The pathophysiology of AHF—New insights from recent studies of novel diuretics and vascular modulating therapies

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ABSTRACT

Treatment of chronic congestive heart failure (HF) has improved substantially during the past decades, with the introduction of modulators of the renin angiotensin aldosterone system (RAAS) such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and aldosterone antagonists and the introduction of the lifesaving beta-blockers as well as device therapy. Despite the dramatic improvement in the treatment of chronic HF, no such progress was achieved in the treatment of acute heart failure (AHF). Diuretics that were never rigorously examined in well controlled large prospective randomized studies remain the cornerstone and almost exclusively the only intravenous therapeutic option for AHF and no further effective therapy as introduced in more than 30 years. As a result, the short term morbidity and most importantly mortality of AHF remains extremely high with up to 20% of patients dying in the first months after admission for AHF and an additional 20% being readmitted to the hospital. In the current manuscript we will address the practical concerns regarding established and novel diuretic and vascular modulating therapies in patients with AHF, examine their recommended use and seek to determine a path to developing better and more effective therapies for AHF.

Keywords: Heart Failure; Treatment; Novel

1. INTRODUCTION

Acute heart failure (AHF) accounts for 1 million hospitalizations yearly and continues to contribute an enormous burden on healthcare services in North America and Europe [1-3]. An admission for AHF represents a major turning point for the heart failure (HF) patient. Not only do symptoms and signs of HF deteriorate or fail to improve fully during the admission [4-8]—10% to 15% experience worsening heart failure (WHF) during the admission and 30% of patients are discharged with persistent congestive symptoms and signs—but during admission and the first months post discharge approximately 20% of patients die and another 20% will be re-admitted, one of the worst outcomes in medicine. Despite this staggeringly poor outcome we have repeatedly failed to develop new therapies for AHF. This failure relates in part to poor selection of candidate interventions to be examined in phase III studies, inappropriate patient selection (attempting to develop drugs that would improve the outcomes of all AHF patients regardless of phenotype) and poor execution of studies (endeavoring to perform the studies in a generic manner engaging non-expert sites and generic operational processes not geared towards AHF).

The importance of making an effort to match novel interventions with the appropriate phenotype of AHF cannot be over stated. Many studies in AHF failed primarily because they were designed to address AHF in all comers regardless of their specific characteristics. Examples abound such as administering drugs with potential hypotensive effects to patients with low blood pressure at admission or ignoring the importance of end organ damage, especially renal impairment, in AHF. About 30% of patients hospitalized with AHF have significant renal impairment, which may further increase risk for in-hospital and post discharge adverse events [6,9-21]. Patients presenting to the hospital with low blood pressure tend to have higher rates of kidney dysfunction at admission [22], and these patients are at significant risk for further renal function deterioration driven by hypotension. Furthermore, until recently AHF was not considered a specific entity and most authorities regarded it just as "chronic heart failure that went slightly bad"—mostly due to non-adherence with dietary and medical recommendations—ignoring the vast increase in mortality and morbidity observed after an AHF episode that cannot be attributed to simple non adherence. This high rate of

adverse outcome may relate to widespread neurohormonal activation and end organ damage that occur during the first days of an AHF episode [15-22]. And hence, their prevention may be of great importance in devising new and effective therapies for AHF.

Another important issue that plagues AHF drug and intervention development is lack of understanding of the importance of study execution in meeting study objectives. Objective criteria are unavailable for diagnosing AHF and assessments of most of the treatment targets (dyspnea improvement, HF specific disease exacerbations) are subjective. Patients are elderly (generally over 65 years) and need to be recruited early in the admission for most intravenous therapy studies. These practical considerations necessitate that study design, site selection, procedures, and data management are critical to the study success as much and sometimes more than the drug to be examined. Regretfully, many AHF studies were performed on general cardiovascular operational platforms with reduced attention to the above mentioned details leading to potential enrolment of inappropriate patients and partial assessment of outcomes, reducing the ability to detect the "true effect" of the intervention.

