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Emerging and Traditional Treatment in Acute Heart Failure: Bad News from Last Interventional Trials

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Abstract

Over last two decades many drugs and Trials have been tested in order to improve Acute Heart failure (AHF) management and outcome. Despite recent findings showing significant improvements in the pharmacological management of chronic heart failure, in AHF patients no consistent benefits in terms of mortality and re-hospitalization rates have been found. Indeed, heart failure remains one of the leading causes of hospital admission in industrialized countries and relative costs is unacceptably high. Thus a therapeutic optimization and drug titration during hospitalization period to prevent future adverse event is one of the primary goals of treatment. Unfortunately, old and new drugs more recently attempted demonstrated contrasting results. In most of cases additional pharmacological treatment showed a transient improvement of some hemodynamic parameters such as wedge pressure reduction stroke volume improvement and congestion relief. Despite these apparently recover the mid and long term outcome revealed an insufficient trend. This is particularly true in patients in more severe hemodynamic picture, more advanced Heart failure and increased congestion burden. Inconsistent results could be due in part to the attempted drug inefficiency and partially to the study design and protocol that tested the same drug in several HF subtypes. In the light of this negative findings, we support the crucial relevance of emphasizing the heterogeneity through AHF clinical profiles, with different medical needs. Accordingly, in this review we report the main finding of the most important trials performed in AHF and we purpose a reappraisal of some attempted drugs looking for the primary HF deterioration mechanism, and the related prevalent pathophysiological disorder.

Keywords: Acute heart failure; Heart failure classification; Outcome; Treatment

Introduction

Acute Heart Failure (AHF) is defined as the rapid onset or worsening of signs and symptoms of heart failure, frequently requiring urgent hospital admission [1]. AHF syndrome can occur as an acute decompensation of an underlying chronic heart failure, or, less often, as a *de novo*, abrupt manifestation [1]. Although much remains unknown about the AHF pathophysiology, recent acquisitions suggest a key role for neurohormonal activation, venous congestion, endothelial dysfunction, myocardial injury and renal dysfunction in determining this disease [2]. AHF is one of the most common causes of hospitalization through patients aged more than 65. This disease has a poor prognosis with high in-hospital mortality rates (3-8%); moreover, post-discharge mortality and re-hospitalization rates can achieve respectively 10% and 20% within 3 months [3-5]. The overall burden of this disease is relevant, with more than one million hospitalizations for AHF annually in the USA and Europe and 1-year mortality at approximately 30% [6]. Severe pulmonary and systemic congestion, due to elevated left ventricular filling pressures, often represent the main reasons why patients with AHF deserve emergency medical care [7]. Acute Coronary Syndrome (ACS) is the major precipitating factor in patients with *de novo* AHF episodes, although there are many causes that could trigger AHF as hypertension, arrhythmias, valvular diseases, kidneys or liver dysfunction or COPD exacerbations [8-10]. AHF patients recognize several clinical profiles related to the main pathophysiological mechanism and clinical scenario. Therefore, AHF manifestations can take the form from different congestion occurrence and blood pressure value: thus, it is universally recognized the classification in: AHF associated with high blood pressure, cardiogenic shock, flash pulmonary edema, ACS, isolated right heart failure from pulmonary hypertension or

intrinsic right ventricular failure, post-cardiac surgery heart failure [11]. AHF is a life-threatening medical condition, thus a timely diagnosis and a correct classification may be extremely helpful to lead an appropriate medical therapy in the early phases. The most prevalent classification for AHF, introduced by Forrester and Waters in 1978, is based on bedside physical examination, in order to detect clinical signs of congestion (wet/dry) and/or systemic organ perfusion (warm/cold). The combination of these characteristics can be applied to identify four different clinical profiles of patients, with different medical needs: wet-warm patients show signs of congestion, in presence of an adequate peripheral perfusion; wet-cold subgroup has both congestion and hypoperfusion signs and symptoms, demonstrating the worst prognosis; dry-cold have signs of hypo perfusion without congestion; and dry-warm present nor congestion neither hypoperfusion signs [1,12-14]. Recent findings from ESC-EORP-HFA Heart Failure Long-Term Registry revealed a prognostic value of this classification in terms of one-year mortality and rehospitalization rates [14] (Figure 1). A careful clinical evaluation has to be promptly performed by specific additional investigations (chest X-ray, lung ultrasound, ECG, echocardiography and laboratory exams) in order to identify major causes of decompensation (e.g. ACS, hypertensive emergency), which should be urgently managed to prevent further clinical worsening [1,15,16]. Mortality during hospitalization may be negatively influenced by elevated heart rate, increasing age, hypotension, and renal impairment; however, *de novo* AHF admissions and pre-hospitalization therapy with ACE inhibitors and beta-blockers are associated with a better prognosis [17-19]. Between 10 and 30% of patients admitted for AHF during the hospitalization, after an initial stabilization, can experience a sudden and unexpected deterioration of the clinical scenario. This clinical status known as Worsening Heart Failure (WHF), represents an extremely dangerous condition, therefore a meticulous monitoring of the patient's vital cardiorespiratory functions is essential during the hospital stay [10,20,21]. Because of the connection between WHF and increased mortality risk, WHF has been a component of the endpoints in clinical trials investigating AHF [22-24].

