

Review of novel therapeutic targets for improving heart failure treatment based on experimental and clinical studies

Kwadwo Osei Bonsu^{1,2}
Isaac Kofi Owusu³
Kwame Ohene Buabeng⁴
Daniel Diamond Reidpath¹
Amudha Kadirvelu¹

¹School of Medicine and Health Sciences, Monash University Sunway Campus, Jalan Lagoon Selatan, Bandar Sunway, Subang Jaya, Selangor, Malaysia; ²Accident and Emergency Directorate, Komfo Anokye Teaching Hospital, ³Department of Medicine, ⁴Department of Clinical and Social Pharmacy, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Abstract: Heart failure (HF) is a major public health priority due to its epidemiological transition and the world's aging population. HF is typified by continuous loss of contractile function with reduced, normal, or preserved ejection fraction, elevated vascular resistance, fluid and autonomic imbalance, and ventricular dilatation. Despite considerable advances in the treatment of HF over the past few decades, mortality remains substantial. Pharmacological treatments including β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists have been proven to prolong the survival of patients with HF. However, there are still instances where patients remain symptomatic, despite optimal use of existing therapeutic agents. This understanding that patients with chronic HF progress into advanced stages despite receiving optimal treatment has increased the quest for alternatives, exploring the roles of additional pathways that contribute to the development and progression of HF. Several pharmacological targets associated with pathogenesis of HF have been identified and novel therapies have emerged. In this work, we review recent evidence from proposed mechanisms to the outcomes of experimental and clinical studies of the novel pharmacological agents that have emerged for the treatment of HF.

Keywords: novel treatment, experimental and clinical studies, therapeutic targets, heart failure

Introduction

Heart failure (HF) is a complex syndrome resulting from disorders in structure and function of the heart associated with a wide variety of cardiovascular diseases and considered a major public health problem owing to its epidemiological transition.¹ HF is typified by loss of contractile function with reduced, normal, or preserved ejection fraction (EF), elevated vascular resistance, fluid and autonomic imbalance, and ventricular dilatation.²

Despite considerable gains in the treatment over the past few decades, mortality and morbidity of HF remain substantial. Pharmacological treatments encompassing β -blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists have been proven to significantly reduce mortality and readmissions in HF.¹ However, the prognosis is still poor, and a large percentage of these patients progress to advanced HF. Further, treatments for many patients remain unsatisfactory as current therapies often fail to control symptoms and restore quality of life.³ The observation that chronic HF progresses to advanced stages despite optimal treatment has increased the quest for alternatives exploring the roles of additional pathways that contribute to the development and progression of HF.⁴

Correspondence: Kwadwo Osei Bonsu
School of Medicine and Health Sciences,
Monash University Sunway Campus, Jalan
Lagoon Selatan, Bandar Sunway, Subang
Jaya 47500, Selangor, Malaysia
Tel +60 35 514 6000 ext 44451
Fax +60 35 514 4451
Email kose1@student.monash.edu

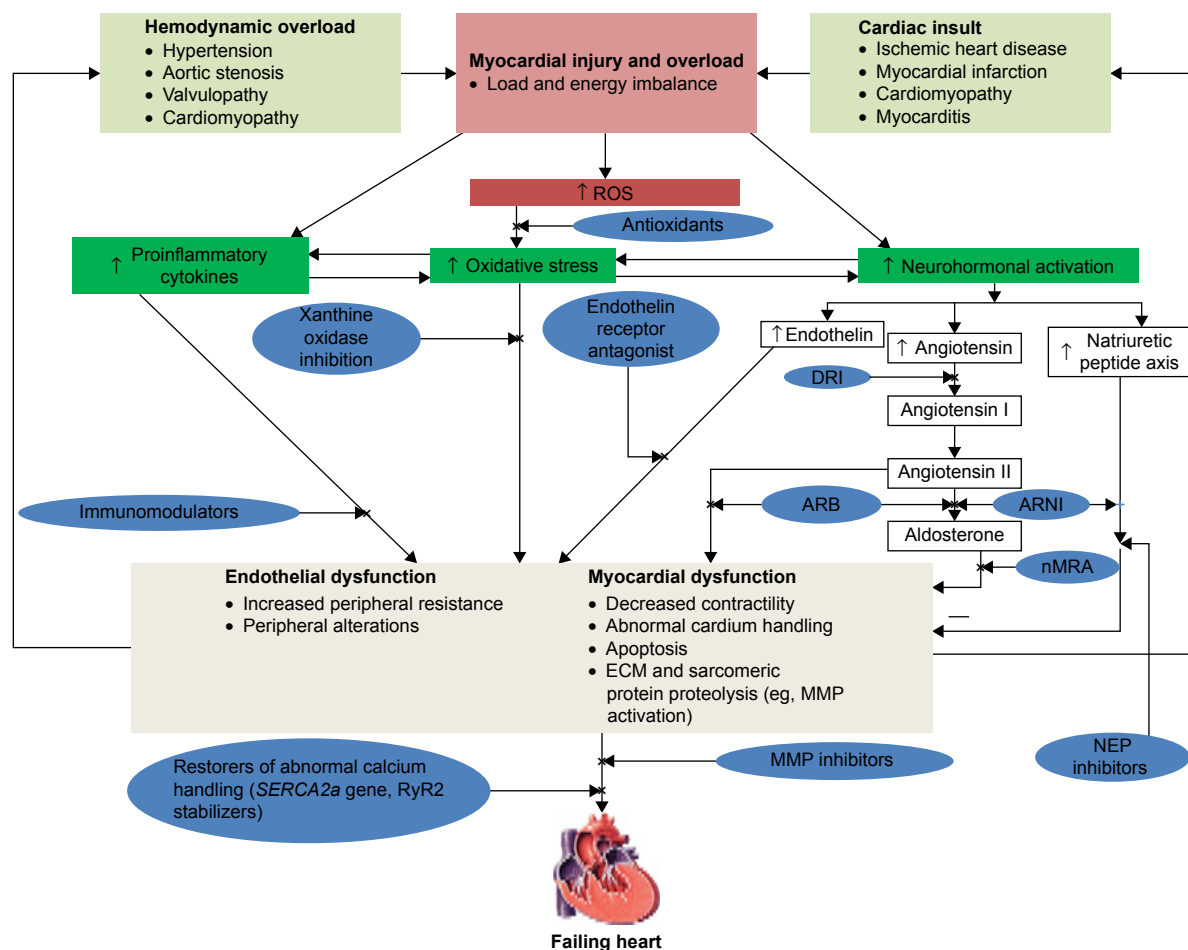


Figure 1 Pathophysiologic mechanisms of HF and novel therapeutic targets of action.

Notes: ARB, ARNI, antioxidants, DRI, endothelin receptor antagonists, immunomodulators, MMP inhibitors, nMRA, NEP inhibitors, restorers of abnormal calcium handling, and xanthine oxidase inhibitors indicate various targets of novel therapeutic agents discussed.

Abbreviations: ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; DRI, direct renin inhibitor; ECM, extracellular matrix; HF, heart failure; MMP, matrix metalloproteinase; NEP, neutral endopeptidase; nMRA, nonsteroidal mineralocorticoid receptor inhibitor; ROS, reactive oxygen species.

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Several pharmacological targets associated with pathogenesis of HF have been identified and novel treatments have emerged. The aim of this article was to review emerging therapies, their proposed mechanisms of action, and outcomes of experimental and clinical studies for these new therapies for HF. Figure 1 shows the pathophysiologic mechanisms of HF and novel therapeutic targets of action of pharmacological agents evaluated in this review.

Novel approaches to myocardial contractility

Targeting sarcoplasmic–endoplasmic reticulum calcium ATPase 2a to treat HF

Calcium (Ca^{2+}) plays a central role in contractile function of cardiomyocytes. Contractility of cardiomyocytes is regulated by excitation–contraction coupling that occurs through

modulation of cytosolic Ca^{2+} concentration encompassing release of Ca^{2+} from sarcoplasmic reticulum (SR) through the ryanodine receptor (RyR), then SR Ca^{2+} reuptake via Ca^{2+} uptake pump, and Ca^{2+} removal from myocytes through Na^+/Ca^{2+} exchanger.⁵ The sarcoplasmic–endoplasmic reticulum calcium ATPase 2a (SERCA2a) is an enzyme responsible for the transfer of Ca^{2+} from the cytoplasm back into the lumen of the SR, thus shutting off contraction and initiating cardiomyocyte relaxation. Calcium released from the SR into the cytosol during systole activates actin, and myosin coupling accounts for myofilament shortening and the production of contractile force. The rate of myocyte relaxation is controlled by reuptake of calcium during diastole.^{5,6}

Dysregulation of Ca^{2+} handling/homeostasis in cardiomyocytes plays a critical role in the contractile and relaxation abnormalities that occur in HF.^{7–10} Deviations from normal

Ca²⁺ handling/homeostasis seen in HF include partial SR Ca²⁺ depletion, elevated diastolic SR Ca²⁺ leak, irregular behavior of SR Ca²⁺ release channels, sarcolemmal Na⁺/Ca²⁺ exchanger upregulation, and downregulation of SERCA2a.⁷⁻¹⁰ Thus, approaches aimed at upregulating and restoring SERCA2a activity are being evaluated as a potential therapeutic target for the treatment of HF.

