Expert Opinion on Investigational Drugs

Current drugs and medical treatment algorithms in the management of acute decompensated heart failure

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Current drugs and medical treatment algorithms in the management of acute decompensated heart failure

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Background: Acute decompensated heart failure (ADHF) is associated with increased hospitalization rates and high in-hospital mortality, and has emerged as a major public health problem over the past decade. In recent years, several new drugs and therapeutic approaches have failed to reduce short- and long-term morbidity and mortality in ADHF patients. New agents and strategies are under investigation in order to effectively reduce the mortality and morbidity in these patients. Objective: To review the recent experimental and clinical evidence on existing therapeutic algorithms and investigational drugs used for the treatment of ADHF. Methods: A systematic search of peer-reviewed publications was performed on Medline and EMBASE from January 1995 to January 2009. The results of unpublished trials were obtained from presentations at national and international meetings. Results: Renal dysfunction and low systolic blood pressure (SBP) remain the main predictors of adverse clinical outcomes in ADHF patients. Thus, therapy should be tailored according to the level of SBP at admission, renal function and fluid retention. ADHF due to hypertensive disease should be treated with intravenous vasodilators and diuretics at low doses, while patients with low output syndrome need mainly inotropic support. However, few agents currently employed in the treatment of ADHF have been shown in large prospective randomized clinical trials to improve clinical outcomes. The calcium sensitizer levosimendan is superior than traditional inotropes in improving central hemodynamics and neurohormonal response in ADHF patients, without increasing their long-term survival. Vasopressin antagonists also seem to be promising and safe drugs in the treatment of ADHF patients, facilitating diuresis on top of standard-care therapy. Encouraging novel therapies include adenosine receptor antagonists, ularitide, istaroxime, cardiac myosin activators and relaxin. Conclusions: Clinical scenarios based on SBP are essential determinants of therapeutic approaches used for the management of ADHF. Traditional drugs (diuretics, dobutamine and milrinone) have several limitations in real clinical practice, and increase mortality rates. Investigational drugs targeting to novel pathophysiologic concepts are promising treatment approaches and ongoing trials will define their clinical efficacy and safety.

Keywords: acutely decompensated chronic heart failure, diuretics, inotropes, investigational drugs, management, treatment algorithms
1. Introduction

Acute decompensated heart failure (ADHF) is a heterogeneous group of clinical syndromes affecting predominantly the elderly, which results in high morbidity, mortality, and hospital admission rate, placing a tremendous burden on healthcare systems worldwide [1-3]. The European Society of Cardiology (ESC) defined ADHF as the rapid onset of symptoms and signs secondary to systolic or diastolic dysfunction, abnormalities in cardiac rhythm, or preload–afterload mismatch [4]. In another description, ADHF was defined as a gradual or rapid change in signs and symptoms characteristic of heart failure (HF), with a need for new and urgent intravenous therapy or urgent augmentation of already existing therapy in patients with chronic or newly developed left ventricular dysfunction [5,6]. Common denominators of the above definitions are a significant deterioration of hemodynamics and clinical condition due to cardiac dysfunction, often necessitating hospital admission; and a need for intensification of medical treatment and occasionally additional institution of mechanical support.

Despite the recent advances in the treatment of ADHF, the vast majority of drugs used for this purpose have failed to reduce morbidity and mortality in patients with this condition. However, a better understanding of the pathophysiology of ADHF has led to more rational use of existing therapeutic approaches, as well as creating novel therapeutic targets and promoting the development of some promising new drugs. This review summarizes the recent experimental and clinical evidence on current therapeutic algorithms and investigational drugs used for the treatment of ADHF.

2. Classification

According to the ESC, acute heart failure (AHF) represents a large spectrum of clinical syndromes and may be classified as:

- ADHF (de novo or as decompensated chronic HF [CHF])
- hypertensive AHF
- pulmonary edema
- cardiogenic shock
- AHF due to acute coronary syndromes
- right HF [4,7].

