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New medications for heart failure

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ABSTRACT

Heart failure is common and results in substantial morbidity and mortality. Current guideline-based therapies for heart failure with reduced ejection fraction, including beta blockers, angiotensin converting enzyme (ACE) inhibitors, and aldosterone antagonists aim to interrupt deleterious neurohormonal pathways and have shown significant success in reducing morbidity and mortality associated with heart failure. Continued efforts to further improve outcomes in patients with heart failure with reduced ejection fraction have led to the first new-in-class medications approved for heart failure since 2005, ivabradine and sacubitril/valsartan. Ivabradine targets the I_f channels in the sinoatrial node of the heart, decreasing heart rate. Sacubitril/valsartan combines a neprilysin inhibitor that increases levels of beneficial vasodilatory peptides with an angiotensin receptor antagonist. On a background of previously approved, guideline-directed medical therapies for heart failure, these medications have shown improved clinical outcomes ranging from decreased hospitalizations in a select group of patients to a reduction in all-cause mortality across all pre-specified subgroups. In this review, we will discuss the previously established guideline-directed medical therapies for heart failure with reduced ejection fraction, the translational research that led to the development of these new therapies, and the results from the major clinical trials of ivabradine and sacubitril/valsartan.

Key words: Heart failure therapies, Funny channel, Neprilysin, Sacubitril/valsartan, Ivabradine.

Introduction

Heart failure is a source of significant morbidity and mortality in the United States [1] and is responsible for billions of dollars spent in direct medical expenditures and lost revenue due to reduced productivity [2]. In the past 3 decades, dramatic advances have been made in the understanding of the pathophysiology of heart failure and the development of pharmacologic therapies that improve functional status and reduce hospitalizations and mortality for patients with heart failure with reduced ejection fraction [3–7]. These advances have led to guideline recommendations for the use of certain beta blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and aldosterone antagonists in patients with symptomatic heart failure with reduced ejection fraction. However, despite these guideline-directed medical treatments, aimed at blockade of the neurohormonal mechanisms of heart failure, heart failure remains the cause of one in nine deaths in the United States [1] and is the number one cause of hospitalization. Recognizing this, effort has continued to identify new pathways in heart failure for modification in patients already receiving the benefit of these proven medications. Secondary analysis of major beta-blocker trials and data from large heart failure registries revealed that heart failure patients with lower heart rates have improved outcomes. This led to the prospective trials that have shown the sinoatrial "funny" current (I_f) inhibitor, ivabradine, improves outcomes in selected patients with

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heart failure [8]. Additionally, while blockade of the renin–angiotensin–aldosterone (RAA) system has been a cornerstone of heart failure therapy, more recent research has noted the important effects of the body's own mechanisms to counter the volume expansion and vasoconstriction seen in heart failure. Efforts to augment these natural systems resulted in the approval of sacubitril, a neprilysin inhibitor, given in combination with the angiotensin receptor blocker (ARB) valsartan in the treatment of heart failure with reduced ejection fraction [9]. In this review, we will summarize the current knowledge of the pharmacologic treatment of chronic heart failure and then explore the first new-in-class medications to be approved by the FDA for the treatment of heart failure since 2005, ivabradine and sacubitril/valsartan (LCZ696).

Guideline-directed medical therapy

Heart failure is the inability of the heart to maintain enough cardiac output to distal organs to meet metabolic demand and is heralded by symptoms that include dyspnea, edema, and fatigue. The decreased perfusion and arterial pressure activate regulatory systems in the body's neural and hormonal pathways designed to compensate for the weakened heart. The most important of these is the RAA system, in which decreased perfusion to the juxtaglomerular cells in the kidney result in an increase in renin levels. Renin is responsible for the conversion of angiotensinogen to angiotensin I (AT I) which is, in turn, converted to angiotensin II (AT II). AT II has a host of effects, including vasoconstriction, promotion of antidiuretic hormone (ADH) and aldosterone secretion, and an increase in sympathetic tone [10]. Baroreceptor feedback in the neural axis further increases the adrenergic drive through direct nerve innervation on the heart and adrenal glands, increasing circulating catecholamines that increase heart rate and cardiac contractility [11]. The physiologic end goal of the neurohormonal cascade is a compensatory attempt to restore organ perfusion through increased systemic vascular resistance, plasma volume, and cardiac output.

