Chapter 2
Novel Therapies for the Prevention and Management of Acute Decompensated Heart Failure

Patrick T. Campbell and Sepehr Saberian

Acute decompensated heart failure continues to be a leading cause of hospital admissions in the U.S. and is the leading cause of hospitalization in patients >65 years of age [1]. Over the past three decades significant advances in understanding the complex pathophysiology has lead to the development of medical therapies that have improved outcome, unfortunately the overall mortality rate remains staggeringly high, 50 % at 5 years [2]. Hospitalizations for acute decompensated heart failure (ADHF) are a huge burden to the already over taxed health care system. Even with the advances in the medical therapies, the 30-day readmission rate for ADHF is 25 % [3]. While the management of chronic stable heart

P.T. Campbell, MD (✉)
Heart Transplant Institute, Baptist Health Transplant Institute, Little Rock, AR, USA
e-mail: Patcamp32@hotmail.com

S. Saberian, MD
Department of Cardiology, University of Illinois College of Medicine at Peaoria, Peoria, IL, USA

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failure has progressed, the management strategies and therapies for ADHF have changed little in the same time period [4]. The mainstay therapies for the management of ADHF are focused on rapidly improving symptoms of dyspnea, peripheral edema and decongesting the patient. Intravenous diuretics are recommended for decongestion and volume removal in all patients with evidence of significant volume overload. Concomitant use of IV vasodilators (nitroprusside, nitroglycerin and neseritide) in patients without evidence of hypotension can aid in decongestion and improve symptoms. In patients with reduced EF and evidence of decreased perfusion and hemodynamic compromise, intravenous inotropes can be used to improve and maintain cardiac output and end-organ perfusion. However none of the therapies have been shown to improve (and may actually increase) morbidity and mortality [5].

The past decade has produced several promising novel therapies for the prevention and treatment acute decompensated heart failure including natriuretic peptides, inotropes and vasodilators.

Modulators of Natriuretic Peptides and Renin Angiotensin Aldosterone System (RAAS)

Vasopeptidase Inhibitors

Vasopeptidase inhibitors (VPIs) are agents that block the activation of the angiotensin converting enzyme (ACE) and neutral endopeptidases simultaneously. ACE, an enzyme that converts angiotensin I into angiotensin II and degrades bradykinin, results in vasoconstriction, along with sodium and water retention. ACE-inhibition decreases the conversion of ANG-I to ANG-II and the degradation of bradykinin. Bradykinin promotes of the vasodilators; NO and prostacyclins [6]. ACE inhibitors are known to improve symptoms, quality of life and reduce hospitalization in the management of patients with congestive heart failure [7]. Neutral endopeptidase (NEP) is

an endothelial; membrane-bound metallopeptidase which catalyzes the degradation of vasodilator peptides, including Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), C-type Natriuretic Peptide (CNP), substance P, and bradykinin [8]. These agents act against the Renin-Angiotensin-Aldosterone System (RAAS), cause vasodilation, promote diuresis and natriuresis. NEP acts on both the vasodilatory peptides and simultaneously on vasoconstrictor peptides such as endothelin-1 and ANG-II [8].

Early trials using NEP inhibitors showed mixed results, with certain formulations caused vasoconstriction rather than vasodilation. The effect of NEP inhibition depends on the substrate available, if ANG-II and ET-1 are predominant the NEP inhibitor may result in vasoconstriction, as has been shown in the vasculature of the forearm [9]. Furthermore, the effects of increased natriuretic peptides (ANP) can be attenuated by upregulation of the RAAS and sympathetic nervous system. In clinical trials evaluating the effect of NEP inhibition on vascular tone, Candoxatril showed inconsistent results with no statistically significant benefit in lowering blood pressure compare to placebo [10]. In patients with congestive heart failure, similar results were observed despite noted elevation of ANP and BNP levels [11]. In the advent of ACE inhibitor agents backed by clinical trials, the potential synergistic effects gained from combination of ACE and NEP inhibition created new possibilities in treatment of congestive heart failure by further additional down regulation of the neurohormonal pathways (i.e. sympathetic nervous system and the RAAS pathway).

Earlier trials using Vasopeptidase inhibitors in animal models with hypertension showed significant long lasting effect in reducing the systolic blood pressure in rat models [12]. In hamster models with congestive heart failure, long-term treatment with omapatrilat improved cardiovascular outcomes compared to ACE inhibition with captopril [13]. The early human based trial; the OCTAVE (Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril) trial enrolled 25,000

hypertensive patients who were randomly assigned to either the NEP inhibitor Omapatrilat, or Enalapril. The study demonstrated a greater reduction in systolic blood pressure in the Omapatrilat treatment arm [14]. A smaller study comparing Omapatrilat to Lisinopril found a similar comparison and validated a dose dependent, long lasting effect of Omapatrilat in reduction of blood pressure [15]. In a limited study designed to evaluate the safety and efficacy of a combined NEP-I and ACEI (Sampatrilat) in African American patients with a history of decreased response to ACEI alone, demonstrated improved blood pressure reduction compared to ACEI mono-therapy [16]. The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial, which enrolled patients with congestive heart failure (NYHA II–III), demonstrated the beneficial clinical and echocardiographic effects of Vasopeptidase inhibitors. Omapatrilat therapy reduced cardiovascular death by 9 % compared to enalapril, however the primary end-point of death and heart failure hospitalization was not different between the groups [17]. In the IMPRESS trial; a head to head comparison between Omapatrilat and Lisinopril in a randomized control trial, noted that Omapatrilat led to lower incidence of hospitalization and reduction in symptoms while being equally well tolerated within a 12 week period [18].

Despite encouraging results, FDA halted the approval of Vasopeptidase Inhibitors due to the incidence of angioedema in the studied patients. The rate of occurrence was noted to be significantly higher in the OCTAVE trial (2.2 % vs. 0.7 %) compared to ACE inhibitor therapy. The cause of angioedema in patients with ACE inhibition and NEP inhibition was evaluated in select studies and partly attributed to the enzymatic activity of other amino and dipeptidyl peptidases. Further studies suggest the possibility of performing bio testing in order to predict the probability of angioedema prior to treatment [19]. Another factor contributing to lack of approval for NEP inhibitors is a lack of sufficient data in different patient populations; accounting for race, gender, age and medication formulations. Despite shown value in the

control of hypertension and clinical benefits in treatment of patient's with congestive heart failure, the risk of unpredictable life threatening angioedema caused a significant set back in the studies and promotion of Vasopeptidase inhibitors.

