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Review

Pharmacologic Options for the Management of Systolic Heart Failure: Examining Underlying Mechanisms

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ABSTRACT

The optimal management of systolic heart failure includes combination therapy to influence myocardial remodelling favourably by affecting neurohormonal activation and underlying maladaptive pathophysiological pathways. These medications include modulators of the renin-angiotensin-aldosterone system (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists) and β-adrenergic receptor blockers. In addition, an agent with a distinct and complementary mechanism of bradycardic action, the selective pacemaker-current (I_f) inhibitor ivabradine, provides further reduction of heart rate. Also, a new drug that incorporates neprilysin inhibition combined with angiotensin receptor blockade shows incremental effectiveness. The primary goal of this

RÉSUMÉ

La prise en charge optimale de l'insuffisance cardiaque systolique comprend le traitement combiné pour influencer favorablement le remodelage myocardique en affectant l'activation neurohormonale et les voies physiopathologiques maladaptatives sous-jacentes. Ces médicaments comprennent les modulateurs du système rénine-angiotensine-aldostérone (p. ex. les inhibiteurs de l'enzyme de conversion de l'angiotensine, les antagonistes des récepteurs de l'angiotensine, les antagonistes du récepteur minéralocorticoïde) et les inhibiteurs des récepteurs β-adrénergiques. De plus, un agent ayant un mécanisme d'action bradycardique distinct et complémentaire, l'ivabradine, un inhibiteur sélectif du courant I_f, réduit davantage la fréquence cardiaque. Également, un nouveau médicament qui

Heart failure (HF) is common, with estimated prevalence in Canada of up to 3.8%.[1] Approximately 60% of all cases are thought to be systolic (heart failure with "reduced" ejection fraction [HFrEF]), with the remainder classified as HF with preserved ejection fraction.[2] Although the incidence of hospitalized HF is on the decline,[3,4] the overall burden is increasing by approximately 1% yearly because of improved survival in Canada and the United States.[5] Ninety percent of HF care is delivered in the outpatient setting, but 80% of costs are incurred during hospitalization; these costs are increasing and might double by 2030.[6] This reality, coupled with the finite resources available, make the optimal management of HF a crucial societal concern.

To accomplish these goals, health providers and their patients need to maximize the use of medical therapies with proven benefit in HF trials, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and β-blockers.[7] Among emerging therapies, evidence now shows that the novel agent ivabradine, a selective I_f-current inhibitor that regulates heart rate (HR), and a drug incorporating

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review is to provide a mechanistic explanation of the complementary role of therapeutic interventions in modulating pathways leading to progressive systolic heart failure. A secondary goal is to summarize the key findings of the pivotal clinical trials that have demonstrated the efficacy of these agents in this population.

combine l'inhibition de la néprilysine au blocage des récepteurs de l'angiotensine montre une efficacité supplémentaire. Le principal objectif de la présente revue est de fournir une explication mécaniste du rôle complémentaire des interventions thérapeutiques dans la modulation des voies menant à l'insuffisance cardiaque systolique. Un objectif secondaire est de résumer les principaux résultats des essais cliniques charnières qui ont démontré l'efficacité de ces agents dans cette population.

neprilysin inhibition with angiotensin receptor blockade augmenting protective peptides, might also have an important role to play in patients with systolic HF.[8,9] The primary goal of this review is to provide a mechanistic explanation of the complementary role of therapeutic interventions in modulating pathways leading to progressive HF (Fig. 1), and to summarize the key findings of the pivotal clinical trials that have demonstrated the efficacy of these agents. This review is based on a conference during the Canadian Heart Failure Summit (May, 2014, Montreal) at which these issues were discussed.

