STATINS AND BEYOND

The Elimination of Coronary Artery Disease

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Special interests: The mechanisms of cholesterol movement through the body and the role of cholesterol in heart disease and in diseases of the central nervous system.

This is to acknowledge that Dr. Dietschy does consult, from time to time, with pharmaceutical companies such as Merck and Schering Plough on various aspects of the basic science of cholesterol absorption, cholesterol metabolism and sterol metabolism within the central nervous system. During this presentation, there may be occasional discussions of "off-label" uses of statins and other agents used to treat elevated plasma cholesterol levels.

The cover illustrates a very early step in the process of coronary artery occlusion. In this illustration the lumen of the coronary artery is open, but there is a large amorphus collection of cellular debris and cholesterol in an atheroma. This atheroma is separated from the lumen of the coronary artery by a delicate fibrous cap that, in this illustration, has just ruptured. Following this rupture, platelets will be rapidly attracted to this area, a clot will form, and coronary artery occlusion will take place.

I. INTRODUCTION

The topic of reduction of coronary artery disease by the use of a group of pharmaceutical agents known as statins was last reviewed at Medical Grand Rounds in 1996. The data available at that time clearly suggested that even in older individuals, significant lowering of the plasma cholesterol level by use of these agents reduced the incidence of coronary artery occlusion and myocardial infarction. Since that time, a considerable amount of new data has been published that bear on this important subject and deal with important aspects of the pharmacology of these agents that are designed to lower the concentration of cholesterol carried in low density lipoproteins (LDL-C). Even though the incidence of coronary artery disease (CAD) is now beginning to decrease (although, not in women), this disease remains