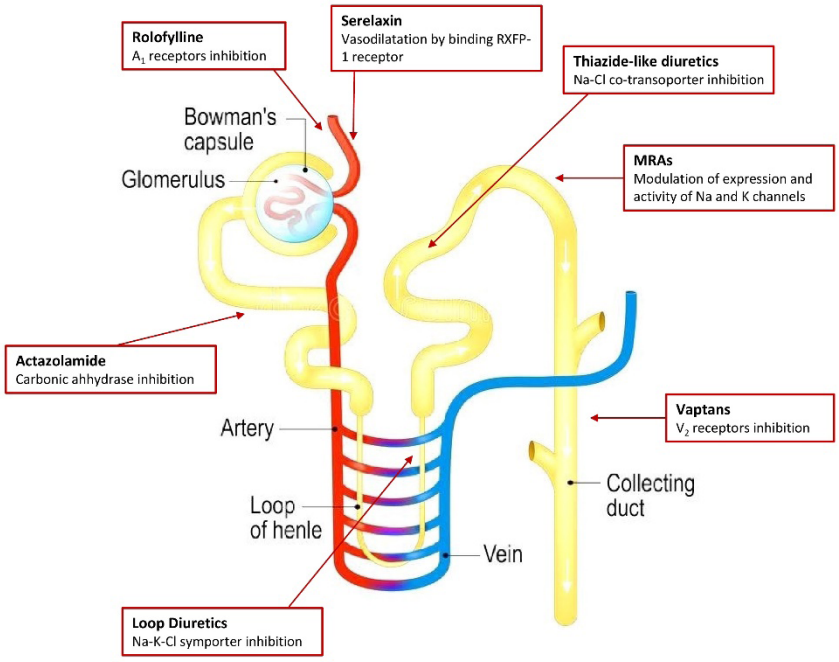

Figure 1: Mode of action at different nephron levels and vasculature of diuretics, inotropes and vasodilators.

In contrast to the improvement in medical therapies and outcomes of patients affected by chronic HF, patients admitted for AHF have not found significant benefits in term of decreased mortality and re-hospitalization rates [6]. The purpose of this review is to analyze traditional and novel pharmacological therapies for AHF syndrome, trying to understand the state of the art of a heterogeneous panorama of therapeutic strategies.

Traditional Therapies

Diuretics

Systemic and pulmonary congestion is the leading cause of hospitalization and consequent signs and symptoms are strictly related to this appearance. The traditional clinical profile in all patients affected by AHF is similar in each specific HF subtypes, and it is independent from ejection fraction [25]. Achieving euvolemia is a primary goal in AHF, by stimulating natriuresis and diuresis. Therefore, diuretics continue to represent a cornerstone for the treatment of acute heart failure related congestion symptoms. Diuretic therapy should be driven by the diuretic response of the patient, defined as the capacity of the diuretic to induce diuresis or natriuresis [7]. The diuretic response can be assessed by dosing urinary sodium content in a urine sample collected after 1-2 hours from the first diuretic administration and evaluating average urinary output after the first 6 hours [7,26]. A careful monitoring of the diuretics efficacy in the early phases can help the clinician to timely detect diuretic resistance and to adjust the decongestive therapy following a stepped pharmacological approach.

Furosemide and torasemide are prototypical loop diuretics, these organic anions are heavily bounded to proteins (>90%) and need to be secreted in the proximal convoluted tubule to directly inhibit Na-K-Cl symporter (NKCC1) at the level of ascending loop of Henle, where 25% of filtered sodium is reabsorbed. Furthermore, loop diuretics inhibit the same symporter on the macula densa cells, stimulating renin secretion [27-30]. Chronic use of loop diuretics promotes resistance phenomena, due to: compensatory distal tubular reabsorption, low plasma protein levels or significant proteinuria, competition with other anions - in chronic kidney disease or metabolic acidosis - for secretion in the proximal tubule [31]. Torasemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) trial (NCT03296813) will compare differences between these two loop diuretics.

Current ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, with regard to loop diuretics administration in AHF, recommend furosemide at the dose of 20-40 mg i.v. (10-20 mg torasemide i.v.) in diuretic naïve patients; patients on a maintenance oral loop diuretic regimen should receive at least their usual dosage administered intravenously [1,27,32].

