LOVASTATIN

by

Scott M. Grundy

Internal Medicine Grand Rounds

University of Texas Health Science Center at Dallas

June 25, 1987

A high plasma cholesterol is a major risk factor for coronary heart disease (CHD). The risk for CHD is proportional to the plasma cholesterol level over a broad range of cholesterol concentrations, and the risk is accentuated at progressively higher concentrations. This relationship is well illustrated by the results follow-up coronary mortality in participants of the Multiple Risk Factor Intervention Trial (MRFIT) (1) (Figure 1). Numerous epidemiological studies--both within and between populations--support this general relationship (2-4). These studies imply that lowering the plasma cholesterol levels should reduce the prevalence of CHD if carried out on a population-wide basis, and at the same time, a lowering should decrease the likelihood of CHD in individuals with high blood cholesterol. For populations such as the U.S. public, in which the prevalence of CHD is high, two approaches have been recommended for the problem of high plasma cholesterol (5). One of these is the population-based strategy, the purpose of which is to lower the average cholesterol level of the population through hygienic means (e.g. modification of the diet, weight reduction, and increasing exercise). The other approach is the high-risk strategy whereby individuals with high plasma cholesterol are identified and plasma cholesterol levels are reduced by medical intervention.

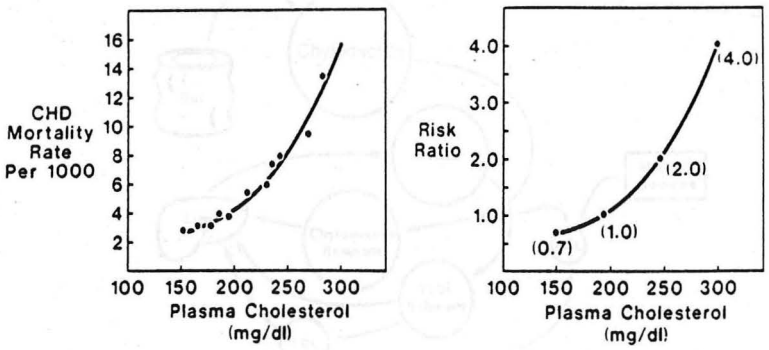


Figure 1. Relation between CHD mortality rates and plasma cholesterol levels in follow-up of participants of the Multiple Risk Factor Intervention Trial. On the right is the risk ratio for different cholesterol levels assuming a risk of 1.0 for a cholesterol level of 200 mg/dl.

Although these general approaches to the problem of high plasma cholesterol have been recommended widely for at least two decades, four significant advances have been made in recent years that have been a great stimulus to control of plasma cholesterol for the purpose of prevention of CHD. One of these has been in the general category, namely, the accumulation of large amounts of information on many fronts--epidemiological, clinical, and basic--that have provided a strong underpinning to the "lipid hypothesis", i.e. the hypothesis that high cholesterol levels are a cause of CHD and lowering the cholesterol level will prevent CHD. Three other advances are of such great importance that they may be considered "breakthroughs" in the field. First was the discovery of the LDL receptor by Goldstein and Brown (6), for which they were awarded the Nobel Prize in Medicine in 1985; this discovery opened the door to our understanding of the way the plasma cholesterol level is regulated. Second was the positive result of the Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT); in

this study (7), it was shown conclusively that lowering the plasma cholesterol level by drug therapy will decrease coronary events. And third was the discovery of a new class of drugs, the inhibitors or 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (8), which will cause a dramatic lowering of the plasma cholesterol (9). The purpose of this review is to specifically examine the HMG CoA reductase inhibitors, but this can be done only in the light of the progress in the whole field of cholesterol and CHD. Particular attention needs to be given to the other "breakthroughs" as they set the stage for the introduction of reductase inhibitors.

Regulation of Plasma Cholesterol Concentrations in Control of Cholesterol Levels

The mechanisms for regulation of plasma cholesterol concentrations can best be understood through the lipoprotein system. The current concepts of this system are outlined in Figure 2. Cholesterol from the diet enters the body with dietary fat associated with lipoproteins called chylomicrons. The triglycerides of chylomicrons are hydrolyzed in peripheral capillaries by the enzyme lipoprotein lipase. Residual particles, called chylomicron remnants, which retain dietary cholesterol, are removed from the circulation by the liver.

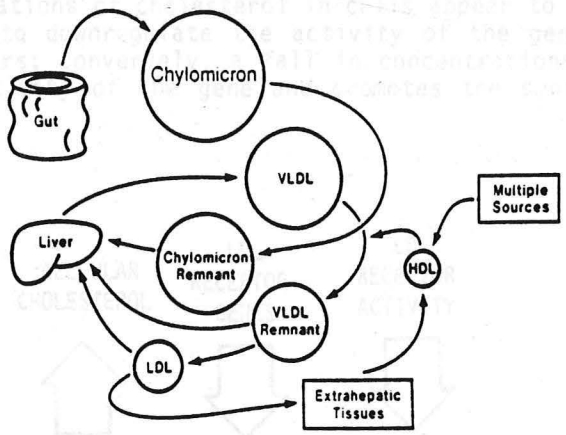


Figure 2. Pathways of lipoprotein metabolism (see text for description).

The liver likewise synthesizes and secretes triglyceride-rich lipoproteins, which are called very low density lipoproteins (VLDL). These too are degraded by lipoprotein lipase into smaller lipoproteins, named VLDL remnants. The latter can have two fates: they can be removed by the liver or converted to low density lipoproteins (LDL). The LDL are the major cholesterol-carrying lipoproteins of plasma. The LDL are cleared from the circulation mainly by specific receptors located on the surface of cells (6), but small quantities of LDL can be removed by nonreceptor mechanisms. Although many tissues of the body contain LDL receptors, most LDL appears to be cleared via the liver (10). VLDL remnants seemingly are removed in large part by LDL receptors as well (11).

A third system for transport of cholesterol in plasma is through high density lipoproteins (HDL). Seemingly, HDL can accept cholesterol from extrahepatic tissues (and other sources) and transfer this cholesterol to VLDL

(and LDL), which are removed via the liver. The movement of cholesterol from peripheral tissues to the liver has been called "reverse cholesterol transport", and it is believed by many that HDL play a major role in this process.

Role of LDL Receptors

Since LDL receptors are mainly responsible for removal of LDL from the circulation, they play a major role in regulating the concentration of plasma cholesterol. As shown in Figure 2, the activity of LDL receptors can reduce plasma LDL concentrations in two ways: (a) by promoting uptake of LDL itself, and (b) by enhancing hepatic clearance of VLDL remnants, the precursors of LDL. By the latter mechanism, the conversion of VLDL to LDL, or production of LDL, is reduced. Thus, the level of plasma LDL depends on the number of LDL receptors expressed.

Normally, two genes encoding for LDL receptors are inherited, one from each parent, and under normal circumstances, both genes activately produce messenger RNA for synthesis of LDL receptors. However, the activity of these genes is modulated by concentrations of cholesterol in cells, particularly, liver cells (12). High concentrations of cholesterol in cells appear to affect the promoter region of the gene to downregulate the activity of the gene and hence reduce synthesis of receptors; conversely, a fall in concentrations of cholesterol in cells stimulates activity of the gene and promotes the synthesis of receptors (Figure 3).

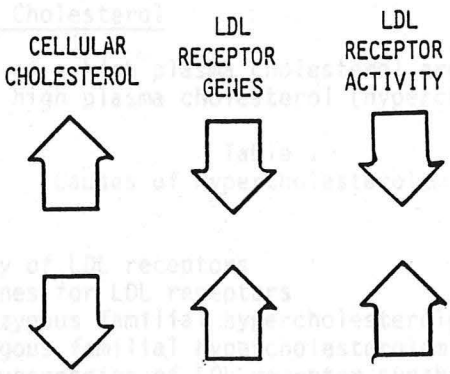


Figure 3. Effects of changes in cellular concentrations of cholesterol suppresses the activity. For example, an increase in cellular cholesterol suppresses the activity of the gene for the LDL receptor which in turn reduces the synthesis of LDL receptors. A fall in cellular cholesterol concentrations has the opposite effect.

Several factors determine the concentration of cholesterol in liver cells (Figure 4). Hepatic cholesterol can be enhanced by increased input from dietary cholesterol and new synthesis of cholesterol from acetate. Hepatic content of cholesterol can be reduced by increased conversion of cholesterol into bile acids or enhanced secretion of cholesterol into bile. The net result of these factors determines hepatic concentration of cholesterol and hence modifies the activity of LDL receptors.

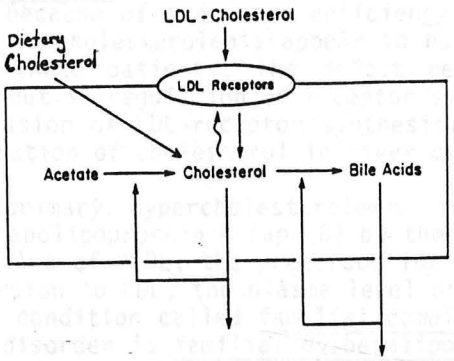


Figure 4. Pathways regulating concentrations of hepatic cholesterol. Hepatic cholesterol is derived from new synthesis from acetate or from dietary cholesterol. It can be secreted into bile as cholesterol itself or converted into bile acids. Both have an enterohepatic circulation which regulates their own synthesis by feedback inhibition. Hepatic cholesterol in turn regulates the synthesis of LDL receptors.

Causes of High Plasma Cholesterol

Potential causes of a high plasma cholesterol are outlined in Table 1. One category of causes of high plasma cholesterol (hypercholesterolemia) is a

Table 1
Causes of Hypercholesterolemia

Primary Disorders
- Reduced activity of LDL receptors
  - Abnormal genes for LDL receptors
    - Heterozygous familial hypercholesterolemia
    - Homozygous familial hypercholesterolemia
  - Metabolic suppression of LDL receptor synthesis
- Overproduction of apo B-containing lipoproteins
  - Familial combined hyperlipidemia
- Altered ligand properties of apolipoproteins
  - Apolipoprotein E4
  - Familial defective apolipoprotein B-100

Dietary Factors
- High intakes of saturated fatty acids and cholesterol
- Obesity

Secondary Disorders
- Hypothyroidism
- Nephrotic syndrome
- Noninsulin dependent diabetes mellitus (NIDDM)

reduced activity of LDL receptors. Such a reduction theoretically can occur by several mechanisms. For example, one in 500 people inherit an abnormal gene for LDL receptors, and the result is a patient with half the normal number of LDL receptors. This abnormality produces the condition called heterozygous familial hypercholesterolemia (FH). Much more rarely, in one in a million people, two abnormal genes are inherited, and patients make essentially no LDL receptors, a condition called homozygous FH. Thus, patients with both forms of FH have elevated levels of LDL because of a genetic deficiency of LDL receptors. Many patients with primary hypercholesterolemia appear to have a reduced activity of LDL receptors, but in these patients, the defect resides not in the genes encoding LDL receptors, but in regulation of receptor synthesis; they seemingly have a metabolic suppression of LDL-receptor synthesis, possibly because of an abnormally high concentration of cholesterol in liver cells (see Figure 3).