The concern for severe angioedema was addressed by combining NEP inhibitors with an ARB rather than an ACEI. The angioedema seen in early trials was related to excessive inhibition of the enzymes that degrade bradykinin including ACE and aminopeptidase P. ARB's do not block these enzymes and therefore reduce the risk of life-threatening angioedema. Entresto (sacubitril/valsartan) a neprilysin inhibitor and angiotensin receptor blocker (ARB) combination received FDA approval in July of 2015 after the PARADIGM-HF [20] (Prospective Comparison of ARNI [Angiotensin Receptor – Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial was stopped early for overwhelming evidence of benefit over standard ACEI therapy. PARADIGM-HF enrolled primarily NYHA Class II-III FC heart failure patients with elevated BNP levels. Patients were required to have been on prior ACEI or ARB therapy and have an EF <40 %. After 2 years of therapy the NEPI-ARB combination demonstrated significant reductions in the primary composite endpoint of death from cardiovascular causes and heart failure hospitalizations compared to enalapril therapy. The benefit was seen in the individual components as well, it significantly reduced death from cardiovascular causes and demonstrated a 21 % reduction in hospitalization for heart failure. Patients on Entresto had improved functional status, decreased heart failure symptoms and better reported quality of life. The angiotensin-neprilysin inhibitor did have higher rates of symptomatic hypotension and non-serious angioedema, but less cough, renal failure and hyperkalemia.

Sacubitril/valsartan has been approved for the treatment of NYHA Class II–IV heart failure with reduced ejection fraction. The recommended starting dose is 49/51 mg twice

daily and can be titrated to a recommended maximum dose of 97/103 mg twice daily. There are recommendations to starting at 24/26 mg twice daily for patients that have severe renal dysfunction, moderate hepatic dysfunction or have never been treated with ACEI/ARB. The significant benefit demonstrated by the PARADIGM-HF study is encouraging for the future of heart failure management. Its full benefits in routine clinical benefits remain to be seen, however ANRI therapy will likely rapidly become standard therapy for the management of chronic heart failure (Table 2.1).

Urodilatin/Ularitide

Natriuretic peptides (NP) have played a large role in the management and understanding of heart failure. Brain-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are released in response to increased myocardial stretch and BNP remains integral in the diagnosis of acute decompensated heart failure (ADHF). Early studies of the recombinant form of BNP (nesiritide) were encouraging, however recent data has failed to demonstrate a significant benefit in the treatment of ADHF [21] and controversy regarding its safety remain [22]. Recent focus has been placed on ANP and its potential therapeutic role in ADHF.

ANP is produced in the atrium primarily in response to increased mycocyte stretch, however ANP can also be released in response to several vasoactive and neurohormones including; epinephrine, vasopression, norepinephrine, angiotensin II and endothelin-1. ANP exerts its biological effects primarily through interaction with the natriuretic peptide receptor type A (NPR-A), the same receptor utilized by BNP. However ANP has up to 70 times the affinity for NPR-A and stimulates ten times greater activity of the NPR-A cyclase [23]. NPR-A receptors are located in a variety of organs and tissues including: vascular smooth muscle, endothelial cells, renal collecting ducts, adrenal glands, kidney, lung, liver and the heart [24, 25]. The binding of ANP to

Table 2.1 Summary of clinical trials for neprilysin inhibitors

Study/trial	Aim of study	Dose	Results
Octave	To evaluate the efficacy of Omapatrilat in patients with hypertension, compared to Enalapril	Omapatrilat 10–80 mg, titrated to reach goal BP < 140/90 Enalapril 5–40 mg, titrated to reach goal BP < 140/90 within 8 weeks, followed for 24 weeks with or without addition of adjuvant therapy to reach target BP goal	Omapatrilat resulted in clinically significant mean reduction of 3–4 mmHg in blood pressure compared to Enalapril Omapatrilat required less up titration of dosage to reach target blood pressure Use of adjuvant therapy post 8 weeks was higher in the Enalapril group Risk of angioedema in the omapatrilat treated patients was (2.17 %) compared to the enalapril treated group (0.68 %) Death and all adverse outcomes were similar between Omapatrilat and Enalapril
Overture	To evaluate the efficacy of Omapatrilat in patients with heart failure (NYHA class II–IV), compared to Enalapril	Enalapril 10 mg twice daily (n – 2884) compared to Omapatrilat 40 mg daily (n – 2886)	No statistically significant reduction in all cause mortality between Omapatrilat, compared to enalapril (hazard ratio 0.94, 95 % confidence interval 0.86–1.03, P = 0.187) Angioedema was more common with Omapatrilat. N = 24 (0.8 %)

(continued)

Table 2.1 (continued)

Study/trial	Aim of study	Dose	Results
Impress	To evaluate the efficacy of Omapatrilat on functional capacity and clinical outcomes in patients with heart failure patients, compared to lisinopril	Omapatrilat 40 mg once daily (n – 289) compared to lisinopril 20 mg daily (n – 284) for 24 week	Week 12 exercise treadmill test results improved similarly in the omapatrilat and lisinopril groups ($p=0.45$) Suggestive trend in favor of omapatrilat on combined endpoints of death or admissions for worsening heart failure ($p=0.052$; hazard ratio 0.53, 95 % Confidence interval 0.27–1.02) Omapatrilat significantly lowered combined death, admission, or discontinuation of study treatment due worsening heart failure ($p=0.035$) Omapatrilat improved NYHA class more than lisinopril in patients who had NYHA class III and IV ($p=0.035$), but not if patients with NYHA class II were included
Paradigm-HF	To evaluate the efficacy of ARB-NEP inhibitor on morbidity and mortality in heart failure patients compared to enalapril	ARB-NEP inhibitor titrated to 200 mg twice daily compared to enalapril titrated to 10 mg twice daily	Significant reduction in combined end-point of death from cardiovascular cause and heart failure hospitalization in the ARB-NEP inhibitor group 21 % ($p<0.001$) reduction in heart failure hospitalizations with ARB-NEPI Improved symptoms and quality of life in ARB-NEPI group

NPR-A results in increased intracellular concentrations of cGMP [23], resulting in natriuresis, diuresis, vasodilation and inhibition of the renal-angiotensin-aldosterone system (RAAS). In the kidney ANP affects both the renal vasculature and the medullary collecting ducts. ANP-NPR activation in the kidney increases sodium excretion by the collecting ducts enhancing natriuresis and diuresis. ANP acts directly on the renal vasculature vasodilating the afferent and vasoconstricting the efferent arterioles. The increased pressure in the glomerular capillaries results in increased glomerular filtration rate (GFR) [26]. The vasodilatory effects of ANP are mediated through direct increase in cGMP in vascular smooth muscle as well as antagonism of RAAS, vasopressin, epinephrine, endothelin and cytokines [27, 28]. ANP causes equal dilation of both the arterial and venous vasculature and some data suggests that it may have a role in vasodilation of the coronary arteries [24]. The metabolism and removal of ANP is primarily through NPR Type C (clearance) and enzymatic degredation by the neutral endopeptidase (NEP) system. In heart failure the effects of ANP are attenuated compared to healthy individuals even in the setting of increased circulating levels. Theories the attenuated effect of ANP in chronic heart failure include: chronic upregulation of ANP production results in the release of less biologically active molecules [29], downregulation of NPR-A receptors and increased NEP activity [30].

