Should We Treat All Primary Prevention Patients With Statins?

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Introduction
In traditional office practice, one of the major responsibilities of practitioners is determining how to screen patients to identify and potentially treat major health risks. Screening for certain malignancies is now routine, and numerous guidelines exist for the identification of other significant medical issues. As coronary heart disease (CHD) has been and should remain our leading cause of mortality, great attention has focused on its identification and treatment. This article focuses on treatment choices that may prevent the initial appearance of CHD in patients at risk.

Statins
In the extensive research on this subject, statins, which the 3-hydroxy-3-methylglutary coenzyme A (HMG-CoA) reductase inhibitors are commonly called, have emerged as premier agents in the treatment of hyperlipidemia. The original primary prevention statin trial was the West of Scotland Coronary Prevention Study (WOSCOPS) [1]. The study enrolled over 6600 Scottish male patients who were free of known CHD. They had an average low-density lipoprotein cholesterol (LDL-C) of 192 mg/dL, with normal high-density lipoprotein cholesterol (HDL-C) of 44 mg/dL and triglycerides of 162 to 164 mg/dL. They were randomized to 40 mg/d of pravastatin or placebo, and they were followed for an average of 4.9 years. The pravastatin-treated patients had dramatic reductions in initial coronary events, including nonfatal myocardial infarction (MI) and death from both CHD and overall cardiovascular disease, and they nearly achieved a significant reduction in total mortality. These dramatic results in a primary prevention trial led to enthusiasm for statin use in patients at high risk for early CHD. Recently, a long-term follow-up evaluation of the former study patients was published, looking at the patients 10 years after the study had been completed [2••]. Even though nearly equal numbers of former statin and former placebo patients were currently on statin therapy, the former statin patients had fewer myocardial events even lower rates of cardiovascular and total mortality throughout the 10-year follow-up period [2••].

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [3] studied a very different primary prevention patient base but had equally dramatic results. AFCAPS/TexCAPS was a trial that enrolled both men and women and included traditional American ethnic groups. LDL-C levels for enrollment were lower than those for WOSCOPS, with an LDL-C of 130 to 190 mg/dL, with a mean of 150 mg/dL. Lower HDL-C levels were required for enrollment (HDL-C < 45 mg/dL for men and < 47 mg/dL for women, with a mean of 36 mg/dL for men and 40 mg/dL for women). Participants were randomized to 20 to 40 mg/d of lovastatin or placebo, with a reduction of LDL-C of 25% and an increase of HDL-C of 6%. Lovastatin treatment significantly reduced a variety of initial coronary events, including MI, new unstable angina, and revascularization procedures. A follow-up analysis of this study showed that much of the benefit of the lovastatin was in the group of patients with an HDL-C of less than 40 mg/dL at baseline [4]. In this group, lovastatin reduced cardiac events by 37% (nearly 50% is probably an overstatement of benefit). This fact offers two extra insights:
HDL-C less than 40 mg/dL is a powerful risk factor for cardiac events, and statin treatment dramatically reduces the effect of low HDL-C [4]. The Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA) [5] was a comparative hypertension treatment trial in northwest Europe that had a primary prevention lipid-treatment arm. In this study, patients with elevated lipids were randomized to 10 mg/d of atorvastatin or placebo [5]. Atorvastatin treatment lowered the LDL-C by 37% but did not affect the HDL-C. In the atorvastatin group, nonfatal MI and fatal CHD were reduced by 36%. These data show the powerful benefit of a dramatic lowering of primary cardiac events through aggressive LDL-C lowering by statin therapy. Because the HDL-C was not altered by atorvastatin, this study also emphasizes the powerful link between LDL-C lowering and reduced cardiac events with statin therapy.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [6] was a trial in northwest Europe that enrolled elderly men and women ages 70 to 82 years. Patients were about an equal mix of higher-risk primary patients (without known vascular disease) and patients with known vascular disease. They were randomized to either 40 mg/d of pravastatin or placebo and followed for 3 years [7]. The pravastatin-treated patients had significant 14% to 23% reductions in cardiac events such as nonfatal MI or CHD, with both the primary and secondary patients benefiting from pravastatin therapy [6]. This very important study demonstrated that the benefit of statin therapy extends to our elderly and very elderly patients.

Two other statin primary prevention studies showed less conclusive, but supportive, results. The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study [8] is a Japanese primary prevention trial using lower doses of pravastatin (10–20 mg/d) in both men and women. The female subset was recently published. It showed that pravastatin therapy reduced initial cardiac events 25% in this extremely low-risk female subgroup. The reduction was comparable to that seen in other studies. However, it failed to reach statistical significance because there were so few total events in this very low risk population. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid Lowering Trial (ALLHAT-LLT) [9] was a hyperlipidemia substudy of a United States (US) hypertension comparison study. The lipid arm compared open-label pravastatin at 40 mg/d to usual care. The substudy was not placebo controlled or double blinded. The pravastatin arm had a nonsignificant trend toward lower cardiac events. However, the validity of the results was severely compromised by the open-label comparison versus usual-care design. Because the usual-care patients were eligible for nonstudy statin treatment by their physicians, the study was not able to achieve enough of an LDL-C difference between the two groups to achieve significance [9,10]. Therefore, this study is invalidated by its nonblinded study design.

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study [12] was a double-blind, placebo-controlled trial using 20 mg/d of rosuvastatin versus placebo in primary patients with low LDL-C (<130 mg/dL) with an elevated level of high-sensitivity C-reactive protein. The trial was stopped prematurely because of “an unequivocal evidence of a reduction in cardiovascular morbidity and mortality” in the treatment group [12]. When this study is finally reported, it should add further support for the use of aggressive statin therapy in primary prevention.

In summary, the comprehensive trials with the statins showed that treating hyperlipidemia to prevent an initial cardiac event, particularly in patients with elevated LDL-C and/or low HDL-C, leads to dramatic reductions in the initial presentation of CHD events. The evidence for the efficacy of this class of agents in the primary prevention of CHD is robust and clear.

Resin Bile Acid Sequestrants
The original US cholesterol medication treatment trial was initiated by the Lipid Research Council in 1973. It was the Lipids Research Clinical Coronary Primary Prevention Trial (LRC-CPPT) [13]. The study used cholestyramine to bind bile acids in the intestines and reduce cholesterol absorption and, therefore, serum cholesterol. The trial enrolled 3810 middle-aged men with very high cholesterol, with an average LDL-C of 216 mg/dL and an HDL-C of 45 mg/dL at enrollment. Patients were randomized to 24 g/d of cholestyramine resin or placebo, and the study ran for 7.4 years. In the on-treatment group, the LDL-C was reduced by 20% and the HDL-C was increased by 3.5%. In the cholestyramine group, there was a 19% reduction in the combined end point of CHD death and nonfatal MI.

In spite of the significant improvements in events seen with this therapy in a primary patient population, bile acid resins are rarely used in primary prevention situations because of their significant gastrointestinal adverse effects. They are used in combination therapy in some very high-risk patients with severe lipid abnormalities that cannot be controlled by statin therapy alone. Whether they reduce events more than statin therapy alone has not been proven, so their use in these combination treatments is intuitive. However, because this class of agents has essentially no systemic absorption, they are generally regarded as safe to use in the very rare instance of a fertile woman who requires lipid-lowering medication [14].

Fibrates
The fibrates, or fibric acid agents, include two preparations on the US market: fenofibrate (soon also to be sold