The DOSE-AHF trial was the largest randomized trial assessing diuretic strategies in patients with acute decompensated heart failure. This study analyzed global assessment of symptoms and changes in serum creatinine level from baseline to 72 hours in 308 patients with AHF, randomly assigned to receive furosemide, administered intravenously, by means of either twice daily boluses or continuous infusion and at either a low dose (equivalent to the previous oral dose) or high dose (2.5 times the previous oral dose). The results of this trial revealed that there was no significant difference in patient's global assessment of symptoms and in the mean change in the creatinine level between the administration of bolus and continuous infusion of furosemide or between high-dose strategy and low-dose. Nevertheless, a non-significant trend was noticed for a greater diuresis resulting in greater net fluid loss, weight loss and relief from dyspnea with a transient worsening of renal function in the high-dose group [33]. However, in the DOSE trial continuous infusions were not preceded by loading doses, for a prompt achievement of steady-state plasma concentration of furosemide; furthermore, furosemide initial infusion velocity was lower than recommended in both high-dose strategy and low-dose strategy [27,34]. Data from a smaller clinical trial demonstrated that continuous infusion of loop diuretics in patients with AHF supply more consistent urine output, with better reduction of BNP levels, as compared with bolus therapy. However, this approach is related to the increased rate worsening renal function, needing additional therapy to avoid hypotension and hyponatremia, and longer hospitalization [35]. In conclusion, an initial treatment with furosemide at a daily dose of 2.5 times the habitual oral dose administered as a bolus every 12 hours appears to be an accepted initial strategy for most patients. A continuous infusion should be approached in case of particular clinical scenario as diuretic resistance and cardio-renal syndrome [27].

As mentioned, timely evaluation of the diuretic response is key to identify patients with diuretic resistance, as the failure of diuretics to achieve the congestion despite the use of maximal recommended doses [36,37]. Several causes may be at the root of loop diuretics resistance, like the indirect stimulation of the distal nephron segments to improve their rates of sodium chloride reabsorption with significant distal tubular remodeling and hypertrophy [38]. Therefore, molecules targeting distal nephron and blocking sodium chloride reabsorption at this site should be useful to achieve decongestion, in a stepped pharmacological approach based on a "sequential nephron blockade" [39]. In the Cardio renal Rescue in Acute Decompensated Heart Failure (CARRESS-HF) the use of a stepped pharmacologic therapy algorithm was compared with ultrafiltration in acute decompensated heart failure patients with worsened renal function. In this trial the stepped pharmacologic approach has proved to be superior to ultrafiltration for preservation of renal function at 96 hours and not inferior in term of weight loss [40]. Although, a per-protocol analysis of CARRESS-HF showed that ultrafiltration was associated with more fluid removal, but also with worsening renal function and neurohormonal activation [41]. The pharmacological algorithm proposed by the CARRESS-HF trial suggests the addition of metolazone for the treatment of fluid overload refractory to loop diuretics. Heart Failure Society of America recommend thiazide as a second-line agent. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure also recommend the combination of loop diuretics with thiazide diuretics or natriuretic doses of

MRAs to enhance diuresis or overcome diuretic resistance [1,42].

Thiazide and thiazide-like diuretics exert their effect in the distal nephron, by inhibiting sodium-chloride co-transporter in the distal convoluted tubule [39]. Increased distal nephron sodium avidity, produced by chronic use of loop diuretics, ideally represent the rationale for targeting this nephron region with thiazide diuretics [43]. Metolazone is the most used thiazide-like diuretic in the United States; most inpatients admitted for AHF refractory to maximal therapy responded to low-dose metolazone in the space of 72 hours; while metolazone non-responders seem to have significantly poor prognosis [39,44]. Presently, the Prospective Comparison of Metolazone Versus Chlorothiazide for Acute Decompensated Heart Failure with Diuretic Resistance trial (NCT03574857) will compare the efficacy of metolazone and chlorothiazide as add-on therapy in patient's refractory to loop diuretics with heart failure with a reduced ejection fraction.

The compensatory activation of the renin-angiotensin-aldosterone system is another well-known mechanism contributing to nephron remodeling. Mineralocorticoid Receptor Antagonists (MRAs) modulate expression and activity of sodium and potassium channels in the late distal convoluted tubule. In the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial, 360 patients with acute decompensated heart failure were randomly assigned to spironolactone (100 mg daily) for 96 hours or placebo/usual care (25 mg spironolactone), evaluating as primary endpoint the change in NT-proBNP levels from baseline to 96 hours. The results of this trial found that, although high dose spironolactone was well tolerated, these did not improve the efficacy endpoints [45]. Even though MRAs demonstrated to have major effectiveness for the treatment of chronic HF with reduced ejection fraction, their role in AHF management needs to be clarified [46]. Nevertheless, MRAs therapy might be helpful in counteracting the potassium loss induced by other classes of diuretics [45].

The proximal tubules of the nephron reabsorb the largest fraction of filtered sodium and chloride (65-80%); when renal blood flow is low the further activation of the renin-angiotensin system, decreases filtration fraction promoting sodium and chloride reabsorption in the proximal tubules [47]. In this framework, the sequential nephron blockade by Acetazolamide is a diuretic agent that inhibits sodium reabsorption, acting on the level of proximal tubules and also on the distal nephron by the inhibition of pendrin; through these mechanisms it may counteract fluid overload and improve loop diuretics effectiveness. Currently, The Acetazolamide in Decompensated heart failure with Volume OveRload trial (ADVOR, NCT03505788) is going to analyze if acetazolamide can boost loop diuretics therapy response to improve decongestion in AHF patients [48].