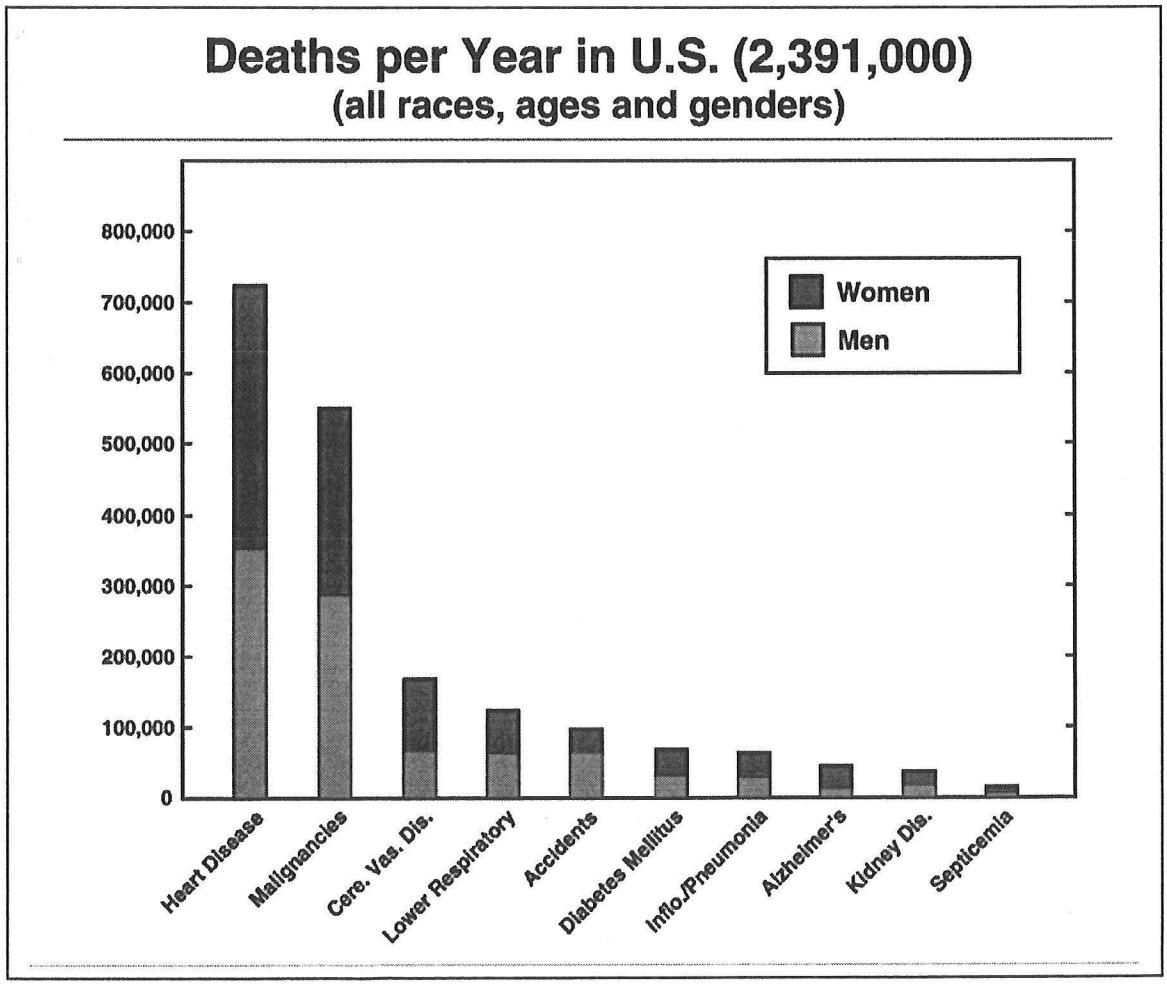

Fig. 1

one of the leading causes of death in the United States. As illustrated in Fig. 1, approximately 2.4 million individuals will die this year in the United States. The leading cause of these deaths by far is atherosclerotic disease of arteries with the associated syndromes of coronary artery and cerebral vascular disease. Deaths from all malignancies combined are significantly lower than deaths from these atherosclerotic diseases. As is apparent in this figure these diseases affect men and women with approximately equal incidence. Furthermore, it should be emphasized that coronary artery disease in women in three times more prevalent than is carcinoma of the breast. Virtually all other diseases are significantly less important as causes of death. These data illustrate how important it is to prevent premature death from atherosclerosis in both men and women.

Since this subject was last reviewed, important new data have appeared in a number of areas which further clarify the pathophysiology of these diseases and the treatment options available for the prevention of cardiac and cerebral vascular disease. These new data will be reviewed in three different sections. The **first** set of data briefly reviews the natural history of atherosclerosis and the new trials that have further supported the concept that lowering the plasma cholesterol level lowers the incidence of coronary events. The **second** section reviews new information on the pharmacology of the various statins and explores the potential limitations and toxicities of the various agents used to treat hypercholesterolemia. Finally, the **third** section introduces a new class of agents that appears to lower the plasma cholesterol level by specifically blocking cholesterol absorption across the gastrointestinal tract.

II. WHAT CONSTITUTES A "NORMAL" CONCENTRATION OF TOTAL-CHOLESTEROL (TC) AND LOW DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C) IN THE PLASMA?

One of the major problems that has plagued this field is the definition of "normal" cholesterol levels in the plasma in Americans. It should be emphasized that the cholesterol carried in lipoprotein fractions in the plasma in humans has little biological function. Rather, this sterol is passing through the blood on route from one organ to another. The cholesterol carried in high density lipoproteins (HDL) is

moving from its sites of synthesis in all peripheral organs to the liver for excretion. The cholesterol carried in LDL is also passing through the plasma on route to the liver for either reutilization or excretion from the body. Unlike such plasma components as sodium, calcium or glucose that must be maintained within narrow concentration ranges, the plasma cholesterol concentration can be virtually any value and not produce symptoms. Thus, there is no such value as a "normal" plasma cholesterol concentration. The more important question is what levels of LDL-C are associated with the formation of atheroma within the walls of the arterial system.

