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Pharmacologic Strategies to Preserve Renal Function in Acute Decompensated Heart Failure

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Abstract Over a million patients get hospitalized with the diagnosis of acute decompensated heart failure which poses an insurmountable financial burden on the health care system. Heart failure alone incurs over 30 billion dollars with half the cost spent towards acute hospitalizations. Majority of the treatment strategies have focused towards decongesting patients which often comes with the cost of worsening renal function. Renal dysfunction in the setting of acute decompensated heart failure portends worse morbidity and mortality. Recently, there has been a change in the focus with shift towards therapies attempting to conserve renal function. In the past decade, we have witnessed several large randomized controlled trials testing the established as well as emerging therapies in this subset of population with mixed results. This review intends to provide a comprehensive overview of the pharmacologic therapies commonly utilized in the management of acute decompensated heart failure and the body of evidence supporting these strategies.

Keywords Acute decompensated heart failure · Cardiorenal syndrome · Loop diuretics · Diuretics efficiency · Vasodilators · Nitroprusside · Nesiritide · Dopamine · Vasopressin antagonist · Recombinant human relaxin-2

Introduction

Acute decompensated heart failure is the leading cause of hospitalization in an elderly patient above age 65 years [1]. Despite advances in therapeutics and improved understanding of the pathophysiology of acute decompensated heart failure (ADHF), the morbidity and mortality associated with this clinical syndrome remains high. There seems to be a complex interplay of neurohormonal activation accompanied with acute renal and myocardial dysfunction underlying this pathologic milieu [2, 3]. There has been relative paucity of randomized trials in this arena, reflected by the general lack of evidence-based recommendations and predominantly expert opinion in the guidelines [4]. Before embarking on evaluating treatment regimens, it would be important to understand the clinical characteristics of this subset in the real world. The prototypes of this population are best described by registries like Acute Decompensated Heart Failure National Registry (ADHERE) and Organized Program to Initiate Lifesaving Treatment in Hospitalized Heart Failure (OPTIMIZE-HF) patients which have been developed to improve the performance metric of the hospitals across the board and the outcomes of patients, admitted with heart failure [5, 6]. These registries have not only helped to improve care processes and facilitate quality improvement across the hospitals, but also at the same time provided valuable insight into understanding the clinical characteristics of this population and has laid the foundation for clinical trials. Patients presenting with ADHF are clearly a heterogeneous group, with majority being of advanced age (mean age of 70); half of them are women and most with multiple co-morbid conditions of hypertension, coronary artery disease, and diabetes. Pre-existing renal failure could be identified in a third of patients with 10 % demonstrating a substantial rise during the index hospitalization. Majority presents with an elevated systolic blood pressure of greater than 140 mmHg, with the chief compliant of dyspnea. The mean ejection fraction in the ADHERE registry was 34 % with a third of patients with heart failure with preserved ejection fraction (HFpEF). These registries highlight the important differences in the patient population enrolled in clinical trials which tend to favorably enroll men with reduced

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ejection fraction with a lower blood pressure. Women with preserved ejection fraction often comprise a small proportion of major clinical trials. It is crucial to keep this in mind as we review landmark clinical trials designed to address the care of ADHF patients.

Currently, the mainstay of treatment for ADHF is diuretic therapy which successfully decongests patients but often at the cost of renal dysfunction. In recent times, the focus has shifted towards therapies which would decongest patients but at the same time, hopefully, preserve or improve renal function. In this review, we intend to provide a concise overview of the existing pharmacologic therapies for ADHF with their indication and limitations.

Diuretics

Loop diuretics have been the cornerstone therapy for treating acute heart failure for several decades. They primarily act on the ascending limb of loop of Henle by blocking the Na-K-2CL co-transporter, leading to excretion of ~25 % of salt load. Multiple, small, mechanistic studies have established that diuretics successfully decongest patients and improve exercise tolerance but usually at the expense of upregulation of the neurohormonal axis leading to electrolytes disturbance, arrhythmias, and worsening renal function and some studies even claim that they adversely affect survival [7]. There has been a lack of consensus and evidence when it comes to deciding the dose and means of administration of the diuretics. Traditionally, physicians have favored the use of low-dose diuretics for the treatment of ADHF patients due to fear of hypotension from intravascular depletion and activation of the vasopressor system. Multiple observational studies and registries have linked higher diuretic dose with impaired survival [8]. Small, observational studies have hinted that diuretics administered via continuous infusion might offer an advantage over the intravenous bolus [9]. Majority of evidence with regard to diuretics come from small, non-randomized, mechanistic studies, leaving us with several unknowns regarding diuretic therapy in ADHF patients.

The Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE-AHF) trial sought to examine the outcomes in ADHF patients and attempted to evaluate treatment with intravenous bolus versus continuous diuretic infusion at low versus high doses, in a 2×2 design [10••]. Low dose was defined as the outpatient dose and the high dose as 2.5 times the daily oral dose. Global symptom assessment based on a visual analogue scale (VAC) and changes in serum creatinine at the end of 72 h were the co-primary end points. Three hundred eight patients were randomized, with mean age of 66 years, a quarter of them being women and black. These patients had moderate left ventricular and renal dysfunction, with mean EF ~35 % and creatinine of 1.5 mg/dL. A quarter of them had preserved function with EF >50 %. Patients with systemic hypotension, defined as systolic blood pressure <90 mmHg, severe renal insufficiency (serum creatinine >3 mg/dL), and use of inotropes or vasodilators were excluded from the study. The results revealed that there was no significant difference between the intravenous bolus versus the continuous infusion cohort for the primary efficacy of global symptom assessment (mean area under the curve, 4239±1440 with boluses and 4373±1404 with infusion; P=0.47) or the safety end point of worsening renal function (mean change in creatinine level, 0.05±0.3 mg per deciliter with boluses and 0.07±0.3 mg per deciliter with continuous infusion; P=0.45). In the high-dose versus low-dose group, there was a trend towards greater symptom relief and improvement in the primary end point (mean AUC, 4430±1401 vs. 4171±1436; P=0.06) with no change observed in the safety end point (mean change in the serum creatinine level, 0.04±0.3 mg per deciliter in the low-dose group and 0.08±0.3 mg per deciliter in the high-dose group; P=0.21). Favorable secondary end points were seen in the high-dose group in terms of greater weight loss, dyspnea relief, and net urinary output with fewer adverse events, although counterbalanced by worsening renal function (increase in creatinine >0.3 mg/dL during the study period), observed in 23 % of patients with high dose versus 14 % in the low-dose group (P=0.04). Worsening renal function was a short term phenomenon and no significant outcome difference was observed at 60 days across the comparison groups. The high-dose group had a significantly better net urine output and weight loss, despite an equivalent dose of furosemide used in both the treatment groups, suggesting a better dose-response relationship in the high-dose group.

Historically, hemoconcentration, urine output, and weight loss have been proposed to be the metrics for successful diuresis. Recently, Testani and Velente et al. proposed a new metric of testing diuretic response, obtained by indexing the urine output to the diuretic dose or achieved weight loss in their respective cohorts [11••, 12]. These studies reveal that patients with low indexed urine output response had a worse survival. These recent observations bring forth a new metric for measuring diuretic efficiency which gives us a better sense of identifying individuals who might have a flat response and perhaps are likely to need higher dose and develop cardiorenal syndrome. When we closely look at the data from DOSE AHF trial, the low-dose diuretic group with a lower diuretic efficiency or dose response relationship had a higher event rate (50 vs. 38 %, P=0.03). However, the clinical composite end point of death, rehospitalization, or emergency department visit did not differ among groups. By convention, high diuretic dose should have had a worse outcome than the low-dose group but it was not the case. This is likely a proof of concept that diuretic efficiency or diuretic response is superior in assessing outcomes in ADHF patients than urine output or weight loss alone. These recent observations open up a whole

new paradigm for assessing outcome when designing future trials keeping these important concepts in mind.

Another dilemma in ADHF patients is the end-point biomarker in assessing renal impairment in these patients. Change in serum creatinine has been the traditional maker used to assess acute kidney injury. Various definitions have been used; however, it is well known that change in creatinine could be due to tubular dysfunction or other factors. There may be a potential role for novel urinary markers like neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18), and cystatin C as they seem to modestly predict acute kidney injury in ADHF patients. There is limited clinical data with these novel biomarkers. Recent publication from Verbrugge et al. compared these novel biomarkers in a head-to-head fashion and demonstrated poor correlation with changes in creatinine in the setting of acute renal failure in ADHF population [13•].

