



## Coadministration Therapy in Hypercholesterolemia: A Novel Approach to Achieving Lipid Goals— Introduction

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**C**oronary heart disease (CHD), including angina pectoris and myocardial infarction, remains a significant clinical and economic burden. Coronary heart disease affects more than 13 million Americans, accounts for 1 in 5 deaths, and consumes more than \$130 billion in direct and indirect medical costs.<sup>1</sup> With the increasing age of the American population, the incidence of CHD is expected to rise, placing an even greater burden on the healthcare system and society at large. Consequently, evidence-based prevention strategies are critical for the successful prevention and treatment of this disease.

Treatment of CHD has shifted in recent years to reflect the increased understanding of atherosclerotic patho-

genesis, with symptom-directed modes of therapy being replaced by approaches that target the underlying causes of CHD and disease progression. Recently, the notion that atherosclerosis results from inflammation within the subintimal space of the vessel wall has generated a significant amount of interest<sup>2,3</sup> and has led to attempts to establish a relationship between markers of inflammation and risk for CHD.<sup>4</sup> Despite this new evidence, however, the cornerstone of both primary and secondary prevention of CHD remains lipid modification.

The third edition of the National Cholesterol Education Program (NCEP) Adult Treatment Panel guidelines (ATP III)<sup>5</sup> recommends that lipid-modification strategies should be matched to the patient's risk for CHD. Patients with a history of CHD, multiple risk factors, and those with CHD risk equivalents such as diabetes are at the highest risk for having a CHD event in the next 10 years and are candidates for interventions that lower low-density lipoprotein cholesterol (LDL-C) levels to less than 100 mg/dL.<sup>5</sup> The recently published ATP III update advocates even more intensified therapy as an option for moderate and high-risk patients. These new recommendations suggest that physicians could revise their LDL-C treatment target from less than 100 mg/dL to less than 70 mg/dL for patients at very high risk.<sup>7</sup>

Clearly, treating patients to LDL-C

levels as low as less than 70 mg/dL presents a challenge to healthcare providers. In addition to lifestyle changes, such as modification of the diet and inclusion of regular exercise, statins are recommended as first-line therapy for lipid lowering owing to their proven effect in lowering CHD risk across multiple patient types.<sup>8-11</sup> However, despite the availability of statins and other lipid-lowering therapeutic modalities such as bile acid sequestrants and fibrates, many patients at high risk for CHD fail to reach their ATP III target LDL-C levels with a single agent.<sup>12,13</sup>

Many explanations are possible for this inability of such patients to achieve treatment goals, including safety concerns reported with high-dose statin therapy; adverse events associated with the use of fibrates, bile acid sequestrants, and other agents; poor patient adherence to therapy; and failure of physicians to increase the intensity of therapy above the starting dose.<sup>14,15</sup> A strategy to overcome these challenges is to coadminister a statin with a second agent with a different mechanism of action that targets another aspect of lipid metabolism. Using lower doses of two agents effectively reduces cholesterol and minimizes the risk of dose-related adverse events.

An example of this approach is the coadministration of simvastatin and the intestinal cholesterol uptake inhibitor ezetimibe. Clinical trial data indicate that the combination of ezetimibe (10 mg) and simvastatin (10 mg) elicits LDL-C reductions similar to those observed with 80 mg of simvastatin.<sup>16</sup> Ezetimibe and simvastatin in combination also increase high-density lipoprotein cholesterol (HDL-C) levels and lower triglyceride concentrations and non-HDL-C levels, including remnant lipoproteins.<sup>16-20</sup>

In summary, the articles in this supplement review CHD pathophysiology, discuss several challenges associated with achieving target lipid levels, and identify new approaches that can potentially enhance the efficacy of existing treatment regimens. Several case studies of patients typically seen by osteopathic physicians are included to illustrate the use of these new approaches in current practice.

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