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Patients who have acute coronary syndrome complicated by heart failure have increased short- and long-term morbidity and mortality. Besides the proven action in reducing cardiovascular events and mortality, statins also reduce the risk of developing heart failure after acute coronary syndrome. The pathways responsible for this benefit are likely a result of the “pleiotropic” actions of statins. The ongoing trials of statins in patients who have heart failure will help to further characterize this benefit.

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The pathophysiologic understanding of chronic heart failure has made significant advances over the last decades. Counterintuitively, high levels of plasma cholesterol are associated with better survival, perhaps because plasma lipoproteins are able to scavenge lipopolysaccharide, a cell-wall component from gram-negative bacteria. A number of similar features are present in patients who have sepsis. This article explores the cholesterol paradox in patients who have chronic heart failure and extends this view to patients who have sepsis. Also discussed is the potential of statins, which might be able to exert beneficial effects in both clinical conditions, despite lowering plasma cholesterol values.

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The syndrome of heart failure is characterized by increased levels of circulating inflammatory mediators, which have been implicated in the pathogenesis of heart failure. Recently, a number of studies have suggested that statins may exert salutary effects in patients who have heart failure by virtue of their pleiotropic (non-lipid lowering)

actions. This article focuses on the non-lipid lowering effects of statins, with an emphasis on the anti-inflammatory properties of these agents.

Potential Autonomic Nervous Systems Effects of Statins in Heart Failure

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Tamara B. Horwich and Holly R. Middlekauff

Sympathetic nervous system activation in heart failure, as indexed by elevated norepinephrine levels, higher muscle sympathetic nerve activity and reduced heart rate variability, is associated with pathologic ventricular remodeling, increased arrhythmias, sudden death, and increased mortality. Recent evidence suggests that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy may provide survival benefit in heart failure of both ischemic and nonischemic etiology, and one potential mechanism of benefit of statins in heart failure is modulation of the autonomic nervous system. Animal models of heart failure demonstrate reduced sympathetic activation and improved sympathovagal balance with statin therapy. Initial human studies have reported mixed results. Ongoing translational studies and outcomes trials will help delineate the potentially beneficial effects of statins on the autonomic nervous system in heart failure.

Investigations of Statins in Heart Failure: Inflammatory Biomarkers and Hormones

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Bobby V. Khan and Sanjay Rajagopalan

The primary role of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) is to treat dyslipidemia. The clinical benefits with statin therapy have been demonstrated in the primary and secondary prevention of atherosclerotic vascular diseases. More recently, it has been observed that pleiotropic effects of statins (which may or may not be associated with lipid lowering) have been described as treatment of various cardiovascular disease processes and in noncardiac disease processes. This article evaluates the potential mechanisms for these effects in the management of heart failure and postulates their clinical and beneficial use.

Clinical Investigations of Statins in Heart Failure: Ventricular Function and Anti-Remodeling

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Henry Krum

This article focuses on the importance of ventricular function as a surrogate end point for clinical outcomes and examines the evidence base for 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as anti-remodeling agents. Overall, the published evidence strongly suggests that statins possess beneficial anti-remodeling effects in the chronic heart failure setting and that these may be additional to those observed with standard therapy, such as angiotensin-converting enzyme inhibitors and beta-blockers. The data are not universally consistent, however, and the doses of agents studied may be important in this regard. Specifically, greater benefits appear to be observed with low doses of statins.

Antiarrhythmic Effects of Statins in Heart Failure

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Chirag M. Sandesara, Hamid Roodneshin, Salam Sbaity, and Brian Olshansky

In vitro heart failure models indicate that statins may be antiarrhythmic, but the mechanisms by which statins are antiarrhythmic are not completely understood. Several retrospective and post hoc analysis studies also indicate that statins can be antiarrhythmic in heart failure populations, but this was not confirmed by a recent large prospective randomized controlled clinical trial. Ongoing and future clinical trials will likely resolve the discrepancies between studies and further the understanding of how pleiotropic properties of statins can be antiarrhythmic in patients who have heart failure.

Observational Studies of Statins in Systolic Heart Failure Wayne C. Levy	201
<p>This article reviews the results of observational statin use in clinical trials of patients who have systolic heart failure, in post-myocardial infarction with left ventricular dysfunction, and in cardiac device trials. This article shows a consistent benefit of statins on mortality (approximately 25%) in heart failure patients of both ischemic and nonischemic etiology. The benefit is not altered by concomitant heart failure medications or device therapy. The benefit of statins in heart failure is being investigated in large prospective trials in a broad range of heart failure patients.</p>	
Observational Studies of Statins in Heart Failure with Preserved Systolic Function Hidekatsu Fukuta and William C. Little	209
<p>This article reviews the available evidence from observational studies concerning the effect of statin therapy in patients who have heart failure and a preserved ejection fraction (diastolic heart failure). Observational studies suggest that statin therapy is associated with lower mortality in patients who have diastolic heart failure. These results emphasize the need for a randomized study of the effect of statins in diastolic heart failure. Until the results of such studies are available, it is recommended to use statins in patients with diastolic heart failure who otherwise have an indication for statin therapy.</p>	
Translating Evidence into Practice: Use of Statins in Real-World Patients with Heart Failure Adrian F. Hernandez and Gregg C. Fonarow	217
<p>Heart failure is a common and serious disorder affecting more than 5 million patients in the United States. Although clinical trials have shown that several therapies improve outcomes, translation of evidence into practice is imperfect. This “quality chasm” ultimately leads to lost opportunities for decreasing morbidity and mortality. As more evidence is gathered for statins in heart failure, it will be important to continuously assess implementation of statins in eligible heart failure patients, as well as to identify opportunities for and barriers to improvement. This article reviews the conceptual basis for driving evidence-based medicine by focusing on quality of care for heart failure patients.</p>	
Randomized Clinical Outcome Trials of Statins in Heart Failure Gregg C. Fonarow	225
<p>Morbidity and mortality in patients who have heart failure (HF) remains substantial, and new therapies are needed. Tantalizing evidence from experimental studies, retrospective analyses, and limited prospective clinical investigations have suggested that statin therapy may improve ventricular function, HF status, and clinical outcomes independently of HF etiology and through mechanisms other than statin effects on dyslipidemia. The Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) is the first prospective randomized clinical outcome trial with statins focused specifically on HF. Over a median follow-up of 33 months, there were no significant differences in the primary end point or in all-cause mortality, the rate of coronary events, effects on New York Heart Association class, or the rate of newly diagnosed diabetes. There were significant reductions in the number of cardiovascular hospitalizations and, in a post hoc analysis, in nonfatal ischemic events. The discrepancy between the results from previous observational studies and the results of the CORONA trial emphasizes the importance of prospective randomized clinical outcome trials.</p>	
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