The role of SERCA2a is of particular importance in the war against HF.¹¹ Experimental and human models with HF have demonstrated that downregulating SERCA2a expression and activity is an important element in cardiomyocyte dysfunction.⁶⁻⁸ It has been further shown that even the modest decrease in SERCA2a reduces its activity to the extent that there is a substantial increase in diastolic calcium concentration in homogenates of human heart.¹² Abnormal Ca²⁺ handling/homeostasis by the failing heart is mostly attributed to the reduction in SERCA2a activity, which adversely affects cardiac function and can be corrected by increasing the expression and activity of SERCA2a.

Augmenting SERCA2a expression and activity has shown various favorable effects in HF.⁶ It has been shown that enhancing SERCA2a activity through a vector-delivered SERCA2a gene improves ventricular metabolic reserve, systolic and diastolic functions, and survival and reduces the probability of developing ventricular arrhythmias during ischemia-induced Ca²⁺ overload.¹³⁻¹⁵ Gene transfer therapy provides a novel strategy for targeting abnormalities in cardiac cells that adversely affect cardiac function. Among the nonviral and viral vector systems developed for tissue and organ gene delivery, adeno-associated viruses (AAVs) have emerged as the most valuable gene transfer agents available today. This is because AAVs are preferentially taken up by cardiomyocytes, minimally immunogenic and have the capacity for long-term transgene expression. In addition, AAVs have demonstrated an excellent biosafety record.¹⁶ The use of AAVs as viral vector to deliver SERCA2a gene therapy to the heart has shown favorable response in both small¹⁷ and large animal models of HF.¹⁸⁻²⁰

The promising outcomes of these experimental studies warranted the initiation of human trials with SERCA2a gene therapy. A Phase I trial with an adeno-associated viral-1 (AAV1) vector used to deliver SERCA2a gene via intracoronary infusion was conducted and subsequently established safety and feasibility of the SERCA2a gene therapy for HF.²¹ A Phase II trial, the Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID), was then conducted to further evaluate the clinical benefits of SERCA2a gene therapy in HF.²² The CUPID was

a double-blind, placebo-controlled trial which enrolled and randomized 39 patients with advanced HF to either AAV1–SERCA2a gene infusions or a matching placebo. The study established the safety of AAV1–SERCA2a gene treatment and exhibited therapeutic response with improved functional status, decreased symptoms of HF, decreased levels of natriuretic peptides (NPs), and attenuated adverse remodeling of the left ventricle in high-dose group. Moreover, a 3-year follow-up study of these patients who received high-dose therapy showed reduction in mortality.²³ However, high titers of adenoviral neutralizing antibodies against the AAV1 seen in some patients remain a problem that needs to be addressed.

Despite the promising outcomes of gene transfer therapy for HF, there remains a number of issues to be addressed. Of particular importance is the presence of adenoviral neutralizing antibodies. There are reports of AAV-associated disease that is common in the population, and many develop titers of neutralizing antibodies in response to these infections. The presence of these antibodies adversely affects the efficacy of treatment, thus the therapy is recommended for patients with titers <1.2.

Approximately 60% of >1,500 participants intended to be enrolled in CUPID were excluded due to antibody titers found in serums drawn from them. It is reported that no specific patterns could be detected although significant variability was observed between study participants from the ten countries. However, patients' age was the only variable that correlated with qualifying AAV1-neutralizing antibody titers.²³ Granted that these results are representative, antibody titers seen in serums of patients will be an important obstacle to AAV-based gene transfer therapy in patients with HF. Studies aimed at reducing antibody titers will need to be carried out in order to make this therapy more widely available.

Although currently available AAV vectors have high affinity for cardiac tissues, uptake into other tissues in the body occurs raising the possibility of off-target effects of therapy that could be harmful. More cardiac-specific vectors need to be developed.

RyR stabilization

RyR is an essential tetrameric protein for contraction of myofilaments via regulating the release of Ca²⁺ from the SR.²⁴ There are three isoforms in mammals. RyR1 is predominant in skeletal muscle,²⁵ and RyR2 is predominant in cardiac muscle.²⁶ RyR3 was first isolated from rabbit brain but known to be more widely distributed in the skeletal muscles, diaphragm, and many other organs.²⁷ Ca²⁺ enters the cell

during the action potential after the voltage-gated L-type calcium channel is activated. The resulting Ca^{2+} influx causes larger amount of Ca^{2+} to be released by stimulating the RyR, which is a channel responsible for the release of Ca^{2+} from the SR membrane. The RyR2 acts as a scaffolding protein which associates with several proteins (protein kinase A, protein phosphatase 1 and 2a, calmodulin, calmodulin kinase II, and phosphodiesterase 4D3 [PDE4D3]) to form a macromolecular complex.^{28,29} This macromolecular complex is vital to regulating and maintaining the integrity of RyR2 and allows tight control of its function via several phosphorylation and Ca^{2+} activation and inactivation sites. The RyR2-binding protein, FKBP12.6 (calstabin 2), stabilizes the tetrameric macromolecular complex. The calstabin increases the likelihood of RyR2 channel to maintain a closed state in a resting myocyte. The RyR2 has the strongest affinity for calstabin 2 in the heart, and detaching the macromolecular complex increases channel open probability.^{9,30} Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) or protein kinase A phosphorylation of RyR increases its open probability in HF. It has been shown that increased β -adrenergic signaling is closely related to malfunction of SR Ca^{2+} release via induction of cyclic AMP-dependent PKA hyperphosphorylation of RyR2, thus resulting in calstabin 2 dissociation from the channel complex and as a consequence destabilizing the closed conformation of RyR, while increasing Ca^{2+} leak.³¹ These processes lead untimely to the release of Ca^{2+} during diastole, known as SR Ca^{2+} leak,^{9,30} which is characterized by a drastic fall in Ca^{2+} content of the SR, with less Ca^{2+} available for release, resulting in weaker muscle contractions. Guo et al³² demonstrated that the activation of CaMKII promotes resting SR Ca^{2+} release events (Ca^{2+} sparks and waves) in permeabilized ventricular myocytes via RyR phosphorylation. Furthermore, increased RyR leak during HF has been linked to CaMKII phosphorylation,³³ and recent evidence indicates that CaMKII-mediated phosphorylation actually promotes HF development.^{34–37} It is noteworthy that CaMKII expression and activity is enhanced during chronic β 1-adrenergic and angiotensin receptor II stimulation in HF.³⁷ Thus, it is clear that in HF, RyRs become leaky and consequently result in increased frequency of Ca^{2+} sparks and waves, which promote arrhythmogenesis.³⁸

Approaches to RyR2- Ca^{2+} leak hypothesis have introduced novel therapeutic strategies for HF.^{9,30} A number of compounds, collectively called rycals, are known to directly bind and modulate RyR, and 1,4-benzothiazepine derivative, JTV519 (K201), is one of the first agents shown to effectively enhance RyR–calstabin binding and restore

abnormal RyR function. These rycals stabilize the closed RyR conformation, but it is unclear whether this action is solely mediated by calstabin 2 binding. An early study in an animal model of HF showed that JTV519-treated hearts restored calstabin 2 binding, inhibited SR Ca^{2+} leak, and eventually reestablished left ventricular (LV) function.³⁹ An experiment with human myocardium indicated improved diastolic and systolic function under Ca^{2+} overload conditions with JTV519,⁴⁰ giving it a great therapeutic promise. Moreover, improved cardiac function could be attributed to the ability of JTV519 to inhibit multiple ion channels.⁴¹ A new derivative of JTV519, S107, with a more selective profile has been developed.⁴² The S107 has been shown to increase the binding of calstabin 2 to RyR, reduce abnormal diastolic Ca^{2+} release in arrhythmias,⁴² and attenuate HF progression.⁴³ Further, irregular spontaneous diastolic SR Ca^{2+} leak resulting from dysfunctional RyR2 is associated with delayed after depolarizations formation, which plausibly accounts for ventricular arrhythmias in HF.⁴⁴ Thus, in a Phase II, placebo-controlled randomized trial, the antiarrhythmic properties of another RyR-modulating agent, S44121, is being assessed in patients with HF at risk of ventricular arrhythmias (ISCRTN register: 14227980).

