Molecular Medicine

# Statins: Definitive Translational Research

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The development of cholesterol-lowering statins is one of the highlights of transitional medicine. Statins reduce serum low-density lipoprotein cholesterol (LDL-C) and other atherogenic lipoproteins. Statin use in clinical practice is the outgrowth of extensive research into cholesterol and lipoprotein metabolism, drug discovery and randomized clinical trials (RCTs). Each of these areas is worthy of some review.

Cholesterol was first discovered in gallstones. It was named cholesterine by the French chemist Chevreul in 1816. In 1856, Virchow found that lipid (cholesterol) is a key component of atherosclerotic plaques. Subsequently, 13 Nobel Prizes have been awarded to scientists who have studied the structure, chemistry, biochemistry and biology of cholesterol. It has been known for 100 years that high serum cholesterol produces atherosclerosis in animals (1). In the 1940s and 1950s, it was observed that high serum cholesterol consistently associates with premature atherosclerotic disease in humans. Shortly thereafter, cholesterol was discovered to be carried in lipid-protein complexes called lipoproteins (2). Among the lipoproteins, LDL is the predominant atherogenic lipoprotein. LDL from the blood filters into the arterial wall and starts the process of atherogenesis (3). All of the steps whereby LDL initiates atherogenesis and produces cholesterol-rich atherosclerotic plaques are still not fully understood. But importantly, in some individuals, a plaque becomes unstable and undergoes rupture. When this occurs, arterial thrombosis follows and precipitates an acute cardiovascular event (4). Coronary thrombosis and stroke are the major killers accompanying atherosclerosis.

The zenith of cholesterol research was the discovery of the LDL receptor by Michael Brown and Joseph Goldstein (5). LDL receptors are located mainly on the surface of liver cells. They recognize the protein component of LDL, known as apolipoprotein B, and remove LDL from the circulation. In a word, LDL receptor expression regulates serum levels of LDL-C. Underexpression leads to hypercholesterolemia; overexpression reduces serum cholesterol levels. LDL receptors also remove some triglyceride-rich lipoproteins but mainly cholesterol-enriched LDL. The discovery of the LDL receptor uncovered a potential pathway for markedly lowering levels of serum LDL and preventing atherosclerosis. The mechanisms underlying the regulation of LDL receptor expression have been worked out in exquisite detail by Brown, Goldstein and their colleagues (6).

One consequence of the discovery of the LDL receptor was the uncovering of the cause of a condition called familial hypercholesterolemia (FH). In this condition, serum LDL-C levels are elevated from birth and remain elevated throughout life. High LDL-C levels cause the buildup of cholesterol in arteries leading to premature atherosclerotic cardiovascular disease (ASCVD). FH occurs in two forms: heterozygous and homozygous. The former confers half the normal number of LDL receptors; in the latter, receptors are absent. Heterozygous FH patients have twice the normal levels of LDL-C, whereas in homozygous FH levels, LDL-C concentrations are about four

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times normal levels. Patients with FH carry mutations that impair the synthesis of LDL receptors (7). Kinetic studies of lipoprotein metabolism show that patients with FH have a defective clearance of LDL from the circulation (8). This clearance defect for LDL, which is due to a deficiency of hepatic LDL receptors, leads to hypercholesterolemia. There are several forms of hypercholesterolemia besides FH. Milder forms appear to have lesser defects in the regulation of LDL receptors, or perhaps other metabolic abnormalities; these lesser forms can be called "polygenic hypercholesterolemia" (9). The degree of hypercholesterolemia also depends not only on genetic factors, but also on the diet. High intakes of saturated fats and cholesterol accentuate polygenic hypercholesterolemia.

Several early attempts to develop cholesterol-lowering drugs were modestly successful. It has subsequently been shown that these drugs act by increasing the removal of serum LDL-C through the receptor pathway. Bile acid sequestrants bind and remove bile acids through the intestine. This process reduces the conversion of cholesterol into bile acids and lowers hepatic cholesterol content. The result is an increase in LDL receptor expression. In a large RCT (10), bile acid sequestrants were shown to reduce the incidence of CHD. Other agents are cholesterol-absorption blockers; they moderately reduce LDL-C levels by preventing the reabsorption of cholesterol from the intestine. They also enhance LDL receptor expression. Cholesterol-absorption blockers have not undergone RCTs for efficacy in preventing CHD. Although both classes of drug act through attractive mechanisms, neither is powerful enough to markedly lower LDL-C levels. Some early investigators believed that if a potent inhibitor of cholesterol synthesis could be developed, it would be more efficacious for reducing serum cholesterol. One person who held this belief was Akira Endo, a scientist at Sankyo Co., Ltd., in Japan.

At about the same time as the discovery of the LDL receptor, Dr. Endo found a fungal metabolite that blocks cholesterol synthesis by inhibiting the enzyme HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase (11). This drug was named compactin. Its structure resembles that of HMG and blocks a rate-limiting step in cholesterol synthesis. Endo further observed that compactin lowered serum cholesterol levels in animals. This finding led his Japanese colleagues (12,13) to test compactin in patients with FH. A marked lowering of cholesterol levels occurred.