In most animals, including most primates, the concentration of LDL-C is in the range of 10-60 mg/dl and the TC concentration is commonly in the range of 100-160 mg/dl. In general, the animals with these cholesterol values are on diets containing very little cholesterol and low amounts of dietary triacylglycerol. When groups of experimental monkeys are placed on diets more typical of those eaten by Americans, both the TC and LDL-C levels increase to the values

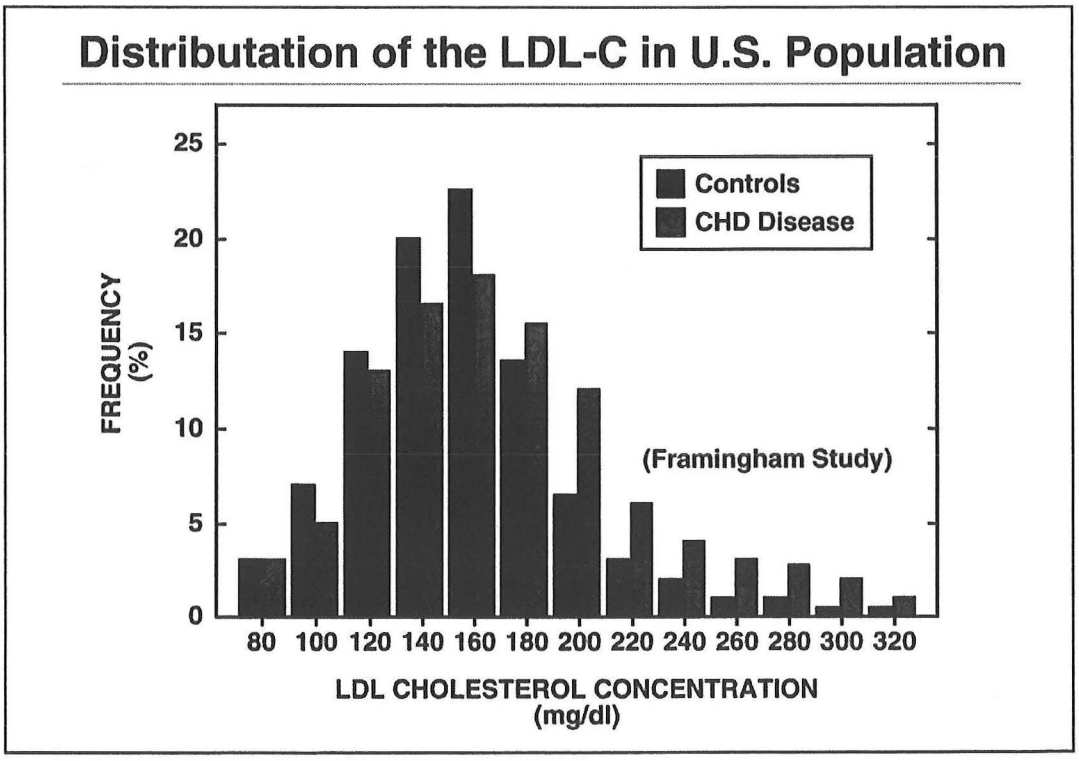

Fig. 2

typical of humans in the Western world. The critical question is not what is the "normal" concentration of cholesterol in the plasma but, rather, what concentrations are associated with the development of

atherosclerosis and, further, is there a threshold concentration below which atheroma formation does not occur?

In the United States (as well as in Europe) the TC concentration in most of the population varies between approximately 220-280 mg/dl. In the earlier literature, therefore, values of 240-260 mg/dl were considered to be "normal." Similarly, the majority of these individuals had LDL-C levels in the range of 120-180 mg/dl, as shown in Fig. 2. As a result of this frequency distribution, values for the LDL-C in the range of 130-160 were considered to be "normal" in the old literature. What was not commonly appreciated was that in very large populations of people around the world, the TC was usually less than 200 mg/dl and the LDL-C was commonly less than 100 mg/dl. There is considerable new data now suggesting that this frequency distribution of the plasma cholesterol level in Western populations is largely due to the intake of diets that contain small amounts of cholesterol and very