Carperitide is a recombinant form of ANP, currently approved in Japan for the treatment of ADHF. A small randomized controlled study (PROTECT) reported significant reductions in death and rehospitalization in patients with reduced EF (<35 %) treated with Carperitide [31], however large scale trials confirming these outcomes are lacking. The hemodynamic benefits of Carperitide are unclear, one study [32] failed to demonstrate improved hemodynamics (PCWP, RAP) with Carperitide compared to traditional intravenous vasodilators, while a more recent study [33] reported improved hemodynamic parameters compared with vasodilator therapy. The conflicting data regarding the hemodynamic

benefits of Carpertide may be due to increased degredation of ANP by the NEP system or the down regulation of NPR-A receptors in chronic heart failure. The two largest observational studies of Carperitide for the treatment of ADHF [34, 35] demonstrated similar results. Caperitide improved dyspnea scores in younger patients (<65 years) with Heart Failure with preserved EF (HFpEF) and mild/moderate decompensation without acute ischemia. The most common adverse event was hypotension, which occurred in 5–10 % of patients. Carperitide was less effective and caused significantly more hypotension in older patients, patients with acute myocardial ischemia and reduced renal function. The limited data regarding Carperitide seems to suggest a possible role in the treatment of patients with ADHF in the setting of hypertensive heart disease and/or HFpEF. Larger studies and more robust data are required before Caperitide can be recommended for routine treatment of ADHF.

Urodilatin is a modified pro-ANP produced in the kidneys, first osilated from human urine [36]. Urodilation binds to NPR-A receptors with equal affinity as ANP, and exerts similar hemodynamic effects as intravenous ANP [25]. Urodilatin differs slightly from ANP in molecular confirmation, which confers resistance to NEP degredation. Early studies of urodilantin demonstrated similar yet sustained hemodynamic effects compared to ANP, suggesting prolonged activity may be due to its resistance to NEP degredation [37]. Ularitide is a synthetic form of Urodilatin that has shown promising results in the management of ADHF. Animal studies demonstrated improved hemodynamic, natriuretic and diuretic effects from Ularitide administration. Early trials in patients with ADHF, both bolus [37] and infusions [38] of Ularitide resulted in decreases in PCWP, systemic vascular resistance and right atrial pressure (RAP). Ularitide favorably affected natriuresis and diuresis. Results from SIRIUS I, a pilot trial [39] demonstrated significant improvement in dyspnea and hemodynamics when Ularitide was added to standard HF therapy including diuretics. There was no difference in urine output between the ularitide and placebo groups, however the

Ularitide group received less frequent and lower doses of diuretics. The hemodynamic and possible diuretic benefits of Ularitide occurred without negative impact on renal function. Hypotension occurred in almost 17 % of the treatment group without impact on clinical outcomes. The highest dose of Ularitide was associated with greater hemodynamic benefits, but resulted in significantly greater hypotension (–17 mmHg in SBP). The follow-up, larger randomized SIRIUS II trial [40] confirm the results of SIRIUS I. Ularitide resulted in favorable reductions in PCWP, right atrial pressure (RAP), systemic vascular resistance (SVR) and improved dyspnea. The effects of ularitide were observed throughout the entire 24 h of infusion without deleterious effects on short-term outcome. An important finding in the SIRIUS II trial was a dose dependent decline in myocardial oxygen consumption in the treatment group. Further analysis of the SIRIUS II [41] data revealed the potential renal protective effects of the intermediate dose (15 ng/kg/min) of Ularitide in HF patients. Ularitide resulted in a favorable effect on the MAP-RAP pressure gradient (an estimate of renal perfusion) which improved renal perfusion and may have contributed to short-term preservation of renal function. Ularitide resulted in sustained MAP while simultaneously reducing RAP. Similar results were not observed in the highest dose, likely due to more substantial reductions in MAP. In patients with ADHF infusions of Ularitide seem to improve hemodynamic parameters, antagonize neurohormonal activity, improve diuresis, preserve renal function and reduce myocardial oxygen demand, however long-term clinical benefits have yet to be demonstrated. Ularitide has not be approved for routine use, however data from the SIRIUS trials suggest that the intermediate dose of 15 ng/kg/min may provide the desired benefits while potentially limiting the incidence and severity of hypotension. With concern regarding the efficacy and safety of other natriuretic peptides, the ultimate role of Ularitide in the treatment of heart failure remains to be seen. Future studies randomized trials are required to assess the long-term risk and benefits associated with natriuretic peptide therapy.

Vasodilator Therapies

Relaxin

Relaxin is a naturally occurring peptide that was first isolated from pregnant guinea pigs and rabbits [42] and later found to have cardiovascular effects including; increased cardiac output, increased arterial compliance and reduced SVR, along with increased renal blood flow, during human pregnancy [43]. Relaxin acts on multiple pathways with possible vasodilatory, angiogenesis and anti-inflammatory effects (Fig. 2.1). Relaxin exerts the majority of its effects through a g-protein coupled receptor, LGR-7, which has been isolated in human systemic vascular, renal vascular and cardiac tissues [46]. Relaxin acts

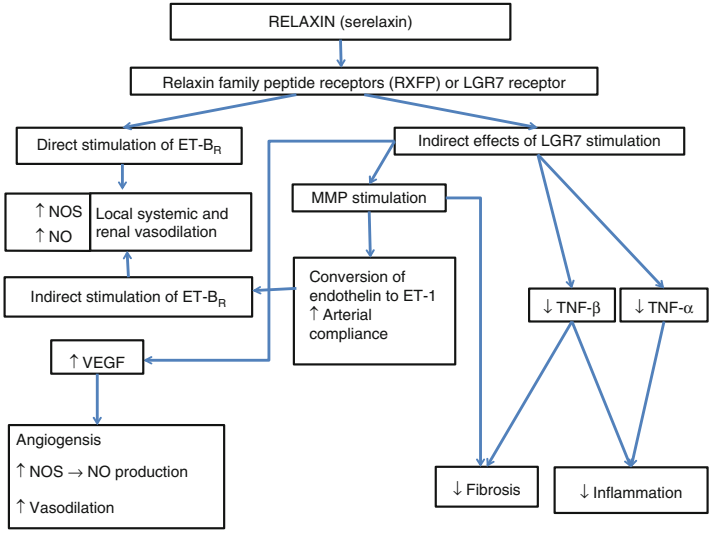

Figure 2.1 Effect of Relaxin Receptor activation by Serelaxin. Notes: *ET-BR* endothelin-B receptor, *NOS* nitric oxide synthase, *NO* nitric oxide, *MMP* matrix metalloproteinase, *VEGF* vascular endothelial growth factor, *TNF* tumor necrosis factor. (Adapted from Teichman [44] and Teichman [45])

through multiple pathways that ultimately result in increased nitric oxide (NO) production and vasodilation. One of the predominant pathways utilized by Relaxin is the endothelin system. The endothelin system comprises two major receptors, Endothelin-A (ET-A) receptors and Endothelin-B (ET-B) receptors. ET-A is responsible for vasoconstriction, while ET-B is primarily responsible for vasodilation in the vascular system. Relaxin has been shown to act both directly and indirectly on the ET system and may increase ET-B receptor expression [47]. The Relaxin-LGR-7 (RLX-7) ligand acts primarily by stimulating matrix metalloproteins 2 and 9 (MMP) which convert Endothelin (ET) into active $ET_{1\text{-}32}$. The activated $ET_{1\text{-}32}$ bind to ET-B receptors which then increase NO production and result in vasoldilation. The increased NO production results in vasodilation of both the systemic and renal vasculature. In the systemic vasculature the RLX-7 ligand can also directly activate the ET-B receptor resulting in increased NO production. There is evidence that RLX-7 increases local phosphatidylinositol 3-kinase and NO resulting in rapid vasodilation [48]. In the kidneys the RLX-7 ligand inhibits the Na/K+ ATPase, which may be the mechanism of the observed natriuresis and diuresis.