Another cause of primary hypercholesterolemia is an overproduction of lipoproteins containing apolipoprotein B (apo B) by the liver. This abnormality leads to an enhanced influx of VLDL, the precursor for LDL, and since more VLDL are available for conversion to LDL, the plasma level of LDL is increased. This defect may underlie the condition called familial combined hyperlipidemia (13). A rare variant of this disorder is familial dysbetalipoproteinemia, a condition in which VLDL remnants bind poorly to LDL receptors because of an inherited defect in the structure of apolipoprotein E (apo E).

Another possible cause of primary hypercholesterolemia is an abnormality in the structure of LDL so that it is a poor ligand for the LDL receptor. Recent studies (14) from our laboratory have revealed the presence of such a defect in some hypercholesterolemic patients which has been named familial defective apolipoprotein B-100 (15).

Finally, LDL levels can be elevated because of other diseases such a hypothyroidism, nephrotic syndrome, and diabetes mellitus. The mechanisms for high concentrations of LDL in these conditions are variable. In hypothyroidism, the clearance of LDL seemingly is reduced because of reduced activity of LDL receptors. The same may be true for the nephrotic syndrome, although many investigators believe that this disorder induces an overproduction of VLDL. An elevated LDL concentration in diabetes likewise may be the result of a combined defect--overproduction of VLDL and defective clearance of LDL.

Evidence of Benefit from Treatment of Hypercholesterolemia

While abundant data indicate that both primary and secondary forms of hypercholesterolemia are associated with increased risk for CHD, less data are available to indicate that lowering of LDL levels by specific therapy will reduce coronary risk. Several clinical trials, using either dietary modification or drug therapy, have provided equivocal data on the efficacy and safety of cholesterol-lowering regimens. Although several trials have produced suggestive evidence for benefit, many investigators have remained skeptical that a benefit of cholesterol lowering has been proven. However, three years ago, the results of the LRC-CPPT were published (7), and the data provided very strong evidence for benefit for coronary prevention by LDL lowering. The LRC-CPPT was a double-blind, placebo-controlled trial to test the effects of a cholesterol-lowering drug, cholestyramine, for the prevention of CHD in middle-aged men with primary hypercholesterolemia. This trial included about 4000 men studied over a period of seven years. The results of the trial

indicated that cholestyramine, compared to placebo, caused a significant reduction in rates of CHD. An overall summary of this trial is presented in Figure 5. Furthermore, the trial indicated that the reduction in rate of CHD in drug-treatment patients was proportional to the magnitude of fall in plasma cholesterol level (Figure 6); this figure shows that a reduction of cholesterol levels of one mg/dl induces a fall in coronary risk of about one percent. The data of this trial thus have provided strong evidence that a therapeutic reduction of cholesterol levels will reduce risk for CHD.

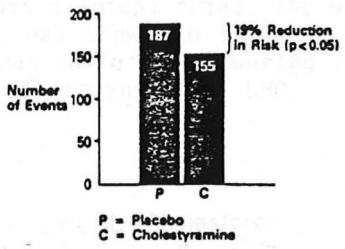


Figure 5. Comparison of incidence of primary endpoints (definite CHD death and/or nonfatal myocardial) in the cholestyramine and placebo groups of the LRC-CPPT.

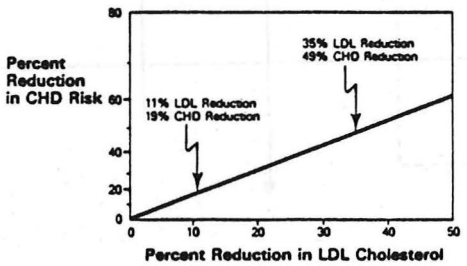


Figure 6. Reduction in risk for CHD compared to the reduction in LDL cholesterol in the LRC-CPPT. Results were calculated by the Cox Proportional Hazards Model. The degree of responsiveness to cholestyramine therapy varied from individual to individual in the study, and change in CHD risk changed proportionally. This study confirms that a one percent reduction in LDL-cholesterol level produced a 2% decrease in CHD risk.

The mechanisms for lowering of plasma cholesterol by cholestyramine and related bile acid-binding resins are shown in Figure 7. These resins inhibit the absorption of bile acids in the intestinal tract and thereby reduce the return of bile acids to the liver. This change releases feedback inhibition of bile acids on bile acid synthesis, and consequently more cholesterol is converted into bile acids; as a result, hepatic levels of cholesterol fall, and the synthesis of LDL receptors is increased. The increase in number of LDL receptors in turn reduces plasma concentrations of LDL. Thus, the bile acid resins lower the plasma LDL by increasing the activity of LDL receptors (16). In the LRC-CPPT, cholestyramine not only reduced the rate of CHD, but it also proved to be safe. Therefore, in this clinical trial, the use of a drug that enhances the activity of LDL receptors was shown to be both safe and effective, a finding which provides a strong rationale for lowering LDL levels via increasing LDL receptors for the purpose of prevention of CHD.

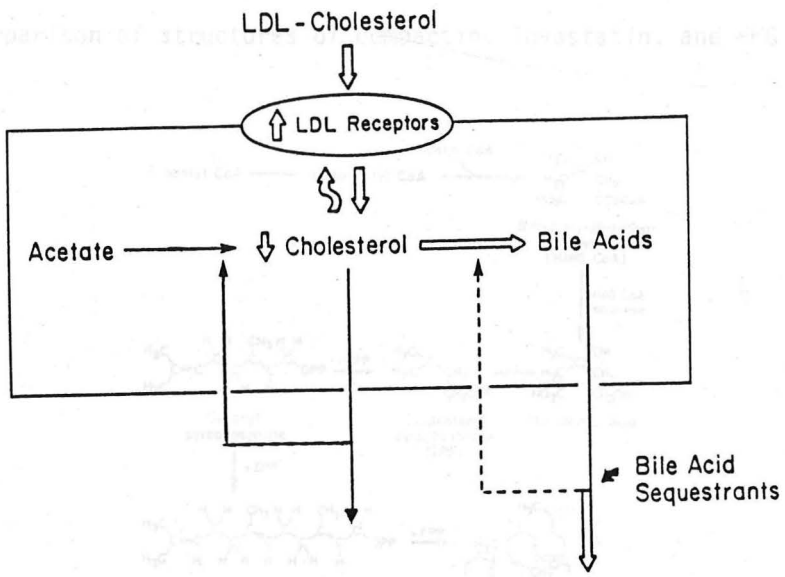


Figure 7. Effects of bile acid-binding resins (sequestrants) on metabolism of cholesterol and LDL. The sequestrants block the reabsorption of bile acids, which releases feedback inhibition on conversion of cholesterol into bile acids; this lowers hepatic cholesterol content which stimulates the synthesis of LDL receptors (see Figure 3), and thereby lowers LDL-cholesterol levels.

HMG CoA Reductase Inhibitors: Mechanisms of Action

The parent compound of this series of new drugs is compactin, which was isolated from Penicillium citrinum (8). A second compound was lovastatin

(previously called mevinolin) which is isolated from the fungus Aspergillus terreus. The structures of compactin and lovastatin are shown in Figure 8, and they are compared to HMG CoA which has a structural similarity. In tissue culture, these agents competitively inhibit the conversion of HMG CoA to mevalonic acid by HMG CoA reductase, the rate limiting enzyme in cholesterol synthesis (Figure 9). Studies in our laboratory have shown that lovastatin can

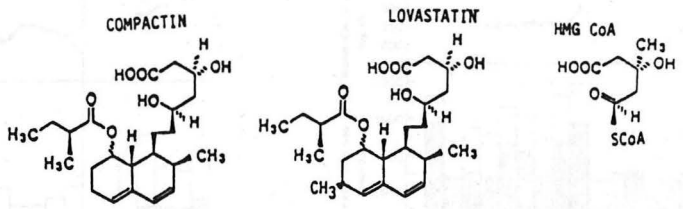


Figure 8. Comparison of structures of compactin, lovastatin, and HMG CoA.

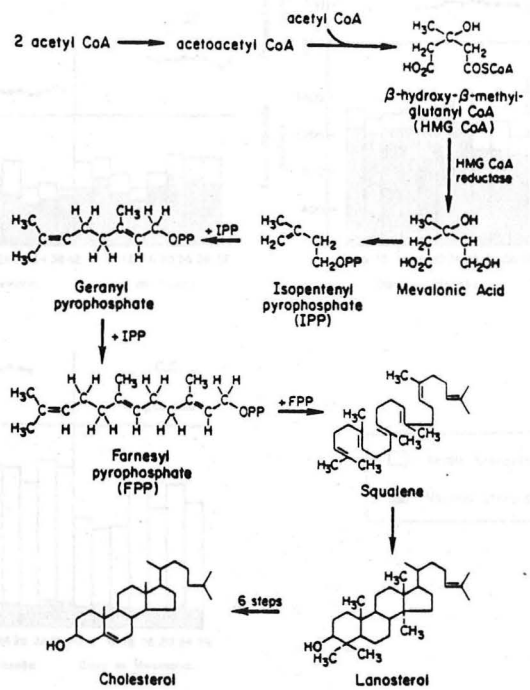


Figure 9. Pathways for synthesis of cholesterol from acetate.

inhibit the synthesis of whole body cholesterol (17). Cholesterol balance studies in five patients showed a reduced fecal steroid excretion in three of five patients treated with lovastatin (Figure 10). This reduced output of fecal steroids strongly suggests a decrease in the synthesis of cholesterol in these patients.

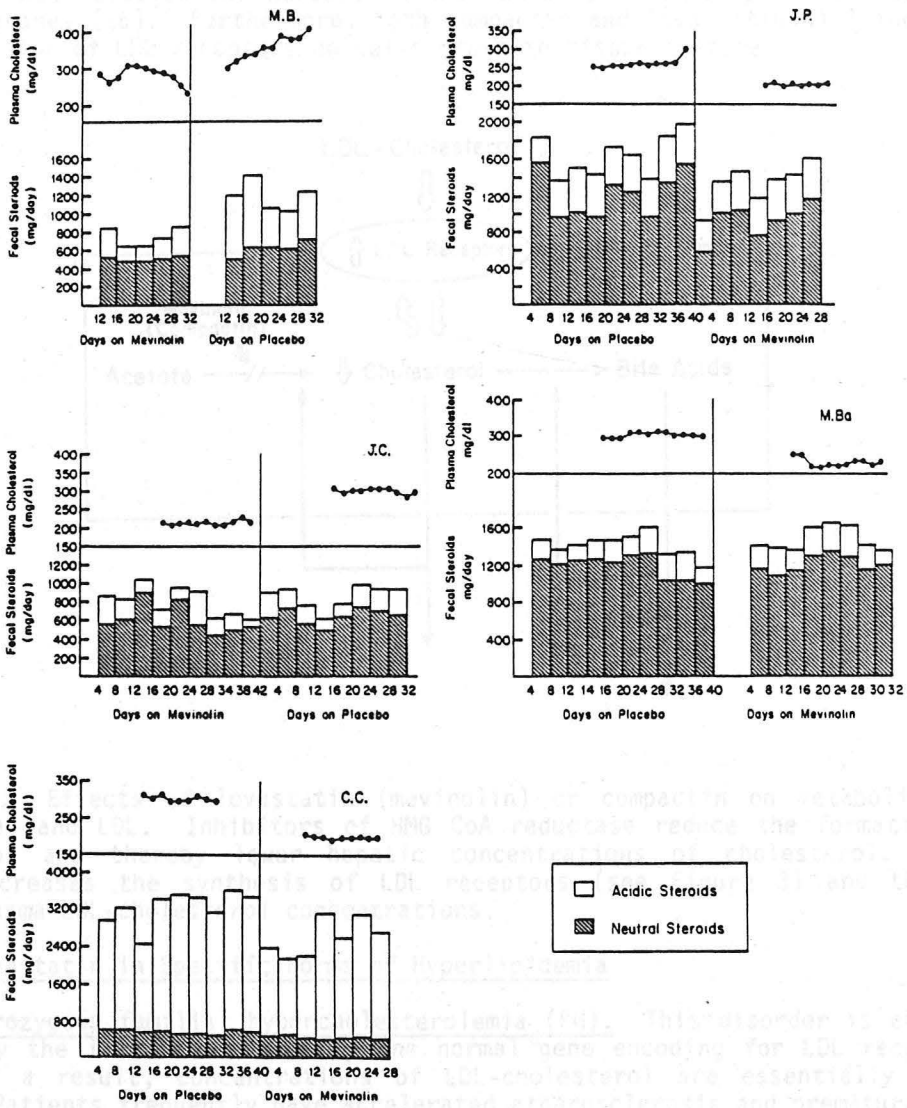


Figure 10. Effects of lovastatin (mevinolin) in excretion of fecal neutral steroids and bile acids in five patients with heterozygous FH. The stripped bars represent fecal neutral steroids, and the open bars, bile acids. The height of the bars should equal whole body synthesis of cholesterol in the steady state.