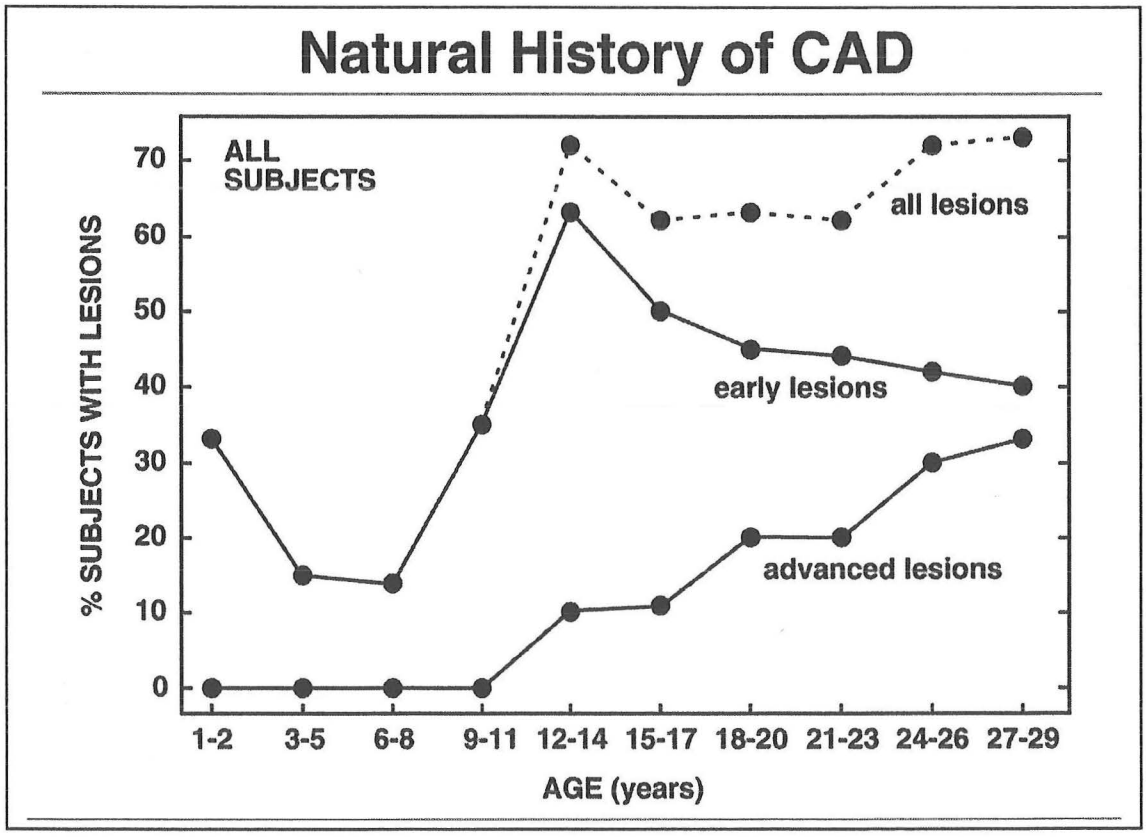

Fig. 3

large amounts of triacylglycerol. Such diets drive the output of cholesterol from the liver in very low density lipoproteins and partially inhibit the uptake of the LDL particle. As a consequence, both the frequency distribution for the TC and LDL-C in such populations is

shifted to higher values than are seen in populations where the triaclyglycerol intake in the diet is less than 10-15%.

There is now little doubt that these high concentrations of circulating LDL-C in the American population has led to widespread atherosclerosis in virtually all Americans. That this is true was first suggested by studies performed in 300 American soldiers (average age 22 years) who were killed in the Korean war in 1951-2. Seventy five percent of these young Americans already had significant coronary artery disease. Similar findings were reported in young men (average age 24 years) killed in the Vietnam war. Much more detailed studies of the natural history of atherosclerosis in the U.S. came from NIH-sponsored studies (Fig. 3) on children and young adults who died from trauma. In these individuals nearly 70% had significant early or advanced coronary atherosclerosis by the age of 30. Finally, a still more recent, ongoing study using intravascular ultrasound to detect atheroma, it has been shown that approximately 85% of Americans reaching the age of 50 years have significant arterial disease. Thus, taken together, all of these studies suggest that approximately 80-85% of the American population has circulating plasma LDL-C concentrations that are greater than 100 mg/dl and the majority of these individuals are continuously developing atherosclerotic disease throughout the early and middle decades of their life. This disease becomes clinically evident in men in their 40's and in women in their 50's, and the incidence increases dramatically in older age groups.