Few randomized clinical trials evaluating the efficacy and safety of relaxin for the management of heart failure have been published. The Pre-RELAX-AHF was a small, randomized pilot study that evaluated a 48 h infusion of escalating doses of Relaxin compared to placebo for the treatment of acute decompensated heart failure and mild to moderate renal dysfunction. The study demonstrated reductions in the composite endpoint of cardiovascular mortality, heart failure hospitalization or hospitalization for renal failure [49].

The larger RELAX-AHF study enrolled 1161 patients with acute decompensated heart failure with evidence of congestion (pulmonary congestion on chest x-ray and elevated BNP) and mild to moderate renal dysfunction (GFR 30–75 mL/min/m^2). Patients were randomized to a 48 h infusion of Serelaxin (30 μg/kg/day) versus placebo. Patients with SBP <125 mmHg were excluded from the trial.

The administration of serealxin resulted in significant declines in early worsening of heart failure, overall length of stay and ICU length of stay. The treatment group reported significantly greater mild reduction in dyspnea and earlier improvement in symptoms. There was a 37 % reduction in cardiovascular and all-cause mortality, however the study was not powered to assess mortality. Serelaxin was associated with greater rates of clinically significant hypotension requiring dose adjustment but less worsening renal function [50]. The major criticism of the RELAX-AHF trial was the generalizability of the data to the larger heart failure population. Patients in the study had significantly higher BP compared to most heart failure studies, almost half of the patients had ejection fraction >40 % and the vast majority (95 %) were Caucasian. While symptomatic improvement is important for the treatment of patients with ADHF, future studies are required to determine if the signal for improved mortality seen is real.

Inotropic Agents

Istaroxime

Istaroxime (Istaroxime-(E,Z)-3-[(2-aminoethoxy)-imino] androstane-6,17-dione is a novel drug with dual action that while unrelated to cardiac glycosides (digoxin) shares one similar mechanism of action. Istaroxime inhibits the Na+/K+ ATPase and simultaneously stimulates the sarcoplasmic endoplasmic reticulum calcium ATPase isoform 2 (SERCA2a), thereby affecting both myocyte contraction and relaxation [51]. The inhibition of Na+/K+ ATPase results in increased cytosolic calcium concentrations during diastole and intracellular Ca2+ concentrations is essential for sarcomere shortening and cardiac myocyte contractions. SERCA2a stimulation results in rapid reuptake of Ca2+ into the sarcoplasmic reticulum (SR) during diastole and enhances myocyte relaxation and lusitropy. The efficient uptake of Ca2+

into the SR also results in sufficient SR Ca2+ concentrations to facilitate subsequent cardiac contractions.

In the heart, calcium cycling is responsible for triggering the interaction between actin and myosin, which result in cardiac contraction. During systole, an action potential stimulates the influx of Ca2+ through L-type Ca2+ channels and the increase in intracellular Ca2+ induces release of Ca2+ from the SR through ryanodine receptor (RyR2) channels. The increased intracellular Ca2+ concentrations is responsible for the contraction of cardiac myocytes [52]. During diastole the RyR2 channels close, the Ca2+ dissociates from the myofilaments and intracellular Ca2+ decline. The rapid decline in intracellular Ca2+ concentrations result in myocardial relaxation, also referred to as lusitropy. There are three mechanisms by which the intracellular Ca2+ concentrations are decreased during diastole, the first is through rapid reuptake of Ca2+ into the SR by SERCA2a, which accounts for approximately 70 %. SERCA2a activity is modulated by phosphorylation of phospholamban (PLB), if unphosphorylated it inhibits the activity of SERCA, while phosphorylated phopholamban activates SERCA. Thus phosphorylated PLB is integral to lusitropy. The second is through the Na+/Ca2+ Exchanger (NCX), which moves Ca2+ extracellularly and is responsible for approximately 28 % of the Ca2+ reuptake. The final mechanism is through the plasma membrane Ca2+ ATPase [51, 53].

In the heterogeneity of heart failure calcium dysregulation has been demonstrated to play a role in certain etiologies. Calcium "leak" from the SR during diastole due to abnormal RyR2 channels has been demonstrated. This "leak" results in decreased Ca2+ availability during systole which decreases the contractile force generated by the myocytes [54]. Abnormal function of the SERCA2a pump has also been shown to impact both contraction and relaxation of the cardiac myocyte. Reduced SERCA activity results in decreased reuptake into the SR which results in creased concentrations of Ca2+ available during systole and sustained levels of intracellular Ca2+ during diastole results in decreased relaxation

and diastolic dysfunction [55]. Finally reduced phosphorylation of the PLB protein may also alter the efficiency of SERCA2a in heart failure, affecting both lusitropy and inotropy [56]. Istaroxime may improve cardiac calcium cycling thereby improving relaxation, contraction and the oxygen demand of the cardiac myocyte. In the mechanically challenged heart the reduction of SERCA2a activity results in upregulation of the NCX channels, extracellular exchange of Ca2+ for Na+. The increased NCX activity results in slower reduction of intracellular Ca2+ concentrations, negatively impacting cardiac relaxation and reducing the available Ca2+ for systole [57]. Furthermore it results in increased energy demands, the NCX pathway requires twice as much energy as the SERCA channels and requires increased Na+/K+ ATPase activity to maintain intracellular Na+ levels, all at an increased energy cost to the strained mycocardium [58].

Istaroxime has dual activity in the cardiac myocyte, it inhibits the Na+/K+ ATPase, which results in increased cytoplasmic concentrations of Ca2+ and simultaneously stimulates SERCA2a affinity for Ca2+. The increased SERCA2a activity improves both cardiac relaxation and contraction. The combined activity of Istaroxime, increasing systolic intracellular Ca2+ concentration and rapid sequestration of Ca2+ during diastole, result in both increased contractility and improved diastolic function. Early animal studies with Istaroxime resulted in improved inotropy and lusitropy. In a hamster model of dilated cardiomyopathy, long-term oral administration demonstrated mortality benefits [59]. The positive inotropic and lusitropic were observed without significant side-effects including arrhythmia, heart rate, blood pressure or myocardial oxygen demand. In a second animal study [60] similar beneficial effects of Istaroxime were demonstrated in hemodynamic and echocardiographic parameters in dogs. Dose-dependent improvement was seen in left ventricular ejection fraction (LVEF), End-diastolic pressures (LVEDP), end-diastolic (EDV), end-systolic volumes (ESV), stroke volume (SV), coronary blood flow (CBF) and deceleration time (DT). The hemodynamic improvements

were obtained without significant increases in myocardial oxygen consumption.