Vasodilators

Vasodilators are an important adjunctive therapy in ADHF patients. Despite the widespread use, HRS guidelines give IIb recommendation to the use of vasodilators (nitroglycerine and nitroprusside) in patients with normal and elevated blood pressure in ADHF. These agents act by reducing preload and afterload, thereby improving cardiac contractility, without an increase in myocardial oxygen demand. In combination with diuretics, they augment natriuresis and suppress neurohormonal activation. Despite robust hemodynamic changes, they have a low level of recommendation which stems from a lack of randomized evidence.

Nitroglycerine is a pro-drug which acts by releasing nitric oxide, thereby relaxing the smooth muscles, increasing venous capacitance and arteriolar dilatation at low doses and decreasing arterial resistance at higher doses. It produces valuable hemodynamic effects by lowering central venous pressure, pulmonary capillary wedge pressure (PCWP), systemic blood pressure, and systemic vascular resistance, resulting in increased cardiac output. Common adverse effects limiting its use are headache, hypotension, reflex tachycardia, and abdominal discomfort. Tachyphylasix occurs with prolonged use of high-dose continuous infusion, at times apparent as early as within 24 h, limiting its use for the intermediate duration. Despite its widespread use, there is very little randomized evidence to support its clinical use. A single, open-labeled randomized trial evaluated the use of high-dose oral nitroglycerine versus diuretics in ADHF patients. The outcome statistically favored nitroglycerine with a reduced need for intubation and improved survival [14]. Small observational studies have reached similar conclusions but there is lack of a double-blind randomized controlled trial (RCT).

Sodium nitroprusside (SNP) has a similar mechanism of action and side effect profile as nitroglycerine. However, it does not have tolerance associated in contrast to nitroglycerine. Some important adverse effects to keep in mind with sodium nitropruside are cyanide toxicity with prolonged use at high doses, ventilation perfusion mismatch, and its ability to degrade on exposure to sunlight. Much of the evidence of efficacy of SNP comes from studies in ischemic cardiomyopathy in the setting of myocardial infarction. An open-labeled RCT demonstrating improvement in hemodynamics revealed no difference in mortality in patients with myocardial infarction at 1 year [15]. Another large multicenter double-blind placebo-controlled trial in heart failure patients with AMI failed to demonstrate any mortality benefit in patients with SNP but did show reduced need for diuretics [16]. Mullens et al. in an observational cohort demonstrated a significant reduction in all-cause mortality in the SNP group versus standard treatment with inotropes; however, the results were criticized due to significant heterogeneity in the population and the lack of randomization and blinding [17]. Despite the relative paucity of evidence in any other setting apart from LV failure with AMI, SNP continues to be used in the ADHF patients off all etiologies, primarily due to its immediate favorable hemodynamic effects. SNP is generic and widely available and has become the standard of care, however still underutilized. There is a need for a large multicenter clinical trial evaluating its role in reducing mortality.

Natriuretic Peptide Analogues

Natreuretic peptide analogues have been shown to have important hemodynamic effects, causing in decrease in PCWP due to reduced pre and after load, resulting in augmentation in diastolic function, cardiac output, and natreuresis. Important adverse effect associated with this class of medication is systemic hypotension. Most well-studied drug in this class is nesiritide, which is a recombinant human B type natriuretic peptide. It was approved for use by FDA in 2001 in ADHF population based on the results of efficacy and comparative trial by Colucci et al [18]. Major societies recommend its use as an adjunct therapy to diuretics in providing symptomatic relief in patients with ADHF. There have been multiple multicenter, double-blind RCTs testing the utility of nesiritide in ADHF population. Vasodilators in the Management of Congestive Heart Failure (VMAC) trial tested nesiritide versus low-dose nitroglycerine versus placebo [19]. Nesiritide resulted in a significant reduction in PCWP at 3 h with some benefits in dyspnea relief; however, there was no reduction in heart failure-related hospitalization or mortality at 6 months. Subsequently, large meta-analyses raised concerns of adverse renal effects and higher mortality associated with the use of nesiritide which led to Acute Study of Clinical Effectiveness