However, a simpler clinical classification of ADHF has been proposed, which involves subdivision into two general types that have different pathophysiology and therapeutic targets and, therefore, require pharmacologic treatments tailored accordingly [8]. Based on this classification, the following types of ADHF are recognized (Figure 1):

- Hypertensive (cardiovascular) ADHF, characterized by high (> 140 mmHg) systolic blood pressure (SBP) accompanied by severe acute dyspnea. Due to rapid symptom development, patients tend to be euvoletic or mildly hypervolemic
- Non-hypertensive (cardiac) ADHF

Two general types of non-hypertensive ADHF have been suggested (see below).

2.1 Normotensive ADHF (SBP 90 – 140 mmHg)

Normotensive ADHF is usually observed in patients with a history of CHF [9,10]. Symptoms and signs develop gradually over days or weeks due to fluid redistribution, probably on top of fluid accumulation. Pulmonary and systemic congestion (jugular venous distension, pulmonary rales and peripheral edema) associated with a reduced left ventricular (LV) ejection fraction (LVEF) are usually present.

2.2 Hypotensive ADHF (SBP < 90 mmHg)

Hypotensive ADHF is associated with low cardiac output and signs of organ hypoperfusion, clinical pulmonary edema, or cardiogenic shock (CS). The definition of CS includes hemodynamic parameters [11]: persistent hypotension (SBP < 80 – 90 mmHg or mean arterial pressure 30 mmHg lower than baseline) with severe reduction in cardiac index (< 1.8 l min\(^{-1}\) m\(^{-2}\) without support or < 2.0 – 2.2 l min\(^{-1}\) m\(^{-2}\) with support) and adequate or elevated filling pressure (i.e., left ventricular end-diastolic pressure >18 mmHg or right ventricular end-diastolic pressure > 10 – 15 mmHg). Hypoperfusion may be manifested clinically by cool extremities, decreased urine output, and/or alteration in mental status. Hemodynamic abnormalities form a spectrum that ranges from mild hypoperfusion to profound shock, and the short-term outcome is directly related to the severity of hemodynamic derangement. The most common cause of CS remains myocardial dysfunction with LV failure.

3. Pathophysiology

Common causes for hospital admission of ADHF patients are summarized in Box 1. Potential mechanisms of ADHF have yet to be fully elucidated.

Hypertensive ADHF has been attributed to neurohormonal and/or cytokine surge leading to an increase in SBP associated with reduced capacitance in the large veins (increased preload) and increased arterial stiffness and resistance (increased afterload) [8]. Cardiac dysfunction contributes to this type of ADHF, as the heart of these patients (usually elderly hypertensive women with preserved LVEF) may have reduced contractile reserve and impaired diastolic function (LV decreased compliance and restrictive filling). Thus, the heart cannot effectively accommodate the fluid redistribution imposed by the altered loading conditions, leading to increased intracardiac pressures transmitted back to the pulmonary veins and lungs.

Non-hypertensive ADHF is a complex phenomenon involving hemodynamic, neurohormonal, ventricular and vascular remodeling, producing the symptoms and signs of congestion [12,13]. The primary cause initiating congestion is not obvious, but could be a constellation of factors, including cardiovascular drugs [14], with involvement of the...
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Acute decompensated heart failure

SBP > 140 mmHg
Hypertensive (cardiovascular)

• 43 – 50% of ADHF cases
• Usually elderly women with preserved LVEF
• In-hospital mortality: < 2%

SBP < 140 mmHg
Non-hypertensive (cardiac)

90 < SBP < 140 mmHg
Normotensive

• 48 – 52% of ADHF cases
• Usually decompensation of chronic HF with depressed LVEF
• In-hospital mortality: 8 – 10%

SBP ≤ 90 mmHg
Hypotensive

• 2 – 5% of ADHF cases
• Includes cardiogenic shock (CS)
• In-hospital mortality: > 15%
(> 30% in CS)

Figure 1. Classification of acute decompensated heart failure (ADHF). Based on data from the EuroHeart Failure Survey II [7], the Italian nationwide survey [9], and the ADHERE registry [10].

LVEF: Left ventricular ejection fraction; SBP: Systolic blood pressure.

Box 1. Common causes for hospital admission of ADHF patients.

- Acute coronary syndromes
- Infections
- Arrhythmias
- Uncontrolled hypertension
- Acute pulmonary embolism
- Noncompliance with medical treatment
- No diet restrictions
- Drugs (NSAIDs)
- Renal dysfunction
- Other comorbidities (anemia, depression, etc)
- Unknown cause

coupled with the increased ROS production, adversely affect excitation-contraction coupling proteins, leading to contractile dysfunction, and promote cardiomyocyte apoptotic death.