The HORIZON-HF was a large randomized, double-blind, placebo controlled study evaluating the effects of Istaroxime in patients admitted for decompensated heart failure with reduced ejection fraction (HFrEF) [61, 62]. The study included 120 patients between 18 and 85 years of age with reduced EF (<35 %) and a pulmonary capillary wedge pressure (PCWP) >20 mmHg on invasive hemodynamic assessment.. Patients were randomized to an infusion of 0.5, 1.0, 1.5 μg/kg/min of Istaroxime or placebo for 6 h. The primary endpoint was change in pulmonary capillary wedge pressure (PCWP) after 6 h infusion. Secondary endpoints included change in cardiac index (CI), right atrial pressure (RAP), systolic BP, diastolic BP, heart rate (HR), along with echocardiographic assessment of systolic and diastolic function. Other parameters assessed included neurohormones, renal function, and troponin. After the 6 h infusion Istaroxime significantly reduced PCWP compared to placebo in a dose dependent manner for all three doses. The greatest decline in PCWP (–4.7 mmHg) was observed in the 1.5 μg/kg/min dose compared to no change in the placebo group. Istaroxime also significantly increased SBP in the highest dose by 15 mmHg compared placebo. During infusion of the highest dose, Istaroxime improved cardiac index (CI) but was not significant at 6 h. Istaroxime improved regional and global myocardial systolic and diastolic function, and LV compliance as assessed by tissue-doppler echocardiography.

The improved PCWP and diastolic function were observed without significant adverse events, changes in neurohormones or increase in troponin. The lack of increase in troponin suggest that the inotropic and lusitropic effects of Istaroxime occurred without significant increase in myocardial oxygen consumption, these findings are consistent with the findings in the animal studies. The only significant adverse events noted were nausea, vomiting and injection site pain.

The data from current available evidence suggest Istaroxime may provide beneficial effects in patients with ADHF, without

significant adverse effects. The combination of increased SERCA2a activity and inhibition of the Na+/K+ ATPase channels results in improved energy balance, decreasing the myocardial oxygen consumption in the failing heart. The increased affinity of SERCA for Ca2+ improves both myocardial relaxation by increasing the rapid reuptake into the SR and improves myocardial contraction through increased availability of Ca2+. The data seems to suggest that Istaroxime improves cardiac Ca2+ cycling and increases intracellular Ca2+ concentrations without the risk of increased arrhythmogenesis [63]. In fact the HORIZON-HF study demonstrated a significant shortening of the QTc in patients treated with Istaroxime [61].

Although not currently FDA approved, recent literature suggest that Istaroxime may be beneficial in patients admitted for acute decompensated heart failure (NYHA Class II–III) with reduced LVEF. Data from the HORIZON-HF suggest doses between 0.5 and 1.5 μg/kg/min may be useful for the management of ADHF. Istaroxime has a 1 h half-life and reached steady state levels at 4 h after of infusion. Istaroxime is metabolized to three less active metabolites and is not excreted by the kidneys [61]. While the most benefit was seen in the highest dose, adverse events were more common at that dose. Future studies focused on in-hospital and long-term clinical outcomes are required to determine the future of this promising drug.

Levosimendan

Commonly used agents in patients with acute decompensated heart failure with systolic dysfunction are intravenous inotropic agents, of which B-adrenergic agonists and phosphodiesterase inhibitors encompass the majority. β-adrenergic agents augment the release calcium into the myocytes by increasing intracellular cAMP levels. Phosphodiesterase inhibitors perform a similar task by inhibiting the degradation of cAMP [64]. Increased intracellular calcium increases contractility, but is also associated with increased risk of arrhythmia and mortality [65]. Levosimendan is a new agent, which acts by sensitizing cardiac troponin C to calcium. This unique mechanism of action strengthens contraction without increasing oxygen demand, cAMP or intracellular

calcium concentrations [66]. Levosimendan functions by binding to the regulatory domain and the charged amino acids in the hydrophobic pocket of the calcium saturated N-terminal domain of the troponin C [67]. In a calcium dependent manner, Levosimendan stabilizes the conformation of calcium–troponin C complex through hydrophobic and electrostatic interactions. This results in accelerated actin–myosin cross bridge formation rate and reduces the speed of dissociation [68]. Levosimendan has also been shown to improve both peripheral and coronary vasodilation. The afterload reduction likely contributes to its effectiveness and the coronary vasodilation may improve cardiac myocyte oxygen mismatch [69].

The effect of Levosimendan is attenuated during diastole due to reduced intracellular Ca2+ concentrations as a result of active Ca2+ reuptake. This allows for appropriate left ventricular relaxation, while maintaining its inotropic properties during the systolic phase of the cardiac cycle [70]. Outside the cardiac myocyte Levosimendan stimulates ATP-dependent potassium channels in myocytes and vascular smooth muscle cells, resulting in vasodilatation [71]. Levosimendan is generally well tolerated in all clinical trials to date. The most frequent adverse effect is headache, hypotension, dizziness and nausea. These side effects are largely attributed to the vasodilatory effect of Levosimendan. Decrease in hemoglobin and hematocrit in higher doses have been reported, as well a mild hypokalemia without significant clinical outcomes.

Levosimendan is an infusion agent with a rapid onset of action, a short half-life of 1.3 h and an active metabolite known as OR-1986 [72]. OR-1986 is formed by the acetylation of Levosimendan metabolites formed by colonic bacteria upon its secretion. It is less plasma bound than its native parent and thus more potent. The peak concentration of OR-1896 is reached within 2–3 days post infusion and its effects may persist for 7–9 days [73]. The initial dosing recommended based on clinical trial is a bolus infusion of 6–12 μg/kg over 10 min, followed by a maintenance dose of 0.05–0.2 μg/kg/min over 24–48 h [74].

Several studies have evaluated the safety, efficacy and hemodynamic outcomes of Levosimendan in humans. An early randomized clinical trial in 146 patients with heart failure NYHA class III–IV, with known cardiac index of

<2.5 L/min/m^2 and elevated wedge pressure (PCWP) showed favorable results. This study concluded that Levosimendan was associated with a dose dependent increase in stroke volume and cardiac index and decrease in PCWP at various doses [75]. Clinical symptoms of dyspnea and fatigue were also improved without any clinical adverse effects. The LIDO (Levosimendan Infusion vs Dobutamine in Severe Low Output Heart Failure) study compared the effect of Levosimendan to Dobutamine. It was found that a significantly higher proportion of Levosimendan patients showed improved cardiac output (≥30 % increase) and a concomitant decrease in PCWP (≥25 %). It was also found that 180-day mortality was lower in the Levosimendan subgroup [76].

