The Past, Present and Future of Heart Failure Medical Therapy

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Heart failure is pandemic with prevalence increasing throughout the world. Patients suffering from heart failure experience frequent hospitalizations, reduced survival and markedly impaired quality of life. Fortunately, medical therapy for heart failure has improved over the past several decades. An increasing number of drugs and devices that have been shown to favorably alter the natural history of patients with heart failure with reduced ejection fraction (HFrEF) are now available. Unfortunately, for patients with heart failure with preserved ejection fraction (HFpEF), currently available medical therapy has not been shown to alter the natural history of the disease. This lecture provides an overview of past, present and future medical therapies, with emphasis on drugs used to treat HFrEF.

Whereas in the past, heart failure was considered a cardiac disorder that resulted in congestion due to the 'back-up' of blood from the heart, it is now recognized as a complex systemic disease involving the vasculature, kidneys, skeletal muscle and brain. Vasodilator drugs to unload the heart were an important breakthrough, as treatment had previously depended on a combination of digitalis glycosides to improve myocardial contractility and diuretics to relieve congestion. Recognition that the renin-angiotensin system (RAS) and its main effector molecule, angiotensin II (Ang II), played an important role in regulating vascular tone, resulted in the development of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). These agents not only improved the clinical course of heart failure patients but also provided insights into the pathophysiology of heart failure, as their beneficial effects transcended their ability to unload the heart. Understanding the central role of neurohormonal activation in promoting cardiac remodeling and progression of heart failure led to the development of additional strategies including the use of beta blockers and mineralocorticoid receptor antagonists, both of which have been shown to greatly alter the natural history of patients with HFrEF.

The role of neurohormones in modulating progression of heart failure, however, is more nuanced than simply blocking activities of maladaptive systems. Counter-regulatory systems that are compensatory including the natriuretic peptides, bradykinin, prostaglandins, adrenomedullin and others are also activated. Angiotensin receptor neprilysin inhibitors (ARNIs) combine blockade of Ang II with neprilysin inhibition which augments levels of compensatory peptides by blocking their breakdown. In the recent PARADIGM-HF study, the combination of valsartan and sacubitril was superior to an ACEI in reducing mortality and mortality as well as improving quality of life in patients with HFrEF. Subsequent studies have demonstrated the safety and efficacy initiating an ARNI during heart failure hospitalization.

Gene and stem cell therapies are novel strategies for treating heart failure. Gene therapy is based on the premise that delivery of a critically important gene that has either been down regulated or in which a mutation has altered the production or function of its product will help restore normal cardiac function. Novel viral vectors that allow the gene of interest to be preferentially taken up by cardiomyocytes are being explored. A variety of stem cells that either promote regeneration of cardiomyocytes or help repair adjacent myocardium through release of signaling molecules are also being tested as therapies for heart failure. Mesenchymal precursor cells, previously shown in early studies to favorably affect clinical outcomes in heart failure, are now being evaluated in the Phase 2b/3 DREAM-HF trial.