Finally, it has been recently suggested that in patients with compensated CHF, an inflammatory insult of varying etiology (infections, noncompliance with diet or medications), acting through biochemical or biomechanical stimulation, may induce or worsen ‘systemic endothelitis’, as characterized by enhanced endothelial oxidative stress and activation [17]. ‘Systemic endothelitis’ may, in turn, offset preferential distribution of limited cardiac output to vital organs, most importantly to the kidneys. Kidney under-perfusion may, in turn, trigger direct vascular, neural and humoral mechanisms that lead to sodium and water retention.

From the above, it is evident that the underlying mechanisms leading to hypertensive or non-hypertensive ADHF share a lot of commonalities (neurohormonal overactivity, endothelial dysfunction, cytokines etc.) and that the final clinical picture of ADHF is largely dependent on the baseline morphologic and functional cardiovascular abnormalities (Figure 2).

4. The cardiorenal connection

Approximately 20 – 40% of patients with ADHF suffer from comorbid renal insufficiency (cardiorenal syndrome) [18]. The combination of heart and renal failure amplifies progression of failure of the individual organ, leading to astounding morbidity and mortality in patients with ADHF [19]. Little is understood about the pathophysiology of renal dysfunction in this patient population, which is much more complex than simply a decrease in cardiac output. An imbalance in
interactions between the failing heart, neurohormonal systems, and host inflammatory responses has been implicated, leading to structural and functional damage to the heart and kidneys [20]. In addition, it has been recently demonstrated that there is a high prevalence of elevated intra-abdominal pressure in ADHF patients, which is associated with impaired renal function. The decrease of this pressure may lead to amelioration of renal dysfunction independent of hemodynamic changes [21]. Finally, recent evidence suggests that elevated systemic venous pressure is the most important hemodynamic factor driving worsening renal function in decompensated patients with advanced heart failure [22].

5. Prognosis

Patients with CHF are at high risk during the period of ADHF, having a significantly greater possibility of death and rehospitalization in comparison with the period of chronic and stable HF [23].

The in-hospital mortality in the EuroHeart Failure Survey II (EHFS-II) was 6.7% [7]. De novo ADHF patients had a higher in-hospital mortality compared with acutely decompensated patients with CHF (8.1 vs 5.8%; p < 0.001). Among clinical groups, in-hospital mortality was extremely high in cardiogenic shock patients (39.6%). In pulmonary edema and right HF, prognosis was also worse than average. The best survival was seen in hypertensive ADHF, as almost all patients were discharged alive. The in-hospital mortality in EHFS-II was similar to that of other European surveys [9], and slightly higher than in reports from the United States (4% mortality in the ADHERE study) [10]. The in-hospital mortality was significantly higher (15%) in the recently published retrospective survey of acute HF admissions in England, Wales and Northern Ireland; this has been attributed to suboptimal use of echocardiography for HF diagnosis and evidence-based management [24]. The mortality risk after an episode of ADHF has been reported to be 11.3% at 30 days and 33.1% at 1 year in the United States. The 1-year mortality rate was 27.4% in the Finnish Acute Heart Failure Study (FINN-AKVA study) [25], 43% in an historical cohort study conducted in Leicestershire, England [26], and 46.5% in the French EFICA study [27].

The high rehospitalization risk is one characteristic feature of ADHF. In EHFS-II [7], 24% of patients were rehospitalized at least once during the 3 months; in a study of 18,000 Medicare recipients, approximately 44%
were rehospitilized ≥ 1 more time in the 6 months after their index hospitalization [28]; and in the OPTIMIZE-HF registry, rehospitalization during the 60- to 90-day period after hospital discharge was 29.6% [29]. The readmission rate seems to be similar between Europe and the United States [30].