As a result, over the last decades, ever since modern therapy for AHF was attempted, the non-potassium sparing diuretics, especially loop diuretics given intravenously, have been the mainstay of therapy for AHF. This therapy is used in the great majority of patients with AHF [23,24] and is recommended as the first-line therapy by the 2010 practice guidelines of the Heart Failure Society of America [25] and 2012 guidelines of the Heart Failure Association of the European Society of Cardiology (ESC) [26] despite the fact that loop diuretics have an established negative side-effect profile (e.g. neurohormonal activation, electrolyte abnormalities, and decreased renal function) and at high doses have been correlated with increased mortality [27-29]. All attempts to develop and introduce new therapies for AHF in the last 30 years failed, leaving the treating physician with virtually no effective therapeutic options to treat these patients and no proven way to improve the dire outcomes facing them. In the current manuscript we examine the therapies currently available for the treatment of AHF and highlight new therapeutic options and pathways to developing interventions that would modify the disease process beyond short term symptom relief.

2. STRATEGIES TO REMOVE FLUIDS AND DIURETICS

Diuretics have been the cornerstone of therapy for heart failure for more than 200 years. Studies examining the role of diuretics in AHF were for the most part small and done 20 - 30 years ago when biomarkers for organ damage were not available. Hence, little is known of the effects of these drugs in this respect. In recent years, loop diuretics and other diuretics and novel strategies to remove fluids were examined in prospective studies.

Loop diuretics: The small DOSE study [30] randomized patients with AHF to either bolus or continuous IV administration and a "low dose" versus an "intensified dose" strategy in which the patients were administered in the initial 24 hours a loop diuretics dose that was the same as the dose administered chronically prior to the admission or a dose 2.5 times higher. The study results showed that continuous administration of IV furosemide was largely equivalent to bolus administration. However, administration of higher doses of IV furosemide was associated with slightly (and borderline statistically significant) increased improvement in dyspnea and partially better decongestion as measured by body weight and other symptoms and signs of HF. These modest effects did not translate into prevention of WHF during admission or shortening of length of stay (LOS). Equally, higher doses of IV furosemide were not associated with less organ dysfunction; to the contrary, markers of renal impairment such as creatinine changes were more pronounced in the high dose furosemide arm during the first few days of admission (but not at later time points). Moreover, high dose IV furosemide had no effect on readmissions or mortality. These results suggest that beneficial effects on further decongestion on the one hand and some more worsening renal function on the other potentially balance each other and lead to an overall lack of improvement in outcomes. A diuretic intervention in AHF should ideally promote decongestion without causing (or preferentially preventing) end organ damage, especially worsening renal function. As symptoms related to congestion are the main reason patients with AHF seek care [23], loop diuretic therapy remains a central key in AHF therapy because they confer fast relief of symptoms. A variety of loop diuretics are currently on the market, of which furosemide tends to be the most often prescribed for patients admitted with AHF. Loop diuretics are recommended by both US (Strength of Evidence B) and European (Class I, level of Evidence B) guidelines to be administered intravenously to patients admitted for AHF [25,26]. Until better therapies are approved that provide both decongestion and symptom relief, as well as protect AHF patient from ongoing organ damage and adverse outcomes, IV loop diuretics at a dose similar or higher than the patients' daily oral dose will remain first line therapy in patients with AHF.

Adenosine blockers: The adenosine receptor blocker rolofylline was shown in small studies to enhance diuresis and protect renal function. In the PROTECT phase III study rolofylline was examined in approximately 2000 patients with AHF and history of chronic HF and renal impairment who were not responsive to an initial dose of

IV loop diuretics. Rolofylline [31] slightly (and statistically significantly) improved decongestion as evident by more relief of dyspnea at 24 and 48 hours from randomization, improvement of symptoms and signs of heart failure and greater weight loss, translating into small decreases in WHF and reduction of LOS. Rolofylline treatment was associated with some trends towards further creatinine increases, and no effects on read-mission and death, again emphasizing the need to both improve congestion and prevent end organ damage as a cornerstone of AHF therapy. Neither rolofylline nor any of the drugs in this class has been approved or considered for further development, mostly due to the adverse neurological side effect profile.

Vasopressin antagonists*: *Tolvaptan is an oral, selective vasopressin V2-receptor antagonist that acts upon the distal nephron to promote aquaresis [32]. Data from phase 2 trials have shown that this agent can relieve signs and symptoms of congestion and correct hyponatremia, without significantly altering BP or renal function [33,34]. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) evaluated the effects of tolvaptan on clinical outcomes in patients hospitalized for AHF [35-38]. Tolvaptan demonstrated very mild effects on decongestion not accompanied by protection from end organ damage and no improvements in either short or long term outcomes. Currently, tolvaptan (Samsca®) is approved by the US FDA (since May 2009) as the only oral selective vasopressin antagonist for the treatment of patients with clinically significant hypervolemic and euvolemic hyponatremia including patients with heart failure, cirrhosis, and the syndrome of inappropriate anti-diuretic hormone (SIADH); and by EMA (since March 2009) for Inappropriate ADH Syndrome. Its use in patients with AHF who are not significantly hyponatremic is not currently recommended and should not be considered given the results of EVEREST. No other vasopressin antagonists have been approved for the treatment of AHF.

