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Review

Management of oral chronic pharmacotherapy in patients hospitalized for acute decompensated heart failure

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ABSTRACT

Acute decompensated heart failure (ADHF) is the most common cause of cardiovascular hospitalization. The presentation is characterized by different clinical profiles due to various underlying causes, volume balance and tissue perfusion status. Currently, a variety of pharmacological therapies, including diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers and digoxin, are usually prescribed in order to treat chronic heart failure (HF) syndromes caused by left ventricular systolic dysfunction. Despite the large number of HF patients with frequent hospitalizations for decompensation, only a few studies have evaluated the management of oral chronic therapies in the clinical setting of ADHF. This article summarizes the information derived from the few published trials on this subject and a therapeutic approach is suggested with respect to the continuation, dose modification or suspension of oral medications.

1. Introduction

Acute decompensated heart failure (ADHF) is a syndrome characterized by rapid or gradual onset of signs and symptoms of heart failure, leading to unplanned hospital admissions or office and emergency room visits [1]. Hospital admission for heart failure represents 1–2% of all hospitalizations in the Western world [2,3]. Patients affected with HF have a high rate of mortality during hospital stay and after hospital discharge, with a high rate of readmission that varies from 15 to 22% within the first 30 days to 35–45% at 90 days [4–7].

ADHF can be differentiated as a new onset of HF (30–40%) or a worsening of chronic HF [8,9]. There is common concern regarding the management of oral therapies in the setting of ADHF due to worsening of chronic HF. This is linked to the fear of worsening the clinical syndrome because chronic treatment could contrast compensatory mechanisms acting to sustain pump function and organ perfusion. There are also doubts on discontinuation or dose reduction of oral therapies that could be unnecessary during the decompensated phase. Another concern is related to the possibility of poor absorption of oral drugs during the acute phases [10]. Recent evidence indicates that continuation with little change in oral therapy may be not only feasible but may also favorably affect the outcome of ADHF patients [11].

This paper aims to consider the physiological background and the rationale of continuing or changing oral therapies in the setting of patients with ADHF related to the worsening of chronic HF and to suggest practical tools for their management.

2. ADHF classification, clinical features and treatment goals

Different classifications have been proposed for ADHF. A common one is based on six categories following clinical and etiological profiles [5,12–14]. This classification, reported in the 2008 edition, but no longer used in the up to date European Society of Cardiology 2012 guidelines, was based on hemodynamic severity and pathophysiological classes and applied to both acute de novo HF patients and to patients with worsening chronic HF [4,5]. The distinction between acute de novo and worsening of chronic HF is important because different mechanisms of adaptations are predominant in the clinical presentation of these two groups of patients. Our paper mainly focuses on the

Abbreviations: ACE, angiotensin converting enzyme; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; B-CONVINCED, beta-blocker continuation vs. interruption in patients with congestive heart failure hospitalized for a decompensation episode; COMET, Carvedilol or Metoprolol European Trial; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESCAPE, evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; OPTIMIZE-HF, organized program to initiate lifesaving treatment in hospitalized patients with heart failure; PDE III, phosphodiesterase III; RAAS, renin–angiotensin–aldosterone system; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial.

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management of oral therapies in patients with acute decompensation of chronic HF.

Another classification, based on the evidence of congestion and adequate perfusion in ADHF patients, is endowed with prognostic significance (Fig. 1) [6,15–17]. This classification better frames the true hemodynamic profile of these subjects and appears more practical to assist in the selection and the titration of treatments. This classification is best suited for patients with acute decompensation of chronic HF [6,17]. ADHF patients are then classified as "warm and dry" if their clinical presentation is characterized by euvolemia and adequate perfusion, as "warm and wet" if they are congested and adequately perfused, as "cold and dry" if they are hypoperfused and euvolemic, and finally "cold and wet" if they are hypoperfused and congested.

The term "wet" of the clinical profiles of patients with ADHF is related to the presence of fluid overload. Pulmonary congestion is not necessarily the same as fluid overload, in fact a hemodynamic derangement with a rise in pulmonary venous pressure without a systemic excess of fluid represents the mechanism of decompensation of HF in acute pulmonary edema: this indicates the need for reduction in filling pressure with a vasodilator more than net fluid removal with a diuretic [18].

There are several precipitating factors responsible for decompensation including poor therapeutic compliance, inadequate pharmacological therapy, administration of inappropriate drugs (such as NSAIDs, COXIBs, antiarrhythmic agents, non-dihydropyridine calcium-antagonists), fluid overload (by excessive salt or fluid ingestion or iatrogenic if the patient is hospitalized), uncontrolled hypertension, arrhythmias (slow or fast), pulmonary infection or COPD exacerbation, sepsis, myocardial infarction, valvular disease progression, cardiac tamponade, aortic dissection, myocarditis, and endocrine or hematologic disorders (anemia, thyroid disorders) [5,19].

The treatment goals in ADHF patients are first, the relief of symptoms and the identification and correction of precipitating factors, and second, the improvement of post-discharge mortality and the prevention of hospital readmission.