The CASINO (Calcium Sensitizer or Inotrope or None in Low Output Heart Failure Study) trial, patients with NYHA-IV classification and reduced left ventricular function showed statistically significant reduction in mortality in a 6-month period compared to patients treated with Dobutamine [77]. From a mortality perspective, The SURVIVE study evaluated 1327 hospitalized patients with acute decompensated heart failure found early benefits from the use of Levosimendan but no difference in mortality and incidence of adverse effects [78]. The REVIVE II study; which evaluated 600 patients with acute decompensated heart failure, demonstrated that Levosimendan in addition to standard therapy was superior to standard therapy alone and resulted in a shorter duration of hospitalization. There was no significant difference in 90-day mortality and concerns were raised regarding an increased rate of arrhythmias [79].

Use of Levosimendan in patients with cardiogenic shock has shown favorable results in those treated in conjugation with catecholamines for restoration of hemodynamics. While studied in a small sample size, Levosimendan treatment resulted in a significant increase in cardiac output together with a decrease in systemic vascular resistance and decreased

mortality at 6 months [80, 81]. The RUSSLAN (Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure due to an Acute Myocardial Infarction) trial evaluated 504 patients with reduced left ventricular ejection fraction due to recent myocardial infarction. Use of Levosimendan was associated with decrease in mortality and worsening heart failure compared with placebo at 6 and 24 h after the infusion with lower all-cause mortality at 14 days in the treatment group. This lower mortality persisted at 180 days but without a statistically significance [82]. On going large clinical trials including the LION-Heart, LAICA and ELEVATE are underway evaluating the role intermittent dosing of Levosimendan in overall mortality and hospitalization rate.

Major contraindications to Levosimendan include moderate to severe renal impairment, severe hepatic impairment, ventricular filling and outflow obstruction, hypotension, tachycardia and a history of Torsades de pointes. No dose change is required for mild renal or hepatic insufficiency. Levosimendan is administered as loading dose of 6–12 μg/kg over 10 min. It is followed by infusion 0.05–0.2 mcg/kg/min for up to 24 h. Levosimendan administration has been well tolerated when co-administered with standard heart failure therapies; ACE inhibitor, B-blockers, Isosorbite mononitrate, warfarin and digoxin, without significant drug-drug interactions [83]. The European society of cardiology recommends against the use of Levosimendan in patients with significant hypotension (SBP < 85 mmHg). Use of Levosimendan is not yet approved by the FDA. Levosimendan has since been approved by many European countries and used when indicated. Current clinical trails have largely been conducted in European countries. Evidence supporting the role of Levosimendan in improving and restoration of hemodynamics in patients with decompensated heart failure are many. Its role in reduction of mortality in long term follow up and appropriate intermittent dosing are current topics in ongoing clinical trials (Table 2.2).

Table 2.2 Summary of Levosimendan clinical trials

Study/study	Aim	Dose	Results
LIDO	To evaluate the effects of Levosimendan on hemodynamic performance and clinical outcomes in heart failure patients, compared to Dobutamine	103 patients assigned to Levosimendan and given an infusion of 24 μg/kg over 10 min, followed by a continuous infusion of 0.1 μg/kg/min for 24 h. 100 patients assigned to Dobutamine and infused for 24 h at an initial dose of 5 μg/kg/min	The primary hemodynamic endpoint (30 % increase in cardiac output or 25 % decrease in pulmonary capillary wedge pressure) was achieved in 29 (28 %) Levosimendan-group patients and 15 (15 %) in the Dobutamine group (hazard ratio 1.9, 95 % Confidence interval 1.1–3.3, p = 0.022) At 180 days, 27 (26 %) Levosimendan-group patients had died, compared with 38 (38 %) in the Dobutamine group (hazard ratio 0.57, CI 0.34–0.95, p = 0.029) Both Levosimendan and Dobutamine increased heart rate by a modest and similar amount Renal and Liver dysfunction declined in the Levosimendan group Clinical symptoms of dyspnea and fatigue improved more so with Levosimendan, however not statistically significant

CASINO	To evaluate the efficacy of Levosimendan on composite of death or re-hospitalization in heart failure patients compared to placebo or Dobutamine	299 patients with decompensated heart failure (Ejection fraction <35 %) receiving 24 h infusion of Levosimendan, placebo or Dobutamine	The study was designed to recruit 600 patients, but it was stopped after 299 patients had been recruited due to clear superiority of Levosimendan versus placebo or Dobutamine 6 months mortality was 18 % in the Levosimendan treatment group, 42 % in the Dobutamine group and 28.3 % for placebo
SURVIVE	To evaluate the effect of Levosimendan on clinical outcomes in patients with heart failure compared to Dobutamine	1327 patients with heart failure (Ejection fraction <30 %) receiving Levosimendan (n – 664) with bolus dose of 12 μg/kg followed by dose increase of 0.1–0.2/kg/min for 24 h or Dobutamine (n – 663) with a continuous dose of 5 μg/kg/min	Mortality rates in patients treated with Levosimendan was not significantly superior to Dobutamine (26 vs. 28 %, respectively, Hazard ratio 0.91 (95 % Confidence interval 0.74–1.13, P = 0.401) Levosimendan use was attributed to higher rates of Atrial Fibrillation compared to Dobutamine (9.1 % vs. 6.1 %) Levosimendan use was associated with lower incidence of heart failure worsening (12.3 % vs. 17 %) compared with Dobutamine Incidence of hypotension and ventricular arrhythmias were similar

(continued)

Table 2.2 (continued)

Study/study	Aim	Dose	Results
REVIVE II	To evaluate the effect of Levosimendan on Clinical outcomes in patients with heart failure as adjuvant therapy to standard therapy	600 patients with heart failure (Ejection fraction <30 %) receiving Levosimendan with bolus dose of 12 μg/kg followed by dose increase of 0.1–0.2 μg/kg/min for 24 h. Patients were followed for up to 4 days post infusion completion	Levosimendan treatment was associated with improved outcomes (19.4 % experienced improvement in clinical findings vs. 14.6 % in placebo, p = 0.015), Levosimendan use was associated with decrease in duration of hospitalization by approximately 2 days ((7.9 vs. 8.9 days in placebo, p = 0.001) No significant reduction in mortality was observed within the follow up period Levosimendan use was associated with higher incidence of hypotension (50 % vs. 36 %), Ventricular Arrhythmias (25 % vs. 17 %) and Atrial Fibrillation (8 % vs. 2 %) compared to placebo

RUSSLAN	To evaluate the effect of Levosimendan on clinical outcomes in patients with left ventricular failure due to as acute myocardial infarction	504 patients treated with Levosimendan with four different loading doses (0.1–0.4 μg/kg/min) for 6 h compared to placebo	The incidence of ischemia with or without hypotension was similar in all treatment groups (P = 0.319) An increase in Incidence of myocardial ischemia and/or hypotension was seen in the highest Levosimendan dose group Levosimendan was associated with lower risk of death and worsening heart failure, compared to placebo during the 6 h infusion (2.0 % vs. 5.9 %; P = 0.033) and over 24 h (4.0 % vs. 8.8 %; P = 0.044) Levosimendan was noted for decreased mortality compared with placebo at 14 days (11.7 % vs. 19.6 %, hazard ratio 0.56, 95 % CI 0.33–0.95, P = 0.031) and the reduction was maintained at the 180-day retrospective follow-up (22.6 % vs. 31.4 %, Hazard ratio 0.67, 95 % confidence interval 0.45–1.00, P = 0.053)