***Ultrafiltration*:** Ultrafiltration as a means to remove fluid without diuresis has been examined in patients with AHF. In the UNLOAD study [39] ultrafiltration improved decongestion and fluid removal but did not lead to more symptom relief. Ultrafiltration was associated with a trend towards fewer post discharge readmissions while leading to some short term creatinine increases. In the CARESS study [40-42] ultrafiltration compared to intensified standard therapy resulted in no further decongestion but led to persistent elevations in creatinine without effects on outcomes.

Taken together these results suggest that, even though as described by Metra *et al*. [43] in some cases more diuresis leads to hemoconcentration and small increases in creatinine that carry limited prognostic value, in general decongestion associated with worsening renal function in patients with AHF does not lead to improved outcome and more importantly reduced mortality. At present, US guidelines recommend to consider ultrafiltration in lieu of diuretics (Strength of Evidence B) and also for AHF patients who have not responded to initial medical therapy (Strength Evidence C) [25]. In the ESC Guidelines on Acute and Chronic Heart Failure, ultrafiltration has a Class IIa recommendation, Level of Evidence: B [26]. However, given the results of the CARESS study [40-42] this use should be considered only in extreme cases where very severe volume overload cannot be controlled by any other means.

***Natriuretic peptides derivatives* (*ASBPN*.1)** Although natriuretic peptides in general have induced effects that are mixed between diuresis and vasodilatation (see below), by alternative splicing B-type natriuretic peptide (BNP), Pan *et al*. [44] generated a unique 34 amino acid carboxyl terminus while maintaining the remaining structure of native BNP (ASBNP.1). ASBNP.1, unlike BNP, failed to stimulate cGMP in vascular cells or relax preconstricted arterial rings suggesting that ASBNP may lack the dose-limiting effects of recombinant BNP but stimulate cGMP in renal cells. In a canine pacing model of heart failure, systemic infusion of ASBNP.1 did not alter mean arterial pressure but increased the glomerular filtration rate [45] Thus, ASBNP.1 enhances GFR associated with heart failure while lacking the vasoactive properties of BNP. These findings will be further explored in human trials phase II and III studies to examine the potential role of ASBNP.1 in AHF. This new promising therapy is not commercially available for the treatment of AHF.

***Electrolyte and water-absorbing drugs*:** This novel therapeutic modality is currently being explored in clinical studies of patients with stabilized AHF. Its main advantage is removal of sodium and fluid through the digestive system bypassing the renal limitations encountered by diuretics. Recently, Costanzo *et al*. presented their study on an orally administered polymer that absorbs water and electrolytes [46]. They found that the drug decreased weight and BNP levels. Larger randomized, placebo-controlled trials are required to confirm the effect of polymers on electrolyte levels and fluid status and whether their use will enable the use of higher dosages of RAAS inhibitors, eventually leading to improved prognosis [47,48]. The effects of this new therapy are being evaluated in a phase IIb program targeting patients recently discharged from an AHF admission (NCT-01736735). This new therapeutic modality is currently not approved.

In conclusion, currently available strategies to remove fluids in patients with AHF are at most mildly to moderately effective in decongesting and relieving symptoms

of AHF, mainly those related to fluid overload. However, they are not effective in preventing (and sometimes exacerbate) end organ damage, most importantly renal impairment, or in preventing WHF, and hence have no effect on outcomes.

3. VASODILATORS

Similarly to studies of loop diuretics, studies of IV vasodilators and especially nitrates were small and hence in general evaluated symptom relief and not effects on end organ damage, WHF or short and intermediate term readmissions and/or death.