6. Patients’ clinical profiles

Data from the European and American surveys and registries have generated important information concerning the characteristics of patients with ADHF [7,9,10,29]. Patients with ADHF are usually elderly (mean age of 75 years in the United States and 71 years in Europe) and 50% are women. Over 75% of hospitalized patients with ADHF have acute decompensation of previously diagnosed HF, and only 15 – 25% are diagnosed with de novo HF during the index admission. Most patients admitted to hospital with ADHF have a normal-to-high SBP (the percentage of patients with an SBP > 140 mmHg was 50 and 43% in ADHERE [10] and the Italian [9] survey on AHFS, respectively), whereas < 8% of patients with ADHF have hypotension associated with low output. The majority (approximately two-thirds) of ADHF patients have a history of coronary artery disease (CAD) and almost one-third of them have a history of myocardial infarction. Very common comorbidities in patients with ADHF are hypertension (more than half of patients), diabetes (more than one-third), renal insufficiency (one-fifth), and atrial fibrillation (more than one-third). Women admitted with ADHF appear to have less CAD and more hypertension than men, but a similar rate of atrial fibrillation and diabetes. The majority of the patients have radiographic evidence of pulmonary congestion and compromised glomerular filtration rates (GFRs < 60 ml/min/1.73m² in > 65% of the patients). The LVEF is preserved in 27 – 54% of ADHF patients; preserved systolic function is associated with advanced age, female sex, a higher incidence of hypertension, LV hypertrophy, and diabetes.

The cause of hospitalization for HF differed between de novo acute HF and acute decompensation CHF groups in EHFS-II [7]. Acute coronary syndrome was the major precipitating factor in patients with de novo AHF, present in 42% of cases, in which this condition was mostly due to myocardial infarction. Arrhythmia was equally prevalent as precipitating factor in AHF patients, regardless of previous history of HF. Valvular disorders, infections, and noncompliance with medication were more common in ADHF. In the recently reported findings of OPTIMIZE-HF, 61.3% of the 48,612 patients had ≥ 1 ADHF precipitating factors identified, with pneumonia/respiratory process, ischemia, and arrhythmia being more frequent. In the same study, two precipitating factors were present in 13.6%, whereas three precipitating factors were present in 4.2% of the patients [29].

7. Current management and treatment algorithms

Despite the socioeconomic cost of ADHF and the probable evolution in chronic, lifelong illness, there are limited numbers of randomized clinical trials on new pharmacological agents. Indeed, the management of ADHF – and consequently, the morbidity and mortality of patients admitted to hospital with this condition – has not significantly changed over the past 30 years [31].

7.1 Noninvasive respiratory support (NIRS)

NIRS can be instituted early in ADHF; it can be provided either by continuous positive airway pressure (CPAP) or by both inspiratory and expiratory support (BiPAP). NIRS augments cardiac output, decreases LV afterload, increases functional residual capacity and respiratory mechanics, reduces the work of breathing, and, most importantly, reduces the need for intubations and decreases mortality in patients with acute cardiogenic pulmonary edema [32,33]. The typical inclusion criteria for NIRS in clinical trials are severe acute respiratory failure, PaO2/FIO2 < 250 mmHg, sudden-onset dyspnea with respiratory rate > 30 breaths/min, and typical physical signs of pulmonary edema.

7.2 Morphine

Morphine use should be avoided in ADHF as it is associated with increased incidence of adverse events, including a greater frequency of mechanical ventilation, prolonged hospitalization, more intensive care unit admissions and higher mortality [34]. However, this drugs seems to be useful in improving symptoms and hemodynamics in patients presenting with acute pulmonary edema and concomitant significant anxiety.

7.3 Hypertensive ADHF

The treatment target is the reduction of SBP with vasodilators, preferably with nitroglycerin (Figure 3) [35]. Tachyphylaxis is common with this agent, necessitating incremental dosing. Elkayam and colleagues have reported that the onset of the nitroglycerin-mediated hemodynamic effect was delayed, and despite the aggressive up-titration, the improvement in central hemodynamics was gradually attenuated because of the early development of tolerance [36]. The major adverse effects of nitroglycerin are hypotension (mean BP should remain > 70 mmHg) and headache. Because of their negative inotropic effects, calcium channel antagonists are in general regarded as inappropriate in CHF patients. However, there are some small trials indicating that short-term use of diltiazem in patients with atrial fibrillation (AF) and moderate-to-severe CHF may be safe and effective [37]. Moreover, hypertensive ADHF is often associated with preserved LVEF and rapid AF with a heart rate > 100 bpm. Thus, diltiazem may be used as an alternative to nitroglycerin in patients with hypertensive ADHF associated with rapid atrial fibrillation,
without evidence of LV systolic function. Moderate doses of intravenous loop diuretics may be used in patients with severe volume overload.

