Statin Therapy in the New Millennium: Is There Room for Improvement?

Introduction

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have ushered in a new era in the treatment of hyperlipidemia. Within the past two decades, statins have become the treatment of choice for patients with hyperlipidemia and are now the most prescribed class of lipid-lowering agents worldwide, with annual sales approaching \$15 billion. The benefits of these drugs in both

primary and secondary prevention settings have been clearly demonstrated in a series of landmark trials, including the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, the West of Scotland Coronary Prevention Study (WOSCOPS), and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).¹⁻⁵ In 4S, for example, simvastatin was associated with a 42% decrease in the risk of coronary mortality in hypercholesterolemic patients with angina or previous myocardial infarction (MI) compared with placebo patients.¹ In AFCAPS/TexCAPS, a primary prevention trial of patients who had average levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) but below average levels of high-density lipoprotein cholesterol (HDL-C), lovastatin-

treated patients had a 37% reduction in the primary composite endpoint of unstable angina, fatal or nonfatal MI, or sudden cardiac death compared with placebo patients.⁵

However, as has been seen all too often with treatments for other chronic conditions such as diabetes, a disturbing gap can arise between the positive results of clinical trials and the translation of these results into "real-world" benefits. Many candidate patients for lipid-lowering therapy are not receiving any treatment at all, while those who do receive treatment often continue to have serum cholesterol levels higher than those recommended by the National Cholesterol Education Program⁶ and the European Joint Task Force.⁷ It seems clear that although we have made great strides in reducing cardiovascular risk in our patients, much work remains to be done if we truly wish to provide optimal lipid-lowering treatment to all those who need it. These issues and more are addressed in the following collection of articles, which are based on the symposium entitled "Statin Therapy in the New Millennium: Is There Room for Improvement?" held prior to the 73rd Scientific Sessions of the American Heart Association in New Orleans.

David Waters, M.D., provides key observations on the basis of results from the large-scale statin trials previously mentioned.¹⁻⁵ He notes that the characteristics of statins—including their efficacy in patients with or without coronary disease, their increasing degree of benefit over time, their ability to reduce stroke and transient ischemic attack, and their efficacy in a wide range of patient subgroups—allow for effective management of hyperlipidemia in current practice while also constituting a foundation for further refinements in statin therapy. *Antonio Gotto, Jr., M.D., D.Phil.*, addresses the critical question of how we can achieve optimal cardiovascular risk reduction, which he believes will require improved application of clinical evidence to patient care and refinement of risk assessment. For example, Dr. Gotto notes that a refinement in global risk assessment can help us to identify high-risk patients who require aggressive treatment more accurately or to identify intermediate-risk patients who appear to be at low risk. *Christie Ballantyne, M.D.*, discusses the use of risk markers, such as cell adhesion molecules and inflammatory markers, to improve and individualize assessment of atherosclerotic disease risk.

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He also suggests that noninvasive imaging procedures such as magnetic resonance imaging may one day permit adoption of new surrogate endpoints in clinical trials. *Anders Olsson, M.D., Ph.D.*, reports clinical results for a new statin, rosuvastatin (Crestor™), which is currently undergoing clinical investigation. Phase III studies suggest that rosuvastatin is more effective than atorvastatin, pravastatin, and simvastatin in improving the atherogenic lipid profiles of hypercholesterolemic patients. Finally, *W. Virgil Brown, M.D.*, provides an overview of new therapies on the horizon for cholesterol reduction. These therapies include statins such as rosuvastatin and NK-104; specific inhibitors of cholesterol absorption, such as ezetimibe; bile acid transport inhibitors; and inhibitors of acyl CoA:cholesterol acyltransferase (ACAT), such as avasimibe, which may work by inhibiting macrophage cholesterol storage.

The title of this supplement asks, "Is there room for improvement in statin therapy?" and, perhaps not surprisingly, we believe the answer to this question is an unqualified yes. However, the purpose of this supplement is not simply to point out the shortcomings of current therapeutic strategies. It is our hope that this supplement will also provide the reader with a clear outline of future treatment options while also stimulating new ideas and research for improving the health of our patients.

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