Nitrates: Nitroglycerin was first synthesized in 1846 and used for the first time by William Murrell to treat angina attacks in 1878. The US Food and Drug Administration (FDA) approved the sale and use of this drug in 1938. Nitrates, administered intravenously in patients with AHF were shown to improve symptoms moderately [49]. However, they are limited by tachyphylaxis occurring early during the first hours of administration [50] requiring frequent up-titrations and eventually rendering them ineffective within the first 24 hours. In a small study early administration of high dose nitrates was demonstrated to be beneficial on early relief of congestion, prevention of myocardial damage and death, however the study was small and no attempt was made to date to replicate its results in a larger cohort [51]. Hence, the effects of nitrates and dose selection in AHF are largely unknown. In the VMAC study [49] IV nitrates administration was compared in the first 3 hours to placebo showing only minor improvement in symptoms and hemodynamics. No other large study was conducted to examine the short term effects of nitrates in AHF. Based on current US recommendations, in the absence of hypotension, intravenous vasodilators (nitroglycerin or nitroprusside) are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension (Strength of Evidence C) and in patients with persistent severe HF (Strength of Evidence B) [25]. Likewise, European guidelines suggest to consider nitrates for the treatment of symptomatic patients with AHF and blood pressure > 110 mmHg (EU-Class IIa level of Evidence B) [26]. These drugs were not shown to prevent organ damage or improve outcomes in large clinical studies and hence their use in clinical practice is limited with less than 20% of patients receiving such therapies.

Natriuretic peptides: Nesiritide—The nesiritide program enrolled >8000 patients in a few clinical studies. The VMAC study [49] had suggested that in patients with AHF, who were for the most part monitored by pulmonary artery catheters, IV nesiritide was associated with short term (3 hours) improvements in dyspnea. The proportion of patients showing a slight to moderate improvement in dyspnea was statistically significantly lar-

ger at 3 hours with nesiritide compared with placebo, though not significantly compared with nitrates. On the basis of these data the drug was approved in the US for the treatment of patients with AHF. However, post-hoc analysis of the early nesiritide studies suggested that this was associated with harmful effects on kidney function and survival [52,53].

In the ASCEND study [54] approximately 7000 patients with AHF were randomized to IV nesiritide versus placebo. Nesiritide administration resulted in a slight improvement in dyspnea at 6 and 24 hours that failed to reach stringent, pre-specified statistical significance levels, caused statistically significantly more hypotension and had no effect on LOS. Importantly, no effects were observed on either end organ damage as measured by creatinine or troponin, or readmissions or death through 30 days [55]. Both the effects of nitrates and nesiritide in the VMAC and ASCEND studies are consistent with slight decongestion, as evident by minimal improvements in dyspnea and signs of congestion, no effects on WHF and LOS and no or negative effects on end organ dysfunction leading to no effects on other outcomes.

Thus, the ASCEND study despite some limitations, could be seen as supportive of the hypothesis that nesiritide does not worsen survival in the patients with AHF. However, it equally demonstrated no benefit in the overall patients. The slight effect on dyspnea and the lack of effects on survival may be explained by the mild effect of nesiritide on congestion with virtually no effects on end organ damage, translating into lack of impact on outcomes. After initial approval in 2001, FDA changed the prescribing information in July 2011 based on the results of ASCEND study. Currently, with limited efficacy in symptom relief and clearly no effect on end organ damage or outcomes US guidelines recommend the use of nesiritide only as an alternative to nitrates in patients with acute decompensated HF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies (Strength of Evidence C) [25]. The drug is currently not recommended by European guidelines in patients with AHF.

Ularitide—Ularitide is a synthetic analogue of urodilatin, a member of the family of atrial or A-type natriuretic peptides (ANP) produced locally in the renal tubular cells which play an important role in sodium and water excretion [56]. Early studies in patients with HF reported favorable hemodynamic effects and possibly enhanced diuresis and natriuresis with ularitide. SIRIUS I [57] and SIRIUS II [58,59] studied three doses of ularitide compared to placebo in 24 and 221 patients hospitalized with AHF, respectively. Ularitide was found to have beneficial symptomatic, hemodynamic (PCWP and cardiac index) and neuro-hormonal effects. The most frequent adverse event was hypotension, reported in up to

5% in active groups. Ularitide has not been studied in a large prospective randomized study examining either symptom improvement or outcome of patients with AHF, although plans are underway to conduct such a study-Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF) (NCT01661634). Hence, this promising molecule is still in clinical development.