Evidence suggests that CaMKII-induced RyR2 phosphorylation accounts for Ca^{2+} leakage through RYR2 channels.^{45,46} In HF, the main cardiac isoform – CaMKII δ – is upregulated in the heart and has been shown to be strongly associated with reduced left ventricular ejection fraction (LVEF). Thus, the administration of CaMKII inhibitors may serve as a novel treatment strategy for HF.⁴⁵ Specific inhibition of CaMKII by agents such as KN-93 also reduces RyR leak³³ and has been shown to improve the force frequency relationship in trabeculae isolated from failing hearts.⁴⁶ KN-93 was additionally shown to prevent arrhythmia in CaMKII δ -overexpressing mice.⁴⁷ Simvastatin increases CAMKK-dependent phosphorylation of AMPK and LKB1 and enhances Rac1 activity in both cultured endothelial cells and mouse aorta.⁴⁸ These findings identify new points of pharmacological regulation of vascular signaling pathways and uncover new complexities in understanding the pleiotropic effects of statins in the vascular wall and by extension cardiovascular diseases.

Approaches to enhancing neuregulin

Neuregulins (Nrgs) are members of a family of growth factors encoded by four structurally related genes (Nrg-1, 2, 3, and 4) and act through tyrosine kinase receptors (ErbB2 and ErbB4) in the epidermal growth factor receptor family⁴⁹ to stimulate cellular proliferation, differentiation,

and survival in many tissues particularly the heart. Nrg-1 has been shown to play a critical role in cardiac chamber differentiation and trabeculation in the developing embryo.⁵⁰ Nrg-1 has two isoforms (Nrg-1 α and Nrg-1 β), which are expressed in the heart; however, β isoforms are more effective in stimulating cardiac myocyte signaling and responses.⁵⁰ Further, it has been shown that Nrg-1 β isoform is required for cardiac development.⁵¹ Nrg-1 β is expressed in the endothelial cells and stimulates the tyrosine kinase receptors on cardiac myocytes to modulate glucose uptake, growth, and survival.^{50,52} An experience of Erb- β 2-targeted antibody trastuzumab (Herceptin) and its associated cardiotoxicity in patients treated for breast cancer^{53,54} has led to the quest for better understanding of the physiological roles of Nrg-1 and its receptors in the myocardium. The early stages of HF are characterized by the activation of Nrg-1/ErbB signaling coupled with increased expression of Nrg-1 in the left ventricle. However, Nrg-1 expression and Nrg-1/ErbB signaling are suppressed during the late phase of HF.⁵⁵

Consequently, experimental and human studies aimed at augmenting Nrg-1 have recently been conducted. A study of recombinant Nrg-1 β showed improved ventricular dimensions, function, and parameters of remodeling in rat model.⁵⁶ Thus, exogenous Nrg-1 β agents have been developed and are being evaluated in clinical trials. An early phase study of exogenous Nrg-1 β showed improved cardiac contractile function via modulating Ca²⁺ handling, thus enhancing excitation–contraction coupling and Ca²⁺ sensitivity.⁵⁷ Further, recombinant human Nrg-1 β 2 has been shown to improve cardiac output, structure, and function by 90 days in a dose-ranging study.⁵⁸

A number of issues have been raised about recombinant NRGs utility in HF since its receptor expression triggers responses in diverse tissues⁵⁰ and, notably, the potential for tumor growth acceleration. The need for continuous intravenous (IV) administration of these agents over several hours on daily basis limits their use in chronic HF. Persistent nausea and central nervous system effects observed with the administration of these agents in almost all subjects may further limit their use in chronic HF. Nonetheless, despite these caveats, this approach remains a solid and an exciting treatment approach in HF requiring further studies.

Novel approaches to renin–angiotensin aldosterone system blockade and neurohormonal modulation

The inhibition of the renin–angiotensin aldosterone system (RAAS) is important to the treatment of HF with known pharmacological agents – ACE inhibitors, ARBs, and

mineralocorticoid receptor (MR) antagonists – already in clinical practice. However, further targets and new pharmacological agents are being discovered and developed to further improve the outcomes in HF.

Direct renin inhibitors

HF is characterized by increased plasma renin activity (PRA).⁵⁹ PRA is closely associated with key adverse events in patients with HF.^{60,61} Moreover, PRA has demonstrated to be a powerful independent prognostic predictor of adverse outcomes in HF.⁶² Direct renin inhibitors (DRIs) block the conversion of angiotensinogen to angiotensin I consistent with the actions and effects of renin. Nguyen⁶³ described a prorenin receptor that has pathophysiological relevance to HF in addition to the action of renin on the RAAS. The activation of prorenin receptor results in prohypertrophic and apoptotic activity through stimulating transforming growth factor- β and several intracellular signaling pathways. Further, it is known that DRI downregulates the RAAS to reduce pro-renin receptor gene expression.⁶³ Several DRIs have been developed; however, their oral bioavailability has been pharmacologically complex and challenging. Aliskiren, the first orally active DRI to be licensed for clinical use, also has very low bioavailability but shows consistent PRA and downstream RAAS inhibition to produce a steady decrease in blood pressure (BP) in hypertension.

Few studies have evaluated DRIs in patients with HF. Neuberger et al⁶⁴ were the first to investigate renin inhibition in nine patients with chronic HF with an IV enalkiren, which suppressed PRA and lowered BP in the previous studies of patients with hypertension. The acute IV administration of enalkiren (1.0 mg/kg) significantly increases cardiac and stroke volume indexes and decreases left ventricular filling pressure, mean right atrial pressure, heart rate, and systemic vascular resistance.⁶⁴ Subsequently, the use of IV remikiren was found to be similar to IV enalapril treatment with regard to reducing pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance in chronic HF.⁶⁵

In recent times, aliskiren – the only orally active DRI – is being studied in chronic HF. The first study randomized 27 patients with HF to ACE inhibitor, ramipril, or aliskiren.⁶⁶ Aliskiren 300 mg/d given for 7 days to patients with low LVEF significantly reduced PRA and angiotensin II compared to ramipril.⁶⁶

To confirm the abovementioned claim, ALiskiren Observation of heart Failure Treatment (ALOFT) study evaluated the efficacy of DRIs in chronic HF.⁶⁷ The ALOFT study randomized 302 patients with chronic HF to aliskiren (150 mg/d) or placebo for 3 months with the change in plasma

brain NP (BNP) levels as the primary efficacy endpoint. At the end of the trial, aliskiren significantly reduced the plasma BNP levels compared to placebo. Further, aliskiren significantly increased plasma renin concentration and decreased PRA compared to placebo. Therefore, DRI could provide extra treatment benefits to existing RAAS inhibitors; however, a careful consideration of possible adverse effects will be required in the treatment of HF. Hyperkalemia is particularly common among patients with chronic HF owing to impaired renal perfusion, comorbidities, and concurrent treatments such as β -blockers and RAAS inhibitors. It is worth noting that, in the ALOFT trial,⁶⁷ hyperkalemia and worsening renal function were slightly higher among patients who received aliskiren than in placebo group. In addition, marginal increase in symptomatic hypotension was seen with aliskiren compared to placebo.

Large-scale trials have been testing aliskiren treatment on major outcomes in HF. The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study⁶⁸ is among the first trial to evaluate aliskiren on outcomes in HF. The ASTRONAUT study randomized ~1,639 patients hospitalized for acute decompensated HF to aliskiren 150 mg (increased to 300 mg as tolerated) or placebo daily in addition to standard therapy for ~12 months. The initiation of aliskiren in addition to optimal treatment failed to reduce mortality or readmissions in patients hospitalized for HF with reduced EF (HFrEF) at 6 months or 12 months after discharge.⁶⁹ Another study evaluating aliskiren in HF is the Aliskiren Trial to Minimize OutcomeS in Patients with Heart FailurE (ATMOSPHERE) trial.⁷⁰ The ATMOSPHERE is currently evaluating the clinical benefit of aliskiren as additional treatment to other RAAS blockers and direct comparison with ACE inhibitor treatment. This clinical trial is expected to clear the doubt about the usefulness of DRIs in chronic HF following the failure of ASTRONAUT and ALTITUDE⁷¹ to show clinical benefit with aliskiren in cardiovascular conditions.