of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial [20]. ASCEND-HF was a large multi-center trial testing the hypothesis of symptom improvement at 6 and 24 h as measured by change in dyspnea and mortality at 30 days in patients receiving nesiritide versus placebo [21•]. Patients reported improvement in dyspnea in the nesiritide group but the pre-specified level of significance could not be demonstrated. However, importantly, the rehospitalization rates, rates of worsening renal function, and all-cause mortality at 30 days were statistically similar in both the cohorts. Most recent RCT which tested Nesiritide was the Renal Optimization Strategy Evaluation (ROSE) trial which studied nesiritide administered as a low-dose infusion to evaluate patients with ADHF with poor or worsening renal within 24 h of presentation. The primary outcome in this study was total urine output and change in serum cystatin C level at 72 h as surrogates for therapeutic efficacy. Nesiritide failed to achieve any statistical significant differences in the primary end points. The clinical end points of heart failure-related morbidity and mortality were statistically comparable among the treatment and the placebo groups with no deaths at 72 h. Hypotension as a side effect was the major reason for discontinuation of the drug and was observed in both the ASCEND-HF and the ROSE trials. Sub group analyses in these trial showed that nesiritide had better diuretic response in patients with HFrEF and lower blood pressure. Collective evidence shows no benefit or harm from nesiritide in ADHF patients when compared to conventional strategy, but the subgroup analysis from recent trials could help us select out the population which might derive benefit, although this needs to be confirmed by a RCT.

Inotropes

Inotropic agents provide beneficial hemodynamic effects in heart failure patients and may facilitate quicker symptom relief. Earlier mechanistic trials suggested potential benefit from low-dose dopamine (so-called renal dose) in conserving renal function in ADHF patients [22]. This has been primarily attributed to increase in renal blood flow, best observed at doses less than 3 μg/kg/min. In conjunction, the activation of dopamine receptors may aid in decreasing peripheral resistance which indirectly contribute to increase in renal blood flow. In the recent years, there have been multiple RCTs evaluating the potential role of dopamine in this selected population. Dopamine in Acute Decongested Heart Failure (DAD HF) trial randomized 60 ADHF patients to receive high-dose furosemide (HDF) infusion versus low-dose furosemide with low-dose dopamine infusion (LDFD) to evaluate total diuresis, worsening renal function, and overall 60-day post discharge outcome [23]. Results favored the dopamine arm in terms of improved renal profile, with no difference in overall outcome at 60 days. This led to the DAD HF II study which included an additional arm of low-dose furesemide (LDF) in addition to HDF and HFFD [24]. The study included 161 patients and was prematurely terminated due to lack of any clear benefit with any particular strategy and slow enrollment process. ROSE is the most recent randomized trial designed to evaluate patients with ADHF with poor or worsening renal function within 24 h of presentation and to investigate the role of low-dose dopamine and nesiritide, individually in decongesting these patients while attempting to preserve and improve renal function [25]. The primary outcome in this study was total urine output and change in serum cystatin C level at 72 h as surrogates for therapeutic efficacy. Patients previously on a loop diuretic received intravenous loop diuretics, a maximum dose of 2.5 times their outpatient treatment dose with bolus treatment for the initial 24 h while diuretic naïve patients received 80 mg of intravenous furosemide daily. Cumulative urine output at 72 h with dopamine was 8524 mL, 95% confidence interval (CI), 7917–9131 versus placebo, 8296 mL, 95%CI, 7762–8830 mL (P=0.59). The change in cystatin C level at the end of 72 h was also insignificant with dopamine 0.12 mg/L, 95 % CI, 0.06–0.18 versus placebo, 0.11 mg/L 95 % CI, 0.06–0.16 mg/L (P=.72). The clinical end points of heart failure related morbidity and mortality were statistically comparable among the treatment and the placebo groups with no deaths at 72 h in any group. Treatment effects were consistent across the pre-specified subgroups for patients receiving dopamine except that HFpEF patients has less urine volume at 72 h compared to placebo (P=0.01). Overall, there seems to be no indication of renal specificity from dopamine as suggested by small mechanistic studies, although its use seems to be safe and comparable to placebo and other currently available therapies.

