

A Prophylactic Application of Statins in Cardiovascular Disease: Statin Use in a “Non-Hyperlipidemic” State

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Abstract

In conventional use, statin pharmacologic intervention was introduced to slow or stop the progression of cardiovascular disease in the initial or early stage, and in doing so limit further complications. Before the introduction of commercially-available lovastatin in 1987, therapeutic interventions were limited to dietary changes, bile acid sequestrants, nicotinic acid, fibrates, and probucol. However, when examined under rigorous studies, these pre-statin interventions showed limited benefits, when used individually and in combination for lowering serum lipid levels. With the introduction of lovastatin, a lipid-lowering HMG-CoA reductase enzyme inhibitor, substantial decreases in cholesterol levels have been observed. However, recently in terms of patients that are at a higher risk for cardiovascular events such as myocardial infarct (MI), statin medications are being recommended regardless of the lipid levels, even in a “non-hyperlipidemic” state.

Keywords: Cardiovascular Disease; Dyslipidemia; Hyperlipidemia; Myocardial Infarction; Statins

Abbreviations

CVD: Cardiovascular Disease; HDL: High-Density Lipoproteins; HPS: Heart Protection Society; LDL: Low-Density Lipoprotein; MI: Myocardial Infarction;

Introduction

History of cholesterol and cardiovascular disease

The connection of cholesterol with atherosclerosis was established in 1910 when Heinrich O. Wieland and Adolf Windaus investigated the relationship of cholesterol and atherosclerotic plaques in humans [1-3]. In 1927 and 1928, they were awarded the Nobel Prize in Chemistry regarding their research in connecting lipids and atherosclerotic plaques.

In the mid-1950s, John Gofman headed an epidemiologic investigation of a cholesterol-coronary corollary. He found that myocardial infarctions corresponded to elevated levels of blood cholesterol. Also, he determined that cholesterol was contained in low-density

lipoproteins (LDLs). Gofman noted that myocardial infarction (MI) was less prevalent when the blood contained a high level of high-density lipoproteins (HDLs) [2-4].

The epidemiologic association between blood cholesterol and coronary atherosclerosis was ultimately settled more than a decade after Gofman’s original work. Beginning in the mid-1960s, Ancel Keys, heading the Seven Countries Study [5], demonstrated that the number of new cases of MI in 15,000 middle-aged men (tracked over ten years) clinically and statistically showed an irrefutable connection between serum cholesterol levels and cardiovascular events [1,3,5].

The Framingham Heart Study (National Heart Institute in Framingham, Massachusetts. 1948–present) proved that people with higher blood cholesterol levels were bound to encounter a heart attack in years to come, compared to those who had normal blood cholesterol levels [6]. Also, the Framingham Heart Study demonstrated that the risk of a cardiovascular event was increased by hypertension and smoking [6].

Discussion

Statin medication and hyperlipidemia

Given the connection between cholesterol and cardiovascular disease (CVD), pharmaceutical companies and researchers around the world began to investigate ways of lowering cholesterol levels (reducing elevated cholesterol levels). In 1978, Alberts and fellow researchers at Merck Research Laboratories discovered a potent inhibitor of HMG-CoA reductase in the fermented broth of *Aspergillus terreus*. They named their discovery mevinolin; later, lovastatin was branded [7,8].

In the early-1980s, a few clinicians including Roger Illingworth and David Bilheimer began treating patients with severe hypercholesterolemia refractory to conventional therapy with cholesterol metabolism-inhibiting agent, lovastatin. In 1987 with positive outcomes, lovastatin, a lipid-lowering HMG-CoA reductase enzyme inhibitor, received FDA approval. Since lovastatin’s entrance into the commercial drug market, six statins—including two semi-synthetic statins (simvastatin and pravastatin) and four synthetic statins (fluvastatin, atorvastatin, rosuvastatin, and pitavastatin)—have been introduced [1-3,7-9].

Fast forward to “prophylactic” statin use in a non-hyperlipidemic state

The Heart Protection Study (HPS) [10] shifted the clinical utilization of statin medications away from patients with hyperlipidemia to the prevention of cardiovascular events. The HPS was the most extensive placebo-controlled randomized study to date, which investigated prescribing statin medications to patients with cardiovascular disease or at a high risk for cardiovascular disease, to prevent cardiovascular events. The HPS was conducted within the United Kingdom, which randomized 20,536 participants and examined individuals with cardiovascular disease or at high risk for cardiovascular disease, due to cerebrovascular or peripheral vascular disease or diabetes [1-4,10].

When the HPS results were published, they offered convincing evidence that adding simvastatin medication to high-risk individuals, such as diabetics or those with peripheral vascular disease (irrespective of their initial cholesterol concentrations), was particularly advantageous in preventing cardiovascular events [1-4,10].

Conclusion

Before the discovery and introduction of the therapeutic application of statins, other interventions such as dietary changes, bile acid sequestrants, nicotinic acid, fibrates, and probucol [11-15] had failed to show significant benefit when utilized separately or in combination to prevent cardiovascular events. Looking forward—given the developments in statin medications and notwithstanding adverse effects on specific patient groups [16–18]—the future of preventing cardiovascular events appears to be statin-oriented, not only in slowing or stopping the progression of cardiovascular disease but also in the prophylactic treatment thereof in a “non-hyperlipidemic” or “non-dyslipidemic” state.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note

While preparing for STEP 3 of the USMLE, Abdullah Hafid, M.D. became interested in this contemporary (and futuristic) application of statins in a non-hyperlipidemic or non-dyslipidemic state in relation to comorbidities in cardiovascular disease, which inspired the investigating and writing of this review.

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