Omecamtiv Mecarbil

Myocardial contraction by the sarcomeres within the myocytes is initiated through the transduction of chemical into mechanical energy. The force generating structures within the sarcomeres consist of actin and myosin, which are regulated by regulatory proteins troponin and tropomyosin. Each myosin complex consists of two myosin heavy chains and two light chains. Each myosin heavy chain head consists of an ATPase complex that cleaves ATP to produce energy, as well as an actin-binding site. Cardiac troponin and tropomyosin form a complex that regulates the interaction of myosin with actin in a calcium dependent process [84]. Increased calcium concentration via depolarization of the myocytes causes binding of calcium to cardiac troponin and dissociation of the troponin-tropomyosin complex. This process allows for actin-myosin cross bridge formation and hydrolysis of ATP to ADP + Pi. The subsequent release of the Pi results in bending of the myosin head, producing a 10-nm stroke. Calcium is then stored in the sarcoplasmic reticulum waiting for the next cycle of myocardial activation. The actin-myosin cycle is quintessential in generation of the myocardial force and contractility [85]. The current drugs that influence the cardiac contractility act by increasing intracellular cAMP and Calcium. These agents have been associated with hypotension and increased myocardial demand due to the increased myocardial oxygen demand. These agents, in the setting of ongoing myocardial ischemia and decompensated heart failure, are associated with increased risk of arrhythmias and mortality [86].

Omecamtiv Mecarbil, known as CK-1827452, is the fourth candidate compound produced which increases the cardiac myosin ATpase activity but not other muscle myosins. It has a half-life that ranges from 17.1 to 21 h. It is the only compound of its class that was studied in human populations and is considered the successor to previous models that showed favorable results in animal models only [87]. Omecamtiv Mecarbil functions by improving energy mobilization and

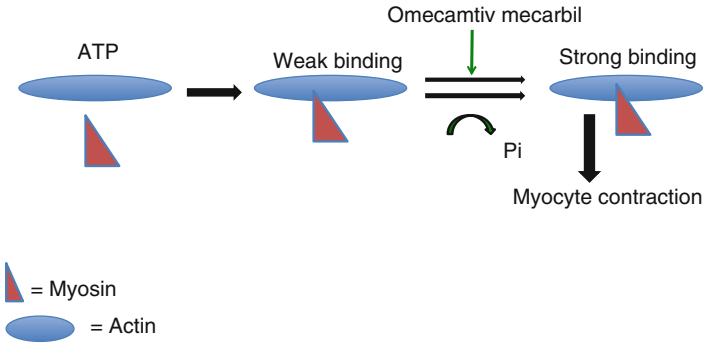

FIGURE 2.2 Mechanism of action: Omecamtiv Mecarbil. *Pi* phosphate (The mechanism of action of Omecamtiv Mecarbil; increasing rate of strong binding through increased rate of phosphate release from myosin, which is the rate limiting step of myocyte activation)

enhancing the myosin-actin cross bridge formation and duration [88]. It also facilitates the release of the phosphate group from myosin heads; thereby increasing the time spent contracting without altering the velocity of the contraction [89]. Omecamtiv Mecarbil increases the rate of transition from weakly bound myosin-actin filaments to the strongly bound state, which enables the myocyte contraction (Fig. 2.2). There are no changes in calcium concentrations within the sarcoplasmic reticulum or the calcium made available for each cycle [90]. Earlier animal studies in rat and dog models with left ventricular hypertrophy and heart failure, utilizing Omecamtiv Mecarbil showed a 20 % increase in left ventricular ejection fraction, systolic time, systolic wall thickening and stroke volume [91]. Interestingly, the studies also showed a reduction in left ventricular end diastolic pressure, mean left atrial pressure and heart rate with no changes in blood flow to the endocardium and myocardial oxygen demand.

In the first human study with Omecamtiv Mecarbil, 34 patients were randomized and received 6-h infusions weekly for 4 weeks. Echocardiograms were obtained prior and post

administration of infusions. Researchers found a linear dose dependent increase in left ventricular systolic time and statistically significant changes in ejection fraction and fractional shortening [92]. Doses that were well tolerated were infusions at 0.625 mg/kg/h and below. Patients receiving higher doses developed signs and symptoms of myocardial ischemia due to severe prolongation of the systolic ejection time, thereby decreasing the diastolic time and coronary perfusion. A second randomized clinical trial evaluated 45 patients with known heart failure with ejection fraction <40 %. This study concluded that Omecamtiv Mecarbil was associated with improved systolic ejection time, stroke volume and fractional shortening in a concentration dependent manner with no changes in the E/E′ or S′ [93]. Three patients were found to have elevated cardiac biomarkers out of the 151 infusions during this study. Two patients showed sign and symptoms of myocardial ischemia; one due to accidental overdose while the other was attributed to poor mechanisms of clearance and therefore increased plasma concentrations beyond predicted values. A phase II clinical trial that evaluated the role of Omecamtiv Mecarbil on patients with ischemic cardiomyopathy found no clinically significant deleterious effect in patients with serum concentrations that improved cardiac function [94]. The ATOMIC-AHF trial randomized 613 patients with left ventricular systolic dysfunction who were admitted for worsening dyspnea. This study showed no significant benefit at lower serum concentrations in improving symptoms. Although the study did not reach clinical significance in the primary end-point, there was improved dyspnea in patients on the highest dose of omecamtiv mecarbil. Interestingly there were also signals of decreases in worsening heart failure and ventricular arrhythmias [95].

Omecamtiv Mecarbil has shown a dose and concentration dependent effect on cardiac function. The recommended initial infusion dosing based on early human studies was 0.125 mg/kg/h; in which increase in systolic ejection time, fractional shortening and stroke volume are noted. Doses up to 0.625 mg/kg/h were well tolerated during studies.

Improvement in ejection fraction was noted at doses of 0.5 mg/kg/h or greater. Adverse outcomes were attributed to plasma concentrations exceeding 1200 ng/mL and were universally attributed to decreased diastolic filling time and coronary perfusion. All research thus far in evaluating the pharmacokinetics and effect of Omecamtiv Mecarbil has provided guidelines for appropriate dosing selection and monitoring for future trials. The role of Omecamtiv Mecarbil in patients with acute decompensated heart failure with NYHA III–IV with inadequate cardiac output remains under evaluated with no answer in sight with regards to clinical effects on quality of life, morbidity and mortality. Required IV infusions and serum concentration monitoring may represent further challenges. Having established grounds regarding appropriate dosing, concentration monitoring, tolerability, and improved cardiac function, further studies are warranted in the evaluation of this novel agent in the management of decompensated heart failure with reduced ejection fraction.