### 7.4 Normotensive ADHF

The treatment target is relief from congestion associated with both fluid retention and fluid redistribution from the systemic to pulmonary circulation. Loop diuretics (furosemide, torsemide) are an extremely important tool in the treatment of normotensive ADHF, as they can effectively give relief to patients in extreme distress from dyspnea. However, the enthusiasm for loop diuretics has been tempered by their association with worsening renal failure and increased mortality \[38,39,40\]. Because of the adverse effects on renal
function and mortality, and the likelihood of development of resistance with chronic use, the loop diuretics must be used judiciously, and their use should be minimized if possible [41].

In patients with the cardiorenal syndrome, the dose–response curve for diuretics is shifted downward and to the right. This results in an increase in the dose required to produce a diuretic response associated with a decrease in the maximum response that can be achieved (‘diuretic resistance’). Some other important causes of diuretic resistance are increased salt intake, use of NSAIDs, and increased reabsorption of sodium by the distal portions of the nephron. If diuretic resistance develops, it is prudent to add a more distally acting diuretic such as metolazone, amiloride, or both.

7.4.1 Nesiritide

Nesiritide is a recombinant human B-type natriuretic peptide that causes venous and arterial vasodilation through increased production of cyclic GMP [42]. Nesiritide induces a balanced vasodilation and an indirect increase in cardiac output, but has no actual inotropic effects and exerts a neutral effect on heart rate. In addition, it inhibits adverse neurohormonal activation and, in some individuals, promotes natriuresis and diuresis. Nesiritide also reduces pulmonary capillary wedge pressure, right atrial pressure and systemic vascular resistance; decreases symptoms of heart failure; and enhances global clinical status in patients with ADHF.

The largest study to date evaluating nesiritide is the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, which randomly assigned 498 patients with New York Heart Association class IV heart failure requiring hospital care for dyspnea to nesiritide, intravenous nitroglycerin. Nesiritide was superior to placebo in reducing the pulmonary capillary wedge pressure at 3 h (nesiritide: -5.8 mmHg [p < 0.001 vs placebo], nitroglycerin: -3.8 mmHg [p < 0.09 vs placebo], placebo: -2.0 mmHg); however, the difference was no longer significant at 48 h. Nesiritide was superior to placebo in reducing dyspnea at 3 h, but this effect waned over time and was not distinguishable from that of placebo on either dyspnea or global status at other future time points when compared with the 3-h placebo measures. Hypotension was more common in the nesiritide group. The 30-day readmission rate was 20% among the patients given nesiritide and 23% among those given nitroglycerin.

Nesiritide was approved by the FDA in 2001 for the treatment of patients with ADHF who have dyspnea at rest or with minimal exertion. However, several questions regarding the risks of nesiritide therapy have recently been raised, and resolution of the safety of nesiritide is a process that remains in evolution [44]. The most frequently reported adverse effect is dose-related hypotension. In addition, nesiritide may cause an acute increase in serum creatinine concentration, which has been attributed to a combination of volume depletion, vasodilation, and neurohormonal inhibition. Finally, recent meta-analyses of existing databases have raised concerns regarding adverse effects of the drug on 30-day mortality [45]. These concerns have recently been muted but not resolved by the results of: i) the small (n = 75) single-center, randomized BNP-CARDS (B-Type Natriuretic Peptide in Cardiorenal Decompensation Syndrome) trial, which showed that nesiritide does not worsen renal function in patients with baseline renal insufficiency and ADHF [46]; ii) the prospective, double-blind NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) trial (n = 303), where nesiritide given to patients with LV systolic dysfunction attenuated renal dysfunction after cardiopulmonary bypass [47]; and iii) the preliminary results of the randomized, double-blind, placebo-controlled FUSION II (Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure) trial (n = 911), which tested the safety and efficacy of serial outpatient administration of nesiritide to patients with advanced heart failure and failed to reveal evidence of renal harm [48]. Until the questions regarding the efficacy and safety of nesiritide are resolved by the ongoing ASCEND HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial [49], it is rational to consider its alternative use in patients not responding to intravenous nitroglycerin and diuretics who have similar characteristics to those enrolled in the VMAC trial.