ACE Inhibitors: The Gold Standard Modulator of the Renin-Angiotensin-Aldosterone System

Recommendations for use

Current Canadian guidelines recommend that an ACE inhibitor should be used for all HF patients with a left ventricular (LV) ejection fraction (LVEF) < 40% (HFrEF). In addition, ACE inhibition is indicated in all patients after an acute myocardial infarction (MI) after the patient has been stabilized, and should be continued indefinitely if LVEF is < 40% or if there is ongoing HF.[7]

Evidence-based agents and doses

The agents that have compelling clinical trial evidence in this setting include captopril, enalapril, lisinopril, perindopril, ramipril, and trandolapril. Starting and target doses for these agents are listed in Table 1.[10]

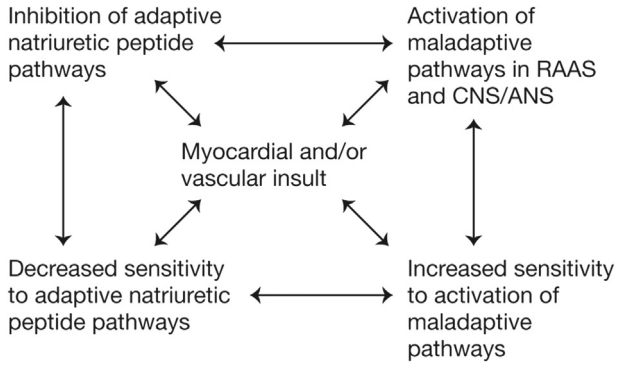

Figure 1. Mechanisms leading to progressive cardiovascular failure. ANS, autonomic nervous system; CNS, central nervous system; RAAS, renin-angiotensin-aldosterone system.

Clinical trial evidence

The evidence supporting the efficacy of ACE inhibition in HF dates back to the **Co**operative **N**orth **S**candinavian **En**alapril **Su**rvival **S**tudy (CONSENSUS), published in 1987.[12] In this study enalapril 2.5-40 mg daily vs placebo was evaluated among 253 patients with severe HF (New York Heart Association [NYHA] functional class IV). Over a mean follow-up of 188 days, there was a 27% relative risk reduction in overall mortality for the active treatment arm ($P = 0.003$). Enalapril treatment was also associated with an improvement in NYHA classification and reduced requirement for other HF medications.

The CONSENSUS data were followed by the important **S**tudies **o**f **L**eft **V**entricular **D**ysfunction (SOLVD) trial, in which 2569 patients with class 2-3 HF were randomized to enalapril 2.5-20 mg per day or placebo.[12,13] At 41 months, there was a relative risk reduction of 16% in mortality in favour of enalapril, associated with a significant reduction in end-diastolic LV volume index at 4 months.[14] Thus began a recurring observation that disease-modifying therapies in systolic HF that reduced mortality also caused reduction in LV volumes, or reverse remodelling.

Other compelling evidence for ACE inhibition accumulated in 3 similar, placebo-controlled clinical trials in the setting after MI, in which patients with evidence of LV dysfunction or a diagnosis of HF were enrolled: the **S**urvival **a**nd **V**entricular **E**nlargement (SAVE; captopril),[15] **A**cute **I**nfarction **R**amipril **E**fficacy (AIRE),[16] and **Tra**ndolapril **C**ardiac **E**valuation (TRACE)[17] studies. A pooled analysis of all 3 study populations yielded a 26% relative risk reduction in all-cause mortality for ACE inhibition vs placebo.[18]

Mechanistic rationale

ACE inhibition has multiple biological effects, with 2 prominent processes: (1) inhibition of the conversion of angiotensin I to angiotensin II; and (2) inhibition of the breakdown of inflammatory mediators like bradykinin. Inhibition of the deleterious effects of angiotensin II (eg, vasoconstriction, abnormal cellular growth, sodium/water retention, prothrombotic effects)[19,20] and the promotion of the beneficial effects of kinins[21] likely contribute. The renin-angiotensin-aldosterone system (RAAS)—of which ACE is a critical component—exists in the circulation, but more importantly, also in the tissues. Some of the potential beneficial effects of ACE inhibition are: modulation of myocyte responses to the intracardiac renin-angiotensin system,[22] attenuation of ventricular remodelling and improvement in ventricular function,[14] reduction in sympathetic activity,[23,24] positive effects on endothelial function,[25,26] cytokine levels,[27]