III. RELATIONSHIP BETWEEN CLINICAL CAD AND THE PLASMA TC AND LDL-C LEVELS

Epidemiologists have looked at a number of populations in the world that have very low LDL-C concentrations and very low incidences of CAD. In the Yandapu-Enga (Fig. 4) for example, 75% of the caloric intake comes from carbohydrate, dietary fat intake is very low and the plasma LDL-C concentrations range from 60-70 mg/dl. This population has virtually no detectable coronary heart disease. There have been similar findings in other populations such as the Tarahumara of Mexico. However, when this group of individuals is placed on a typical Western diet or when they immigrate to the United States and become integrated into American society, their LDL-C

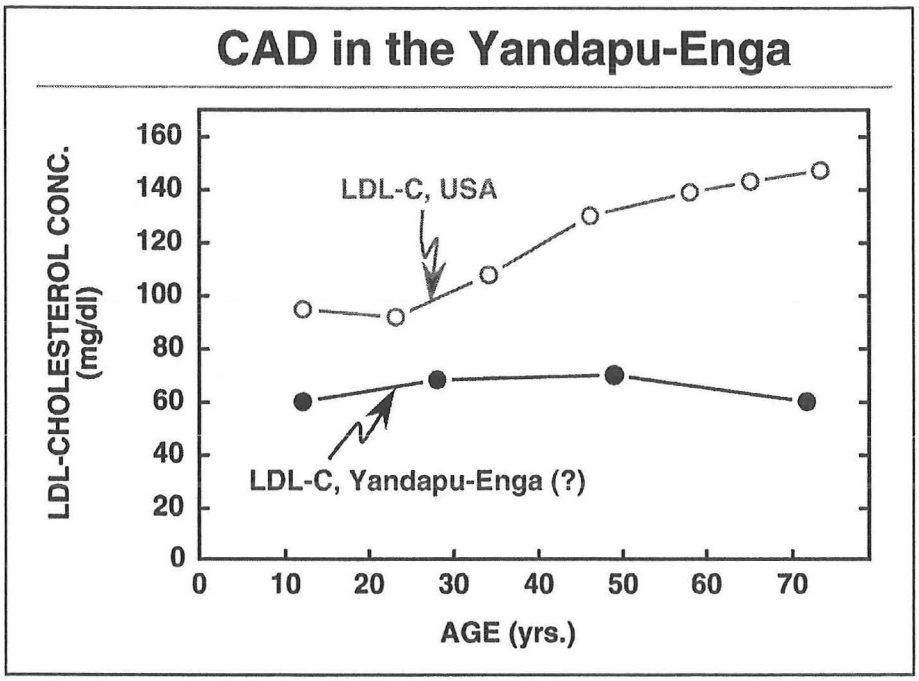

Fig. 4

levels rapidly rise to the same levels seen in other Americans and they develop the same, high incidence of CAD.

The classic relationship between CAD mortality and plasma cholesterol levels is shown in Fig. 5. It is noteworthy that the increase in coronary events is a constant percentage at any incremental increase in the plasma TC concentration. Thus, there is about a 50% increase in events for each incremental increase of 40 mg/dl in the plasma cholesterol concentration. More recent epidemiological data have shown this same relationship even in societies with very low plasma cholesterol levels and very low incidences of coronary events. In the urban Chinese, for example, the absolute incidence of heart attacks