Vasodilators

The 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure assert that i.v. vasodilators should be useful in acute heart failure for symptomatic relief in patients with Systolic Blood Pressure (SBP) >90 mmHg, while these should be avoided in case of symptomatic hypotension and should be used with caution in patients with significant mitral and aortic stenosis; symptoms and blood pressure should be strictly monitored during the intravenous infusion of vasodilators (calss of recommendation IIa; level of evidence B) [1]. Data from Acutely Decompensated Heart Failure National Registry (ADHERE) and Acute Heart Failure Survey of Standard Treatment (ALARM-HF) revealed that traditional vasodilators (e.g. nitroglycerin and nitroprusside) still remain the second most used class of medications in acute heart failure [49,50]. Nitrates (nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, and sodium nitroprusside) activate the nitric oxide receptors, soluble Guanylate Cyclase (sGC), facilitating the conversion of GTP to cGMP; cGMP promotes the entrance of calcium through cells, resulting in smooth muscle relaxation and subsequent vasodilatation [51]. These drugs demonstrated a dose-dependent mechanism of action: producing venous vasodilatation at low dose, while higher doses determine arterial dilatation with afterload decrease [52] (Table 1).

Pharmacological Class	Mechanism of Action	Main Findings
Diuretics		
Loop Diuretics	Na-K-Cl symporter inhibition at the level of ascending loop of Henle	Congestion reduction symptoms improvement; high dose related with increased adverse events risk
Thiazide and Thiazide-like	Na-Cl co-transporter inhibition at the level of distal convoluted tubule	Improve diuresis in loop diuretics resistance; increased rate for hypokalemia
Acetazolamide	Carbonic anhydrase inhibition in the proximal tubule	May boost loop diuretics response and avoids tubular resistance; no data on mortality

MRAs	Modulation of expression and activity of Na and K channels at the level of distal convoluted tubule	Do not Improve NT-proBNP levels in AHF and increased risk for WRF. Maintain K+ levels into range in patients with low levels
Vasodilators		
Nitrates	Activation of nitric oxide receptors, promoting calcium intake through cells	No significant results in symptoms relief and outcome, improve blood pressure value in hypertensive HF
Nesiritide	Recombinant B-type natriuretic peptide with vasodilator properties	Neutral effect on mortality and rehospitalization despite a reduction in NP levels
Serelaxin	Recombinant form of human relaxin-2, exerting vasodilatation by binding RXFP-1 receptor	No effect on mortality; dyspnea relief according VAS AUC, trends toward hypotension
Ularitide	Synthetic form of Urodilatin. Improves natriuresis, diuresis and vasodilatation by binding natriuretic peptide receptor-A	No effect on CV mortality and disease progression; more rapid reduction of NT-proBNP
Clevidipine	Rapid anti-hypertensive effect exerted by selective arteriolar vasodilatation	SBP reduction and dyspnea relief in hypertensive AHF
TRV027	Biased ligand of the angiotensin II type I receptor, producing arterial pressure reduction	No effect on clinical status at 30 days
Inotropes and Vasopressors		
Norepinephrine	α and β agonist properties, resulting in a positive inotropic and chronotropic effect with peripheral vasoconstriction	Lower rate of death compared with Dopamine in cardiogenic shock, increased rate for arrhythmic risk
Dopamine	**Low dose:** prevalent action on DA_1 receptors with vasodilatation and improved renal function **Intermediate dose:** prevalent action on β_1 receptors with inotropic and chronotropic effects **High dose:** prevalent action on α_1 and 5HT determining intense vasoconstriction	Improve diuresis in patients with lower ejection fraction and SBP, no signify-cant data about short term mortality
Dobutamine	β_1 receptors stimulation in the heart, improving cardiac function	Increases in hospital mortality and readmission rates vs nesiritide
Milrinone	Phosphodiesterase III inhibition, increasing cAMP intracellular concentration which improves myocardial contractility and vasodilatation	No significant difference on mortality and readmission rates vs placebo
Levosimendan	Increases the sensitivity of cardiomyocyte to ionic intracellular calcium, determining an inodilator effect	Symptomatic relief; increases cardiac output and reduces PCWP; no effect on long term mortality
Omecamtiv Mecarbil	Inotropic action by directly activating S1 domain of cardiac myosin	No effect on dyspnea relief
Rolofylline	Synthetic A_1 receptor antagonist	No changes in survival, HF status and renal function despite congestion improvement
Aquaretics		

Vaptans	V_2 receptors inhibition at the level of collecting duct	Improves dyspnea and congestion by diuresis increase; no effect on long term mortality.
Abbreviations: AHF: Acute Heart Failure; WRF: Worsening Renal Function		

Table 1: Mechanism of action of the discussed pharmacological classes.

Nitroglycerin's usefulness has been evaluated in several clinical trials; the retrospective study reported by Aziz, et al. analyzed patients with chronic kidney disease and AHF dividing them in three groups: treated with both nitroglycerin and diuretics, treated with diuretics only and those who received neither diuretics nor nitroglycerin [52-55]. The safety endpoint regarding 24-month survival reached statistical significance in favor of the nitroglycerin group, even if it has been pointed out that patients in the nitroglycerin group have significantly higher values of blood pressure, when low blood pressure is a well-known marker of poor prognosis in AHF [56].