Studies in normal subjects by Tobert et al (9) showed that lovastatin will induce reductions in LDL-cholesterol levels by 35 to 45% in normal subjects when given in doses of milligrams per day (6.5 to 50 mg). One mechanism whereby lovastatin might lower the LDL level is presented in Figure 11. It could inhibit the synthesis of cholesterol in the liver, which should reduce cholesterol concentrations in hepatocytes, and in so doing, stimulate the synthesis of LDL receptors. In accord with this hypothesis, treatment of dogs with lovastatin has revealed an increase in the number of LDL receptors on isolated liver membranes (16). Furthermore, both compactin and lovastatin will increase the expression of LDL receptors on cells grown in tissue culture.

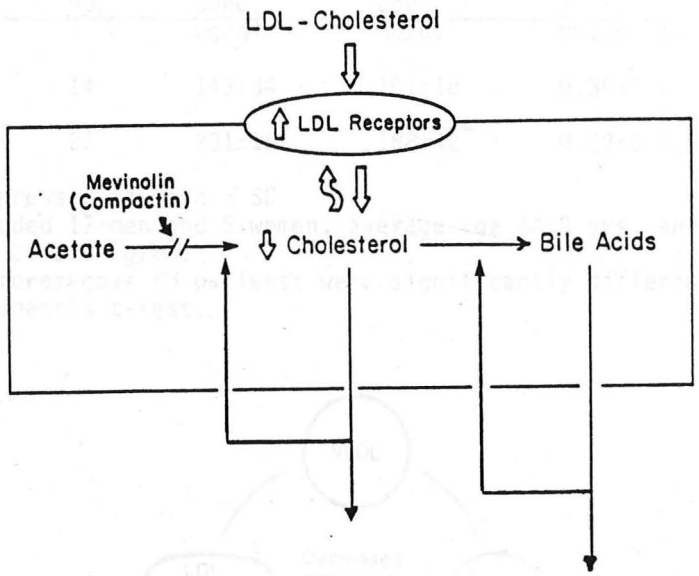


Figure 11. Effects of lovastatin (mevinolin) or compactin on metabolism of cholesterol and LDL. Inhibitors of HMG CoA reductase reduce the formation of cholesterol and thereby lower hepatic concentrations of cholesterol. This change increases the synthesis of LDL receptors (see Figure 3) and thereby lowers plasma LDL-cholesterol concentrations.

Use of Lovastatin in Specific Forms of Hyperlipidemia

Heterozygous familial hypercholesterolemia (FH). This disorder is characterized by the inheritance of only one normal gene encoding for LDL receptors (18). As a result, concentrations of LDL-cholesterol are essentially twice normal. Patients frequently have accelerated atherosclerosis and premature CHD. Men often develop myocardial infarction in their 30's and 40's, while women frequently have CHD in their 50's and 60's. Tendon xanthomas are common. The

mechanisms of hypercholesterolemia in patients with heterozygous FH are shown in Table 2 and illustrated in Figure 12. Turnover studies of LDL-apo B in these

Table 2

LDL Kinetics in Heterozygous
Familial Hypercholesterolemia (FH)

		LDL-chol	Apo LDL*		
Group	No.	Conc.	Conc.	FCR	Transport
		mg/dl	mg/dl	pools/day	mg/kg-d
Normal men	14	143±34	101±18	0.30±0.04	13.5±2.5
Heterozygous FH†	22	281±15*	168±42*	0.22±0.02*	16.5±6.1*

*Results are expressed as mean ± SD
† Patients included 17 men and 5 women, average age 44±9 yrs, and mean body mass index of 26.5±9 kg/m^2.
* Values for heterozygous FH patients were significantly different from normal men at $p<0.02$, student's t-test.

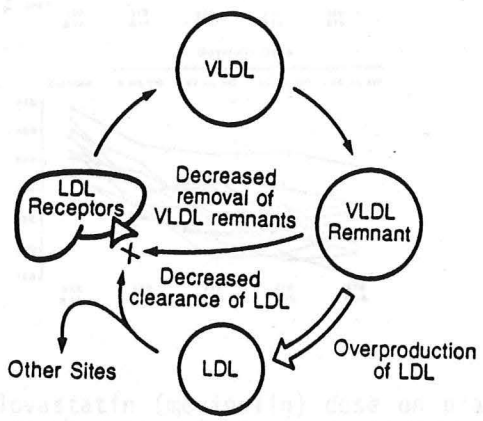


Figure 12. Influence of a reduction in activity of LDL receptors on the metabolism of LDL. When receptor activity is decreased, the clearance of LDL from the circulation is delayed, which raises the LDL level. Simultaneously, hepatic uptake of VLDL remnants by LDL receptors likewise is retarded, which allows more VLDL to be converted to LDL. The latter, leading to overproduction of LDL, also contributes to the rise in LDL concentrations.

patients reveal that they have a reduced fractional clearance rate (FCR) and an increased production rate for LDL-apo B, both of which contribute to the elevated LDL-cholesterol concentration. The reduced FCR for LDL-apo B is due to a reduced number of LDL receptors, and the increased production rate of LDL-apo B might have two causes: (a) increased synthesis of VLDL-apo B, the precursor of LDL, and/or (b) reduced uptake of VLDL remnants and enhanced conversion of VLDL to LDL. The latter seems most likely, since VLDL remnants are removed mainly by LDL receptors.

Illingworth and Sexton (19) has carried out a thorough investigation of the effects of lovastatin on concentrations of plasma cholesterol in patients with heterozygous FH. His results are summarized in Figure 13. Increasing doses of lovastatin produced progressive reductions in plasma total cholesterol; in 13 patients, cholesterol levels fell from a baseline of 450±14 (SEM) to 300±15 mg/dl on lovastatin (40 mg BID). Parallel reductions were found in concentrations of LDL-cholesterol.

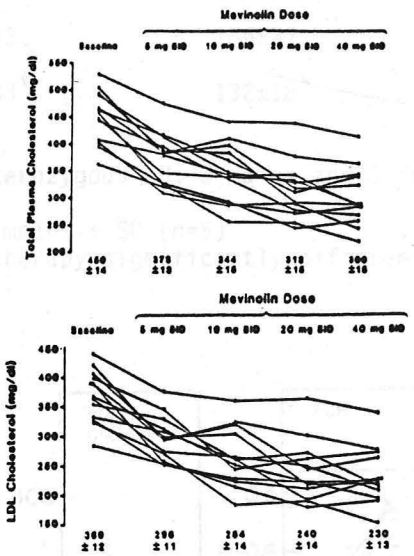


Figure 13. Effects of lovastatin (mevinolin) dose on plasma concentrations of total cholesterol and LDL-cholesterol in patients with heterozygous FH. A maximum lowering of LDL-cholesterol was obtained at 40 mg BID. Data are those of Illingworth and Sexton (19).

The mechanisms for lowering of LDL levels in heterozygous FH by lovastatin have been studied by Bilheimer, Grundy, Brown and Goldstein (20). Investigations were carried out in six patients with heterozygous FH. To distinguish between receptor-dependent and receptor-independent pathways of LDL catabolism, the simultaneous clearance rates of native LDL and LDL that was modified by in vitro glycosylation were compared. Previous work had demonstrated that glycosylated LDL does not bind to LDL receptors in vivo or in vitro, and for this reason, the catabolism of glycosylated LDL can be used to estimate the FCR of receptor-independent clearance of LDL.

All six patients with heterozygous FH had markedly elevated concentrations of LDL-cholesterol in the control period of this study (Table 3). After treatment of the patients with lovastatin (20 mg BID) for 3 to 6 weeks, the mean concentration of LDL-cholesterol fell by 27% (Figure 14). In these patients, the FCR for native LDL increased by 37%, while the production rate for LDL,

Table 3

Effects of Lovastatin on LDL Kinetics
in Heterozygous Familial Hypercholesterolemia *

Period	LDL Cholesterol Conc.	Apo LDL†		
		Conc.	FCR	Transport
	mg/dl	mg/dl	pools/day	mg/kg-d
Control	262±43	186±37	0.30±0.03	19.2±64
Lovastatin (20 mg BID)	191±33‡	132±18‡	0.41±0.05‡	18.4±6.0

* Six patients with heterozygous FH; 3 males and 3 females; average age 43±9 (SD) yrs.
† Results expressed as means ± SD (n=6)
‡ Values on mevinolin therapy significantly different from control at $p<0.001$ by paired t-test.

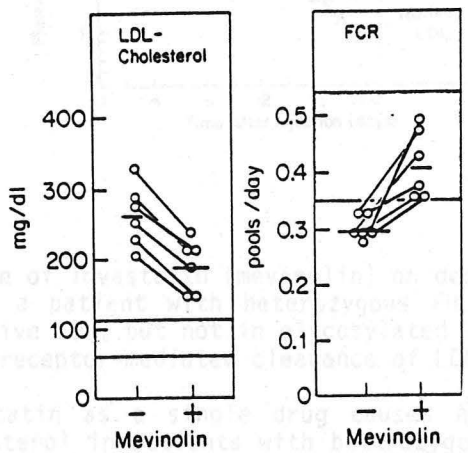


Figure 14. Effects of lovastatin (mevinolin) on concentrations of LDL-cholesterol (left) and fractional catabolic rates (FCRs) for LDL-apo B (right). Normal ranges are shown in the stippled areas.

which was elevated in the control period, did not change during lovastatin therapy. The data for simultaneous studies of catabolism of ^{131}I-native LDL and ^{125}I-glycosylated LDL in one patient with heterozygous FH during control and lovastatin-treatment periods are presented in Figure 15. In the absence of drug, the FCR for native LDL was 0.29 pools/day, whereas the FCR for glycosylated LDL was 0.16 pools/day. The difference of 0.13 pools/day presumably represented the FCR for the receptor-mediated component. When lovastatin was administered, the FCR for native LDL increased to 0.48 pools/day, while the FCR for glycosylated LDL (i.e. 0.18 pools/day) was essentially unchanged. In this patient, it appeared that the FCR for the receptor-mediated pathway increased from 0.13 to 0.18 pools per day on lovastatin, which of course meant that lovastatin stimulated the receptor-mediated clearance of LDL but did not change the nonreceptor-mediated pathway. This finding confirms the postulated mechanism for lovastatin discussed in the preceding.