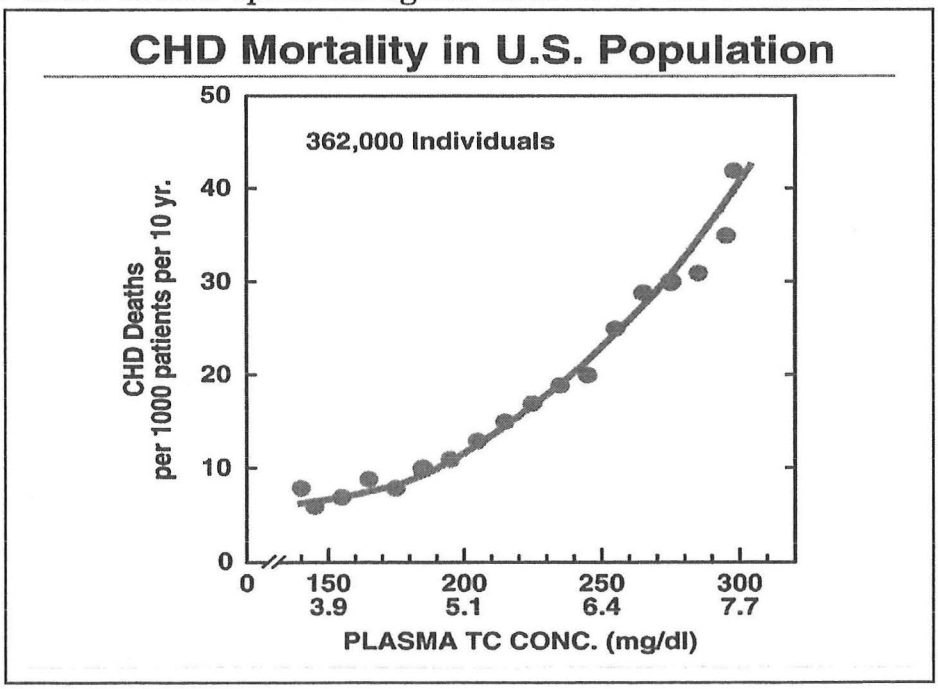

Fig. 5

is very low. Nevertheless, an increase in the plasma cholesterol concentration of 40 mg/dl is again associated with an approximate 50% increase in the relative risk of a coronary event. Thus, all of these data together have failed to demonstrate a "threshold" concentration at which atherosclerosis and CAD fail to develop. Apparently, at any concentration of LDL-C above about 60-70 mg/dl there is essentially a log linear relationship between the risk of coronary artery disease and the plasma cholesterol concentration.

IV. MAJOR TRIALS IN WHICH THE PLASMA CHOLESTEROL CONCENTRATION WAS LOWERED WITH STATINS

Over the last 15 years, there have been a number of major trials in different populations of patients in which the effectiveness of lowering the plasma cholesterol concentration in preventing CAD has been assessed. The six largest and most important of these trials are summarized in TABLE I. These trials are divided into two groups:

TABLE I. Major Trials Using Statins To Reduce CHD Events in Normal (Primary) Individuals and in Patients (Secondary) with Established CHD

STUDY	Number Subjects n	Total Cholesterol (Mean ± 2SD) mg/dl	LDL-C (Mean ± 2SD) mg/dl
Primary Prevention			
WOSCPS	6595	226-318	158-226
AFCAPS/TexCAPS	6605	180-263	116-184
Secondary Prevention			
4S	4444	209-313	163-213
LIPID	9014	162-274	96-204
CARE	4159	175-243	109-169
High Risk (CHD, Diabetes, HT)			
HPS	20,536	150-316	104-168

those that were undertaken in patients who already had obvious clinical coronary artery disease (Secondary Prevention) and those individuals who had not yet manifested clinical disease (Primary Prevention). The first of these studies was directed at patients with very high plasma cholesterol concentrations. The 4,444 patients entered into the 4S study had plasma total cholesterol concentrations of 209-313 mg/dl and LDL levels of 163-213 mg/dl. Later, two other important secondary prevention trials (LIPID and CARE) looked at groups of patients with much lower plasma cholesterol levels. Two other trials evaluated the prevention of the first myocardial event in patients with very high cholesterol levels (WOSCPS) or in individuals with somewhat lower plasma cholesterol concentrations (AFCAPS). Preliminary results have just been published from the most recent, and largest, of these prospective trials. In the HPS study patients were considered to have a "high risk" of developing a coronary event because they had preexisting CHD, hypertension, vascular disease or diabetes. The total plasma cholesterol concentrations in this group of nearly 21,000 patients varied from 150 to 316 mg/dl. Importantly, in this study fully one-third of the patients had an initial LDL-C concentration of less than 116 mg/dl and a smaller group of patients had initial LDL-C concentrations of less than 100 mg/dl.