Modulation of NPs

NPs are cardiac hormones which are stimulated and produced by the atrium, ventricles, or endothelial cells after myocardial infarction, LV hypertrophy, and HF. Four major isoforms, such as atrial NP, BNP, C-type NP, and dendroaspis NP, have been described to be produced by the heart after injury. These peptides have various favorable hemodynamic, neurohormonal, cardiac, and renal properties, which are believed to further enhance the beneficial RAAS-blocking effects in HF.

A synthetic analog of BNP – nesiritide – has been extensively studied in clinical trials and proven to increase cardiac indexes and reduce cardiac filling pressures and eventually improve the clinical status of patients with acute decompensated HF. Nesiritide is now clinically available for the management of acute decompensated HF although no primary endpoint benefit was reported.^{72,73} However, adopting this approach to treatment in chronic HF has been problematic because of poor oral bioavailability of NPs.⁷⁴

Endothelin receptor antagonism

Endothelin activation is considered an integral part of the neurohormonal response in HF.^{75,76} The vascular endothelial cells produce endothelin, a potent vasoconstrictor, higher plasma levels of which induces adverse ventricular remodeling and worsens HF symptoms via reducing coronary flow and exhibiting direct harmful myocardial effects.^{75,77} It is well established that higher plasma levels of endothelin-1 is associated with functional impairment and worsening prognosis in HF.⁷⁶⁻⁷⁹ Driven by these pathophysiological insights, bosentan, an orally active nonselective endothelin receptor antagonist which interferes and inhibits endothelin-mediated effects was developed. Experimental studies evaluating the long-term treatment effects of bosentan in HF have reported significant benefits in hemodynamic variables, ventricular remodeling, and survival.^{80,81} This claim was confirmed in clinical studies where patients with symptomatic HF on standard therapy had short-term benefits of bosentan on hemodynamics reported.⁸² However, two long-term studies, Endothelin Antagonist Bosentan for Lowering Cardiac Events in HF (ENABLE) and Research on Endothelin Antagonism in Chronic HF (REACH), assessing bosentan were terminated ahead of schedule owing to the increased number of adverse events, with no improvements in clinical status in patients with symptomatic HF.^{83,84}

Neutral endopeptidase inhibition

Neutral endopeptidase (NEP) is an enzyme which degrades NPs, and the inhibition of NEP persistently increases plasma concentration of NPs. Candoxatril has been shown to induce diuresis and natriuresis, improve exercise capacity, and lower PCWP, but produces no effects in PRA. Ecadotril increases plasma concentration of NPs and reduces PRA and PCWP.⁸⁵ Further, the treatment effects of ecadotril were evaluated in ~280 patients with chronic HF in a multicenter dose-ranging study.⁸⁶ There were no symptomatic benefits,

but rather pancytopenia and deaths were reported among patients treated with ecadotril.

Vasopeptidase inhibition

Among the NEP inhibitors, omapatrilat (a dual antagonist of ACE and neprilysin) is the most widely studied particularly in HF and/or hypertension. The IMPRESS randomized trial⁸⁷ was the first Phase II evaluation of 40 mg daily omapatrilat versus 20 mg daily lisinopril in 573 New York Heart Association (NYHA) Functional classes II–IV patients with HF with LVEF $\leq 40\%$ in a head-to-head randomized fashion for 24 weeks. Fewer cardiovascular events were seen in the patients who received omapatrilat compared to the lisinopril group. Omapatrilat treatment significantly reduced composite endpoint of death, admission for HF, or discontinuation of treatment due to worsening symptoms compared to lisinopril. However, both treatment and lisinopril groups were comparable regarding exercise tolerance which was the primary endpoint of the study.

The promising outcomes of these studies prompted the conduct of Phase III study, OVERTURE,⁸⁸ which evaluated 5,770 patients comparing enalapril (10 mg twice daily) to omapatrilat (40 mg once daily), over a mean duration of 14.5 months. A marginal but nonsignificant decrease in composite endpoint of death or HF hospitalization requiring IV treatment was seen with omapatrilat compared to enalapril treatment. The design of the OVERTURE study is believed to have accounted for the neutral outcomes reported. The twice-daily dosing of enalapril may have led to pharmacokinetic variations than with a daily dosing of omapatrilat which produced significant lowering in BP. In addition, the definition of “hospitalization for HF” as admissions for HF requiring IV diuretics may have underrated the omapatrilat treatment benefits in the OVERTURE study. Finally, angioedema reported in few patients in the IMPRESS and OVERTURE studies are undoubtedly a source of concern and worth investigating.

Angioedema associated with ACE/NEP inhibitor treatment is believed to be due to the accumulation of bradykinin resulting from concurrent ACE and NEP inhibition, both of which play critical roles in the breakdown of bradykinin.⁸⁹

In addition to single daily dose of omapatrilat failing to show any significant clinical benefit in comparison to twice-daily dosing enalapril, omapatrilat was associated with serious angioedema and hypotension leading to early termination of the OVERTURE study. In contrast to omapatrilat treatment, LCZ696 (sacubitril – neprilysin inhibitor

and valsartan – an ARB) has no or minimal effect on ACE and therefore angioedema associated with inhibition of bradykinin breakdown was limited.

Angiotensin receptor blockade and neprilysin inhibition

Driven by the abovementioned pharmacological insights and experiences, newer approaches aimed at inhibiting NEP to enhance RAAS blockade have been developed. The combination of NEP inhibition with ARBs is suggested to be less likely to cause angioedema because the degradation of bradykinin would be lower compared to ACE inhibitors.

LCZ696 is a single molecule consisting of neprilysin inhibitor sacubitril (AHU377) and ARB valsartan designed to curtail the risk of angioedema.^{90,91} LCZ696 concurrently inhibits RAAS and impairs NP breakdown due to its specific moieties which modulate both pathways.⁹² Clinical studies have demonstrated that LCZ696 exhibits greater but favorable neurohormonal and hemodynamic effects compared to ARB alone in patients with hypertension or HF with a preserved EF.^{93,94} These studies established the tolerability and safety in chronic HF.

The PARADIGM-HF is a large trial that evaluated the efficacy and safety of LCZ696 in chronic HF.^{95,96} This study compared LCZ696 with enalapril in patients who had HF with a reduced LVEF. In this double-blind trial, 8,442 patients with classes II–IV HF and an LVEF $\leq 40\%$ were randomly assigned to either LCZ696 or enalapril in addition to the recommended therapy. LCZ696 was superior to enalapril in reducing the risks of HF hospitalization and all-cause and cardiovascular mortality after 27 months of follow-up.⁹⁶ However, higher proportions of patients had hypotension and nonserious angioedema, but lower proportions were seen with renal impairment, hyperkalemia, and cough in the LCZ696 group than the enalapril group.⁹⁶ Now, LCZ696 is registered as Entresto™ (Novartis International AG, Basel, Switzerland) (sacubitril/valsartan) in the US and has entered the clinic for the treatment of patients with HFrEF and NYHA classes II–IV. Entresto™ is indicated for reducing the risk of HF hospitalizations and cardiovascular mortality and currently being reviewed by health authorities around the world.

NP analogs

Augmenting endogenous NPs is another approach to finding treatment options for HF. The use of chimeric NP (CD-NP) which is a chimeric designer peptide made up of a complete string of C-type NPs fused to the carboxyl-terminal tail of

Dendroaspis NP is one of such approaches being evaluated. C-type NP selectively binds to natriuretic peptide receptor-B and results in the reduction in cardiac filling pressures to lessen hypotension. The C-terminus of dendroaspis NP is responsible for a greater percentage of renal activity via promoting natriuresis and diuresis.⁹⁷ CD-NP has been shown to be safe and improves cardiovascular and renal function without inducing significant levels of hypotension in animal and human studies. This approach is now being evaluated in Phase II trials in HF (NCT01750905 and NCT00620308). Nonetheless, large clinical trials are needed to further validate CD-NP as an effective treatment option for HF.⁹⁸

Arginine vasopressin receptor antagonism

Arginine vasopressin (AVP) is a neuropeptide hormone synthesized in the nuclei of the hypothalamus in neuronal cell bodies and released from the posterior pituitary into the bloodstream. Circulating AVP levels are significantly elevated in patients with HF compared to healthy controls, and much higher levels found in congestive patients with HF with significant cardiac decompensation and hyponatremia.⁹⁹ Its actions are linked to free water reabsorption (V_2) and arteriolar vasoconstriction (V_{1A}). Novel approaches being developed for the treatment of HF target vasopressin receptor antagonism. Antagonizing V_{1A} receptor produces vasodilation and lessens afterload, while V_2 receptor antagonism increases aquaresis with minimal or no sodium loss.⁴ Two vasopressin antagonists – conivaptan and tolvaptan – have received the approval for the treatment of hyponatremia in HF.⁴ Tolvaptan, a selective V_2 receptor antagonist, promotes diuresis and as a consequence reduces edema, jugular venous pressure, and lessens or relieves congestion in HF. Conivaptan – dual V_{1A} and V_2 receptor antagonist – inhibits pressor response, stimulates aquaresis, and significantly reduces PCWP in HF.^{100–102} Thus, AVP antagonists provide important options for the treatment of patients with volume-overload HF.