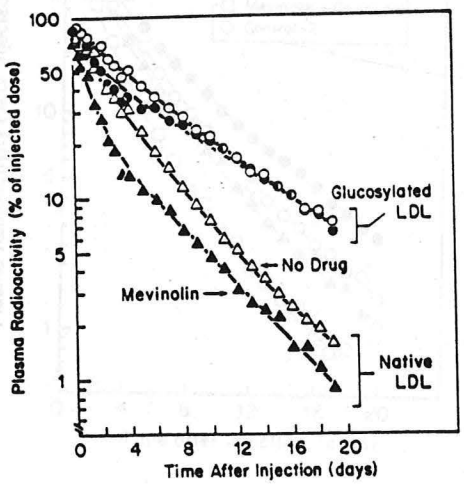


Figure 15. Influence of lovastatin (mevinolin) on decay rates of native LDL and glycosylated LDL in a patient with heterozygous FH. Lovastatin enhanced the rate of decay of native LDL, but not in glycosylated LDL. The data suggest that lovastatin promotes receptor-mediated clearance of LDL.

Although lovastatin as a single drug causes a significant reduction in levels of LDL-cholesterol in patients with heterozygous FH, in most patients it does not produce a complete normalization of LDL-cholesterol concentrations (Figure 14). Therefore, we questioned whether the reduction in levels of LDL can be enhanced by adding a second drug. One such drug is a bile acid binding resin. Since both lovastatin and bile acid-binding resins appear to enhance the activity of LDL receptors, their action might be additive (or even synergistic). A previous study from Japan by Mabuchi et al (21) demonstrated that compactin plus cholestyramine produced a marked lowering of LDL-cholesterol levels in

patients with heterozygous FH. In a pilot study, we carried out four sequential studies of LDL turnover in a 45-yr-old FH heterozygote (22). Treatment with lovastatin alone lowered his level of LDL-cholesterol from 340 to 208 mg/dl, and the addition of the bile acid-binding resin colestipol further reduced LDL-cholesterol to 136 mg/dl. When the two drugs were discontinued, the FCR for LDL returned to the original level. As shown in Figure 16, the rate of decay of radioactivity for LDL increased during lovastatin therapy, and it increased even more when colestipol was added.

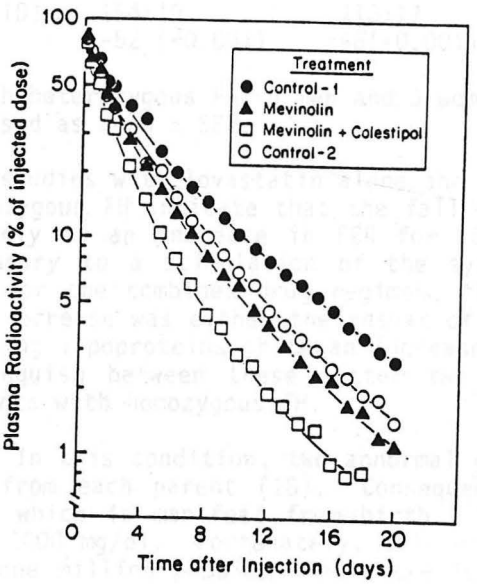


Figure 16. Trial of lovastatin (mevinolin) alone and lovastatin (mevinolin) + colestipol on decay rates of radiolabeled LDL in a patient with heterozygous FH. Lovastatin alone enhanced the catabolism of LDL, but the change was even greater with the drug combination.

After these encouraging results in a single patient, the study of combined therapy was extended to eight patients with heterozygous FH in a study by Grundy, Vega, and Bilheimer (23). These patients received the combination of lovastatin (20 mg BID) and colestipol (10 gm BID). Their data are summarized in Table 4. The combination of the two drugs caused a decrease in levels of total cholesterol averaging 43%, and the reduction in LDL-cholesterol averaged 52%. The level of LDL-apo B (apo LDL) fell by 46%, while the FCR for LDL rose by 40%. On the average, the production rate for LDL-apo B fell by 25%.

Table 4

Effects of Lovastatin + Colestipol on LDL Kinetics*†
in Heterozygous Familial Hypercholesterolemia

Period	LDL Cholesterol Conc. mg/dl	Apo LDL Conc. mg/dl	Apo LDL FCR pools/day	Apo LDL Transport mg/kg-d
Control	321±32	209±24	0.25±0.02	18.2±2
Lovastatin (20 mg BID) + Colestipol (10 g BID)	154±19	113±17	0.35±0.03	13.7±2
% Change (p-value)	-52 (<0.001)	46(<0.001)	40(<0.002)	25(<0.003)

* Eight patients with heterozygous FH; 5 men and 3 women.
† Results are expressed as mean ± SEM.

The results of studies with lovastatin alone and lovastatin + colestipol in patients with heterozygous FH indicate that the fall in LDL-cholesterol concentrations is due mainly to an increase in FCR for LDL. This increase in FCR appears to be secondary to a stimulation of the synthesis of LDL receptors. However, especially for the combined drug regimen, the production rate of LDL usually fell. This decrease was either the result of a decrease in the synthesis of apo B containing lipoproteins or to an increase in the clearance of VLDL remnants. To distinguish between these latter two mechanisms, studies were carried out in patients with homozygous FH.

Homozygous FH. In this condition, two abnormal genes for the LDL receptor are inherited, one from each parent (18). Consequently, patients has severe hypercholesterolemia which is manifest from birth. Cholesterol levels are in the range of 700 to 1000 mg/dl. Fortunately, this disorder is rare, occurring only once in about one million people. There are two kinds of homozygous FH. In one form, called receptor-negative homozygous FH, both abnormal forms of LDL receptors are completely nonfunctioning, and patients has essentially no LDL receptor activity. In a second form, LDL receptors are defective, and while LDL receptor activity is greatly reduced, it is not totally absent.

Since the major action of lovastatin appears to be to increase the synthesis of LDL receptors, the drug theoretically should not lower concentrations of LDL-cholesterol in patients with receptor-negative homozygous FH. However, if lovastatin also interferes with the synthesis of apo B-containing lipoproteins, it could reduce LDL levels by reducing the formation of LDL. Receptor-negative patients thus may provide a unique opportunity to learn something fundamental about the mechanism of action of lovastatin. For this reason, a study was carried out by Drs. Ricardo Uauy, G.L. Vega, D.W. Bilheimer and S.M. Grundy for the effects of lovastatin on lipoprotein metabolism in three patients with receptor-negative homozygous FH. These patients included two 6-yr-old girls and one 9-yr-old boy.

As shown in Table 5, plasma levels of total cholesterol were markedly elevated in all three patients in the control period. Lovastatin apparently lowered total cholesterol levels slightly but not statistically significantly. LDL-cholesterol levels were unchanged during lovastatin therapy, although

Table 5

Lipoprotein Profiles
(Homozygous FH Patients)

Patient		Plasma			Lipoprotein Cholesterol		
		Cholesterol	Triglyceride	Apo-B	VLDL*	LDL	HDL
		mg/dl±SD (n = 4)†					
1. (GE)	C	791±44	174±54	393±32	39±17	735±28	18±3
	L	755±18‡	138±18‡	404±27	12±5‡	728±52	15±1
2. (JH)	C	949±38	120±11	437±17	47±5	868±37	34±5
	L	858±25‡	104±12‡	371±19	6±1‡	816±20	36±5
3. (RH)	C	770±57	101±9	371±16	32±7	710±48	29±5
	L	755±53‡	138±18	343±8‡	12±5‡	728±52	15±1
Mean±SE	C	837±56	132±22	400±19	39±4	771±49	27±5
	L	789±34	127±11	373±18	10±2	757±29	22±7
	Δ(%)	-48(-5.7)	-5(-3.8)	-27(-6.8)	-29(-74.4)‡	-14(-1.8)	-5(-18.5)

*VLDL = [VLDL+IDL]-cholesterol
†Four pools of plasma were made for these determinations.
‡Significantly lower than levels during control period by Student's t-test ($p<0.05$)

VLDL-cholesterol levels were reduced by the drug. In these same patients, turnover rates of LDL-apo B were measured (Table 6). The concentrations of LDL-apo B were not affected by the drug. FRCs for LDL-apo B were low before lovastatin therapy (mean = 0.12±0.01 pools/day), and they were unchanged by lovastatin (mean = 0.12±0.01 pools/day). Transport rates for LDL-apo B were high before therapy and were not altered by the drug.

Table 6

Kinetic Parameters of LDL-apo B
(Homozygous FH Patients)

		LDL-apo B			
Patient	Period	Concentration mg/dl±SD* (n = 4)	Pool Size mg	FCR pools/d	Transport Rate mg/kg-day
1 (GE)	Control	384±28	4992	0.13	28.5
	Lovastatin	402±27	5236	0.14	32.9
2 (JH)	Control	425±18	3183	0.11	24.7
	Lovastatin	369±19	2764	0.11	20.1
3 (RH)	Control	364±15	3716	0.11	19.3
	Lovastatin	340±8	3471	0.11	17.4
Mean±SE	Control	391±18	3964±537	0.12±0.01	24.2±2.7
	Lovastatin	370±18	3824±735	0.12±0.01	23.5±4.8
	Δ(%)	-21(-5.4)	-140(-3.5)	0(0)	-0.7(-2.9)

*Four pools of plasma were made for these determinations.

In this study, in spite of relatively high doses of lovastatin for children, none of the three patients had significant reductions of LDL-cholesterol levels. Since these patients had essentially no capacity to synthesize functioning LDL receptors and showed no change in LDL levels on lovastatin therapy, we concluded that the cholesterol-lowering response to lovastatin in other hypercholesterolemic patients is due almost entirely to an increase in the number of LDL receptors. Our findings further suggest that lovastatin has little if any effect on production rates of lipoproteins containing apo B. If this conclusion is correct, then the high rate of input of LDL in homozygotes (Table 6) can be explained by their absence of LDL receptors, most VLDL remnants are converted to LDL. Although the claim has been made that there is an excessive synthesis of LDL in FH heterozygotes to account for the overproduction of

LDL in these patients, other interpretations of isotope kinetic data are possible. For example, the WHHL rabbit, which likewise has an inherited absence of LDL receptors, also has an increase in production rates of LDL, as determined by isotope kinetic methods; however, in these rabbits, the excessive input of LDL has been shown to be due to increased conversion of VLDL remnants to LDL. Further, perfusion studies on livers of WHHL rabbits have failed to show an excessive synthesis of apo B-containing lipoproteins, or more specifically, LDL-apo B.

It is of interest that in our apparently receptor-negative FH homozygotes, lovastatin was found to reduce concentrations of VLDL-cholesterol. The mechanism for this effect is not readily apparent. Lovastatin may have had a small effect on the synthesis of VLDL because of its action to inhibit the synthesis of cholesterol a constituent of VLDL. On the other hand, these patients may have had a very small residue of LDL receptor activity that was stimulated by lovastatin and was adequate to promote clearance of circulating VLDL. Nonetheless, on the basis of the findings of LDL turnover, it appears as though the major effect of lovastatin is to enhance the activity of LDL receptors.