Adjunctive Therapies

Tolvaptan

Vasopressin is a 9 amino acid peptide, which is produced by the magnocellular neurosecratory cells of the supraoptic nucleus and the paraventricular nucleus of the hypothalamus. It is stored in the posterior pituitary and secreted into the systemic circulation [96]. The release of Vasopressin is primarily driven by changes in serum osmolality as detected by specialized sensors in the brain, and changes in circulating blood volume as perceived by baroreceptors in the carotid sinus, the atria, pulmonary trunk and stretch receptors in large veins [97, 98]. Vasopressin functions by acting on the cells within the collecting ducts of the kidneys, where the insertion of unique water channels (called aquaporin 2) into the luminal membrane allow for free water reabsorption into the systemic circulation [99]. Vasopressin receptors are

G-protein receptors of which three types are known, V_1, V_2 and V_{1B}. V_1 receptors are abundant in vascular smooth muscles and cause vasoconstriction upon activation. V_2 receptors mediate the antidiuretic response in the collecting ducts of the renal tubules while the V_{1B} receptors in the anterior pituitary mediate the release of adrenocorticotropic hormone and endorphins [100, 101].

Tolvaptan is an oral Vasopressin antagonist first described in 1998 [102] and approved by the FDA in 2009 for the treatment of hypervolumic or euvolumic hypotonic hyponatremia (Defined as serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has persisted despite adequate volume restriction). Tolvaptan antagonizes the V_1 and V_2 receptors, thereby preventing free water reabsorption. It binds V_2 receptors with an affinity 1.8 times greater than inherent Vasopressin and 29 times greater than V_1. Tolvaptan has a half-life of approximately 9.4 h. It is plasma protein bound with a peak concentration of 2 h with no alteration in effect by food intake [103]. The majority of the metabolism occurs in the liver through the CYP3A4/5 enzymatic mediated process, while a small fraction of its clearance is medicated by the renal system. Vasopressin is primarily released in response to a hypovolemia and hypotension. In a seemingly paradoxical response vasopressin levels are not suppressed and may even be elevated in heart failure. The up regulation of vasopressin in heart failure results in increased vasoconstriction, increased salt and fluid retention. These effects are similar to the effects seen as a result of the up regulation of the RAAS system, which has been associated with a poor prognosis in patients with known systolic dysfunction via retention of free water and resulting hyponatremia [104].

The SALT-1 and SALT-2 trials were the initial large randomized clinical trials, which evaluated the effect of Tolvaptan on euvolemic and hypervolemic, hyponatremic patients. Heart failure patients comprised 33 and 29 % of enrolled patients in the SALT-1, and 29 % in the SALT-2 trial, respectively [105]. Both trials concluded that Tolvaptan could be safely administered in a 30-day period to increase serum NA^+ concentrations

through removal of excess free water. The role of Tolvaptan in heart failure patients has been analyzed in many clinical trials. Early randomized studies in patients with heart failure symptoms showed weight reduction and normalization of sodium concentrations without amendments in quality of life, reduction of systolic or diastolic blood pressures or negative impact on renal function [106]. The ACTIV in CHF (Acute and Chronic Therapeutic Impact of Vasopressin Antagonist in Congestive Heart Failure) trial studied the effect of Tolvaptan in hospitalized individuals with known LV dysfunction who presented with worsening symptoms of their heart failure. Gheorghiade M et al. showed a statistically significant reduction in weight and dyspnea in the treatment group compared to placebo in a short-term analysis (up to 10 days) with no significant difference in worsening HF between the two groups during the outpatient follow up period of the study [107]. The EVEREST (Efficacy of Vasopresin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial randomized 4133 patients presenting with HF symptoms and reduced EF to either tolvaptan or placebo. The authors found improvements in dyspnea, weight loss and edema in the treatment group. Importantly these benefits occurred without significantly higher incidence of adverse events including hypotension, hypernatremia or renal failure [108]. The ECLIPSE (Effect of tolvaptan on hemodynamic Parameters in Subjects with Heart Failure) trial analyzed the hemodynamic effect of Tolvaptan in heart failure patients with NYHA III & IV. It concluded that no significant changes in cardiac index, pulmonary vascular resistance, and systemic vascular resistance were noted in the treatment group while a statistically significant decrease in peak change in PCWP was noted from 3 to 8 h after Tolvaptan administration [109]. The METEOR (Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction) study subsequently failed to show a significant change in LV ejection fraction post 1 year of therapy with Tolvaptan 30 mg/daily in 240 patients with LV function <30 % [110].

While trials showcasing the effect of Tolvaptan in treatment of heart failure are lacking clinical findings in reduction of mortality, quality of life and re-hospitalization; other studies have evaluated its role as an adjuvant therapy in patients with volume overload and hyponatremia. An independent study in Japan showed favorable results, including increased diuresis, using Tolvaptan in patients with congestive heart failure in patients unresponsive to loop diuretics without electrolyte abnormalities within 7 days of therapy [111]. Another single center trial validated the role of Tolvaptan in the treatment of acute decompensated heart failure in addition to loop diuretics; in preventing renal injury, decreasing the required doses of diuretics and reducing the time to achieve euvolemia [112]. The AVCMA trial which studied the role of Tolvaptan vs. Carperitide (An intravenous natriuretic peptide), showed favorable results in maintaining electrolyte balance in conjunction with loop diuretics without significant hypernatremia or hemodynamic derangement [113].

The efficacy of Tolvaptan in patients with hyponatremia is well defined. Hyponatremia has been evaluated as an independent risk factor attributed to poor outcomes in patients admitted for decompensated heart failure [114]. In an era where the mainstay therapy for acute decompensated heart failure are loop diuretics; of which the most profound side effect is electrolyte abnormalities, Tolvaptan may offer a novel strategy to alleviate hyponatremia while assisting in diuresis. As mentioned before, several studies have shown the benefit of Tolvaptan in addition to loop diuretics. These studies are performed in Japan and as such cannot necessarily be generalized to other patient populations without further studies. FDA has approved the use of Tolvaptan for durations less than 30 days with recommendations against use in patients with hepatic insufficiency. It is mandated that Tolvaptan be initiated and or restarted in an inpatient setting where serum electrolytes can be monitored closely as rapid reversal of sodium concentrations can precipitate osmotic demyelination, leading to seizures, coma and death.

It is available in 15, 30 and 60 mg dosing. The recommended initial dose is 15 mg daily with titration to 30 mg after 24 h and subsequently 60 mg daily as needed to reach appropriate levels of sodium concentration. Tolvaptan is contraindicated in patients who are anuric, need an urgent rise in serum sodium, in those unable to respond to thirst, hypovolemic hyponatremia and in patients with concomitant use of strong CYP 3A inhibitors. The most common side effect of Tolvaptan noted in all clinical trials included thirst, dry mouth and polyuria. It is generally well tolerated with no significant increase in adverse effects on renal function. There are currently no guidelines for the treatment of heart failure with Tolvaptan; as such its use has been dependently driven on the comfort level of individual providers. Its efficacy in conjunction with loop diuretics, duration of therapy and the appropriate dosing remain understudied in larger patient populations within the United States. Given its relative safety profile; it is imperative for randomized clinical trials to evaluate the role of Tolvaptan from an inpatient perspective in patients with heart failure to further evaluate its efficacy in reducing symptoms, length of hospitalization, electrolyte abnormalities, renal and hepatic dysfunction and all cause mortality as an adjuvant therapy.

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