The results of these six studies are summarized in Tables II and III. In general, in the two primary prevention studies treatment with a statin lowered the LDL-C concentration about 25% and this was associated with a reduction in CAD events by approximately 30-37%. The results in the HPS study are particularly important in that subgroup analysis showed a similar reduction in CAD events regardless of the initial concentration of the LDL-C. In particular, in a small group of these patients, a reduction in the initial plasma LDL-C concentration of 97 mg/dl to only 65 mg/dl produced a similar reduction in the event rate. Thus, these studies revealed no "threshold" effect but, rather, there was a similar favorable effect of lowering the plasma LDL-C concentration regardless of the initial concentration of cholesterol in the plasma.

There were similar findings in the three secondary prevention trials (Table III). The absolute risk of having another CAD event was much higher in these patients than in those in the preceding trials. However, regardless of the initial level of the LDL-C, lowering the plasma cholesterol level by use of a statin significantly reduced the incidence of the next myocardial event.

TABLE II

WOSCPS (Normal, ~55 y.o., ~4.9 yr. R_x)

	Cholesterol (mg/dl)		Patients And Events (Rates)		
	TC	LDL-C	Total	CV Events	CV Deaths
Control	272	192	3293	248 (154)	52 (32)
	↓ 20%	↓ 26%		↓ 30%	↓ 27%
Statin	218	142	3302	174 (107)	38 (23)

AFCAPS/TexCAPS (Normal, ~ 57 y.o., 5.2 yr. R_x)

	Cholesterol (mg/dl)		Patients And Events (Rates)		
	TC	LDL-C	Total	CV Events	CV Deaths
Control	228	156	3301	183 (107)	25 (16)
	↓ 19%	↓ 26%		↓ 37%	↓ 32%
Statin	184	115	3304	116 (67)	17 (10)

HPS (High Risk, ~ 40-80 y.o., 5.3 yr. R_x)

	Cholesterol (mg/dl)		Patients And Events (Rates)		
	TC	LDL-C	Total	CV Events	CV Deaths
Control	236	132	10237	1212	707
	↓ 23%	↓ 30%		↓ 26%	↓ 17%
Statin	182	92	10232	898	587

TABLE III

4S (CAD, ~60 y.o., 5.4 yr. R_x)

	Cholesterol (mg/dl)		Patients And Events (Rates)		
	TC	LDL-C	Total	CV Events	CV Deaths
Control	261	188	2223	502 (417)	189 (157)
	↓ 25%	↓ 35%		↓ 30%	↓ 41%
Statin	196	122	2221	353 (294)	111 (92)

LIPID (CAD, ~ 60 y.o., 6 yr. R_x)

	Cholesterol (mg/dl)		Patients And Events (Rates)		
	TC	LDL-C	Total	CV Events	CV Deaths
Control	219	150	4509	708 (262)	373 (138)
	↓ 18%	↓ 27%		↓ 22%	↓ 23%
Statin	177	110	4509	554 (205)	287 (106)

CARE (CAD, ~ 50 y.o., 5 yr. R_x)

	Cholesterol (mg/dl)		Patients And Events (Rates)		
	TC	LDL-C	Total	CV Events	CV Deaths
Control	209	139	~2080	269 (258)	116 (112)
	↓ 20%	↓ 30%		↓ 24%	↓ 19%
Statin	167	98	~2079	206 (198)	97 (93)

The results in all of these studies are best visualized by plotting the average results as shown in Fig. 6. Several points should be emphasized. First, the absolute risk of having the next cardiac event is 3-4 times higher in those patients who had already had one major coronary event (the upper curve) as compared with those patients in the primary prevention trials (the lower curve). Second, in both cases, however, there was essentially a linear relationship between the incidence of a coronary event within the five year period of observation and the plasma LDL-C concentration. Third, and most important, there was no evidence of a "threshold" effect. That is to say, there was a significant reduction in the incidence of coronary events regardless of the initial plasma LDL-C concentration. This was true even when the initial cholesterol concentration was less than 100 mg/dl.