Endothelin antagonists: Endothelin (ET)-1 is a powerful vasoconstrictor that is increased in heart failure. Higher ET-1 levels are observed in patients with more symptomatic heart failure [60] and were shown to correlate with the outcome of patients admitted for decompensated AHF [61]. Tezosentan is an intravenous dual ET_A and ET_B receptor competitive antagonist of ET-1 that was extensively studied in AHF. It is associated with vasodilatory effects that result in increased cardiac index and reduced PCWP. The Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study (VERITAS) was a large-scale international trial designed to study the effects of tezosentan added to conventional therapy on dyspnea relief and worsening HF events in patients with AHF hospitalized for dyspnea [62,63]. VERITAS results showed that tezosentan did not improve patients' symptoms, prevent WHF or end organ damage and hence had no effect on outcomes, preventing the sponsoring company from seeking regulatory approval of this drug for the treatment of AHF.

Guanylate cyclase activators: Cinaciguat (BAY 58-2667) is the first of a new class of soluble guanylate cyclase activators in clinical development for acute decompensated heart failure. Binding of nitric oxide (NO) to the ferrous heme iron of soluble guanylate cyclase (sGC) activates the enzyme and leads to conversion of GTP to cGMP, which leads to vasodilatation. Cinaciguat activates sGC not only independently of NO but also independently of the prosthetic heme group. In a dog-model of tachycardia pacing-induced severe heart failure, cinaciguat caused a dose-dependent reduction in blood pressure, right atrial pulmonary artery, and pulmonary wedge pressure and an increase in cardiac output and renal blood flow, with no change in glomerular filtration rate, urine flow and urine sodium excretion [64]. Similar effects were observed in a small proof of concept study in patients with acute decompensated heart failure [65].

Recently, a Phase IIb study evaluated the hemodynamic effect and safety of cinaciguat added to standard therapy in 139 patients with AHF. In this study cinaciguat decreased wedge pressure, as well as pulmonary and systemic vascular resistance and mean arterial pressure, and increased cardiac index. No adverse effects on 30-day mortality were seen; however, the trial was stopped prematurely due to an increased occurrence of hypotension at cinaciguat doses ≥ 200 µg/h [66].

Theoretically, cinaciguat may induce predictable and easily reversible effects on vascular tone that are endothelium independent, and hence reproducible, even in patients with severe endothelial dysfunction; however such effects would need to be examined in larger studies with emphasis on safety with regard to blood pressure and renal effects and this drug is not approved for the treatment of AHF at this time.

TRV120027, a Novel *β*-Arrestin-Biased Ligand at the Angiotensin II Type I Receptor (AT1R): TRV027 is a novel modulator of AT1R with the unique properties of antagonizing angiotensin-stimulated G-protein activation, while acting as a stimulator of *β*-arrestin. In a dog model of heart failure, TRV027 appeared to be a potent, balanced vasodilator that enhances cardiac output and preserves glomerular filtration rate (GFR) while decreasing renal vascular resistance and increasing renal blood flow [67,68]. The hemodynamic effects of TRV-027 were evaluated in patientswith chronic heart failure (NYHA class 3-4) in a phase 2 study (CP120027.2001). TRV027 pharmacokinetics in patients with heart failure appear to be similar to those observed in healthy subjects and in preclinical species (unpublished data). These properties suggest that it will be beneficial in the treatment of patients with AHF and another Phase 2 study with this compound is planned, and hence this drug is not approved for the treatment of patients with AHF.

CXL-1020, a nitroxyl donor CXL-1020 is a pro-drug that breaks down under physiological conditions and liberates nitroxyl (HNO). A Phase IIa dose-defining study to evaluate the hemodynamic effects, safety and tolerability of CXL-1020 in patients with AHF (NCT-01096043), as well as Phase I/IIa Dose-Escalation Study evaluating the safety and tolerability of CXL-1020 and specific effects on electrocardiographic and non-invasive hemodynamic parameters in patients with CHF (NCT-01092325) were recently completed. Currently the company is developing a second generation of the HNO donor in patients who are hospitalized with severe heart failure. Based on all pre-clinical studies to date, CXL-1020 is anticipated to improve the symptoms, hemodynamics and clinical status of patients with ADHF, although large studies will be required to assess these potential effects [69].

