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**Editorial correspondence** — Burton E. Sobel, M.D., Editor, Washington University School of Medicine, 660 South Euclid Ave., Box 8055, St. Louis, Missouri 63110.

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# New developments in lipid-lowering therapy: the role of inhibitors of hydroxymethylglutaryl-coenzyme A reductase

J. A. TOBERT, M.B., PH.D.

ABSTRACT HMG-CoA reductase catalyzes the conversion of hydroxymethylglutarate to mevalonate, an important early rate-limiting step in the cholesterol biosynthesis pathway. Since the discovery of compactin, the first HMG-CoA reductase inhibitor, by Endo et al. in 1976, several other inhibitors have been described. Those that have been investigated in the clinic include mevastatin (compactin), lovastatin (mevinolin), simvastatin (synvinolin), eptastatin (CS-514, SQ-31,000), and SRI-62320. These compounds are competitive inhibitors, with $K_i$ values of the hydroxyacid forms of around $10^{-9}$M. Lovastatin (mevinolin, Mevacor*), which is in the late stages of clinical development and has been administered to over 1000 subjects for up to 4 years, is the inhibitor on which the most information is available. It is given in single or divided doses of 20 to 80 mg/day, and is a very effective and usually well-tolerated lipid-lowering agent. At 40 mg bid, lovastatin produces the following approximate mean changes: total plasma cholesterol, −33%; low-density lipoprotein (LDL) cholesterol, −40%; very low-density lipoprotein cholesterol, −35%; plasma triglycerides, −25%; high-density lipoprotein cholesterol, +10%; apolipoprotein B, −20%. The substantial reduction in both LDL cholesterol and apolipoprotein B (the principal protein component of LDL) indicates a reduction in the number of circulating LDL particles. The mechanism probably involves both decreased LDL production and increased LDL clearance.

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THE ROLE OF hypercholesterolemia, or more accurately hyperbetalipoproteinemia, as a risk factor for atherosclerosis in general and ischemic heart disease in particular is supported by a wealth of clinical, epidemiologic, and pathologic studies. A National Institutes of Health Consensus Development Panel recently concluded[1] that the ideal blood cholesterol for all Americans over the age of 30 is 200 mg/dl or less, and that attempts should be made to lower blood cholesterol when it exceeds the 75th percentile, or approximately 240 mg/dl, in middle-aged American men. Therapy should always start with a lipid-lowering diet, but diets acceptable to most patients typically lower blood cholesterol by 10% or less. Drug therapy has been limited by insufficient efficacy at tolerated doses, and in some cases a high instance of side effects and/or significant safety problems.[2]

In individuals eating a typical Western diet, approximately one-third of total body cholesterol is derived from the diet, and two-thirds is synthesized, mainly by the liver and intestine. The biosynthetic pathway for cholesterol involves more than 25 different enzymes, and is summarized in figure 1. An important rate-limiting step in this pathway is the conversion of hydroxymethylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is catalyzed by HMG-CoA reductase.[3] Early attempts to inhibit cholesterol synthesis were centered on the late stages of the pathway. One such inhibitor, triparanol (MER/29), was used briefly in the clinic, but was withdrawn in 1962 after reports of serious toxicity, including cataracts, ichthyosis, and alopecia.[4] Triparanol inhibited the conversion of desmosterol to cholesterol, and consequently caused the buildup of desmosterol in plasma and tissues.[5] It is believed that the toxicity of triparanol and other late-stage inhibitors can be attributed, at least in part, to the accumulation of abnormal sterols in tissues.

Inhibitors of HMG-CoA reductase inhibit the pathway at a much earlier stage, and therefore cannot cause buildup of sterol intermediates. Five inhibitors have been studied in the clinic: mevastatin (compactin), lovastatin (mevinolin, Mevacor*), simvastatin (synvi-

From the Department of Clinical Research, Merck Sharp & Dohme Research Laboratories, Rahway, NJ.

Address for correspondence: J. A. Tobert, M.B., Ph.D., Department of Clinical Research, Merck Sharp & Dohme Research Laboratories