Primary Moderate Hypercholesterolemia. Moderate hypercholesterolemia can be defined as a plasma total cholesterol in the range of 240 to 300 mg/dl, or more precisely, as an LDL-cholesterol level (with normal plasma triglycerides) in the range of 160 to 200 mg/dl. While cholesterol-raising diets probably contribute to many cases of moderate hypercholesterolemia, genetic factors likely play a significant role in most individuals. Goldstein et al (24,25) used the term "polygenic" hypercholesterolemia for an elevated plasma LDL that does not originate from a single mutant gene, as occurs with heterozygous FH. The term "polygenic" was used to indicate that abnormally high levels of LDL are the result of the interaction of multiple genes. This category of hypercholesterolemia is 10 to 15 times more common than heterozygous FH; it differs from FH in two ways: (a) elevated levels of cholesterol are present in no more than 10% of first-degree relatives, in contrast to 50% in heterozygous FH; and (b) tendon xanthomas do not occur. However, the word "polygenic" might be applied in two ways. First, the inheritance of multiple genes may be required to produce high LDL-cholesterol in some patients, and other family members who inherit fewer genetic abnormalities may fail to develop elevated levels of LDL. Alternatively, a single metabolic defect may exist in the propositus, and failure to detect a monogenic mode of inheritance in the family may be the result of incomplete penetrance of the genetic defect. The other affected members of the family may have only mild increases in LDL that are not classified as distinct hypercholesterolemia. The physiological abnormalities responsible for primary moderate hypercholesterolemia could be twofold, both of which may be the result of abnormalities in the liver. The first abnormality could be overproduction of VLDL, the precursor of LDL. The second could be reduced activity of LDL receptors.

To differentiate between these two mechanisms, Grundy and Vega (26) have carried out a study of LDL kinetics in a group of 12 middle-aged men with primary moderate hypercholesterolemia. The results are summarized in Table 7 and are compared to data from 12 normal men with "normal" concentrations of LDL. Concentrations of LDL-cholesterol and LDL-apoprotein were significantly higher in the group with moderate hypercholesterolemia. In addition, the FCRs for LDL in the two groups were not different. This finding strongly implies that elevated levels of LDL in most hypercholesterolemic patients were the result of

Table 7

LDL Kinetics in Middle-Aged Men

with Primary Moderate Hypercholesterolemia

Group	n	LDL-chol*	Apo LDL*		
		Conc.	Conc.	FCR	Transport
		mg/dl	mg/dl	pools/day	mg/kg-day
Normal	14	144±23	101±18	0.30±0.04	13.5±2.5
Moderate hypercholesterolemia	12	199±24†	129±11†	0.24±0.03†	12.9±2.3

* Results are expressed as mean ±SD

† Values for hypercholesterolemia men are significantly different from normal men (student's t=test, $p<0.05$).

reduced clearance of LDL through the receptor pathway and not to overproduction of VLDL, the precursor of LDL. On the other hand in other patients, we have found that hypercholesterolemia can sometimes be the result of overproduction of VLDL.

Because most patients with primary moderate hypercholesterolemia seemingly have a reduced activity of LDL receptors, a logical therapy for these patients is to use an agent that enhances receptor activity. One such drug could be a bile acid-binding agent, e.g., colestipol or cholestyramine. The fact the cholestyramine was shown to reduce the risk for CHD in such patients in the Lipid Research Clinics Coronary Primary Prevention Trial (7) speaks in favor of this approach. Another drug is lovastatin. To determine if lovastatin is effective in the treatment of primary moderate hypercholesterolemia, 11 patients with this disorder were studied by Vega and Grundy (26). Treatment with lovastatin caused significant reductions of plasma total cholesterol and LDL-cholesterol (Table 8). The average reduction of LDL cholesterol was 32%. Furthermore, in these same patients lovastatin caused a significant increase in HDL-cholesterol levels (averaging 23%). Thus total cholesterol/HDL-cholesterol ratios were distinctly reduced, from an average of 6.7 to 4.3.

Table 8

Effects of Lovastatin on Plasma Lipids and Lipoproteins in Primary Moderate Hypercholesterolemia*

Period	No. Determ	Total Cholesterol	Total Triglycerides	LDL Cholesterol	HDL Cholesterol
		mg/dl±SEM			
Placebo	7	261±7	131±10	197±7	39±3
Lovastatin (20 mg BID)	7	204±10†	133±10	134±11†	48±3†
% change		-22	+1	-32	+23

* Eleven patients with primary moderate hypercholesterolemia, i.e. with cholesterol levels exceeding 250 mg/dl at entry into the study. Their age averaged 59±9 (SEM) yrs, and their weights averaged 113±5% of desirable body weight.
† Results on lovastatin significantly different than on placebo at $p<0.02$ by paired t-test.

Although lovastatin consistently lowered LDL levels, a surprising finding in this group of patients was that it did not dramatically increase the FCRs for apo-LDL (Table 9). Instead, the drug mainly reduced production rates for LDL. This finding is contrary to what might have been expected if the primary action of lovastatin is to increase the number of LDL receptors. If the activity of LDL receptors in fact is not increased by lovastatin, the decrease in LDL levels on the drug would have to be explained by a decrease in the production of VLDL or IDL, the precursors of LDL. Certainly, a decrease in the synthesis of

Table 9
Effects of Lovastatin on LDL Kinetics* in Primary Moderate Hypercholesterolemia

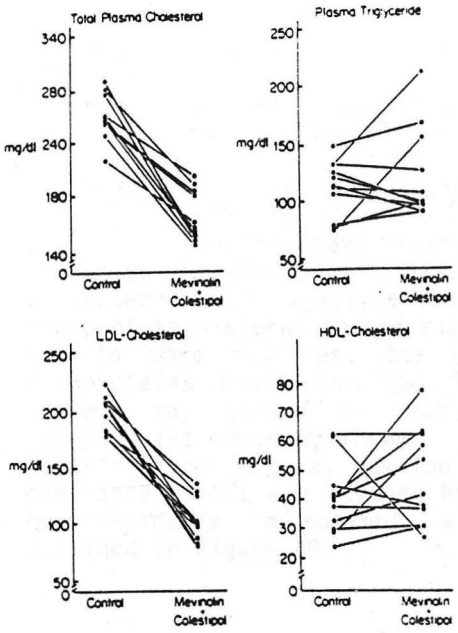
Period	Apo LDL† Conc.	FCR	Transport
	mg/dl	pools/day	mg/kg-d
Placebo	116±3	0.25±0.01	12.1±0.5
Lovastatin (20 mg BID)	75±5‡	0.27±0.01	8.5±0.2‡

* Eleven patients with primary moderate hypercholesterolemia (see Table 5)
† Results expressed as mean ± SEM.
‡ Values on lovastatin therapy significantly different than placebo at $p<0.01$ by paired t-test.

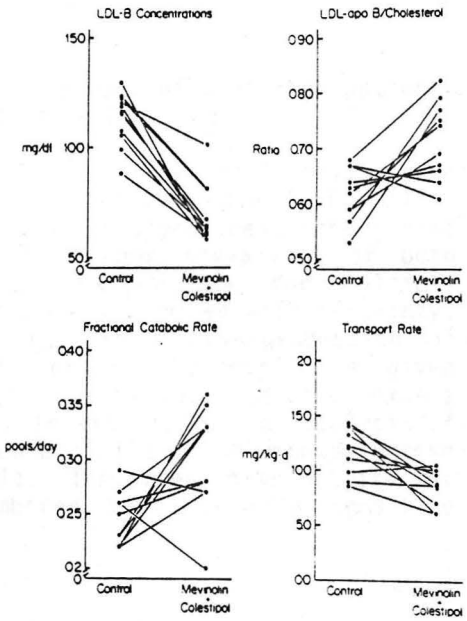
precursor lipoproteins is consistent with the observed decrease in production rates of LDL during lovastatin therapy. To detect a change of this type, however, simultaneous measurements of VLDL and LDL turnover would be necessary, and these measurements were not made in this study. It should be pointed out that most of the patients on lovastatin did have small but apparently real increases in FCRs for LDL; thus from this finding alone it seems likely that lovastatin increased the activity of LDL receptors. Furthermore, for the reasons discussed above, the decreased LDL production during lovastatin therapy could have been due to an increase in activity of LDL receptors. An enhanced uptake of VLDL remnants would leave few remnants to be converted to LDL, and consequently the production rate of LDL would decline. The increases in FCRs for LDL during treatment with lovastatin could have been relatively small because enhanced uptake of VLDL remnants competed with uptake for LDL; if so, a high rate of uptake of VLDL remnants may interfere with removal of LDL and prevent a striking rise in FCR for LDL. This reasoning, combined with our findings of effects of lovastatin in patients with receptor-negative homozygous FH, make it unlikely that lovastatin has a major effect on the hepatic synthesis of lipoproteins.

Finally, the failure of lovastatin to raise the fractional clearance of LDL as much as might have been expected could have been the result of differences in affinity of LDL subpopulations for receptors. A heterogeneity of LDL for receptors uptake need not be the result of a true metabolic defect. For example, Witztum et al (27) have noted that cholestyramine-fed guinea pigs appear to have more rapid removal of some LDL than others. Consequently, poorer-binding LDL may accumulate in plasma, and these LDLs would be mainly labeled in turnover studies. If so, their FCRs would be lower than those of all LDL entering the LDL fraction. A similar phenomenon may occur during lovastatin therapy. If so, FCRs for LDL might not increase markedly on treatment with the drug. Yet another possibility is that the whole fraction of LDL in some patients with primary moderate hypercholesterolemia has a reduced affinity for LDL receptors. For instance, if some patients have an abnormality in the apo-B molecule, the apo-B could be a pool ligand for the LDL receptor; this situation could account for the failure of lovastatin to markedly increase the FCR for LDL. Thus a variety of mechanisms might be responsible for elevated LDL levels in patients with primary moderate hypercholesterolemia. Whatever the causes, most patients appear to have a decrease in fractional clearance of LDL as the underlying cause of their hypercholesterolemia (Table 7); further these patients respond to lovastatin with a striking reduction in LDL levels.

The question can be asked whether the combination of lovastatin and a bile acid-binding resin will be just as effective in patients with primary moderate hypercholesterolemia as it is in patients with heterozygous FH. To examine this question, lovastatin and colestipol were administered together to ten patients with primary moderate hypercholesterolemia by Drs. Vega and Grundy (28). The results for this study are shown for individual patients in Figures 17 and 18, and they are summarized in Table 10. Compared with a control period, the combined-drug therapy caused a 36% reduction in plasma total cholesterol, a 48% decrease in LDL-cholesterol level, and a 17% increase in HDL-cholesterol level (Figure 16). The reduction in LDL-cholesterol concentration was the result of three changes: (a) a 27% decrease in the production rate of LDL, (b) a 20% increase in the FCR for LDL, and (c) a 15% depletion of cholesterol in LDL particles (Figure 18). Overall, the data indicate that the combination of lovastatin and colestipol is highly effective in primary moderate



(Fig. 17)



(Fig. 18)

Figure 17. Influence of lovastatin (mevinolin) + colestipol on plasma concentrations of total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol in patients with primary moderate hypercholesterolemia.