7.4.2 Peripheral ultrafiltration

Peripheral ultrafiltration is an alternative method of sodium and water removal that safely improves hemodynamics in HF patients. The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial enrolled 200 patients with ADHF and showed that peripheral ultrafiltration compared with diuretics alone increased weight loss at 48 h (5.0 vs 3.1 kg; p < 0.001), decreased the need for vasoactive drugs (3 vs 13%; p = 0.02) and reduced the rate of readmission to hospital at 90 days (18 vs 32%; p = 0.02) [50]. Thus, ultrafiltration offers the potential of greater volume and sodium removal as compared with conventional therapies in a more expeditious manner. However, it relies on earlier discharge with reduced readmission rates to be economically feasible.

It has been recently demonstrated that low-dose dopamine results in an increase in renal blood flow due to dilation of both the large conductance and the small resistance renal blood vessels associated with a marked increase in cardiac output [51]. However, no controlled randomized trial to date has shown the effects of dopamine on either clinical symptoms or outcomes in ADHF patients. Although beneficial effects of intravenous dopamine both on the systemic and renal circulation are encouraging, more clinical data are needed concerning the efficacy and safety of dopamine in patients with ADHF. Finally, low-dose dopamine together
with loop diuretics may be considered in cases with diuretic resistance due to renal dysfunction, if peripheral ultrafiltration is not available.

7.5 Hypotensive ADHF

The treatment target is restoration of cardiac output and maintenance of organ perfusion. Early use of inotropic/vaso-pressor therapy is appropriate in patients with this type of ADHF, who present with cardiogenic shock or with evidence of low output (hypotension, cold extremities, clammy skin, renal impairment, liver dysfunction, or impaired mentation).

7.5.1 Inotropes

Inotropes are often used in patients with persistent impaired hemodynamics. Unfortunately, their use is controversial due to potential harmful effects as they increase oxygen demand and intracellular calcium, thereby increasing myocardial ischemia and the risk of progression to ventricular dysfunction and arrhythmias [52]. Dobutamine is a synthetic sympathomimetic amine with predominantly β-1 and some β-2-adrenergic effect producing both dose-dependent inotropic and chronotropic response [53]. Milrinone is a type of phosphodiesterase inhibitor that also has inotropic and vasodilatory effects, with a more prominent effect on pulmonary vasculature [54]. Both dobutamine and milrinone improve contractility by promoting cellular calcium influx, thereby stimulating actin–myosin cross-bridging and myocyte formation. It should be noted that in patients with systolic ADHF who had been receiving beta-blocking agents, the favorable hemodynamic effects of dobutamine are blunted and alternative inotropic agents, such as milrinone or levosimendan, should be used [55-59].

Levosimendan is a new inotrope that enhances myocardial performance by increasing the affinity of troponin C to calcium (calcium sensitizer). The prolonged, enhanced contractility during systole (half-life of 80 h) does not impair ventricular relaxation, and is not cleared by the kidneys [57,58]. The LIDO (Levosimendan Versus Dobutamine in ADHF) trial was a double-blind, parallel-group study that randomized 203 patients with ADHF defined as LVEF < 35%, cardiac index (CI) < 2.5 l/min/m² and pulmonary capillary wedge pressure (PCWP) > 15mmHg [59]. The primary end point of the study was the improvement of the hemodynamic profile of the levosimendan group (defined as > 30% increase in cardiac output and > 25% decline in PCWP), which was observed in 28% of patients on levosimendan versus 15% of those on dobutamine.

In the recent Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study, 1327 patients hospitalized with ADHF who required inotropic support were allocated to intravenous levosimendan (n = 664) or intravenous dobutamine (n = 663) [60]. Despite an initial reduction in plasma B-type natriuretic peptide level in patients in the levosimendan group compared with patients in the dobutamine group, levosimendan did not significantly reduce all-cause mortality at 31 and 180 days. However, a post-hoc subgroup analysis of the SURVIVE trial showed that levosimendan may improve short-term mortality in patients with a previous history of CHF and on beta-blockers at hospital admission [60-62]. According to the recent guidelines of ESC, levosimendan is indicated in patients with symptomatic low cardiac output HF secondary to cardiac systolic dysfunction without severe hypotension (class IIa, level of evidence B) [4,63].