A single-center retrospective analysis compared isosorbide dinitrate in bolus and standard of care in elderly patients with AHF, but no significant differences in in-hospital mortality were found between two groups [57].

Two randomized controlled trials revealed beneficial hemodynamic effects in patients with left ventricular failure after myocardial infarction treated with sodium nitroprusside, even though no significant differences in mortality were found [58,59]. An observational study by Mullens, et al. evaluated the efficacy of sodium nitroprusside for patients with acute decompensated heart failure and low-output states, noticing lower rates of all-cause mortality in patients treated with nitroprusside [60].

However, an extensive review regarding the use of vasodilators in AHF by the Cochrane library concluded that no significant differences in symptoms relief and hemodynamic variables between intravenous nitrates and alternative interventions have been found in AHF patients [61]. Currently, the Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensated Study (GALACTIC; NCT00512759), an ongoing randomized clinical trial, is purposed to assess if an early decrement of preload and afterload with a target SPB 90-110 mmHg, reached by aggressive vasodilatation, in the non-ICU setting is safe, and leads to a better clinical and economical outcome.

Inotropes and Vasopressors

The latest ESC guidelines for the diagnosis and treatment of acute and chronic heart failure claim that vasopressors (e.g. norepinephrine, dopamine) should be accounted to achieve blood pressure and organ perfusion in patients with cardiogenic shock; a close ECG and blood pressure monitoring is recommended while using inotropic agents and vasopressors, as these can cause arrhythmia, myocardial ischemia and also hypotension because of the preload reduction related to the potential presence of B receptors in pulmonary circulation. Inotropic agents could be used in patients with hypotension and signs or symptoms of hypo perfusion despite adequate filling status, to improve cardiac output, blood pressure and peripheral perfusion [1].

Norepinephrine is an endogenous catecholamine with both α and β agonist properties, resulting in a positive chronotropic and inotropic effect, with peripheral vasoconstriction; due to the risk of arrhythmias and tachycardia norepinephrine should be use carefully, and should be avoided in patients with recent myocardial infarction [62]. A subgroup analysis of a multicenter, randomized trial investigating efficacy of dopamine and norepinephrine as first-line vasopressor agents in the treatment of shock, revealed that dopamine is associated with an increased rate of deaths, compared to norepinephrine, through patients with cardiogenic shock [63].

Dopamine is an endogenous catecholamine with dose-dependent effects. Low doses of dopamine (<3 μg/Kg/min) cause vasodilatation, with a prominent action on DA_1 receptors. The role of low-dose dopamine in improving renal function is discussed; 2013 ACCF/AHA Guidelines for the Management of Heart Failure recommend to consider the use of low dose dopamine in association with loop diuretics to improve diuresis avoiding systemic pressure fall (class of recommendation IIb; level of evidence B), whereas ESC guidelines do not comment on renal dopamine effects [1,64]. ROSE-AHF trial is a multicenter, double-blind, placebo-controlled randomized trial that randomized 360 patients with AHF and renal dysfunction to be treated with dopamine or nesiritide strategy, within each strategy, patients were randomized in a double-blind, 2:1 ratio to active treatment or placebo. This study evaluated, as co-primary endpoints, decongestion (in terms of daily diuresis 72-hour cumulative urine volume) and renal function (by measurement of change creatinine and change in serum Cystatin-C from enrollment to 72 hours); no significant difference was found between low dose dopamine and placebo. Interestingly, a lower 72 hours' urinary volume was noticed with low dose dopamine as compared to placebo in subgroup of patients with higher ejection fraction and higher blood pressure, although ROSE trial was not powered to assess subgroup differences [65]. Intermediate doses of dopamine (3-10 μg/Kg/min) have prevalent action on β1 receptors, with inotropic and chronotropic effects, leading to a potential increase in pulmonary capillary artery pressure (PCWP); higher doses of dopamine exert a predominant α1 and 5HT mediated vasoconstriction, with disadvantageous effects in case of severe ventricular dysfunction [62].

Dobutamine is a catecholamine that stimulates β1 receptors in the heart to improve cardiac function that can be considered in the management of cardiogenic shock, although it could induce elevated myocardial oxygen demand and tachyarrhythmias, determining dangerous effects [66,67]). A recent met analysis by Wang XC, et al. examined the effectiveness of dobutamine and nesiritide in reducing mortality and readmission rate in acute decompensated heart failure; this study found that dobutamine is associated with significantly increased in-hospital mortality and higher readmission rates compared with nesiritide therapy [68]. For these reasons this drug has been downgraded by the latest ESC Guidelines in class II B.