Figure 18. Effects of lovastatin (mevinolin) + colestipol on kinetics of LDL-apo B in patients with primary moderate hypercholesterolemia.

Table 10

Concentrations of Lipids and Kinetics of Low-Density Lipoprotein (LDL)-Apolipoprotein in Ten Patients

	Control	Lovastatin Plus Colestipol Hydrochloride Therapy	Normal Subjects*
Plasma concentration, mg/dL (mmol/L)†			
Cholesterol	260 ± 6 (6.72 ± 0.16)	166 ± 5 (4.29 ± 0.13)‡	214 ± 10 (5.53 ± 0.26)
Triglyceride	107 ± 8 (1.21 ± 0.09)	116 ± 12 (1.31 ± 0.14)§	140 ± 14 (1.58 ± 0.16)
LDL cholesterol	196 ± 6 (5.07 ± 0.16)	101 ± 5 (2.61 ± 0.13)‡	144 ± 7 (3.72 ± 0.18)
HDL‖ cholesterol	42 ± 4 (1.09 ± 0.10)	49 ± 5 (1.27 ± 0.13)§	45 ± 4 (1.16 ± 0.10)
Total cholesterol-HDL cholesterol ratio	6.5 ± 0.5	3.7 ± 0.4‡	4.7 ± 0.4
LDL-apolipoprotein kinetics†			
Concentration, mg/dL (mmol/L)	113 ± 4 (2.92 ± 0.10)	68 ± 3 (1.76 ± 0.08)‡	101 ± 5 (2.61 ± 0.13)
Pool size, mg	3349 ± 185	2013 ± 128‡	2993 ± 155
Fractional catabolic rate, pools/d	0.25 ± 0.01	0.30 ± 0.02‡	0.30 ± 0.02
Transport rate, mg/kg-d	11.7 ± 0.07	8.5 ± 0.5‡	13.5 ± 0.7
LDL-apolipoprotein-cholesterol ratio†	0.60 ± 0.02	0.69 ± 0.03‡	0.72 ± 0.04

*Fourteen middle-aged, normal men.
†Mean (± SEM) of ten patients, taken from the means of seven determinations for each period for each patient.
‡Significantly different from control period ($P < .02$; paired t test).
§Not significantly different from control period.
‖HDL indicates high-density lipoprotein.

hypercholesterolemia, and it could be useful in treatment of high risk patients in this category, especially patients who already have CHD.

Familial Combined Hyperlipidemia. Another familial form of hyperlipidemia is characterized by elevations of both VLDL and LDL in the same family (13). Some family members have increased concentrations of triglycerides; others have increases in cholesterol levels; and still others have elevations of both cholesterol and triglycerides. The mechanisms responsible for multiple lipoprotein patterns in the same family have not been determined with certainty, but in some families, the underlying defect may be an overproduction of lipoproteins containing apo B. The actual lipoprotein pattern of a given patient may depend on that patient's capacity to catabolize the excess lipoproteins entering plasma. For example, patients with defective lipolysis of VLDL-triglycerides may develop hypertriglyceridemia, while those with defective clearance of LDL can develop hypercholesterolemia. The proposed mechanisms for hyperlipidemia in patients with familial combined hyperlipidemia thus are outlined in Figure 19.

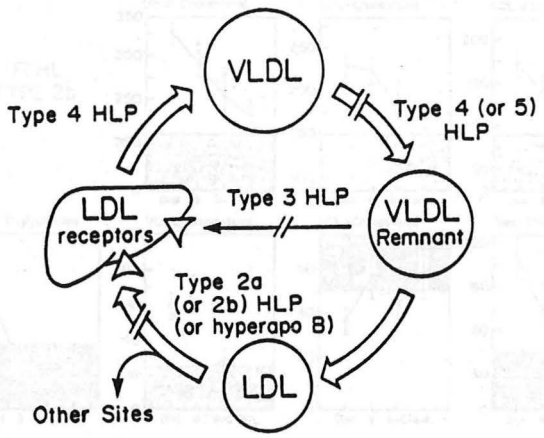


Figure 19. Proposed mechanisms for hyperlipidemia in patients with familial combined hyperlipidemia. Many patients with familial combined hyperlipidemia appear to have an overproduction of lipoproteins containing apolipoprotein B. If there is a simultaneous overproduction of VLDL-triglycerides or a defect in lipolysis of VLDL-triglycerides, the patient will have an elevated VLDL [and possibly chylomicron) concentration i.e. types 4 or 5 hyperlipoproteinemia (HLP)]. If there is an abnormality in apo E, the result will be an increase in VLDL remnants (beta-VLDL). Further, if the patient has a reduced activity of LDL receptors, LDL levels will be increased to produce hyperlipidemias of types 2a or 2b, or an increase only in LDL-apo B (hyperapobetalipoproteinemia or hyperapo B).

The role of lovastatin in treatment of familial combined hyperlipidemia has been examined recently by Drs. East, Bilheimer, and Grundy. In this study, the effects of three drug regimens were examined in seventeen patients with familial combined hyperlipidemia. Half the patients had elevations in both VLDL-triglycerides and LDL-cholesterol levels [type 2b hyperlipoproteinemia (HLP)] and the others had increase in VLDL-triglycerides and normal LDL-cholesterol levels (type 4 HLP). The drug regimens included gemfibrozil alone, gemfibrozil plus colestipol, and gemfibrozil plus lovastatin.

The data for patients with type 2b HLP are summarized in Figure 20. In these patients, gemfibrozil alone reduced total cholesterol by 11%, but LDL-cholesterol by only 3%; however, LDL-apo B fell by 18% and total triglycerides by 54%. When colestipol was combined with gemfibrozil, further reductions were noted: reductions compared to baseline were total cholesterol 22%, LDL-cholesterol 20%, LDL-apo B 23%, and triglyceride 44%. When lovastatin replaced colestipol, even better results were obtained: total cholesterol fell by an overall 29%, LDL-cholesterol by 28%, LDL-apo B by 34%, and triglyceride by 56%.

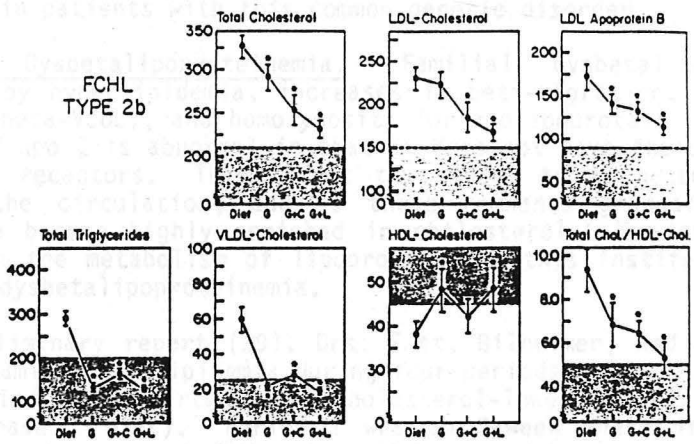


Figure 20. Drug therapy in familial combined hyperlipidemia (FCHL) of the type 2b (increased VLDL + LDL) variety. Abbreviations: G = gemfibrozil alone; G + C = gemfibrozil + colestipol; G + L = gemfibrozil + lovastatin. Stippled areas represent the desirable range.

In FCHL patients with type 4 HLP (Figure 21), gemfibrozil alone lowered triglyceride by 40%, failed to affect total cholesterol or LDL-apo B, but actually increased the significant reductions of total cholesterol, LDL-apo B, and LDL-cholesterol, but partially reversed the triglyceride lowering of gemfibrozil alone. Again, the combination of gemfibrozil plus lovastatin produced the best overall changes (reducing total cholesterol by 25%, LDL-cholesterol by 14%, LDL-apo B by 29%, and triglycerides by 56%).

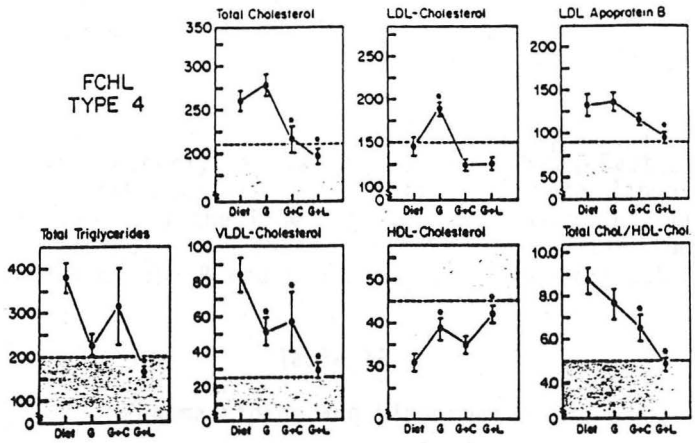


Figure 21. Drug therapy in familial combined hyperlipidemia (FCHL) of the type 4 (increased VLDL) variety. See Figure 20 for abbreviations.

The findings of this study show that lovastatin holds considerable promise for the treatment of patients with familial combined hyperlipidemia when it is combined with gemfibrozil. This combination favorably affects all three lipoprotein fractions---VLDL, LDL, and HDL, and in so doing it should reduce coronary risk in patients with this common genetic disorder.

Familial Dysbetalipoproteinemia. Familial dysbetalipoproteinemia is characterized by hyperlipidemia, increases in beta-migrating, very low density lipoproteins (beta-VLDL), and homozygosity for apolipoprotein E2 (apo E2). The apo E2 form of apo E is abnormal in that it does not have the usual affinity of apo E for LDL receptors. This defect thus leads to an accumulation of VLDL remnants in the circulation, and as these remnants gradually acquire more cholesterol to become highly enriched in cholesterol. Two studies have been carried out on the metabolism of lipoproteins in this institution in patients with familial dysbetalipoproteinemia.

In a preliminary report (29), Drs. East, Bilheimer, and Grundy studied a patient with familial dyslipidemia during four periods. At the beginning of the study the patient was started on a cholesterol-lowering diet (American Heart Association Phase I diet). Period I was an 8-week phase in which baseline values were obtained on the diet but without medication. In period II (16 weeks) the patient received lovastatin 20 mg twice daily; in Period II (12 weeks), he received placebo; and in Period IV (12 weeks) he was given lovastatin (20 mg twice daily) again. Steady-state values during the last 4 weeks of each period are shown in Table 11. Compared to the baseline (I) and placebo (III) periods, lovastatin caused marked reductions of cholesterol in total plasma, VLDL, LDL, and HDL. Levels of VLDL-triglycerides also fell on lovastatin. Ratios of VLDL-cholesterol to total triglycerides were markedly increased in baseline and placebo periods and fell with lovastatin therapy. Since lovastatin probably acts to enhance clearance of VLDL remnants, it may partially overcome the primary metabolic defect in dysbetalipoproteinemia.

Table 11

Plasma Lipoproteins in R.R.*

	Plasma Cholesterol (mg/dL)				Plasma Triglycerides (mg/dL)		VLDL-C: Total TG Ratio
	Total	VLDL	LDL	HDL	Total	VLDL	
Period I Baseline	420 ± 33	280 ± 28	112 ± 24	29 ± 1	486 ± 8	396 ± 37	0.58 ± 0.08
Period II Mevinolin	183 ± 22†	66 ± 10†	84 ± 17‡	33 ± 2	250 ± 30†	164 ± 20†	0.27 ± 0.08†
Period III Placebo	413 ± 39	233 ± 31	152 ± 16	29 ± 6	382 ± 29	288 ± 25	0.61 ± 0.05
Period IV Mevinolin	173 ± 22†	70 ± 16†	75 ± 25‡	29 ± 5	222 ± 36†	139 ± 28†	0.31 ± 0.04†

*Values are the means ± SD of the last four measurements (ie, one month) in each study period. Data analyzed by Neuman-Keuls multiple comparisons procedure.