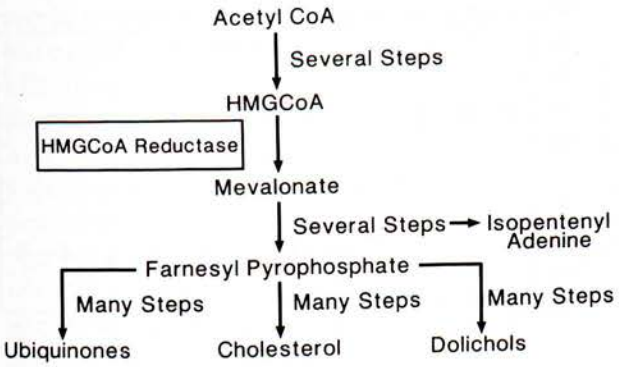
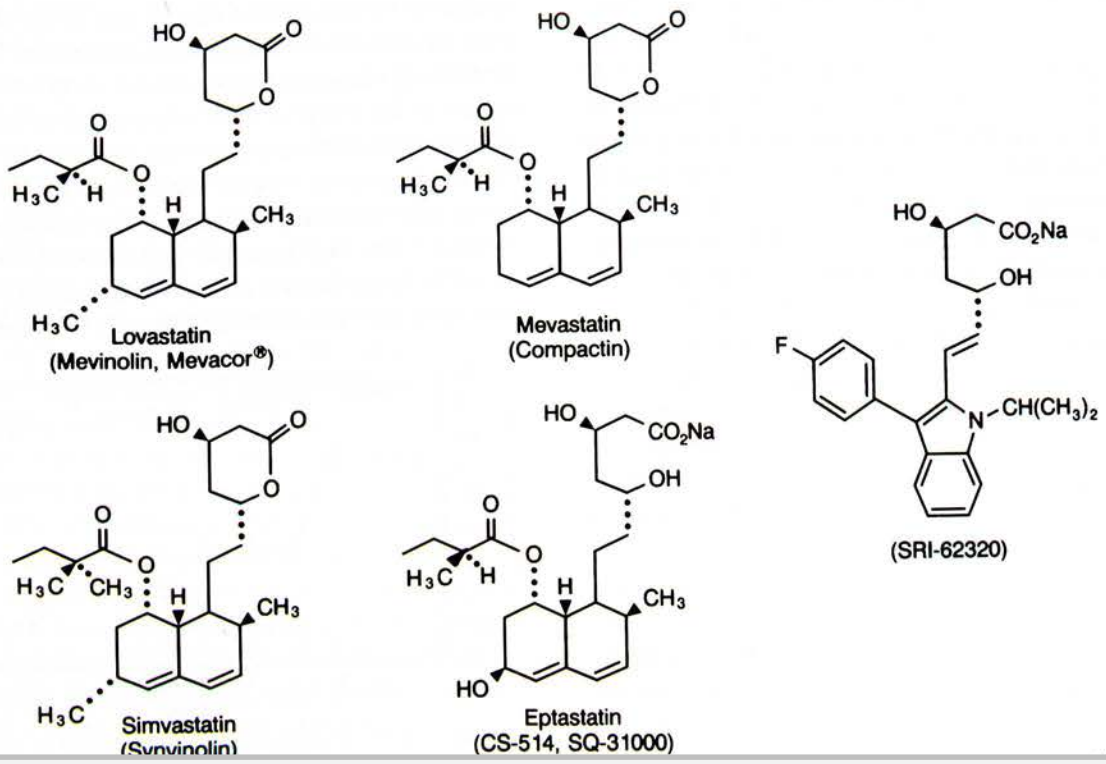



**FIGURE 1.** The cholesterol biosynthesis pathway.

nolin), eptastatin (CS-514, SQ-31,000), and SRI-62320 (figure 2). Mevastatin, lovastatin, and simvastatin are prodrugs; in vivo, the lactone ring is hydrolyzed to the corresponding $\beta$-hydroxyacid, which is the principal active form of these drugs. These compounds are competitive inhibitors of HMG-CoA reductase, with $K_i$ values of approximately $.10^{-9}$M. Mevastatin, which was discovered by Endo et al.[6] in Japan, is the prototype of this class of compounds. However, lovastatin is the agent that has been most extensively studied, having been given to more than 1000 subjects for up to 4 years. Approval by the U.S. Food and Drug Administration is expected in 1987. Because much more information is available on lovastatin than on the other inhibitors, this review will summarize the clinical evaluation of this agent.

**Effect of lovastatin on lipoproteins.** The first human studies on lovastatin were carried out in normocholesterolemic volunteers eating an unrestricted diet. In these subjects, the hypocholesterolemic effects of the drug were evident after 3 days, and mean reductions in low-density lipoprotein (LDL) cholesterol between 35% and 45% were obtained after 4 weeks at doses of 6.25 to 50 mg bid.[7] Similar reductions in LDL cholesterol were subsequently demonstrated in heterozygous familial hypercholesterolemia (FH)[8–12] and in patients with primary nonfamilial hypercholesterolemia.[10, 13, 14] In all these studies, patients were on lipid-lowering diets before starting treatment with lovastatin. Illingworth and Sexton[8] obtained dose-related decreases in LDL cholesterol in 13 patients with FH that ranged from 20% on 5 mg bid to 38% on 40 mg bid. In six patients with heterozygous FH, Bilheimer et al.[9] noted a 27% decrease in LDL cholesterol on 20 mg bid; in another group of six patients with heterozygous FH, Hoeg et al.[10] reported a 34% reduction in LDL cholesterol at the same dose. In a multicenter, double-blind, placebo-controlled study in 101 patients with FH, Havel et al.[11] observed mean reductions in LDL cholesterol ranging from 17% on 5 mg bid to 39% on 40 mg bid. The corresponding mean changes



in total cholesterol ranged from 14% to 34%. In two patients with homozygous FH undergoing treatment by plasma exchange,[12] lovastatin was relatively ineffective, producing reductions in serum cholesterol of only 7% and 12%. The effects of lovastatin in patients with nonfamilial primary hypercholesterolemia are similar to those in patients with FH. Hoeg et al.[10] obtained a 34% reduction in LDL cholesterol at 20 mg bid in 18 patients with nonfamilial hypercholesterolemia, and Grundy and Vega[13] reported a 31% reduction in 12 patients at the same dose. In another multicenter study using the same double-blind, placebo-controlled design as that of Havel et al. in their study of patients with FH, Hunninghake et al.[14] reported very similar results in 100 patients with nonfamilial hypercholesterolemia. At 40 mg bid, total and LDL cholesterol fell by 32% and 39%, respectively.

