STATINS IN THE REDUCTION OF CARDIOVASCULAR EVENTS

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1 DISCOVERY OF STATINS

In the 1960s, physicians became aware of cholesterol's role in the development of atherosclerotic heart disease. Several agents, such as nicotinic acid, cholestyramine, and clofibrate were developed, but these agents failed to substantially lower low-density lipoprotein (LDL)-cholesterol levels. Akira Endo, a Japanese scientist who had done years of research on fungi, realized that fungi could hold a solution to the cholesterol problem because bacteria—like humans—required cholesterol to maintain cell wall integrity. He reasoned that certain fungi produce a substance that destroys cholesterol in bacterial cell wall as an evolutionary adaptation. With this fundamental understanding, he set about testing more than 6000 fungal broths. In 1973, he identified the mold *Penicillium citrinum* that produced a substance that appeared to inhibit HMG-CoA reductase enzyme, a key step in LDL-cholesterol synthesis. This substance, named compactin, was the first known statin. It successfully lowered LDL-cholesterol levels in animal studies, and similar success was seen in early human trials. Interestingly enough, the first patient treated with Dr. Endo's new drug developed severe muscle cramps and weakness, now a well-known side effect of this class of drugs, and had to discontinue therapy. However, interest in this agent continued to grow as its success in lowering LDL-cholesterol became public knowledge, and several pharmaceutical companies developed several variations of this formulation. Merck was first to market lovastatin (Mevacor) in the United States in 1987. Today the world's most widely selling drug is a statin (atorvastatin, Lipitor; Pfizer), with annual worldwide sales of $12 billion [1].

2 STATINS: BIOCHEMISTRY AND MECHANISMS OF ACTION

Acetyl-CoA is produced from glucose, fatty acids, or essential amino acids, with three molecules of acetyl-CoA combining to form 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA). HMG-CoA reductase catalyzes the reduction of HMG-CoA to produce mevalonate. Mevalonate produces isoprene units that condense to form squalene, and the cyclization of squalene produces the steroid ring system, with subsequent reactions generating cholesterol. HMG-CoA reductase is the rate-limiting step in the formation of cholesterol in the liver and intestine, though cholesterol formation does occur in most cells of the body (Fig. 1).

Statins compete with normal substrate for the enzyme's active binding site and once bound alter the conformation of the enzyme. This binding is reversible, but once statin binds to HMG-CoA reductase, the enzyme is prevented from attaining a functional conformation. The inhibition of HMG-CoA reductase by statins reduces the hepatocyte cholesterol content,

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