†Values are significantly different from baseline and placebo periods by $P < 0.001$.

‡Values are significantly different from placebo periods by $P < 0.05$.

Another study was recently carried out by Drs. Vega, East, and Grundy. In this investigation, three patients with familial dysbeta lipoproteinemia were treated with lovastatin, and the kinetics for apo B were determined in control and drug treatment periods. In these patients, lovastatin therapy generally lowered concentrations of apo B and cholesterol in VLDL and LDL (Table 12). Of

Table 12

PLasma Lipids and Lipoproteins

(Familial Dysbetalipoproteinemia)

Patient	Total Cholesterol	Triglyceride	Lipoprotein-Cholesterol VLDL	LDL	HDL
		mg/dl±SD*			
No. 1					
Control	341±35	403±37	252±34	69±9	20±1
Lovastatin	111±9†	161±51†	49±15†	28±9†	33±1†
No. 2					
Control	284±10	257±67	172±12	82±9	30±1
Lovastatin	228±13†	241±19	135±11†	60±8†	31±1
No. 3					
Control	577±28	851±71	447±28	117±10	19±1
Lovastatin	391±25†	557±64†	299±31†	72±5†	25±3†

*Mean±SD for four 3-day pools of fasting plasma for day 2-14 of the turnover study.

†Significantly different from control by Student's t-test ($p<0.05$).

interest, the reductions in concentrations in both fractions were mainly due to a decrease in production rates for these fractions (data not shown). Indeed, the FCRs for LDL-apo B were reduced during lovastatin therapy (Figure 22); further, the direct removal of labeled VLDL-apo B was not enhanced. The decreased input of VLDL-apo B and LDL-apo B might have been due to a suppression in the synthesis of apo B-containing lipoproteins. An alternate explanation, which seems more consistent with current and previous results, is that lovastatin promoted direct removal of a nonidentifiable, rapidly-catabolized fraction of VLDL-apo B that is a precursor for longer-lived lipoproteins in the circulation. This mechanism could explain the decreased input rates of identifiable lipoprotein species which should retard the clearance of the latter lipoproteins because of "saturation" of LDL receptors by rapidly removed lipoproteins.

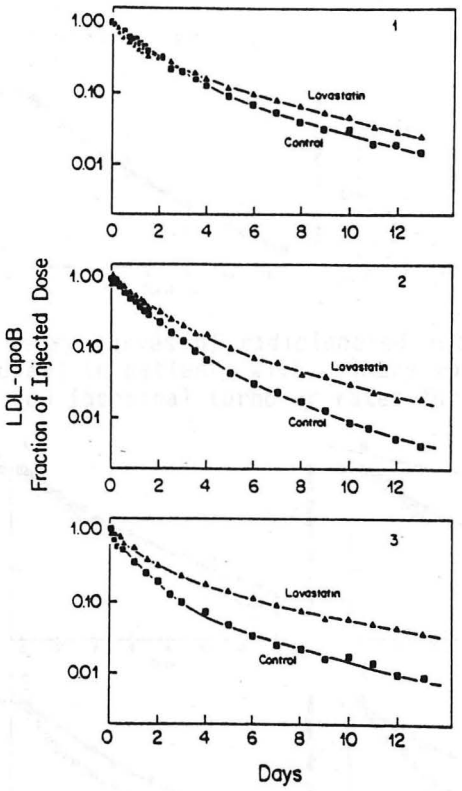


Figure 22. Influence of lovastatin on decay of radiolabeled LDL in patients with familial dysbetalipoproteinemia. In all three patients, lovastatin slowed the turnover rate of LDL.

Familial Defective Apolipoprotein B-100. Recent studies by Drs. Vega and Grundy (14) have shown that some patients with hypercholesterolemia have an abnormality in the structure of LDL so that it is a poor ligand for LDL receptors. This was revealed by comparing the turnover rates of autologous and homologous LDL in patients with hypercholesterolemia. In the majority of patients, turnover rates of the two forms of LDL are identical indicating that the patient's own LDL is not uniquely abnormal in its binding to LDL receptors (Figure 23). On the other hand, in some patients (Figure 24), autologous LDL is cleared more slowly than normal (homologous) LDL which indicates that the autologous LDL is abnormal and binds poorly to LDL receptors. In these patients, the hypercholesterolemia appears to be due to the presence of abnormal LDL. When these patients were treated with lovastatin, the clearance of the

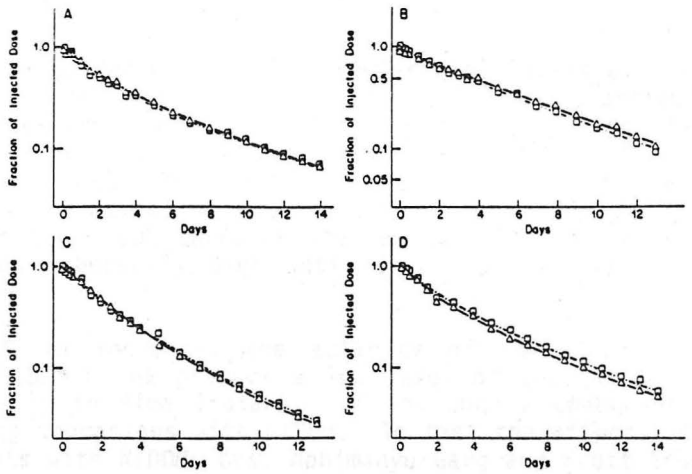


Figure 23. Plasma decay curves of radiolabeled autologous LDL (triangles) and homologous LDL (circles) in patients with primary moderate hypercholesterolemia. These four patients had identical turnover rates for the two types of LDL.

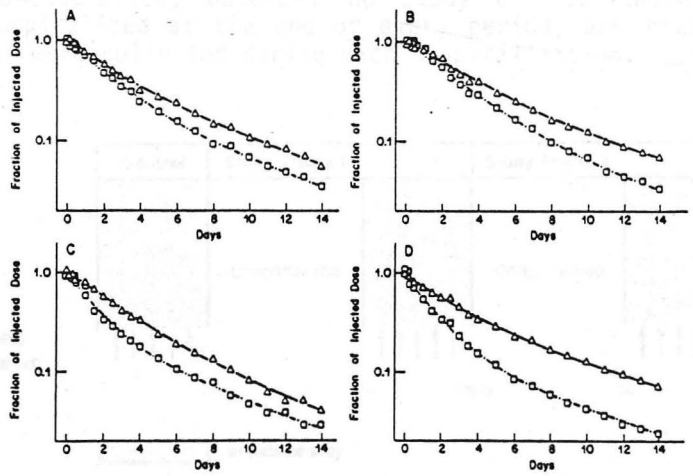


Figure 24. Plasma decay curves of radiolabeled autologous LDL (triangles) and homologus LDL (circles) in patients with primary moderate hypercholesterolemia. These four patients had a slower turnover ate of autologous LDL than of homologous LDL.

normal LDL is increased markedly, while that of the abnormal LDL was increased to a lesser extent. This finding provides additional evidence that these patients have an abnormal form of LDL that binds poorly to LDL receptors.

Non-Insulin Dependent Diabetes Mellitus (NIDDM). Patients with NIDDM are at increased risk for CHD. The mechanisms responsible for this enhanced risk are not known, but abnormalities in plasma lipoproteins may be a contributing factor. The most striking feature of NIDDM is an increase in VLDL-triglyceride levels, but LDL-cholesterol concentrations frequently are moderately increased and HDL-cholesterol levels are reduced. All three abnormalities may contribute to premature CHD.

The importance of increases in LDL-cholesterol levels as a risk factor for CHD is suggested by the situation in American Indians, particularly the Pima Indians. The Pimas are a genetically homogenous population that have a high prevalence of NIDDM and the expected microvascular complications, but they have a low prevalence of CHD (30). Their low rate of CHD may be the result of relatively low concentrations of LDL-cholesterol which are the result of a high catabolic rate of LDL. LDL turnover studies carried out in the Pimas suggest that they have an inherently high activity of LDL receptors, possibly on a genetic basis (31).

Since lovastatin increases the activity of LDL receptors, its use in Caucasians with NIDDM might produce a low level of LDL-cholesterol similar to those found normally in Pima Indians. If so, such a change might reduce the risk for CHD among Caucasians with NIDDM. To test the effects of lovastatin in non-Indian patients with NIDDM, Drs. Abhimanyu Garg and Scott Grundy studied 15 patients with NIDDM. Their age averaged 60±2 yrs; their BMI was 26.8±1.0 kg/m^2; plasma cholesterol exceeded 200 mg/dl at entry to the study. The patients were under good glycemic control with either glyburide (n=9) or insulin (n=6). The experimental design of the study is outlined in Figure 25. This was a randomized, placebo-controlled, double-blind study of lovastatin (20 mg BID). Patients were hospitalized at the end of every period, and five blood samples (shown by arrows) were collected during each hospitalization.

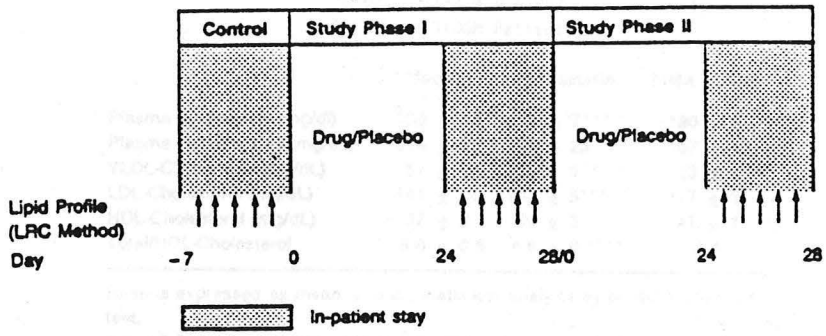


Figure 25. Experimental design for study; of effects of lovastatin (drug) vs. placebo in patients with NIDDM. Stippled areas indicate periods of hospitalization. Arrows indicate points of sampling of blood for lipids and lipoproteins.

The metabolic variables in the study during placebo and lovastatin periods are presented in Table 13. The effects of lovastatin therapy on plasma levels of lipids and lipoproteins are given in Table 14, and the results on lovastatin are compared to those of middle-aged Pima Indians. Lovastatin produced a marked lowering of plasma total cholesterol and LDL-cholesterol levels. It also reduced plasma triglycerides and raised the total cholesterol/HDL-cholesterol ratio. The levels of LDL-cholesterol in non-Indians during treatment with lovastatin were similar to those obtained in the Pima population. Thus, on the basis of the findings in patients with NIDDM, lovastatin could greatly lower the danger for CHD in this high-risk population.