Vasopressin Antagonist

Among several neurohormones which are upregulated during ADHF, arginine vasopressin is one which is secreted by the posterior pituitary in response to reduced blood pressure, contracted plasma volume, and increased osmolality. It acts via various receptors to cause fluid retention and contribute to heart failure and electrolyte deregulation. V2 receptors, located in the renal collecting ducts, promote sodium reabsorption. Tolvaptan, a selective V2 receptor antagonist, causes augmented dieresis at the same time preserving renal function by antagonizing endogenous AVP. Initial studies demonstrated increased sustained weight loss with Tolvaptan, thereby suggesting improved dieresis and renal preservation [26]. EVEREST study was a large multi- center study, enrolling 4133 patients, assigned to Tolvaptan versus placebo. The primary end point of the study was to evaluate all-cause mortality and the composite of cardiovascular death and rehospitalization [27]. Results revealed no difference in primary

outcome, thereby demonstrating non-inferiority and no harm to the study population in comparison to placebo. There was statistically significant benefit with respect to the secondary end points of sustained weight loss, improvement in dyspnea, quality of life, and maintenance of renal function. This large study was a good example of the limitations of drawing conclusion from underpowered studies. Tolvaptan was approved for use by Food and Drug Administration (FDA) for use in patients with hypervolemic and euvolemic hypornatremia, resistant to fluid restriction.

Adenosine Antagonist

Adenosine has been incriminated as an intrarenal mediator of diuretic resistance and worsening renal function. Adenosine acts on the A1 receptor in the afferent arteriole to reduce blood flow and the GFR, thereby stimulating rennin release and causing reabsorption of sodium in the proximal tubules. As a result, A1 receptor antagonist has attracted interest as a means to decreasing diuretic resistance and thereby improving renal function. PROTECT 1 trial was a dosing and safety study which established that 30 mg of Rolophylline, a selective A1 adenosine receptor antagonist, caused symptom improvement with preservation of the renal function [28]. PROTECT 2 trial sought to study the drug against placebo to evaluate primary efficacy and safety end point of improvement in the symptom as well as death or readmission from cardiovascular/renal causes within 7 days of treatment initiation. Secondary end points evaluated all-cause mortality and readmissions from cardiovascular and renal causes at day 60. Rolophylline failed to meet primary efficacy as well as safety end point, and there was no difference in all-cause mortality, worsening renal failure, or cardiovascular readmissions at 60 days [29].

Recombinant Human Relaxin-2

There is an unmet need for emerging treatment options for ADHF patients, as little has changed in the past few decades in the management of these patients. Serelaxin is a recombinant human relaxin-2, a natural vasoactive protein which regulates maternal changes in pregnancy. It has been tested in phase 2 trials for dosing and safety [30]. The mechanism of action is thought to improve arterial compliance, cardiac output, and renal blood flow. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX AHF) study randomized 1161 patients to serelaxin versus placebo in an effort to evaluate primary efficacy end points of improvement in patient reported dyspnea quantified by (1) area under the curve of visual analogue scale and (2) seven-level Likert scale. Composite heart and renal failure-related rehospitalizations and cardiovascular death was analyzed as a secondary end point. Serelexin did show a significant improvement in dyspnea based on the VAC scale but failed to demonstrate any difference in symptoms based on the Likert scale. The rate of reduction of composite cardiovascular death and heart and renal failure readmissions was not significant as the reduced rate of cardiovascular death at 180 days was offset by the increased readmissions reduced in the serelaxin at 180 days. The fact that Serelexin reduced the rate of cardiovascular death at 180 days along with improvement in dyspnea is encouraging. Patients on placebo had a higher adverse events related to renal impairment compared with serelaxin (placebo, 51 patients (9 %); serelaxin, 32 (6 %); P=003). Serelaxin reduced the use of diuretics and rate of worsening renal function which could be a potential mechanism of reduction in mortality. Hypotension was the major adverse event and occurred infrequently and equally in both the populations [31].

Conclusion

Cardiorenal syndrome is the ‘Achilles heel’ of patients with acute decompensated heart failure, portending worse short- and long-term morbidity and mortality. Despite overall improvement in understanding the pathophysiology, contemporary therapies have failed to make an impact. The biggest limitation of testing and proving efficacy of therapy is the significant heterogeneity in the population, presentation, and care these patients with ADHF receive, besides the complex underlying mechanism involving cardiorenal syndrome. It has become imperative that we carefully select the population to be studied and then strategize appropriate therapies using targeted biomarkers to evaluate outcomes and reach valid conclusions.

Compliance with Ethics Guidelines

Conflict of Interest Sachin Kumar and David O. Taylor declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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