Shortly thereafter, Merck & Co. in the United States identified a related compound named mavinolin (14). Its name was later changed to lovastatin. HMG-CoA inhibitors of this class are now called statins. Merck & Co. did a preliminary study in humans with lovastatin that showed potential for cholesterol lowering (15). Just at this time, the development of statins as cholesterol-lowering drugs was stopped because of reports from Japan that compactin causes intestinal tumors in dogs. Merck & Co. decided to discontinue its investigation of lovastatin.

A group of investigators in the cholesterol field still recognized the potential for statins. Among them were researchers at the University of Texas Southwestern Medical Center in Dallas; they included this author (Grundy). We expressed a willingness to carefully explore the potential of lovastatin if approval for testing could be obtained through the U.S. Food and Drug Administration (FDA). This author was able to obtain investigational new drug (IND) approval to test lovastatin in patients with hypercholesterolemia. A similar IND was given to Dr. Roger Illingworth at the University of Oregon. Dr. Sol Sobel, then director of the Division of Metabolic and Endocrine Drugs at FDA, saw the potential of statins. His support for the testing of these drugs was recently recounted by the FDA historian, Dr. Suzanne White Junod (http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm082054.htm). This article speculates that, without the foresight of Dr. Sobel, the development of statins might have been greatly delayed.

In a study in patients with heterozygous FH, this author together with Drs. David Bilheimer, Goldstein and Brown found that lovastatin is a powerful cholesterol-lowering drug (16). In this study, lovastatin was shown to increase LDL receptors in the liver and to remove circulating LDL-C through this pathway.

Subsequently, our group carried out a series of studies with lovastatin and confirmed its efficacy in patients with several types of dyslipidemia. Besides further research in FH (17–19), we were the first group to investigate statins in polygenic hypercholesterolemia (20,21), dysbetalipoproteinemia (22,23), postmenopausal hypercholesterolemia (24), combined hyperlipidemia (25–27), hypertriglyceridemia (28–30), hypoalphalipoproteinemia (31), nephrotic dyslipidemia (32) and diabetic dyslipidemia (33). It is our view that these investigations contributed to the development of large-scale statin trials in these conditions.

Fortunately, the claim that compactin causes cancer in animals was shown to be incorrect. Subsequent research found no evidence of carcinogenesis. Our testing and that of others found that statins are well tolerated. For this reason, Merck & Co. moved forward with more extensive testing of efficacy and safety of statin therapy. On the basis of these studies, in 1987, the FDA approved statins for treatment of hypercholesterolemia. At the same time, they encouraged further exploration of statins to determine their efficacy in prevention of cardiovascular disease.

The first major end-point trial was the Scandinavian Simvastatin Survival Study (4S) (34). This trial included 4,444 patients with angina pectoris or previous myocardial infarction and elevated serum cholesterol. Patients were randomized to double-blind treatment with a newer statin, simvastatin, or placebo. Over the 5.4 years of treatment, simvas-

tatin reduced LDL-C by 35%. The drug additionally reduced total mortality by 30%, coronary heart disease (CHD) mortality by 42% and major CHD events by 34%. These dramatic results in the 4S trial opened the door to further clinical trials with simvastatin and other statins.

Both primary and secondary prevention trials have been carried out with several different statins. Virtually all have shown risk reduction for CHD in the range of 25–40% (35–50). Meta-analysis of these trials further showed that for every 1% reduction in LDL-C levels, risk for CHD events is reduced by 1% (51). This observation indicates that newer and more potent statins (for example, atorvastatin and rosuvastatin) should lower risk for future CHD by approximately 50%.

Fortunately, statins have proven to be largely safe. Serious side effects are extremely rare. A variety of lesser adverse side effects have been reported; these include mainly myalgias, glucose intolerance and cognitive dysfunction. In most cases, these lesser side effects can be eliminated by either reducing the dose of the statin or by switching to another statin.

Thanks to the discovery of the LDL receptor, other agents besides statins have the potential for reducing risk for ASCVD by acting through this pathway. At present, the most promising among these are inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a circulating protein that blocks uptake of LDL by LDL receptors (52). By binding PCSK9 to an antibody, it is possible to remove this receptor blockade and to markedly lower LDL-C levels (53). Several new PCSK9 inhibitors are currently being tested to determine whether they will reduce risk for ASCVD beyond what can be obtained with statins alone.

Statins are the most prescribed drug in the world. Millions of people are taking these drugs, and new guidelines are expanding their use to many more people. This author had the privilege of overseeing the development of U.S. national cholesterol guidelines in the first two decades of the statin era (54–56). More recently, recommendations for use of statins to prevent ASCVD have been expanded to include more people (57).

In summary, basic science has uncovered the potential for cholesterol lowering through regulating pathways of cholesterol metabolism. These discoveries have been appropriately recognized through Nobel Prizes and other awards. But in addition, drug discovery has made it possible to regulate cholesterol metabolism in a way to markedly reduce serum cholesterol concentrations. Several pre-statin drugs demonstrated that serum cholesterol can be lowered, but their efficacy was limited. The discovery of statins opened the door to marked reductions of serum cholesterol. Statins have proven without a doubt the validity of the "cholesterol hypothesis" for atherosclerotic disease and promise to go a long way to eliminating its scourge. It may be possible to extend this protection even more with newer cholesterol-lowering drugs that act via the LDL receptor pathway.

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## DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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