Table 13
Metabolic Variables
(NIDDM Patients)

	PLACEBO	LOVASTATIN
Plasma Glucose (mg/dl) (3,7,11,16,21 hrs qd X 5)	125 ± 4	133 ± 6
Insulin Requirements (Units/d; n = 6)	81 ± 12	82 ± 13
Glyburide Dose (mg/d; n = 9)	8.3 ± 1.4	8.3 ± 1.4
Glycosylated Hemoglobin (%)	8.9 ± 0.2	8.7 ± 0.4
Body Weight (kg)	85.1 ± 3.8	84.4 ± 3.8

p Values not significant for all comparisons. Results expressed as mean ± S.E.

Table 14
Plasma Lipids and Lipo-
Proteins (NIDDM Patients)

	Placebo	Lovastatin	PIMA Values*
Plasma Cholesterol (mg/dl)	236 ± 10	173 ± 7***	180 ± 5
Plasma Triglycerides (mg/dL)	314 ± 52	213 ± 25*	167 ± 13
VLDL-Cholesterol (mg/dL)	57 ± 12	32 ± 5**	23 ± 2
LDL-Cholesterol (mg/dL)	141 ± 10	101 ± 5***	117 ± 5
HDL-Cholesterol (mg/dL)	37 ± 2	39 ± 3	41 ± 1
Total/HDL-Cholesterol	6.6 ± 0.5	4.6 ± 0.3***	4.4

Results expressed as mean ± S.E., statistical analysis by paired student's t test.
* $p < 0.01$ ** $p < 0.005$ *** $p < 0.0001$
* Howard et al. Arteriosclerosis 4: 462-471, 1984. values reported here are for 50 Male diabetic Pima Indians, ≥ 55 years, mean BMI 27 kg/M², and fasting Plasma Glucose 180 ± 10 mg/dL.

Side Effects of Lovastatin

Thus far the HMG CoA reductase inhibitors have been remarkably free of serious side effects. In laboratory animals, they have not been shown to be carcinogenic, and numerous laboratory studies in animal testing have failed to reveal significant toxicity. Nonetheless, the potential for side effects exist in several areas that might be considered.

First, it can be asked whether inhibition of cholesterol synthesis by lovastatin and similar drugs might interfere with either the production of

cholesterol required for membrane formation or vital products of cholesterol (e.g. steroid hormones or bile acids). Our own cholesterol balance studies indicate that lovastatin does not cause a marked reduction in synthesis of cholesterol in the doses normally used. Therefore, it is highly unlikely that lovastatin will cause a severe depletion of whole-body cholesterol. Certainly, in laboratory animals, when lovastatin is given in very large doses, there may be an inhibition of cholesterol synthesis to the point that normal cellular function is adversely affected, particularly in the nervous system, but such an effect seems highly unlikely in the doses used in humans. Further, available data suggest that lovastatin does not significantly interfere with the formation of steroid hormones or bile acids.

The primary action of lovastatin appears to be in the liver. Indeed, the drug seemingly is removed almost completely during its first pass through the liver. It has been postulated that its effects on body synthesis of cholesterol are limited exclusively to the liver, but this remains to be proven with certainty. Thus far, the major side effects of lovastatin appear to be "hepatotoxicity". In a small but perhaps significant portion of patients, the drug causes abnormalities in plasma concentrations of hepatic enzymes, particularly the transaminases. The clinical significance of these findings is not clear. Whether lovastatin might produce a silent but progressive injury to the liver in some patients is unknown. While this seems unlikely, more investigations on the effects of the drug on hepatic structure and function are needed.

Another question that has arisen is whether lovastatin can cause cataracts. One notorious example of this side effect was found with the cholesterol-lowering drug MER-29 (triparanol). This drug blocked the last step in the formation of cholesterol (from desmosterol), and by mechanisms that have not been determined, it cause cataracts in humans. Further, when dogs are given very high doses of lovastatin, cataracts have been noted. On the other hand, from data available on effects of lovastatin in humans, an increase in formation of cataracts has not been demonstrated. Nevertheless, this is an issue that must continue to be examined carefully.

Still another question is whether the drug will interfere with the formation of sperm. Studies on this question have not been done. Further, a variety of other possible side effects can be visualized, but so far, they have not materialized. Thus, while safety is currently of major concern about lovastatin, the drug has not been used in enough patients for long enough to either validate it safety or to identify long-term adverse effects.

Future for Lovastatin

The discovery of HMG CoA reductase inhibitors must be considered a major breakthrough in the control of high blood cholesterol. These agents have many characteristics of an "ideal" cholesterol-lowering drug. First, they are highly potent and are effective in low doses. Second, they induce a lowering of the plasma cholesterol through a mechanism that has already been proven to be efficacious for prevention of CHD, namely, the enhancement of activity of LDL receptors. Third, the drugs are specific; they apparently have a single metabolic effect--to competitively inhibit HMG CoA reductase. And fourth, they appear to be relatively nontoxic.

The most obvious use of lovastatin is for the treatment of patients with severe hypercholesterolemia, especially those with heterozygous FH. There are at least half a million Americans with heterozygous FH, and most of these should be candidates for HMG CoA reductase inhibitors sooner or later. At the present time, it probably would not be wise to use reductase inhibitors for treatment of FH children, but as we gain more experience with the safety of these drugs, they should be appropriate for young adults with heterozygous FH, particularly for young men.

Perhaps the major question is whether reductase inhibitors will be appropriate therapy for individuals with primary hypercholesterolemia who have cholesterol levels in the range of 240 to 300 mg/dl. We have shown that these drugs are highly effective in such individuals, but in the absence of greater proof that reductase inhibitors are entirely safe, many investigators will question their use in this group. A logical approach to patients with primary hypercholesterolemia is to employ a stepwise plan of therapy. Individuals in this category should first be tried on a cholesterol-lowering diet. If this fails to bring LDL-cholesterol levels down to an acceptable range, the patient can be advanced to bile-acid binding resins. Only after it has been shown that this more conservative approach has failed should the physician give serious consideration to use of lovastatin.

On the other hand, for high-risk patients with primary hypercholesterolemia, consideration can be given to using lovastatin at an earlier stage. For example, for patients with established atherosclerotic disease (such as CHD or carotid atherosclerosis), it is not unreasonable to use lovastatin to obtain a maximal reduction of risk. Not only may a marked reduction of cholesterol levels prevent the further development of atherosclerosis in these patients, but it conceivably might cause a reversal of existing atherosclerotic plaques. Certainly, in experimental animals, atherosclerotic lesions can be reversed by lowering cholesterol levels. Whether the same can occur in humans remains to be proven, although preliminary evidence of several types suggests that human atherosclerosis can be reversed.

Another high-risk group that might be candidates for lovastatin therapy is NIDDM. Patients with NIDDM are at increased risk for CHD, and this heightened risk may be due partly to dyslipidemia and relatively high cholesterol levels. If we can use the Pima Indians as a guide, a reduction of cholesterol levels to the low-normal range may prevent development of CHD. Our studies indicate that Caucasians with NIDDM are responsive to lovastatin, and thus they are candidates for further investigation.

What about smokers with primary hypercholesterolemia? Are they candidates for lovastatin therapy. Since cigarette smoking increases risk considerably, the combination of smoking and high cholesterol levels (in the range of 240 to 300 mg/dl) imparts a risk for CHD equivalent to that of a patient with heterozygous FH. Thus, it is not unreasonable to consider smokers with other forms of primary hypercholesterolemia as candidates for lovastatin therapy.

Now that it has been well established that lovastatin (and related HMG CoA reductase inhibitors) are powerful cholesterol-lowering drugs, the key issue about these agents is their long-term safety. Their use in patients with severe hypercholesterolemia (and perhaps in high-risk patients with moderate hypercholesterolemia) can be justified in the absence of data on long-term safety, but until such data have been obtained, it probably would be better not to extend their use to other individuals with less-severe forms of hypercholesterolemia.

REFERENCES

1. Stamler, J., Wentworth, D., Neaton, J. JAMA 256:2823, 1986.
2. Kannell, W.B., Castelli, W., Gordon, T. et al. Ann. Intern. Med. 74:1, 1971.
3. Pooling Project Research Group. J. Chronic. Dis. 31:201, 1978.
4. Goldbourt, V., Holtzman, E., Neufeld, H.N. Br. Med. J. 290:1239, 1985.
5. Grundy, S.M. JAMA 256:2849, 1986.
6. Brown, M.S. and Goldstein, J.G. Science 232:34, 1986.
7. Lipid Research Clinics Program JAMA 251:259, 1980.
8. Endo, A., Kuroda, M., Tsujita, Y. J. Antibiot. (Tokyo) 29:1346, 1976.
9. Tobert, J.A. et al J. Clin. Invest. 69:913, 1982.
10. Bilheimer, D.W., Goldstein, J.L., Grundy, S.M., Brown M.S. N. Engl. J. Med. 311:1658, 1984.
11. Brown, M.S. and Goldstein, J.L. J. Clin. Invest. 72:743, 1983.
12. Goldstein, J.L. and Brown, M.S. Ann. Rev. Biochem. 46:897, 1977.
13. Grundy, S.M., Chait, A., Brunzell, J.D. Arteriosclerosis 7:203, 1987.
14. Vega, G.L. and Grundy, S.M. J. Clin. Invest. 78:1410, 1986.
15. Innerarity, T.L., Weisgraber, K.H., Arnold, K.S., Mahley, R.W., Krauss, R.M., Vega, G.L. and Grundy, S.M. Proc. Natl. Acad. Sci. (USA) (in press)
16. Kovanen, P.T., Bilheimer, D.W., Goldstein, J.L., Jaramillo, J.J. and Brown, M.S. Proc. Natl. Acad. Sci. (USA) 78:1194, 1981.
17. Grundy, S.M. and Bilheimer, D.W. Proc. Natl. Acad. Sci. (USA) 81:2538, 1984.
18. Goldstein, J.L. and Brown, M.S. The Metabolic Basis of Inherited Diseases. McGraw Hill, New York, 1983, pp. 672-712.
19. Illingworth, D.R. and Sexton, G.J. J. Clin. Invest. 74:1972, 1984.
20. Bilheimer, D.W., Grundy, S.M., Brown, M.S., Goldstein, J.L. Trans. Assoc. Am. Physicians 46:1, 1983.
21. Mabuchi, H., Sakai, T., Sakai, Y. et al N. Engl. J. Med. 308:609, 1983.
22. Bilheimer, D.W., Grundy, S.M., Brown, M.S., Goldstein, J.L. Proc. Natl. Acad. Sci. (USA) 80:4124, 1983.
23. Grundy, S.M., Vega, G.L., Bilheimer, D.W. Ann. Int. Med. 103:339, 1985.
24. Goldstein, J.L., Hazzard, W.R., Schrott, H.G. et al. J. Clin. Invest. 52:1533, 1973.
25. Goldstein, J.L. Schrott, H.G., Hazzard, W.R. et al. J. Clin. Invest. 52:1544, 1973.
26. Grundy, S.M. and Vega, G.L. J. Lipid Res. 26:1464, 1985.
27. Witztum, J.L., Young, S.G., Elam, R.L. J. Lipid Res. 26:221, 1985.
28. Vega, G.L. and Grundy, S.M. JAMA 257:33, 1987.
29. East, C.A., Grundy, S.M., Bilheimer, D.W. Metabolism 35:97, 1986.
30. Ingelfinger, J.A. et al. Diabetes 25:561, 1976.
31. Howard, B.V. et al. J. Lipid Res. 27:11, 1986.