8. New and investigational drugs

ADHF remains a complex entity with therapeutic challenges due to limited mortality data on current approved and recommended pharmacological regimens. Recently developed pharmaceutical agents that have shown some promise are summarized in Box 2 and described in more detail below.

8.1 Vasopressin antagonists (vaptans)

The vaptans are non-peptide vasopressin receptor antagonists that are orally and intravenously active. There are three types of vasopressin receptors [64]. The V1a receptors are widely distributed, mainly on vascular smooth muscle, and stimulation of these receptors is associated with vasoconstriction and cardiac hypertrophy, together with a range of other effects. The V1b receptors have little selective distribution and their activation is part of the adaptive reaction to stress. The V2 receptor is expressed predominantly in principal cells of the renal-collecting-duct system, in which its activation leads to increased resorption of free water.

Two V2-receptor antagonists, tolvaptan and lixivaptan, and one combined V1a- and V2-receptor antagonist, conivaptan, have shown promise for use in patients with heart failure [65]. All three agents increase free water excretion and serum sodium levels without adversely affecting the serum potassium levels, GFR, and renal function. Based on data from available clinical trials [66-69], vasopressin antagonists may offer a new treatment option for ADHF, facilitating diuresis on top of standard-care therapy, especially in patients with resistance to classical diuretics and/or hyponatremia. However, these agents do not currently appear to have a persistent effect on symptoms and do not seem to delay the progression of HF or decrease mortality [65].

8.2 Adenosine antagonists

Adenosine is an ATP breakdown product that in most vessels causes vasodilatation and which contributes to the metabolic control of organ perfusion (i.e., to the match between oxygen demand and oxygen delivery). In the renal vasculature, in contrast, adenosine can produce vasoconstriction, a response that has been suggested to be an organ-specific version of metabolic control designed to restrict organ perfusion when transport work increases (Figure 4). The renal adenosine system employs vasoconstrictor adenosine A1 receptors (A1R) on
the afferent arteriole and vasodilatory adenosine A2 receptors (A2R) on the efferent arteriole. Activating either population of glomerular adenosine receptors will suffice to reduce the filtration fraction, whereas nuances in their relative activities will determine the impact of endogenous adenosine on single-nephron GFR and glomerular blood flow [78].

The A1R antagonists induce a euclidean natriuresis and diuresis by blocking A1R-mediated NaCl reabsorption in the proximal tubule and the collecting duct. Normally, suppressing proximal reabsorption will lower GFR through the tubuloglomerular feedback (TGF) mechanism. But as the TGF response itself is mediated by the A1R in the pre-glomerular arteriole, blocking A1R allows natriuresis to proceed while GFR remains constant or increases. The influence of A1R over vascular resistance in the kidney is augmented by angiotensin II while A1R activation, directly suppresses renin secretion [71]. These interactions could modulate the overall impact of A1R blockade on kidney function in patients taking angiotensin II blockers. A1R blockers may increase the energy utilized for transport in the semi-hypoxic medullary thick ascending limb, an effect that could be prevented with loop diuretics. Finally, while the vasodilatory effect of A1R blockade could protect against renal ischemia, A1R blockade may act on non-resident cells to exacerbate reperfusion injury, were ischemia to occur [72]. Despite these uncertainties, the available data on A1R antagonist therapy in patients with ADHF are promising [73] and warrant confirmation in further studies.

Figure 4. Effects of adenosine on renal function. A. Structural organization of the nephron. The distal tubule, when it emerges from the medulla, is adherent to the glomerulus. The conglomerate of cells at the site of contact is called the juxtaglomerular apparatus (JGA) and it includes the macula densa (MD). B. The MD is located within the end portion of the thick ascending limb (TAL) of the loop of Henle, mediating contact between the TAL and the vascular pole of its parent glomerulus. The MD senses the tubular NaCl load at the end of the thick ascending limb, where about 85% of the filtered NaCl has been reabsorbed and 15% is left in the tubular fluid. C. An increase in NaCl load sensed by the MD elicits local adenosine production, which increases NaCl reabsorption in the proximal tubule and causes adenosine A1 receptor (A1R)-mediated constriction of the efferent arteriole, leading to a decrease in renal blood flow (RBF) and glomerular filtration rate (GFR) (tubuloglomerular reflex).