The four clinical profiles described above may also define different prognostic categories. The clinical profile "warm and dry", representing almost one third of patients, describes a group of patients with a good overall prognosis, generally related to ADHF due to uncontrolled hypertension. In the "warm and dry" clinical profile group, the objective is the treatment of uncontrolled hypertension and the titration of oral beta-blockers and renin–angiotensin–aldosterone system (RAAS) active therapies. The worst prognosis group is represented by the "cold and wet" clinical profile, which holds a two-fold higher death risk when compared with the "warm and dry" profile [17].

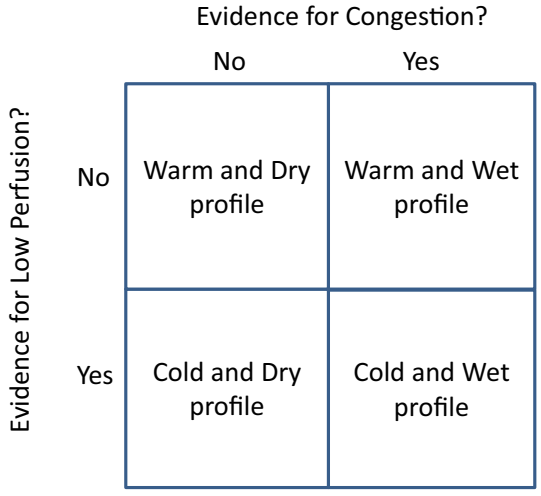

Fig. 1. Classification scheme for assigning clinical profile in patients with ADHF. Patients may be defined "warm" when there is adequate tissue perfusion, or "cold" when the perfusion is compromised, evaluating the extremities temperature-status. The patients may also be defined "wet", indicating pulmonary congestion or "dry" in the absence of pulmonary congestion, evaluating the presence of lungs edema or rales.

About half of the ADHF patients are admitted with a "warm and wet" clinical profile, and they carry a better prognosis when compared with the "cold and wet" group [6]. They need relief from congestion and therefore the initial treatment should be focused on diuretic therapy. The "cold and wet" clinical profile of ADHF (around 20% of ADHF patients) presentation requires a more intensive therapy to achieve adequate perfusion and to solve the congestion. Vasodilating inotropes may be helpful as initial treatment.

The clinical "cold and dry" profile represents the few patients with ADHF who have significantly reduced cardiac reserve without significant congestion [6,17]. They need an intervention aimed at tissue perfusion and the emphasis should be on inotropic support and careful fluid repletion with hemodynamic monitoring.

3. Oral pharmacological therapy management

The medical treatment for chronic HF patients is based on preload and afterload reduction (using ACE-inhibitors, ARBs and diuretics), and inhibition of deleterious neurohormonal activation (RAAS and sympathetic nervous system) using ACE-inhibitors, ARBs, mineralocorticoid receptor antagonists (MRAs) and beta-blockers. The mentioned therapies have been demonstrated to prolong survival and reduced hospital readmission in HF patients with reduced left ventricle ejection fraction (EF) [4,20–28]. None of these treatments has convincingly been shown to reduce mortality and hospital admission in HF patients with preserved EF.

Afterload reduction obtained by inhibiting both the RAAS and sympathetic nervous systems produces vasodilation, thereby increasing cardiac output and decreasing myocardial oxygen demand, which represents another fundamental goal [4,20]. Diuretics are the main treatment to relieve symptoms induced by positive fluid balance; they are effective in preload reduction by increasing urinary sodium excretion and decreasing fluid retention, which improves cardiac function and exercise tolerance [4]. In addition, preload reduction results in decreased pulmonary capillary hydrostatic pressure and reduction of fluid transudation into the pulmonary interstitium and alveoli. All these effects of diuretics on preload and afterload reduction provide symptomatic relief.

An issue of major concern in all patients admitted to the hospital for ADHF is related to the necessity to maintain, modify or stop ongoing oral medical treatments.

3.1. Diuretics

Diuretics remain the cornerstone of standard therapy for ADHF, and the intravenous administration of a loop diuretic (i.e., furosemide, bumetanide, torsemide) is initially preferred because of the potentially lower absorption of the oral form in the presence of bowel edema in HF [10]. Given the potential reduced intestinal absorption of diuretics during the hypervolemic status of ADHF ("warm and wet" and "cold and wet" clinical patient profiles) and altered pharmacokinetics and pharmacodynamics of diuretics, intravenous administration of loop diuretics is needed. In fact, patients admitted for ADHF and already on therapy with oral diuretics should be switched to an i.v. loop diuretic [4,20].

Loop diuretic use should always be associated with a correct monitoring of fluid balance including intake and excretion. After i.v. administration of loop diuretics, the transition to oral therapy is possible when the patient reaches a near-euvolemic state. The oral loop diuretic dose is usually equal to the i.v. dose except for furosemide, whose mean oral bioavailability is 60%, and so the dose should be doubled to obtain a similar diuretic effect. In most cases, 40 mg/day of furosemide is equivalent to 20 mg of torsemide and 1 mg of bumetanide. Body weight, diuresis, signs and symptoms of heart failure, fluid balance, electrolyte