Milrinone produces the inhibition of phosphodiesterase III, leading to increased intracellular concentration of cAMP, which increases myocardial contractility and vasodilatation in vascular smooth muscle; differently from dobutamine, milrinone has a positive inotropic action that is independent of β receptors stimulation, making this drug particularly useful when adrenergic receptors are blocked [69]. OPTIME-CHF trial randomized 951 patients admitted for acute exacerbations of heart failure with reduced ejection fraction, evaluating clinical outcomes of the addition of milrinone to standard medical therapy: while milrinone was associated with sustained hypotension and new atrial arrhythmias, no significant differences were found with regard to in-hospital mortality, 60 days' mortality and readmission as compared to placebo [70]. Furthermore, data from ADHERE registry showed significantly higher in-hospital mortality rates in AHF patients treated with milrinone or dobutamine with respect to nitroglycerine or nesiritide [17].

Levosimendan

Levosimendan is a calcium sensitizing drug, it has an inodilator effect acting by increasing the sensitivity of cardiomyocyte to ionic intracellular calcium. The inotropic mechanism occurring without a rise of intracellular calcium levels, leads to increase in myocyte contractility and strength, with low risk of arrhythmias [71,72]. Furthermore, Levosimendan has vasodilator properties, due to the opening of adenosine triphosphate (ATP)-dependent potassium channels on vascular muscle cells [71]. The use Levosimendan in congestive heart failure patients reached initial positive results demonstrating rapid improvements in cardiac output, stroke volume and decrease pulmonary artery pressure, pulmonary capillary wedge pressure and total peripheral resistance [73]. The Levosimendan Infusion versus Dobutamine (LIDO) Trial compared effects of levosimendan and dobutamine in 203 severe low-output heart failure patients [74]. The primary endpoint evaluated hemodynamic effects within 24 hours (increased cardiac output >30% and decreased PCWP >25%). The study revealed levosimendan improved cardiac output and reduced PCWP; furthermore, lower mortality rates at one month were observed as a secondary endpoint; these data were confirmed in over six months' follow-up [74,75]. The RUSSLAN study was a safety evaluation of levosimendan in patients with left ventricular failure due to acute myocardial infarction [76]. Results from this study revealed that levosimendan decreased worsening heart failure, reducing both short (14 days) and long-term (180 days) mortality [76]. Conversely, The SURVIVE randomized trial compared the efficacy of i.v. levosimendan or dobutamine in 1327 patients admitted for acute decompensated heart failure with reduced ejection fraction during longer follow up period showed contrasting findings [77]. No significant differences in short and long-term mortality have been demonstrated, although BNP levels decreased more consistently in the levosimendan group in the first 5 days [77]. Subgroup analysis from SURVIVE data pointed out the higher 31-days survival rate in the levosimendan treated patients with a history of HF; furthermore, a reduction in the early phase mortality was noticed in the levosimendan group of patients assuming a concomitant beta-blockers therapy [78]. The REVIVE trial revealed that the use of levosimendan vs. placebo in ADHF patients provide relevant symptomatic relief, despite an association with increase rate of adverse events was observed [79]. Subgroup analysis from REVIVE II dataset identified an increased mortality risk in administering levosimendan in patients with baseline low blood pressure (SBP<100 mmHg or DBP<60 mmHg) [79]. Evidence from ALARM-HF registry showed that levosimendan was associated with lower mortality rate in the studied population as compared with traditional adrenergic, calcium-mobilizing inotropes [80].

In conclusion, in a recent extensive review on the use of levosimendan in acute heart failure by Harjola, et al. authors concluded that levosimendan should be more often considered as a preferable alternative to conventional adrenergic inotropes, specifically in such situations: AHF patients who are on beta-blockers, cardiogenic shock or cardiorenal syndrome [75].

Novel Therapies

Aquaretics

Vasopressin is a peptide neuroendocrine hormone with an important role in the maintenance of water and electrolyte balance. Vasopressin secretion is regulated by osmotic and non-osmotic pathways: hyperosmolar states, hypotension and activation of renin-angiotensin-aldosterone system stimulate vasopressin release [81]. There are three classes of vasopressin receptors: V_{1a}, expressed on vascular smooth muscle, V_{1b} on pituitary and V_2 located on collecting duct in the kidney; vasopressin ensures water balance regulation by V_2 receptors stimulation, determining water reabsorption through the collecting duct [81]. Therefore, selective V_2 receptors inhibition determines free water clearance (aquaresis) with a concomitant serum sodium concentration rising

[82]. Tolvaptan is a selective V_2 antagonist, thoroughly studied for its effects on patients affected by congestive heart failure. The EVEREST outcome trial (The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) comprised 4113 patients representing the most comprehensive investigation on the use of vaptans in hospitalized HF patients. This report, showed no significant differences in terms of long-term mortality or heart failure-related morbidity between tolvaptan and placebo groups; nevertheless, tolvaptan significantly improved secondary endpoints of patients-assessed dyspnea, body weight and edema [83]. Randomized controlled trials conducted by Gheorghiade, et al. and Shanmugam, et al., assessed the effectiveness of tolvaptan in increasing urine output and restoring serum sodium concentration in hyponatremic patients affected by congestive heart failure [84,85]. Currently, tolvaptan is indicated for volume overload in HF patients with inadequate response to other diuretics in Japan, differently it is approved for the indications of hyponatremia and SIADH in the USA, and for SIADH only in EUROPE [86].

