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Based on overwhelming data demonstrating reduced morbidity and mortality, ACE inhibitors form a mainstay of therapy in all patients with symptomatic left ventricular systolic dysfunction. Furthermore, ACE inhibitors may be beneficial in the prevention of heart failure in patients with high-risk cardiovascular profiles. However, definite benefit from the use of ACE inhibitors in all patients with heart failure and preserved ejection fraction has not been demonstrated. Even though ACE inhibitors probably have a class effect in patients who have heart failure, it is recommended that ACE inhibitors that have been shown to reduce morbidity and mortality in clinical trials (captopril, enalapril, lisinopril, and ramipril) be used because studies have clearly defined a dose for these agents that is effective in modifying the natural history of the disease. Attempts should be made to up titrate patients to target doses of ACE inhibitors that have been used in clinical trials, if tolerated.

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Aldosterone blockade has been shown to be effective in reducing mortality in patients who have severe heart failure because of systolic left ventricular dysfunction (SLVD) and those who have heart failure and SLVD post-myocardial infarction. Aldosterone blockade also may be beneficial in patients who have New York Heart Association class II heart failure, asymptomatic left ventricular dysfunction, and heart failure with preserved or normal left ventricular function. Considering the beneficial effects of aldosterone blockade on improving nitric oxide availability, endothelial function, and atherosclerosis, it can also be postulated that an aldosterone blockade would add to the benefits of an angiotensin-converting enzyme inhibitor in patients who have coronary artery disease. However, these hypotheses must be confirmed in well-designed, large-scale, prospectively randomized studies.

Role of Neurohormonal Modulators in Heart Failure with Relatively Preserved Systolic Function	23
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Cardiovascular disease remains the leading cause of mortality in the developed world. It is estimated that 5 million Americans suffer from heart failure (HF), and roughly 550,000 new cases are diagnosed annually. Studies have found that 40% to 71% of patients who have HF have relatively preserved systolic functions, or diastolic heart failure (DHF). Although there are abundant data to guide the treatment of heart failure and systolic dysfunction (systolic HF), evidence-based data are lacking in the management of DHF. This article examines the role of neurohormonal modulators in the management of DHF.

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The current treatment paradigm for heart failure revolves around the central theory of neurohormonal antagonism. With the success of angiotensin-converting-enzyme inhibition, beta-blockade, and aldosterone antagonism in heart failure, alternative areas of the hormonal cascade have been targeted for potential benefits. Two such agents, neutral endopeptidase inhibitors and endothelin antagonists, have demonstrated promising initial results in animal models and small, human-based studies but have fallen short when examined in larger clinical trials. The reasons for these shortcomings are varied and require analysis of the design of the studies as well as the intrinsic functions of these agents.

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The existing guidelines for the treatment of patients who have heart failure limit the administration of antiplatelet and anticoagulant agents to patients who have specific comorbidities, including coronary artery disease, atrial fibrillation, history of thromboembolic events, and left ventricular mural thrombus. Retrospective analyses of large clinical trials or smaller nonrandomized studies indicate that the use of statins may be beneficial both in ischemic and idiopathic dilated cardiomyopathy. This article outlines the current knowledge regarding the use of antiplatelet and anticoagulant agents and statins in patients who have heart failure.

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Although considerable progress has been made in the pharmacologic and device management of chronic heart failure in recent decades, heart failure patients continue to remain symptomatic, with high hospitalization and mortality rates. A number of novel agents, including endothelin antagonists and tumor-necrosis factor blockers, have recently failed to improve the clinical outcomes of patients with heart failure. Have we reached a ceiling in preventing the progression of the disease? This article reviews successes and late-stage clinical trial disappointments in the treatment of patients with heart failure. Furthermore, the article discusses how agents that have beneficial effects in heart failure also generally attenuate or reverse ventricular remodeling, whereas the newer agents that have failed to improve clinical outcomes either had no effect on remodeling or have been associated with adverse remodeling.

IV: Management of Post-Myocardial Infarction Left Ventricular Dysfunction

Angiotensin-Converting Enzyme Inhibitor and/or Angiotensin Receptor Antagonist for the Postmyocardial Infarction Patient

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Robert L. Scott

The utilization of angiotensin-II attenuating agents is the standard of care in the management of patients with left ventricular dysfunction regardless of the etiology. The most effective agents of this group includes both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARB). Given the worse outcomes noted in those patients who have coronary artery disease, efforts to optimize appropriate pharmacotherapy in this population is imperative. There does appear to be some advantage in the combination of ACE+ARB in chronic left ventricular dysfunction patients. In those patients that have sustained a recent myocardial infarction with concomitant left ventricular dysfunction, the combination of ACE+ARB does not improve survival and in fact might exacerbate renal dysfunction as well as hypotension. The appropriate employment of agents that attenuate the effects of angiotensin-II should be a priority in the care and management of the left ventricular dysfunction patient.