Approaches to modulation of catecholamine synthesis and release

Nolomirole is a selective dopamine 2- α 2 receptor agonist which inhibits the release of catecholamines from sympathetic nerve endings.⁴ This inhibition of catecholamines further inhibits the release of tumor necrosis factor (TNF)- α with the improvement of ventricular function. Although nolomirole reduces cardiac hypertrophy and lessens the symptoms of HF in animal models, a large randomized

controlled trial in humans did not show clinical benefit in patients with HF.^{103,104}

Further, 5-HT₄ receptor antagonist (SB207266) has been found to significantly reduce LV remodeling and improve diastolic function in postinfarction rat model. These favorable effects suggest important contributions of 5-HT₄ receptor antagonism in HF.¹⁰⁵ A proof concept of double-blind randomized control trial (RCT) showed that the treatment with piboserod (5-HT₄ receptor antagonist) 80 mg marginally but significantly improved LVEF in patients with chronic HF in 24 weeks of follow-up.¹⁰⁶ However, the study did not show any significant changes in exercise tolerance, neurohormones, and quality of life but reported increases in adverse events. The clinical relevance of piboserod remains unclear since no significant changes in other efficacy parameters was reported.

Novel approaches to aldosterone blockade

Aldosterone is critical to HF progression and MRs are shown to be overexpressed in failing hearts.¹⁰⁷ Aldosterone enhances sodium retention, stimulates loss of potassium and magnesium, and is associated with sympathetic activation, parasympathetic inhibition, fibrosis of the myocardium and vascular walls, and impaired arterial compliance.¹⁰⁷ ACE inhibitors suppress aldosterone through the inhibition of angiotensin II formation; however, they do not prevent the release of aldosterone from non-ACE-dependent angiotensin II production or activation of aldosterone receptors.¹⁰⁷ Thus, aldosterone has become a well-established independent target for the treatments of systolic HF. Pharmacological agents that inhibit MR reduce the mortality in chronic HF. However, clinical use of these approaches is limited by increased risk of hypotension, hypokalemia, and worsened renal function when used together with other RAAS-blocking agents in HF. Several approaches aimed at addressing the concerns of adverse events limiting the clinical use of these agents have been developed.

PF3882845 (Pfizer, Inc., New York, NY, USA)¹⁰⁸ and BR-4628 (Bayer AG, Leverkusen, Germany)¹⁰⁹ are among several nonsteroidal MR antagonists which have recently been developed. PF3882845 demonstrated greater decreases in BP, albumin, and renal protection compared to eplerenone in an experimental model.¹⁰⁸ The BR-4628 is a dihydropyridine (DHP) derivative which was developed as a result of recent discovery that classic dihydropyridine-based L-type calcium channel blockers antagonize MRs in *in vitro* and *in vivo* studies.¹⁰⁹ BR-4628 is known to prevent or treat

renal injury induced by ischemia/reperfusion using Wistar rat models¹¹⁰ and it is currently in clinical trials.¹¹¹

Another nonsteroidal MR antagonist – BAY 94-8662 – has recently been developed and has been found to be more selective for MR than spironolactone and showed improved affinity for MR compared to eplerenone in experimental models.¹¹² Further, BAY 94-8662 shows a more evident cardiorenal end-organ protection than steroidal MR antagonists in hypertension-driven HF and renal dysfunction model.¹¹³

The mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) was a double-blind randomized, controlled, Phase II trial which evaluated the safety and tolerability of oral BAY 94-8662 in patients with chronic HFrEF and mild or moderate chronic kidney disease (CKD). The ARTS reported that BAY 94-8662 5–10 mg/d was as effective as spironolactone 25 mg/d or 50 mg/d in decreasing hemodynamic stress indicators and was associated with lower incidences of hyperkalemia and worsening renal function in patients with HFrEF and moderate CKD.¹¹³ The promising result of ARTS affords a firm reason for further research into the role of BAY 94-8662 in patients with HFrEF and concomitant CKD. This study further guides dosage selection for Phase III clinical trials.

Blockade of aldosterone synthesis is an alternative strategy to MR antagonism. In a failing heart, local aldosterone production is proportionate to the severity of disease. Aldosterone synthase or angiotensin II induces local aldosterone production in the failing ventricles in a manner comparable to disease severity. A number of novel agents targeting aldosterone synthase inhibition have been developed. One such agent is FAD286, an aldosterone synthase inhibitor, which has been shown to improve hemodynamics and the function of the heart in a rat model of HF.¹¹⁴ A selective aldosterone synthase inhibitor – LCI699 – showed a significant lowering BP similar to that of 50 mg twice-daily dosing of eplerenone and further substantial reductions in 24-hour ambulatory BP monitoring compared to placebo in mild-to-moderate hypertension.¹¹⁵ Thus, inhibiting aldosterone synthase may provide alternative or complementary strategies to MR antagonism in chronic HF.

Novel agents targeting cytokines and inflammation

Increased inflammation resulting from the activation of proinflammatory cytokines, cardiac myocytes, cardiac autoantibodies, cell adhesion molecules, and endothelial cells produced by activated macrophages is common in HF.² Elevated levels of proinflammatory cytokines – TNF- α ,

interleukin (IL)-1, IL-6, IL-10, IL-12, IL-17, IL-18, and C-reactive protein – have been linked to adverse outcomes in HF.² Several chemokines such as monocyte chemoattractant peptide-1, IL-8, and macrophage inflammatory protein-1 α are also elevated in HF. Established treatments for HF have shown marginal effects on the cytokine network. Consequently, a number of immunomodulatory agents have been developed as novel treatments due to evidence that attenuated inflammation enhances cardiac function in HF.^{116,117}

TNF- α plays a substantial role in HF progression as elevated plasma levels has been linked to extracellular matrix (ECM) remodeling, myocyte hypertrophy, and increased apoptosis.¹¹⁷ Etanercept (TNF- α receptor antagonist) and infliximab (anti-TNF- α antibody) are two agents known to inhibit TNF- α activity and have been widely studied in various clinical trials.¹¹⁸ However, both agents failed to show outcome benefits in patients with HF and several explanations have been proposed for the failure of anti-TNF- α therapy. One such reason is that low plasma concentrations of TNF- α is essential for the repair of tissues and it is possible that infliximab may have reduced TNF- α to concentrations below optimal levels which may be required for the observed favorable effects. In addition, infliximab may have induced apoptosis and other harmful effects on cardiomyocytes via antibody-dependent cellular toxicity and complement-dependent cytotoxic mechanisms. Further research into anti-TNF- α therapy should clarify the appropriate pharmacological agent, optimal dose, and subgroup of patients likely to benefit from treatment.^{116,117}

The inhibition of TNF- α synthesis via competitively inhibiting the TNF- α -converting enzymes (anti-TACEs) has been explored as a therapeutic target in HF. TACEs are important enzymes required for the conversion of pro-TNF- α into matured form. Studies have shown that macrophage inflammatory proteins and aprotinin decrease the processing of TNF- α via nonselective inhibition of TACE. Two selective TACE inhibitors – DPH-067517 and GM 6001 – are being assessed as novel therapeutic agents for the treatment of HF.¹¹⁹