Cardiorenal syndrome is a contemporary renal and heart disorder frequently occurring in patients with acute decompensated heart failure often associated with diuretic resistance and hyponatremia [87]. Vasopressin antagonists can efficiently counteract neurohormonal activation by avoiding tubular sodium avidity. Thus, the drug could have a potential rationale application and good safety profile in heart failure treatment to improve net fluid loss and congestion, avoiding electrolyte unbalance in patients prone to hyponatremic states [88].

Inotropes

Current available traditional inotropes mechanism of action is based on altering the concentration of intracellular Ca^{2+}, increasing cardiac contractility [89]. Although these agents can improve symptoms and have a role in shock clinical settings, they are affected by several adverse reactions for AHF patients, including increased myocardial oxygen demand and risk of malignant arrhythmias [62,90]. Based on these considerations, current research focused on the development of novel inotropic molecules acting through different myocardial intracellular pathways, with calcium-independent mechanisms.

Myosin represents a new and interesting therapeutic target, performing work of myocardial contraction; Omecamtiv Mecarbil (OM) exerts an inotropic action by directly and selectively activating the S1 domain of cardiac myosin [91]. The clinical effectiveness of Omecamtiv Mecarbil in patients with chronic heart failure with reduced ejection fraction is presently being evaluated in the GALACTIC-HF randomized trial. The ATOMIC-AHF trial randomized 606 patients admitted for acute heart failure with reduced ejection fraction (<40%) and dyspnea to receive a double-blind 48-h infusion of Omecamtiv Mecarbil or placebo [92]. Results from this study found that OM did not meet the primary endpoint of dyspnea relief, despite the fact that it was well tolerated and improved the ejection fraction time [92].

Another attractive therapeutic target concerns mitochondrial energy production, which plays a central role in the myocardial metabolism [89]. Currently, several molecules affecting myocardial metabolism are under clinical development: studies regarding perhexiline, trimetazidine and elamipretide have provided promising results in term of improvements in myocardial performance and contractility, although no adequately sized trials confirmed these results [93-95].

Vasodilators

Traditional vasodilators, despite continuing to be widely used in clinical practice, are lacking significant evidence to improve clinical outcomes in acute heart failure patients [96]. Therefore, recently, multiple novel agents with vasodilator action have been provided for the treatment of AHF [96].

Nesiritide is a recombinant B-type natriuretic peptide with vasodilator properties [97]. The ASCEND-HF trial was a randomized controlled trial of niseritide in addition to standard care. 7000 patients admitted for acute decompensated heart failure were enrolled and randomly assigned to receive either nesiritide or placebo; two coprimary endpoints were evaluated: assessment of acute dyspnea at 6 or 24 hours and 30 days' mortality and rehospitalization rates for heart failure [98]. Results from this large trial showed that nesiritide has a neutral effect, neither increasing nor decreasing the rate of death and rehospitalization, although a non-statistically significant effect on dyspnea relief was noticed [99].

Serelaxin is a recombinant form of human relaxin-2 with vasodilator properties; this new molecule has two G-protein coupled receptors (RXFP1 and RXFP2), activation of these receptors can result in triggering NO synthase, that appears to be central in the vascular modulation effects of serelaxin [100-102]. The RELAX-AHF trial randomized 1161 patients, admitted for acute heart failure, to receive standard care plus 48 hours intravenous infusion of placebo or serelaxin (30 µg/Kg per day) [103]. Data from this study demonstrated that serelaxin meets the primary endpoint of VAS AUC dyspnea relief, but did not reach statistically significance on the other primary endpoint of dyspnea improvement measured by Likert scale during the first 24 hours; no significant effects were noticed on the secondary endpoints of cardiovascular death and all-cause mortality at 60 days, even if the serelaxin treated group had statistically significant decrease in all-cause mortality at 180 days as compared with placebo [103]. However, subsequent analysis from RELAX-AHF trial found that serelaxin reduced markers of cardiac and hepatic damage and NT-proBNP levels [104]. On the basis of these positive findings

it was decided to conduct the RELAX-AHF-2 trial, to evaluate serelexin administration effects on post-discharge cardiovascular mortality and in-hospital worsening heart failure in AHF patients; in parallel, the RELAX-AHF-EU trial was similarly conducted across 26 countries in Europe as a PROBE [105,106]. The RELAX-AHF-2 failed to meet both co-primary endpoints, leading to early termination of RELAX-AHF-EU [107,108].

Ularitide is the chemically synthetized form of the human natriuretic peptide urodilatin. Exerting his action by binding natriuretic peptide receptor-A, it produces natriuresis, diuresis, vasodilatation and inhibition of renin-angiotensin-aldosterone system [109]. Ularitide demonstrated hemodynamic and clinical benefits in decompensated heart failure patients in two previous clinical trials [110,111]. The TRUE-AHF double-blind trial randomized 2157 AHF to receive ularitide or placebo, in addition to accepted care. The co-primary endpoints of this study were death from cardiovascular causes over the entire duration of the trial (median follow-up at 15-months) and a hierarchical composite endpoint evaluating the initial 48 hours' clinical course [112]. Results from this study showed that ularitide did not influence disease progression, not affecting both cardiovascular mortality and clinical composite endpoint, while it produced a more rapid reduction of NT-proBNP levels as compared with placebo [112].