AArt: Afferent arteriole; EArt: Efferent arteriole.
8.3 Cardiac myosin activators

Cardiac-specific myosin ATPase activators are a novel class of agents designed to improve myocardial contractility by accelerating the productive phosphate-release step of the cross-bridge cycle [74]. The results of a study reporting the first administration of the selective myosin activator CK-1827452 to human volunteers support the initiation of clinical trials in heart failure patients [75].

8.4 Istaroxime

Istaroxime is an inhibitor of the sodium-potassium adenosine triphosphatase pump and also increases sarcoplasmic reticular calcium adenosine triphosphatase isoform 2a (SERCA 2a) activity. Evidence that improving SERCA 2a activity may constitute a promising therapeutic strategy for AHF derives from positive results in animal models with either SERCA 2a overexpression or reduction in phospholamban activity [76]. The initial results with the use of istaroxime are encouraging. In a recent Phase II study including 120 patients admitted with systolic HF instrumented with a pulmonary artery catheter, istaroxime decreased PCWP, increased SBP, and decreased heart rate [77].

8.5 Ularitide

This agent is a synthetic analogue of urodilatin. Urodilatin is a molecule produced by tubular renal cells that promotes sodium and water excretion; it belongs to the family of A-type natriuretic peptides [78]. Moreover, this agent causes peripheral vasodilation through the production of cyclic guanosine monophosphate. In recent placebo-controlled randomized clinical trials SIRIUS (Safety and Efficacy of an Intravenous Placebo-Controlled Randomized Infusion of Ularitide in a Prospective Double-Blind Study in Patients with Symptomatic Decompensated Chronic Heart Failure) I and II, a short-term infusion of ularitide in patients with ADHF had a beneficial effect on their clinical status, central hemodynamics and neurohormonal response [79]. The ongoing Ularitide Global Evaluation in Acute Decompensated Heart Failure (URGENT) trial will investigate the safety and efficacy of ularitide in a larger patient population, defining the exact role of this drug in the management of ADHF.

8.6 Relaxin

This molecule is a pregnancy-related polypeptide hormone that promotes nitric oxide release and stimulates atrial natriuretic peptide secretion [78,80]. Thus, relaxin has potent vasodilatory and antifibrotic properties, also regulating fluid distribution and preventing platelet aggregation into the cardiovascular system. Experimental evidence suggests that relaxin mRNA is overexpressed in failing hearts in relation to the severity of the syndrome [81]. The ongoing randomized placebo-controlled RELAX-HF trial will clarify the safety and efficacy of this drug in the treatment of hospitalized patients with ADHF [79].

9. Conclusion

Treatment algorithms based on SBP and the presence of congestion and/or the low-output state are essential approaches for the current management of ADHF. Traditional drugs have several limitations in real clinical practice and may increase mortality rates. Investigational drugs targeting novel pathophysiologic concepts are promising treatment approaches without significant adverse effects, and ongoing trials will define their clinical efficacy and safety.

10. Expert opinion

ADHF is a condition that manifests mainly as signs and symptoms of congestion; it leads to increased hospitalization rates, and high short- and long-term mortality. Existing therapies have failed to improve morbidity and mortality in ADHF patients. Thus, treatment should be individualized according to SBP, renal function and the existence of fluid retention. The new cardiac enhancer, levosimendan, seems to cause greater improvement of congestion and central hemodynamics than dobutamine and may improve short-term mortality in special patient subpopulations such as those with a previous history of heart failure and on beta-blockers at hospital admission. The vasopressin antagonists are another promising class of vasoactive drugs that seem to improve congestion on top of standard-care treatment in patients with resistance to traditional diuretics. The new cardiac enhancer with positive lusitropic effects, istaroxime, the renal protectors, adenosine antagonists, and the potent vasodilator ularitide are all novel agents with very promising results in small clinical trials; ongoing trials will define their efficacy and safety in larger patient populations. A better understanding of the pathophysiology...
of ADHF will invite novel therapeutic approaches and drugs aimed not only at symptomatic improvement but also at reducing the high morbidity and mortality of ADHF patients.

**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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