Serelaxin: The recently completed RELAX-AHF study [70] that followed the phase II Pre-RELAX-AHF [71] was a prospective randomized study in which 1161 patients with AHF, systolic blood pressure > 125 mmHg at baseline and some renal impairment were randomized to continuous IV infusion of either serelaxin or placebo for up to 48 hours. Serelaxin is a naturally occurring peptide that is elevated during pregnancy and has effects on vascular resistance and compliance, induces renal vasodilatation and has anti-inflammatory activity [72]. In

Pre-RELAX-AHF 234 patients were randomized to receive either placebo or one of 4 doses of IV serelaxin for up to 48 hours. In the RELAX-AHF study less decongestion and end organ damage were associated with increased 180 days mortality [73]. IV serelaxin administration was shown to improve symptoms and signs of congestion including dyspnea, WHF, and NT-pro-BNP levels, and to shorten LOS despite a progressively higher use of IV loop diuretics (50% more), nitrates and inotropes in the placebo arm. This increase in concomitant therapies in the placebo arm created a de facto situation in which serelaxin administration was compared to placebo and intensified background IV therapy for AHF, suggesting first that IV serelaxin is more effective in decongestion and improvement of symptoms and signs of HF then intensification of traditional IV therapies and second that investigators cognizant of the reduced improvement in patient's' status in the placebo treated patients have attempted to improve this lack of response by up titrating other IV AHF therapies. More importantly, serelaxin administration was effective in reducing some organ damage including renal dysfunction (as measured by changes in creatinine, BUN, Cystatin C and uric acid), cardiac damage (as measured by troponin release at 48 hours from randomization) and hepatic impairment (as measured by levels of AST, ALT during the first days of the study) and substantially reduced 6 months cardiovascular and all-cause mortality [73]. These ground breaking results suggest for the first time that short term IV therapy administered during the first days of admission in AHF by improving congestion and preventing end organ damage may improve longer term outcomes. Although, the results of the RELAX AHF-1 study are promising, serelaxin is currently not approved for the treatment of AHF.

In summary, although promising the effects of vasodilators in AHF are largely unknown. Nitrates which are the most commonly used IV vasodilators were never examined in large prospective studies and their effects may be limited beyond the first hours of administration by tachyphylaxis. However, newer compounds and especially the naturally occurring peptide hormone serelaxin suggest that therapies that are targeted to improve vascular function especially when administered to patients with "vascular" phenotype of AHF (*i.e.*, presenting with high blood pressure) may help both in improving congestion and symptoms as well as preventing end organ damage, hence reducing mortality in AHF.

4. INOTROPES

Although probably effective in improving symptoms, especially in patients with severe systolic HF, inotropes administration has been consistently associated with poorer outcomes. However, similar to most studies of diuretics and vasodilators, studies examining different inotropes were mostly performed 10 - 30 years ago, and many were small retrospective analyses and have assessed limited endpoints.

Milrinone: The OPTIME-CHF study [74] examined the effects of IV milrinone in almost 1000 patients with AHF. IV milrinone administration was associated with some trends to improved decongestion such as a reduction of treatment failures at 48 hours and less need for IV therapy in the active treatment arm, suggesting improvements in "backward failure". However, IV milrinone did not reduce LOS or improve end organ damage or post-discharge readmissions and was associated with a substantial increase in mortality, especially in patients with ischemic heart disease [74]. A post-hoc analysis of OPTIME-CHF has suggested that the increase in mortality associated with milrinone administration was more pronounced in patients with coronary artery disease, with the composite endpoint of death or re-hospitalization occurring in 36% versus 42% of the ischemic patients treated with placebo and milrinone, respectively, and no significant differences between the two treatments amongst the nonischemic patients (p = 0.01 for interaction) [75]. It seems that administration of IV milrinone (similar to other inotropes, see below) in AHF results in better decongestion and dyspnea relief, but probably at the price of some myocardial damage leading to increased rather than decreased short and intermediate term mortality. Similarly to all inotropes (see below) US guidelines suggest that milrinone be considered in extreme cases of low output AHF where all other options to control patients' symptoms have failed and patients are developing progressive hypoperfusion with signs of end organ dysfunction (Strength of Evidence C) [25]. European authorities recommend to consider milrinone mainly if necessary to counteract the effects of beta blockers (Class IIb level of Evidence C) [26].

Dobutamine: The effects of dobutamine in patients with AHF were never examined in detail [76,77]. The CASINO study [78] evaluated 24 hours intravenous infusion of levosimendan against dobutamine and placebo in patients with AHF and reduced ejection fraction of 35% or below. The study was stopped prior to completion of enrollment by the data safety monitoring board due to increased mortality in both the placebo (24.7%) and the dobutamine arms (39.6%) compared to levosimendan (15.3%). Similarly to all inotropes (see below), US guidelines recommend that dobutamine may be considered in extreme cases of low output AHF where all other options to control patients' symptoms have failed and patients are developing progressive hypoperfusion with signs of end organ dysfunction (Strength of Evidence C) [25]. Similarly, the ESC recommends to consider dobutamine in patients with low blood pressure <

85 mmHg and signs of hypoperfusion (Class IIa level of Evidence C) [26].