Comprehensive Adrenergic Blockade Post Myocardial Infarction Left Ventricular Dysfunction

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Gregg C. Fonarow

Practice guidelines recommend that post myocardial infarction (MI) patients should be started and continued indefinitely on oral beta-blocker therapy unless absolutely contraindicated or not tolerated. Patients with post-MI left ventricular dysfunction (LVD) are at particularly high risk for recurrent cardiovascular events, heart failure, sudden death, and mortality and have been shown to derive substantial benefit from certain beta-blockers. Nevertheless, many of these patients are not prescribed beta-blockers, and some patients are treated with agents whose long-term use has not been shown to be effective. This article discusses the clinical trial evidence supporting the use of beta-blockers in patients post MI with LVD, provides the rationale for choosing specific beta-blockers, and presents practical approaches to implement this evidence-based therapy in the acute and chronic post-MI period.

Aldosterone Receptor Blockade in Patients with Left Ventricular Systolic Dysfunction Following Acute Myocardial Infarction

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Filippo Brandimarte, John E.A. Blair, Amin Manuchehry, Francesco Fedele, and Mihai Gheorghiade

Left ventricular systolic dysfunction (LVSD) is a common complication of acute myocardial infarction (AMI) that occurs in approximately 30% of post-AMI patients, and results in a threefold increase in in-hospital and 6-month mortality, regardless of type of AMI. Post-AMI care has evolved to include early reperfusion, antiplatelet therapy, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Despite these therapies, however, there is still an excess of sudden cardiac death (SCD), especially in patients with severe LVSD and in the first 30 days post-AMI. Aldosterone has been shown to be elevated in patients with post-AMI LVSD and to have deleterious effects on the myocardium, including endothelial dysfunction, collagen deposition, inflammation, apoptosis, and autonomic instability, leading to left ventricular remodeling and SCD. Aldosterone blockade with eplerenone has been shown to reduce mortality even in the presence of optimal post-AMI therapy in patients with post-AMI LVSD. Despite this, eplerenone is underutilized in real-world clinical practice. Care must be taken to follow renal function and potassium balance in patients treated with eplerenone.

V: Heart Failure in Perspective

Differences in European and North American Approaches to the Management of Heart Failure

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Philip A. Poole-Wilson

In recent years many guidelines on the treatment of specific medical conditions have been published with the goal of advising physicians, promoting good clinical care, and achieving a degree of equity and equality in the delivery of care. Differences exist between European and American guidelines for the management of heart failure not just because of differences in health systems but also because there is little agreement on how to assess clinical trials and convey conclusions in a clear format. Current recommendations can be confusing and often do not reflect the complexities of modern personalized medicine.

Heart Failure: Who We Treat Versus Who We Study

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Leslie W. Miller

The prevalence of patients with the diagnosis of heart failure continues to increase, with recent data suggesting that the current estimate in the United States should now be over 7 million patients. There are many sources of information about the patients with heart failure. Many patients have been enrolled in pharmaceutical and devices trials in heart failure, but the patients enrolled are often not reflective of the patients being managed outside of these trials in terms of age, gender, race, and comorbidities. And yet, investigators have extrapolated the results of these trials to all patients with heart failure. This article offers a comparison of the demographics and outcomes of the patients with heart failure that investigators treat and those studied.

Pharmacogenomics for Neurohormonal Intervention in Heart Failure

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Dennis M. McNamara

Neurohormonal activation is an important driver of heart failure progression, and all pharmacologic interventions that improve clinical outcomes inhibit this systemic response to myocardial injury. Functional polymorphisms affecting mediator levels and signal transduction are present in genetic loci critical to renin-angiotensin and sympathetic activation. Clinical investigations have demonstrated that these neurohormonal polymorphisms influence heart failure outcomes and alter the effectiveness of drug therapy. Genetic variation of disease modifiers such as angiotensin-converting enzyme (ACE) and β -adrenergic receptors influences ACE inhibitor and β -blocker effectiveness. The investigation of functional genomics will allow pharmacologic therapeutics to be tailored to an individual's specific genetic background. This article explores how genetic variation in genes involved in neurohormonal activation influence heart failure outcomes and the impact of pharmacotherapy.

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