Clevidipine is a rapid acting intravenous anti-hypertensive, acting by selective arteriolar vasodilatation [113]. The PRONTO study, a prospective, randomized open label trial enrolled 104 patients admitted to the emergency department for hypertensive acute heart failure; it compared clevidipine with standard vasodilator therapy with two endpoints: SBP reduction in a target prespecified range and dyspnea relief. Data from this trial revealed that clevidipine provided a more rapid reduction in SBP and improvements in dyspnea, although more studies are need to clearly assess the effectiveness of clevidipine in this clinical setting [114].

TRV027 is a biased ligand of the angiotensin II type I receptor (AT1R), this drug could selectively antagonize negative effects of angiotensin II, while preserving the potential pro-contractility effect of AT1R stimulation; in animal models TRV027 provided afterload reduction and increased cardiac performance [115]. Prior studies on healthy volunteers and HF patients revealed that TRV027 was well tolerated and produced a reversible and dose-dependent reduction of mean arterial pressure [116,117]. The BLAST-AHF dose-finding, clinical trial randomized 621 patients to receive placebo or three different doses of TVR027, evaluating a composite primary endpoint: time from baseline to death through day 30; time to baseline to heart failure rehospitalization through day 30; the first assessment time point following worsening heart failure through day 5; change in dyspnea VAS AUC score from baseline through 5 days; length of hospital stay [118]. Data from this study showed that TRV027, regardless of the dose, did not improve clinical status through 30-day follow-up, revealing no significant difference in the composite primary endpoint as compared with placebo [118].

Rolofylline

Data in literature demonstrated an important role for adenosine as a mediator of worsening renal function and diuretic resistance, acting on A_1 receptors in the afferent arterioles it can reduce renal blood flow and increase proximal tubular sodium reabsorption [119,120]. Rolofylline is a synthetic, highly selective A_1 receptor antagonist; this drug demonstrated to enhance diuresis and increase GFR, respectively in AHF and HF patients, in Phase II studies [121,122]. The PROTECT trial enrolled 2033 patients hospitalized for AHF with impaired renal function, randomly assigned to rolofylline or placebo group [123]. The primary endpoint of this study was treatment success/failure or no change in clinical condition, according to survival, HF status and changes in renal function [123]. Unfortunately PROTECT trial was unsuccessful, given that rolofylline failed in achieving primary and secondary endpoints [121].

A recent post hoc analysis, based on the PROTECT population, by Liu, et al. found that additional analysis based on plasmatic levels of a set of circulating biomarkers, already measured in the PROTECT trial, showed significant interactions between treatment and biomarkers plasmatic levels [124]. Higher levels of the majority of the measured biomarkers were related to a better treatment response to Rolofylline [124]. Authors of this study considered that biomarkers could be used to identify subgroups of patients with different treatment response, emphasizing the heterogeneity through acute heart failure patients and the importance to provide more tailored therapeutic strategies [124].

Conclusions and Future Perspectives

In the last two decades many drugs with different potential mechanisms have been attempted in order to improve AHF management. Despite initial positive findings in terms of hemodynamic and congestion signs improvement, long term outcome has been disappointing for the most tested drugs. Current findings provide several concerns regarding the gap existing between the hypothesis of potential benefit and the real life scenario. Indeed, independently of the pharmacological action there is a tremendous range occurring between theory and practice. The reasons of this debacle could be explained by several features: first of all, the concept the "one size fits all" cannot be translated in medicine and particularly in the treatment of HF. Notably each drug needs to be customized in relation to the clinical presentation blood pressure value and HF subtype. Secondly, HF with reduced or preserved ejection fraction need a specific consideration and

management: in the former, medicament focused on contractility improvement and pressure perfusion stabilization are potentially indicated; in the latter, same drugs can be inappropriate and potentially deleterious by increasing ventricular arterial coupling, peripheral vasoconstriction and cardiac overload. Thirdly, despite the congestion solution together with symptoms improvement are two primary goals in HF treatment, all the interventional Trials put as primary endpoints these two items, failed to demonstrated significant prognostic benefit during long term period. Lastly, the treatment should be focused on the primary cardiac pathophysiological disorder, the timing occurrence of the syndrome, and the underlying specific mechanism leading to HF re-acutization.

Overall, these issues need to be investigated in order to tailor the optimal treatment for each patient on the basis of the specific clinical history, the main cardiac defect, and the clinical presentation picture. Therefore, the endpoints guided the literature by now, need to be revised looking for less ambitious aims such as natriuretic peptide reduction, congestion score solution and optimal diuretic titration before discharge.

Until researches do not concentrate their efforts on the type of HF to treat and on the better type of drug to test in each singular situation based on the underlying pathophysiological disorder, the findings about AHF treatment will continue to be negative.

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