TNF- α activates the p38 MAPK pathway to suppress contractility and promote inflammation and ECM remodeling.¹²⁰ P38-mediated proinflammatory properties via cytokines (eg, IL-1 β and IL-6) and TNF- α have been shown to play significant roles in the progression of HF.¹²¹ SB203580 and FR167653 are p38 inhibitors which have shown significant decreases in fibrosis, apoptosis, LV hypertrophy, and dilatation as well as improvement in EF and contractility in experimental models.¹²¹ Despite being promising agents for

the treatment of HF, these agents have not been tested in clinical studies.¹²⁰

Pentoxifylline (PTX) is a phosphodiesterase inhibitor which downregulates TNF- α synthesis through suppressing gene transcription of TNF- α . Furthermore, PTX is known to have TNF- α -independent immunomodulatory properties and prevents apoptosis to protect the myocardium and subsequently slowing down the progression of HF. A number of trials of PTX therapy have reported improved clinical symptoms, whereas others fail to show any benefits in patients with HF.¹²² Lysophosphatidic acid acyl transferase inhibitor – lysofylline – is another pharmacological agent which acts by decreasing lipopolysaccharide-induced TNF- α synthesis. Lysofylline is being evaluated for the treatment of sepsis, thus establishing its contribution to HF treatment may be required.¹¹⁹

Myocardial dysfunction,¹²³ dilated and ischemic cardiomyopathy, and the severity of HF are associated with elevated levels of IL-18.¹²⁴ The IL-18 is shown to be upregulated in the heart and consequently increasing the production of proinflammatory mediators (IL-1 β , IL-8, TNF- α , and inducible nitric oxide synthase) in HF. IL-18 coupled with these mediators is associated with reduced contractility of the myocardium, increased β -adrenergic signaling, ECM remodeling, and apoptosis.¹²⁴ Thus, inhibiting IL-18 may serve as a potential target for the treatment of HF. Recently, trials evaluating the safety and efficacy of the recombinant human IL-18BP (r-hIL-18BP) and agents blocking IL-18 antibody have been designed and initiated in healthy volunteers and patients with various conditions.^{125–127} Favorable safety profiles with mild-to-moderate adverse effects were observed in healthy volunteers and patients with moderate-to-severe rheumatoid arthritis or plaque psoriasis with r-hIL-18BP treatment.^{125–127} The longer elimination half-life of IL-18 neutralizing/blocking antibody is a primary advantage which may allow monthly or quarterly administration.

IL-converting enzyme inhibitor has been shown to attenuate inflammation and ultimately cardiac dysfunction in experimental diabetic cardiomyopathy.⁸⁵ Moreover, a selective IL-converting enzyme inhibitor, pralnacasan, has demonstrated favorable effects in diabetic cardiomyopathy.¹²⁸ This may present a novel therapeutic approach to HF.

IV immunoglobulin treatment lowers plasma levels of inflammatory mediators (eg, IL-8 and IL-1), upregulates anti-inflammatory mediators (eg, IL-10 and IL-1Ra), and ultimately improves EF and hemodynamic variables and exercise capacity in HF.¹²⁹ However, IV immunoglobulin therapy did not reduce LV remodeling compared to placebo

when 62 patients with myocardial dysfunction during hospitalization after acute myocardial infarction were randomized in a double-blinded fashion for 26 weeks.¹³⁰

Celacade immune modulation therapy downregulates proinflammatory cytokines and upregulates anti-inflammatory cytokines by inducing apoptosis in human blood sample exposed to oxidative stress. The outcomes of animal and human studies evaluating celacade in HF and other conditions have so far been encouraging. Subsequently, celacade has been approved for use in the European Union for the treatment of HF in all NYHA class II patients and in classes II, III, and IV patients with no prior history of myocardial infarction.^{131,132}

Novel approaches to targeting myocardial fibrosis and remodeling

Fibrosis of the myocardium is an important pathology in cardiac dysfunction. Matrix metalloproteinases (MMPs) play critical roles in myocardial fibrosis and remodeling by directly breaking down matrix components and subsequent release of biologically active factors from the ECM. Further, enhanced TNF- α and IL-1 β expression is shown to be related to improved MMPs activity. Thus, altering the activities of MMPs by direct inhibition or anti-cytokine treatment could modulate myocardial remodeling and function.^{133,134} Several MMP inhibitors including batimastat, ilomastat, marimastat, and prinomastat have been developed for the treatment of HF.¹³³ Treatment with batimastat reduces collagen synthesis and denaturation, prevents cardiac hypertrophy and dysfunction, and improves the survival of TNF1.6 HF mice.¹³⁵ Moreover, a selective inhibitor of MMP – PG-53072 – was found to attenuate LV dysfunction and cardiac remodeling in the HF model.¹³³ From these promising findings, further research to determine the efficacy of MMP inhibitors in humans with HF may be required.

TGF- β 1 is critical to immune system suppression and tissue repair as well as inducing fibroblasts to produce and remodel ECM. Thus, broadly targeting TGF- β signaling may improve outcomes in HF.¹³⁴ Experimental studies have shown that local angiotensin II generation correlates with expression and synthesis of TGF- β . Moreover, inducing TGF- β via stimulating angiotensin II type 1 receptor (AT₁R) is important to developing myocardial fibrosis.¹³⁴ Thus, ACE inhibitors may have suppressed TGF- β induction to improve outcomes in HF. Thalidomide reduces post-infarction myocardial remodeling and fibrosis via mechanisms that could plausibly be due to its direct anti-fibrotic effects on the expression of myocardial TGF-h1 gene leading to a sudden decrease in major stimuli for ECM remodeling. In addition,

thalidomide may have directly affected the proliferation and survival of fibroblasts.¹³⁶ These anti-fibrotic effects could present a potential treatment approach which needs to be harnessed to improve outcomes in HF.

Novel approaches to modulating metabolism

Myocardial metabolism may be normal in the early stages of HF but as disease advances, oxidative metabolism reduces, and glycolysis increases and as a consequence downregulating glucose and fatty acid oxidation.¹³⁷ Fatty acid oxidation remains a dominant source of energy production in LV dysfunction. However, increased fatty acid oxidation inhibits glucose oxidation via the Randle cycle phenomenon which ultimately results in proton overload and intracellular acidosis and further decreases cardiac efficiency.¹³⁷ Studies have shown that a shift of metabolism from fatty acid toward glucose oxidation improves myocardial contractility, thus slowing down the progression and improving the prognosis of HF.¹³⁸ The growing evidence of substrate metabolism in HF has provided a strong impetus for thorough studies into optimizing myocardial energy metabolism as novel therapeutic targets.^{137,139} Several novel agents that modulate myocardial substrate metabolic pathways to optimize myocardial energy production have been developed. These agents include carnitine palmitoyl transferase (CPT) inhibitors (perhexiline maleate, etomoxir), malonyl CoA decarboxylase (MCD) inhibitors, 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors (trimetazidine [TMZ], ranolazine), pyruvate dehydrogenase kinase (PDK) inhibitors (dichloroacetate, DCA), incretins, and thiazolidinediones.

TMZ is a piperazine compound which is a clinically effective antianginal agent and selectively inhibits long-chain 3-KAT enzyme, which plays a critical role in the β -oxidation pathway. A number of RCTs have shown outcome benefits in both short- and long-term evaluation of TMZ in HF.^{140–144} These clinical studies show that TMZ improves cardiac function, clinical status, and survival in HF. Recent meta-analyses have indicated that TMZ improves clinical symptoms and cardiac function and reduces cardiovascular hospitalization and mortality in patients with HF.^{145–147} The meta-analyses revealed a compelling evidence for outcome benefits of TMZ in HFrEF since all RCTs included in the analysis enrolled patients with EF >50%.

Ranolazine is a piperazine derivative which is similar but less potent compared to TMZ. The cardioprotective properties of ranolazine are suggested to be mediated via stimulating glucose oxidation and partially blocking fatty acid oxidation

through the inhibition of 3-KAT.¹³⁷ In addition, there are suggestions that the observed beneficial effects with ranolazine are partly due to its ability to inhibit the late inward sodium current and thus averting the sodium-dependent Ca^{2+} overload in ischemic HF.^{137,148}

CPT-1 catalyzes an important step in the mitochondrial uptake of long-chain fatty acids during fatty acid metabolism. CPT-1 inhibitors (etomoxir, oxfenicine, and perhexiline) suppress fatty acid oxidation while promoting glucose oxidation. Perhexiline maleate is an antianginal agent which inhibits CPT-1 and CPT-2 enzymes,¹⁴⁹ to shift the use of muscle substrate from free fatty acids toward carbohydrates.¹⁵⁰ A perhexiline-induced shift in metabolism improves cardiac function, exercise capacity, skeletal energetics, and quality of life in HF.¹⁵¹ However, perhexiline inhibition of CPT-1 leads to the accumulation of phospholipids, resulting in peripheral neuropathy and hepatotoxicity, which could be lessened by sustaining constant therapeutic concentrations.^{137,152} Etomoxir that was previously introduced as a potential hypoglycemic agent acts by inhibiting the enzyme CPT-1 which favors the oxidation of glucose over fatty acid during metabolism.¹³⁷ Etomoxir improves the oxidation of glucose and reduces oxygen consumption in the myocardium while preserving contractile function in animal models.¹³⁷ In a clinical study, etomoxir improved the LVEF and clinical status of patients with HF.¹⁵³ However, this study had a major limitation of the lack of placebo as control. Subsequently, the Etomoxir for Recovery of Glucose Oxidation (ERGO) study randomized 347 patients with chronic HF to etomoxir (80 mg and 40 mg) or a matching placebo for 6 months. The ERGO study did not report any significant changes in exercise tolerance, ventricular dimensions, and quality-of-life assessment scores between treatment and placebo groups. However, ERGO was stopped prematurely, because investigators detected an unacceptably high liver transaminase levels in four patients in the treatment group.¹⁵⁴