In addition to reducing LDL cholesterol, lovastatin increases high-density lipoprotein (HDL) cholesterol by 5% to 10%,[10, 11, 14] although this effect is too small and variable to be reliably detected in small studies. As a result of the large decreases in LDL cholesterol coupled with the small increases in HDL cholesterol, the ratio of LDL cholesterol to HDL cholesterol, which some consider to be the best predictor of atherogenic risk,[15] is almost halved during therapy with lovastatin.[11, 14] Very low-density lipoprotein (VLDL) cholesterol is also reduced almost as much as LDL cholesterol,[10, 14] and plasma triglycerides have been reported to fall about 25% in most studies.[8, 10, 11, 14] Apolipoprotein B also falls substantially.[7, 10, 11, 13, 14] Since each LDL particle contains one molecule of apolipoprotein (apo) B[16] and since little apo B is found in the other lipoproteins,[17] the indication is that lovastatin reduces the concentration of circulating LDL particles. Consistent with the effects on HDL cholesterol, the concentrations of apo AI and apo AII (which are carried in HDL) also tend to rise slightly.[11, 14]

The time course of the therapeutic response is shown in figure 3. The maximum therapeutic response is obtained in 4 to 6 weeks, after which the response is quite stable. The effects of progressive increases in dose on plasma cholesterol are shown in figure 4. Lovastatin is given with meals, in single or divided doses. Divided doses are slightly more effective,[14, 18] but single daily doses are more convenient and may be adequate for patients with milder forms of hypercholesterolemia. If the drug is given once a day, a dose given in the evening is more effective than the same dose given in the morning,[18] probably because

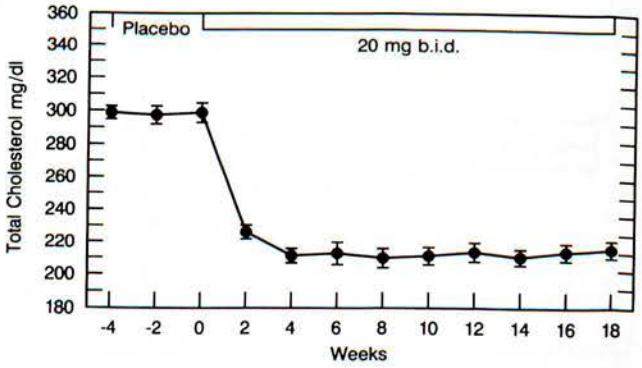



**FIGURE 3.** Effect of a fixed dose of lovastatin (20 mg bid) on plasma cholesterol. (Reproduced, with permission, from Hunninghake et al.[14])

**Mechanism of action.** Lovastatin is a potent competitive inhibitor of HMG-CoA reductase,[20] and this action can be demonstrated in human subjects by measuring plasma and urinary mevalonate. In normocholesterolemic volunteers, plasma and urinary mevalonate clearly fall after administration of lovastatin.[21, 22] In a limited number of patients with FH, however, Illingworth et al.[22] observed increases in plasma mevalonate. This paradoxical effect is not understood at the present time.

It is clear that the mechanism of action of lovastatin is not simply and solely due to inhibition of cholesterol synthesis. In five patients studied by sterol balance techniques, Grundy and Bilheimer[23] showed a modest decline in fecal output of neutral and acidic sterols in three patients but no changes in another two. Changes in the fecal output of sterols did not correlate with the degree of lowering of LDL cholesterol. Bilheimer et al.[9] had earlier shown that lovastatin could increase the fractional catabolic rate of LDL in patients with FH, which may indicate an increase in the number of LDL receptors. The importance of the LDL receptor is supported by limited data in patients with homozygous FH, who have very few or no functioning LDL receptors,

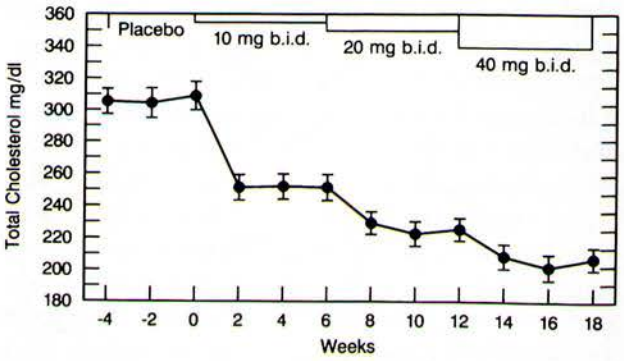



**FIGURE 4.** Effect of progressive increases in dosage of lovastatin on

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