While these mechanisms may help in an acute setting, over time the chronic, continuous feedback becomes deleterious, leading to pathologic ventricular remodeling, worsening heart failure, and perpetuating a downward spiral. Extended beta-receptor activation increases myocardial metabolic demands, contributes to adverse ventricular remodeling, predisposes to dangerous arrhythmias, and speeds myocyte death [11]. The continuous activation of the RAA system leads to remodeling of the ventricle, volume overload, and increased ventricular fibrosis [10]. In light of this, current guideline therapy in chronic heart failure aims to interrupt this process. The Studies of Left Ventricular Dysfunction (SOLVD) and Vasodilator-Heart Failure Trial II (V-HeFT II) trials showed that ACE inhibitors reduced the risk of death by 17% and death or hospitalization by up to 30% compared to placebo, and they were superior to the non-specific vasodilators hydralazine and isosorbide dinitrate [6,12]. Other trials showed that angiotensin receptor antagonists could improve outcomes in patients intolerant of ACE inhibitors, but they did not reduce mortality when added on to an ACE inhibitor. Studies testing beta-blockade in heart failure with reduced ejection fraction, including the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials, showed an additional mortality decrease of up to 35% when added to background ACE inhibitor therapy [3,4]. The Randomized Aldactone Evaluation Study (RALES) trial showed a remarkable, additional 30% all-cause mortality reduction with the aldosterone antagonist spironolactone when added to ACE inhibitor and beta-blocker therapy [7], and subsequent trials showed benefit in mild heart failure with reduced ejection fraction. Taken together, pharmacologic therapy aimed at interrupting the neurohormonal feedback system can decrease 2-year mortality by 50% and the risk of hospitalization by 64% in patients with heart failure with reduced ejection fraction [13]. It is on this background of guideline-directed medical therapies that new classes of heart failure therapies were evaluated.

Ivabradine

Resting heart rate has long been shown to have prognostic significance. Follow-up from the Framingham Heart Study demonstrated in an adult population without previous myocardial infarction or heart failure that a higher resting heart rate was associated with increased risk of cardiovascular and all-cause mortality. Each standard deviation of increase in baseline heart rate was associated with a 17% increase in the risk of all-cause mortality over a median follow-up of 19 years, even when adjusted for comorbidities and activity level [14]. Multiple studies have demonstrated heart rate to be a predictive and modifiable marker in patients with heart failure in sinus rhythm. Although there has been some question as to whether there is a mechanistic relationship between elevated heart rate and worse cardiac function [15] or whether heart rate is secondary in importance to dose of beta blockers [16], most analyses suggest that heart rate reduction is associated with lower risk.

Given the relationship between heart rate and mortality in heart failure it may be expected that beta blockers with higher chronotropic suppression would have a larger benefit in heart failure patients. There was essentially only one large, randomized, and double-blind study, the Carvedilol or Metoprolol European Trial (COMET) [17], in which there were similar long-term heart rate reductions. Outside of head-to-head trials, there are limitations in comparing differences in heart rate reduction and mortality reduction relative to placebo among different trials of various beta blockers under varying conditions. However, it appears that the beta-blocker trials that showed the largest heart rate reduction, even with similar agents, had the largest impact on mortality. In a meta-analysis of 23 beta-blocker trials, there were greater mortality reductions as a function of the magnitude of heart rate reduction achieved within the trial [18]. For every heart rate reduction of 5 bpm with beta-blocker treatment, a commensurate 18% reduction [confidence interval (CI): 6–29%] in the risk for death occurred. If heart rate reduction is independent of the other protective effects of beta blockers, then