DCA inhibits pyruvate dehydrogenase (PDH) kinase, an enzyme which deactivates PDH in the mitochondrion. The PDH activation enhances carbohydrate oxidation partly by improving glycolysis and glucose oxidation coupling and as a result lessening acidosis and contractile dysfunction.⁴ Conversely, studies evaluating DCA failed to improve exercise tolerance and LVEF in patients with HF.^{155,156}

MCD regulates fatty acid oxidation in the myocardium by altering intracellular levels of malonyl CoA. Agents inhibiting MCD increases the levels of malonyl CoA which in turn inhibit CPT-1, thus slowing down fatty acid oxidation.¹⁴⁸ CBM-301940 inhibits MCD to speed up glucose

oxidation and decelerate fatty acid oxidation.¹⁵⁷ Moreover, a direct inhibitor of fatty acid oxidation – CVT-4325 – has been shown to improve cardiac work without increasing cardiac oxygen consumption, thus increasing myocardial efficiency.¹⁵⁸

Novel approaches to oxidative stress reduction

Oxidative stress is a state characterized by excess production of reactive oxygen species (ROS) relative to antioxidant defense and plays important roles in the pathophysiology of LV remodeling and HF.^{159,160} Cyclooxygenase, cytochrome c oxidase, lipoxygenase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, uncoupled nitric oxide synthase, and xanthine oxidase (XO) are likely ROS sources in HF.¹⁶⁰ Excessive production of ROS causes DNA damage and protein and lipid peroxidation, which results in permanent cell damage or death, and these detrimental effects have been implicated in various cardiovascular conditions.¹⁶⁰ In addition, ROS impairs contractile function by modulating proteins responsible for excitation–contraction pairing. Excess ROS cause apoptosis via activating diverse hypertrophy signaling kinases and transcription factors. Elevated ROS production leads to ECM remodeling by stimulating proliferation of cardiac fibroblasts and activating the MMPs.^{159,160} These cellular events play critical roles in the HF progression. Enzymatic (superoxide dismutase and catalase) and nonenzymatic antioxidants such as β -carotene, lipoic acid, vitamins C and E, and ubiquinone (coenzyme Q10) minimize the deleterious effects of oxidative stress.¹⁶⁰ However, studies evaluating the proposed benefits of typical antioxidants such as vitamins C and E have been disappointing.¹⁶¹

Ubiquinone is depleted in HF and has been shown to independently predict mortality.¹⁶⁰ Treatment with ubiquinone has marginally but significantly improved LV function in a few clinical studies.¹⁶¹ Further, long-term ubiquinone treatment has been found to reduce cardiovascular events in patients with moderate-to-severe HF who were randomized to ubiquinone 100 mg thrice daily or a matching placebo on optimal treatment for 2 years of follow-up.¹⁶² Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a free radical scavenger, which was found to produce significant treatment benefits in various disease conditions, but its proposed beneficial effects in HF are less clear and yet to be evaluated.^{160,161}

XO inhibitors – allopurinol and oxypurinol – suppress XO activity to improve myocardial function.^{161,163} XO inhibitors reduce ROS levels and decrease $\text{Na}^+/\text{Ca}^{2+}$ ion exchange but enhance SERCA2a production to increase

myocardial contractility.¹⁶³ Further, XO inhibition produces anti-inflammatory effects.¹⁶⁰ Allopurinol treatment (acute and chronic) shows variable outcome benefits in HF. Acute IV administration improves LV function and ameliorates endothelial dysfunction, whereas chronic oral treatment did not improve exercise capacity.¹⁶⁴ Thus, large clinical trials were required to evaluate the beneficial effect of XO inhibition in HF.¹⁶¹

Cingolani et al were the first to evaluate the inhibition of XO in congestive HF. This study was a single-center, double-blind, placebo-controlled, randomized trial of 60 patients with NYHA classes II–III congestive HF, comparing 600 mg daily oxypurinol with a matching placebo, in addition to optimal treatment for 1 month.¹⁶⁵ The trial reported that XO inhibition by oxypurinol in congestive HF decreases serum uric acid (SUA) and improves LVEF in patients with LVEF $\leq 40\%$ after 1 month of treatment.¹⁶⁵

The Oxypurinol Compared to Placebo for classes III–IV NYHA Congestive HF (OPT-CHF) study is a proof-of-concept trial which randomized 405 patients with NYHA classes III–IV HF due to systolic dysfunction on optimal medical therapy to oxypurinol (600 mg/d) or a matching placebo for 24 weeks.¹⁶⁶ Oxypurinol did not show any clinical benefit after 24 weeks of follow-up in moderate-to-severe HF. Nonetheless, further analysis suggests that oxypurinol shows outcome benefits in patients with higher SUA in a manner that correlates with the scale of SUA reduction.¹⁶⁶

In a trial conducted by Nasr and Maurice,¹⁶⁷ allopurinol (300 mg/d) was evaluated in comparison to a matching placebo in 59 patients with NYHA classes III–IV HF on standard treatment after 36 weeks of follow-up. In agreement with the earlier trial, allopurinol did not show any significant outcome benefits in patients with HF.¹⁶⁷ However, further analysis suggest that allopurinol will be beneficial in patients with elevated SUA in a manner correlating with the degree of SUA reduction and thus SUA may serve as a valuable biomarker to target HF therapy.¹⁶⁷

A more recent trial, the Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients (EXACT-HF) study tested the hypothesis that patients with HF with hyperuricemia may have composite clinical benefits with high-dose allopurinol treatment.^{168,169} The EXACT-HF, which is a multicenter, randomized (1:1), double-blind, placebo-controlled trial enrolled and randomly assigned 253 patients with symptomatic HF, LVEF $\leq 40\%$, and SUA levels ≥ 9.5 mg/dL to allopurinol 600 mg daily or placebo for 24 weeks. The primary composite endpoint was based on survival, worsening HF, and patient global assessment, whereas secondary

endpoints were change in LVEF, exercise capacity, and quality of life at 24 weeks. SUA levels were significantly reduced with allopurinol treatment in comparison to placebo at 12 weeks and 24 weeks (both $P < 0.0001$). However, allopurinol did not show any improvement in the major endpoints at 24 weeks in high-risk HFrEF and elevated SUA levels.¹⁶⁹

Studies have shown that a cholesterol-lowering agent, probucol, reduces oxidative stress and myocardial remodeling and improves LV function.^{170–172} Despite the promising effects of probucol, there are no clinical trials evaluating its proposed beneficial properties in HF. ACE inhibitors, ARBs, and β -adrenoceptor blockers particularly β 1 blockers (carvedilol, nebivolol) as well as statins have been proven to reduce oxidative stress and may have contributed to their improved outcomes in patients with HF.

Hydroxymethylglutaryl-coenzyme A reductase inhibitor (statins)

Statins have demonstrated significant decrease in adverse outcomes in both primary¹⁷³ and secondary¹⁷⁴ prevention studies and remain the mainstay treatment for preventing HF as well as other cardiovascular conditions. Recent meta-analyses showed significant reductions in cardiovascular events with statin use notwithstanding of patients' lipid profiles. These studies further demonstrated that the treatment benefit of statins exceeds identified risks.^{175,176}

While the benefit of statin therapy in prevention is well established, their role in the treatment of “established” HF is less clear. A number of non-randomized studies reported that statin therapy improved clinical outcomes in patients with HF^{177–181} and benefits were also shown in several small RCTs identifying improved surrogate (cardiac function and inflammation) and mortality outcomes in HF.^{182–185} In contrast, two recent large RCTs – the Controlled Rosuvastatin Multinational Study in HF (CORONA)¹⁸⁶ and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure (GISSI-HF)¹⁸⁷ – did not show statistically significant outcome benefits in primary endpoints compared to placebo. Nonetheless, the CORONA trial reported a significant reduction in hospitalizations for worsening HF. Furthermore, secondary analyses of CORONA data showed improved survival in patients with low galectin-3¹⁸⁸ and N-terminal prohormone brain natriuretic peptide (NT-proBNP)¹⁸⁹ levels with rosuvastatin therapy.

