effect may therefore be that of coronary ischemia because of reduced filling during diastole.  

Istaroxime is a novel intravenous inotropic agent that inhibits Na+/K+ adenosine triphosphatase activity while stimulating the sarcoplasmic reticulum Ca2+-adenosine triphosphatase isofrom 2a. The combined mechanism of istaroxime allows for cytosolic calcium accumulation during systole, creating a positive inotropic response, as well as rapid sequestration of calcium during diastole, creating a beneficial lusitropic response.  

HORIZON-HF was a randomized controlled study evaluating the short-term effects of istaroxime to test the hypothesis that istaroxime improves diastolic stiffness in hospitalized ADHF patients. According to pressure–volume analysis and tissue Doppler imaging, istaroxime increased contractility and decreased diastolic stiffness compared with placebo.

#### Myocardial Fibrosis and Matrix Remodeling

Following myocardial injury, LV remodeling manifests a phenotype characterized by thinning of the myocardium at the site of injury, compensatory hypertrophy of viable myocardium and dilatation of the ventricular chamber. Reparative deposition of extracellular matrix (ECM) in the injured region occurs in an attempt to maintain the structural integrity of the heart. Fibrosis also appears in regions at the border of, and remote

<table>
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<th>Table 1. Direct Cardiac Myosin Activators</th>
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<td>1. Prolonged duration of systole</td>
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<tr>
<td>2. Increased stroke volume</td>
</tr>
<tr>
<td>3. No change in dP/dt max</td>
</tr>
<tr>
<td>4. No increase in MVO2</td>
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<tr>
<td>5. No increase in heart rate</td>
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<td>6. No increase in catecholamines</td>
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<td>7. No increase in cAMP</td>
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dP/dt max, maximum rate of pressure development; MVO2, maximal oxygen capacity; cAMP, cyclic adenosine monophosphate.
from the injury, and can be considered to be “reactive” or “pathological”, contributing to increased myocardial stiffness and systolic dysfunction. In particular, a complex interrelated process involving the production of collagen by cardiac fibroblasts, together with the enhanced degradation of the ECM by MMPs, appears to take place during cardiac remodeling (Figure 3). Pathological fibrosis has emerged as a key target for pharmacological intervention in HF.

Conventional HF therapies, such as neurohormonal blocking agents, have been demonstrated to reduce pathological fibrosis, both indirectly by improving hemodynamic status, but also directly via effects on collagen synthesis (Table 2).

Pirfenidone (PFD) is an orally active, antifibrotic drug shown to significantly attenuate and potentially reverse collagen deposition. Lee et al investigated the effects of PFD on arrhythmogenic atrial remodeling and AF vulnerability in canines with ventricular tachypacing (VTP)-induced CHF. They evaluated arrhythmogenic atrial remodeling by electrophysiological studies, atrial fibrosis measurements, and atrial cytokine expression. PFD treatment resulted in a significant reduction in atrial fibrosis, conduction heterogeneity, and AF vulnerability. Those results suggest broad effects of PFD on potent profibrotic mediators. Pharmacological therapy targeted at the underlying fibrotic substrate may therefore play an important role in the management of CHF and concomitant AF.

Many of the profibrotic effects occurring in the remodeling process are mediated via growth factors and cytokines such as transforming growth factor-β (TGFβ), interferon-γ, and TGFα. The TGFβ1 signaling pathway offers a variety of sites at which pharmacological interventions may be directed to inhibit its profibrogenic actions. A number of compounds have been developed that may be useful.

Tranilast (N-(3',4'-dimethoxycinnamoyl)-anthranilic acid) has been used in the treatment of a variety of allergic conditions, including allergic conjunctivitis, atopic dermatitis and bronchial asthma. Tranilast inhibits the release of chemical mediators, such as cytokines and prostaglandins from inflammatory cells in response to antibody–antigen interactions to effect its anti-allergic actions. The inhibitory effect of tranilast on the release of cytokines, including TGFβ1 and prostateglandin E2, may also be a mechanism by which the agent exerts its documented antifibrotic and antiproliferative effects on a variety of cells, including cardiac fibroblasts.

In the PRESTO study, tranilast was disappointing for preventing post-percutaneous transluminal coronary angioplasty restenosis. Kelly et al evaluated the effect of tranilast on diabetic rats with impaired diastolic function in association with fibrosis, apoptosis, and hypertrophy. Treatment with tranilast prevented the development of diastolic dysfunction of diabetic cardiomyopathy, with evidence of attenuation of pathological fibrosis in the heart (also in kidney).

Knowledge of structure–activity relationships has been used to improve the antifibrotic efficacy of tranilast while reducing adverse events. Fibrotech Therapeutics is currently exploring this approach with FT-011 and similar drugs.

Table 2. Inhibition of Cardiac Fibrosis

| 1 | Neurohormonal antagonists |
| 2 | Cardiac resynchronization therapy |
| 3 | Antagonism of TGFβ1 pathways |
| 4 | Naturally occurring eg decorin |
| 5 | Antisense/monoclonal antibody to TGFβ1 |
| 6 | TGFβ1 inhibitors eg, Alk-5inh. |
| 7 | Blockade of downstream pathways |
| 8 | Inhibition of relevant intracellular signaling pathways |
| 9 | Direct antifibrotic growth factor inhibitors |

TGFβ1, transforming growth factor-β1; inh., inhibitors; CTGF, connective tissue growth factor; MAPK, mitogen-activated protein kinase.
Other Pharmacological Approaches

**Direct Sinus Node Inhibitors** Resting HR strongly correlates with major cardiovascular outcomes. Preclinical studies suggest that resting HR is prospectively related to the development of atherosclerosis and of major cardiovascular events. In the INVEST study of elderly coronary heart disease (CAD) patients with hypertension, high resting HR was associated with increased risk of adverse outcomes, regardless of treatment and underlying comorbidity such as diabetes or prior MI. It is unclear, however, whether slowing of HR alone results in significant improvements in ventricular function and major outcomes in HF, and whether these are incremental to that of β-blocker therapy. A large-scale clinical trial (BEAUTIFUL) with ivabradine, a selective h channel blocker in patients with CAD and systolic LV dysfunction (with and without background β-blockade) examined this question. Ivabradine failed to reduce the primary composite endpoint of cardiovascular death, admission to hospital for acute myocardial infarction and admission to hospital for new-onset or worsening HF. The SHIFT study, evaluating the effect of ivabradine in patients with established systolic CHF is currently underway.

**Summary**

The Future of HF Pharmacological Therapy

We have reviewed the future directions that HF drug therapy may take. The focus has been on optimizing the use of existing therapies; however, new drugs acting on novel targets will continue to be explored. There will be a renewed focus on prevention of HF using proven and perhaps novel drugs as well. Treatment will also focus on comorbid conditions that may influence the progression of heart failure. Improvements in diagnosis and prognostication may lead to earlier use of effective therapies in specific patients. Improving the targeting of specific drug therapies based on pharmacogenomics, and perhaps hormone-guided therapy, will be critical to the optimization of pharmacological therapy. Interaction of drug therapy with devices, as well as the coming era of cell transplantation/gene therapy, will also be important considerations moving forward.

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