Levosimendan: Levosimendan, a calcium sensitizer with both vasodilatory and inotropic effects, was examined in a few studies. In the LIDO study [79] IV levosimendan administration was associated with hemodynamic improvements as compared to dobutamine as well as improvements in dyspnea and reduced mortality. This study was followed by two further controlled studies. In the REVIVE II study [80] 600 patients with AHF were randomized to IV levosimendan or placebo. Levosimendan administration was associated with greater dyspnea relief and faster resolution of plasma levels of natriuretic peptides (BNP) suggesting faster decongestion but without effects on LOS, end organ dysfunction or readmissions. Importantly, there was a trend towards a slight increase in early mortality, especially in patients with low pre-randomization blood pressure. In the SURVIVE study [81] comparing levosimendan to dobutamine treatment, contrary to results observed in the LIDO study, no differences in mortality were found. These diverging results (LIDO vs REVIVE and SURVIVE) may, however, be related to different trial design, *i.e.* in REVIVE and SURVIVE, therapy was started late in the admission and administered as a bolus, leading to some hypotension, which may have been associated with the less favorable effects. Levosimendan is only approved in some European countries and similarly to milrinone should only be used to reverse the effects of beta blockade if beta-blockade is thought to be contributing to hypoperfusion. (EU recommendations Class IIb level of Evidence C) [26].

Istaroxime: Istaroxime is a novel agent, with both inotropic and lusitropic effects. It inhibits the sarcolemmal Na-K ATPase, thus increasing cytosolic calcium and stimulating sarcoplasmic reticulum calcium ATPase isoform-2 (SERCA-2) [82,83]. A recently published study assessed the hemodynamic effects of istaroxime in 120 patients admitted for AHF with left ventricular ejection fraction <35% randomized to a 6 hours continuous infusion of 3 different doses of istaroxime (0.5, 1.0 and 1.5 μg/kg/min) or placebo [84]. Istaroxime infusion was associated with a reduction in pulmonary capillary wedge pressure, the primary end-point of the study (p < 0.05 for all 3 doses vs placebo), and with an increase in stroke work index (at 1.5 μg/kg/min). Unlike traditional intravenous inotropic agents, istaroxime was associated with a dose-dependent reduction in heart rate and an increase in systolic BP [84]. Hemodynamic and echocardiographic analyses also showed a decrease in left ventricular volumes and an improvement in left ventricular ejection fraction with istaroxime administration in addition to some lusitropic effects [85]. However, despite this unique hemodynamic profile these results were not examin-

ed in larger trials as a phase III study of istaroxime was stopped before recruitment commenced.

Cardiac Myosin Activators: These agents directly tar-get myocardial myosin ATPase, increasing the rate of effective myosin cross-bridge formation, and hence the duration and amount of myocyte contraction with increased myocyte energy utilization, and no effect on intracellular calcium or cAMP [86,87]. CK-1827452, known as omecamtiv mecarbil, is the first agent to be tested in humans [88]. In pre-clinical studies this drug was shown to lengthen the contractile period without increasing oxygen demand and hence contributing to a safe increase in cardiac pumping capacity (896). In a phase I trial, Teerlink *et al.* [88] examined its effect in 34 healthy volunteers. Omecamtiv mecarbil, at the dose of 0.5 mg/kg/min given as a 6-hour continuous infusion, induced a significant 6.8% and a 9.2% absolute increase in EF and in fractional shortening, respectively [88]. In a Phase II multi-center, double-blind, randomized, placebo-controlled trial, omecamtiv mecarbil was administered to 45 stable heart failure patients exposed to a total of 151 dosing periods divided among 5 cohorts [90]. This study confirmed the findings of the Phase I study, with concentration-dependent increases in the systolic ejection time accompanied by improvements in fractional shortening, stroke volume, and ejection fraction with associated decreases in heart rate. No difference in these effects has been found between patients with ischemic and non-ischemic cardiomyopathy. Additional Phase II trials are currently underway in patients with AHF [91] and ischemic heart disease. Cardiac myosin activators may be expected to play a substantial role in the quest for a safe and effective inotropic agent, and the availability of a highly bioavailable oral formulation suggests that these benefits may be extended to therapy of chronic heart failure. This new exciting therapeutic option is not yet approved for the treatment of patients with AHF.