Two meta-analyses of RCTs,^{190,191} which evaluated statin versus placebo, did not report any significant outcome benefit in HF. The outcomes of the two large trials together with these two meta-analyses appear to weigh against the evidence

for statin treatment in HF. Nonetheless, a careful scrutiny of the RCTs in the meta-analyses show that the researchers did not compare effects of statin types utilized in each trial but treated them as a uniform class of drugs. Within the statins, there are two different types which can be identified by their hydrophilicity or lipophilicity. Rosuvastatin (hydrophilic statin) evaluated in CORONA and GISSI-HF is suggested to have played a part in the neutral outcome in both large RCTs and possibly skewed both meta-analyses toward the results of these two large trials.

Following CORONA and GISSI-HF, several studies still show statins to improve outcomes and prolong life in patients with HF.^{192–194} These studies, although non-randomized, again suggest that lipophilic statins may be better than hydrophilic statins in improving clinical outcomes in HF.² Moreover, a meta-analysis that did not show improved overall survival with statin treatment demonstrated that, in subgroup analysis, lipophilic statins may improve survival in HF.¹⁹⁰ Pharmacological properties inherent to the two statin types^{195,196} may have accounted for the differences in clinical outcomes seen in patients with HF. A closer observation of these data attributes the debatable outcomes obtained in HF trials to the hydrophilicity or lipophilicity of statins. Indeed, lipophilic statins have been shown to improve cardiac function and reduce inflammation better than hydrophilic statins in an indirect adjusted comparison meta-analysis involving ~6200 patients with HF from 19 RCTs.^{197,198} Given that the evidence from the comparisons favors lipophilic statin therapy, it is plausible that their superior pleiotropic effects coupled with cholesterol-lowering properties may have accounted for better clinical outcomes seen with many trials that evaluated lipophilic statins in HF and studies subsequent to CORONA and GISSI-HF.^{197,198} More recently, Bonsu et al¹⁹⁹ have shown in another study involving ~11,000 patients in 13 RCTs that lipophilic statin treatment significantly decreases hospitalizations for worsening HF and all-cause and cardiovascular mortality compared to rosuvastatin treatment.

In addition to well-known effects, statins have shown important modulation of a number of proposed pathways of novel approaches being evaluated for HF treatments. Several experimental studies have shown that, aside well-established pleiotropic properties, statins modulate novel pathways in the pathogenesis of HF.^{200–204} Statins have earlier been proven to improve cardiac function via increased expression of SERCA and RyR2 gene and protein in rat hearts.²⁰⁵ Further, rosuvastatin therapy attenuated both structural and functional deterioration of decompensated heart in the spontaneously hypertensive rat models. These

actions of rosuvastatin occurred together with decreases in collagen deposition but without changes in BP, LDL-C concentrations, or action potential prolongation, to prevent HF progression.²⁰³ Moreover, simvastatin treatment increased CaMKK β -dependent phosphorylation of AMPK and LKB1 and enhanced Rac1 activity in vascular walls, establishing an important role for statin in activation Rac-1-dependent signaling to possibly attenuate arterial stiffness in HF with a preserved EF.⁴⁸

In another spontaneously hypertensive rat model study, atorvastatin preserved cardiac dysfunction by positively altering calcium regulatory proteins and upregulating expression and activity of SERCA2a. Thus, the favorable effects of statins on calcium regulatory proteins may, in part, explain the mechanisms underlying their beneficial effect on cardiac function.²⁰⁶ Further, rosuvastatin has been shown to be effective in preventing LV remodeling and cardiac dysfunction via normalizing pSer16-phospholamban (PLB) levels, expression and activity of SERCA2a and SERCA, respectively, as well as elevating IL-10 levels and depleting IL-6 levels, independent of the lipid-lowering effect.²⁰⁷ Simvastatin was shown to prevent decreased SERCA2a activity as it inhibited sympathetic activity via β -adrenergic signaling. This occurred primarily by inhibiting sympathetic outflow and preventing reduced β 1-Adrenoreceptor density and intracellular cAMP levels in nonischemic HF rabbit models.²⁰⁸

Recently, a number of studies have further demonstrated diverse mechanisms by which statins improve cardiac function in various HF models. Rosuvastatin therapy exerts cardioprotective effects in end-stage hypertension via dephosphorylation of protein kinase C (PKC) α/β 2, causing resultant dephosphorylation of PPI-1 and augmented CaMKII expression. As a consequence, these mechanisms increases the expression of SERCA2a, RyR2, and Na⁺/Ca²⁺ exchanger but decreases PLB expression to exhibit the beneficial effects seen with statin treatment in HF with hypertension.²⁰¹

Rosuvastatin significantly reduces hypertrophy via AT₁R-PKC β 2/ α -ERK-c-fos pathway and prevents apoptosis of the myocardium via Akt-FOXO1, Bcl-2 family, and survivin pathways, consequently suppressing caspase-3 activity in the end-stage hypertensive heart disease.²⁰² Statin impairs LV remodeling and improves cardiac function of diabetic rats via mechanisms which are directly linked to repair of Ca²⁺ dysregulation and recovery of repolarizing K⁺ currents resulting from the inhibition of RhoA signaling pathway, independent of cholesterol-lowering effects.²⁰⁹ Simvastatin has been proven to prevent the progression of LV hypertrophy in nonischemic HF model through the inhibition of the

RhoA-PPAR γ -NF- κ B signaling axis associated with blockade of RhoA and Rho GTPase activity in the heart.²¹⁰

In a more recent study, pitavastatin was found to ameliorate the cardiac dysfunction in mice with dilated cardiomyopathy by reversing the changes in the ratios of phosphorylated PLB to total PLB, SERCA2a, and RyR2 via reducing the plasma AngII concentration and the expressions of myocardium AT₁R and PKC β 2. The possible underlying mechanism was proposed to be the regulation of myocardial AT₁R-PKC β 2-Ca²⁺ handling proteins.²⁰⁰

In clinical studies, the debate continues about statin treatment in HF since their role remains controversial following neutral outcomes of the two large RCTs – CORONA and GISSI-HF – which evaluated low-dose rosuvastatin. Several studies subsequent to these large trials have shown improved outcomes in HF and thus have raised issues about the design and the type of statins evaluated in CORONA and GISSI-HF.²

A recent meta-analysis of 15 prospective studies (n=45,110) assessing statin treatment in both HF with a preserved EF and HFrEF²¹¹ showed a significant reduction in all-cause mortality (risk ratio [RR] 0.71, 95% confidence interval (CI) 0.61–0.83) and rehospitalization rate for HF (RR 0.84, 95% CI 0.74–0.96) with statin treatment.²¹¹ The study reported that atorvastatin treatment appeared to reduce all-cause mortality (RR 0.61, $P=0.05$) and rehospitalization for HF (RR 0.44, $P=0.04$) compared to other statin treatment.²¹¹ Moreover, statin treatment has recently been reported to be associated with the reduced risk of HF hospitalization, all-cause, and cardiovascular mortality in a nationwide population of patients with HF (n=21,864) from the Swedish HF Registry.²¹²

Statin therapy is known to be clinically safe in HF contrary to earlier assertions and thus remains better alternative to be properly evaluated.^{175,176} Work on novel agents is worth commendation; however, these agents may not be clinically and commercially available until several years. In addition, new molecules require ample time to study and fully understand their safety in clinical use, thus making statins a better novel approach if they indeed modulate both conventional and several novel pathways to HF pathogenesis. Overall, statins have shown outcome benefits that require recommendation to treatment guidelines while we wait for novel agents that have shown huge promise in the treatment of HF to become clinically and commercially available. Statins may have significant outcome benefits for subgroups of patients with HF, if not all. Thus, a prospective study into whether statins improve outcomes in patients with HF and comorbid conditions such as diabetes where β -blocker treatment is contraindicated may be necessary. Further, the evaluation of

statins on outcomes in categories of patients who are known to be underrepresented in major clinical trials such as patients of Black African descent whom the efficacy of mainstay treatments – ACE inhibitors/ARBs and β -blockers – remain controversial may be considered.

Disclosure

The authors report no conflicts of interest in this work.

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