In conclusion, prospective and retrospective analyses of multiple randomized trials have consistently shown the association between the administration of inotropic agents and increased mortality. Despite this fact, these agents are currently recommended in the US to relieve symptoms and improve end-organ function in patients with advanced HF with a low cardiac output and signs of peripheral hypoperfusion (US-Strength of Evidence C); supported by similar recommendation by ESCII a Level C. The effects of these agents are important in demonstrating the association between early drug administration in the acute phase of AHF and long-term mortality. Although the cause of this detrimental effect is not known, it is possible that the mechanism of action of these drugs mostly associated with an increase in cyclic AMP and increased free cytoplasmic calcium leads to more myocardial (end organ) damage and hence increased

adverse outcomes. Through these mechanisms, inotropic agents may cause arrhythmias, tachycardia, hypotension, and increased oxygen consumption and, hence, increased mortality. The studies with inotropic agents are therefore supportive of the concept that organ damage during an AHF event may translate into increased mortality. Indeed the findings of the effects of milrinone on mortality are an exact inverse image of the findings of improved outcomes with serelaxin. *i.e.*, milrinone increases end organ (myocardial) damage and hence increases 6 months mortality progressively (**Figure 1**) whereas serelaxin reduces end organ damage and reduces 6 months mortality (**Figure 2**).

5. CONCLUSION

As our knowledge of the new therapeutic options for patients admitted with AHF grows, we are faced with an understanding that severe short term adverse outcomes observed after an AHF admission reflect that AHF is a turning point in the course of HF. Intense neuro-hormonal and inflammatory activation lead through cardiac and
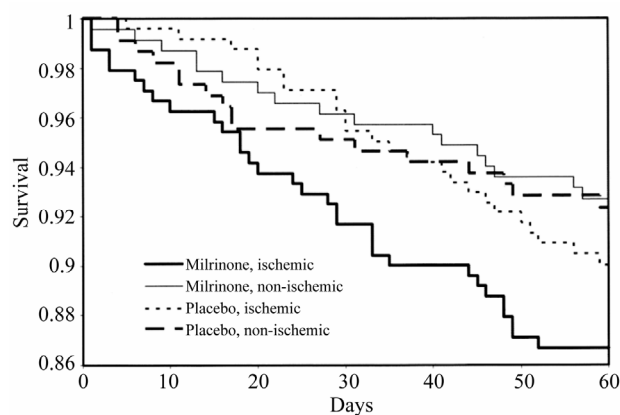
Figure 1. Kaplan-Meier survival curves to 60 days by heart failure etiology and treatment assignment [75].
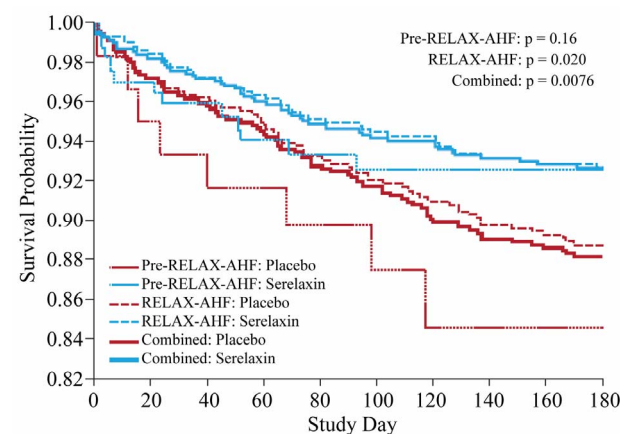

Figure 2. Risk for all-cause mortality in Pre-RELAX-AHF,

RELAX-AHF, and combined [73].

vascular mechanisms to significant congestion and end organ damage causing high rates of morbidity and mortality during the first months after admission. Regretfully all agents available to date for the treatment of AHF have no or sometimes deleterious effects on these core mechanisms and hence have no effect or may have in some cases (especially inotropic agents) negative effects on clinical outcomes. New therapeutic agents that confer organ protection and improve the adverse outcomes of AHF are urgently needed. The path towards developing such agents requires both that treatments are effective and that they are developed targeting appropriate AHF phenotypes and using robust research platforms that are AHF specific.

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