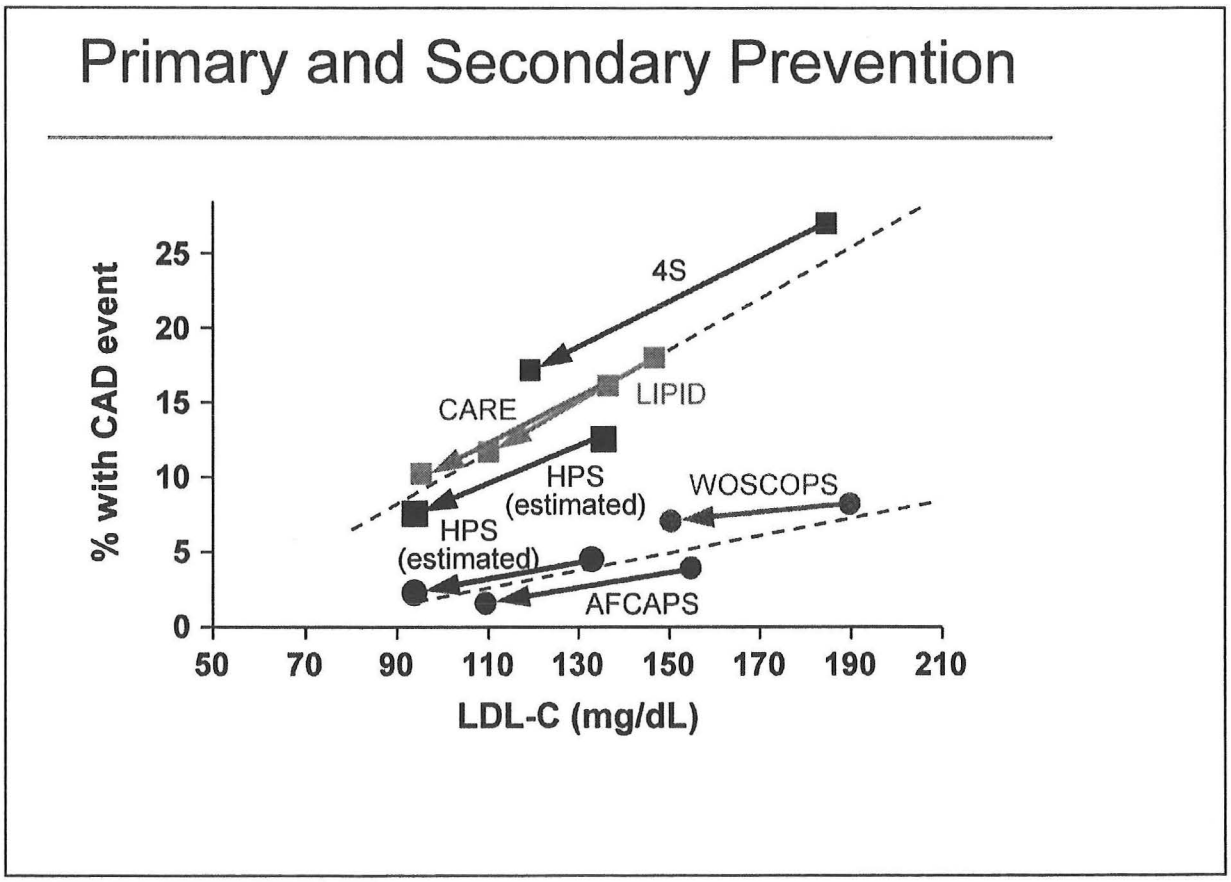

Fig. 6

V. MERGING OF THE EPIDEMIOLOGICAL DATA WITH THOSE FROM THE PRIMARY AND SECONDARY PREVENTION STUDIES

As is apparent in Fig. 5, the curve that describes the relationship between CAD and the plasma TC has the form of a first order, growth curve. When such curves are plotted in semi-logarithmic fashion there is a straight line function between CHD incidence and the plasma TC level. The lower curve in Fig. 7 represents such a plot for the epidemiological data where the log of the relative risk for

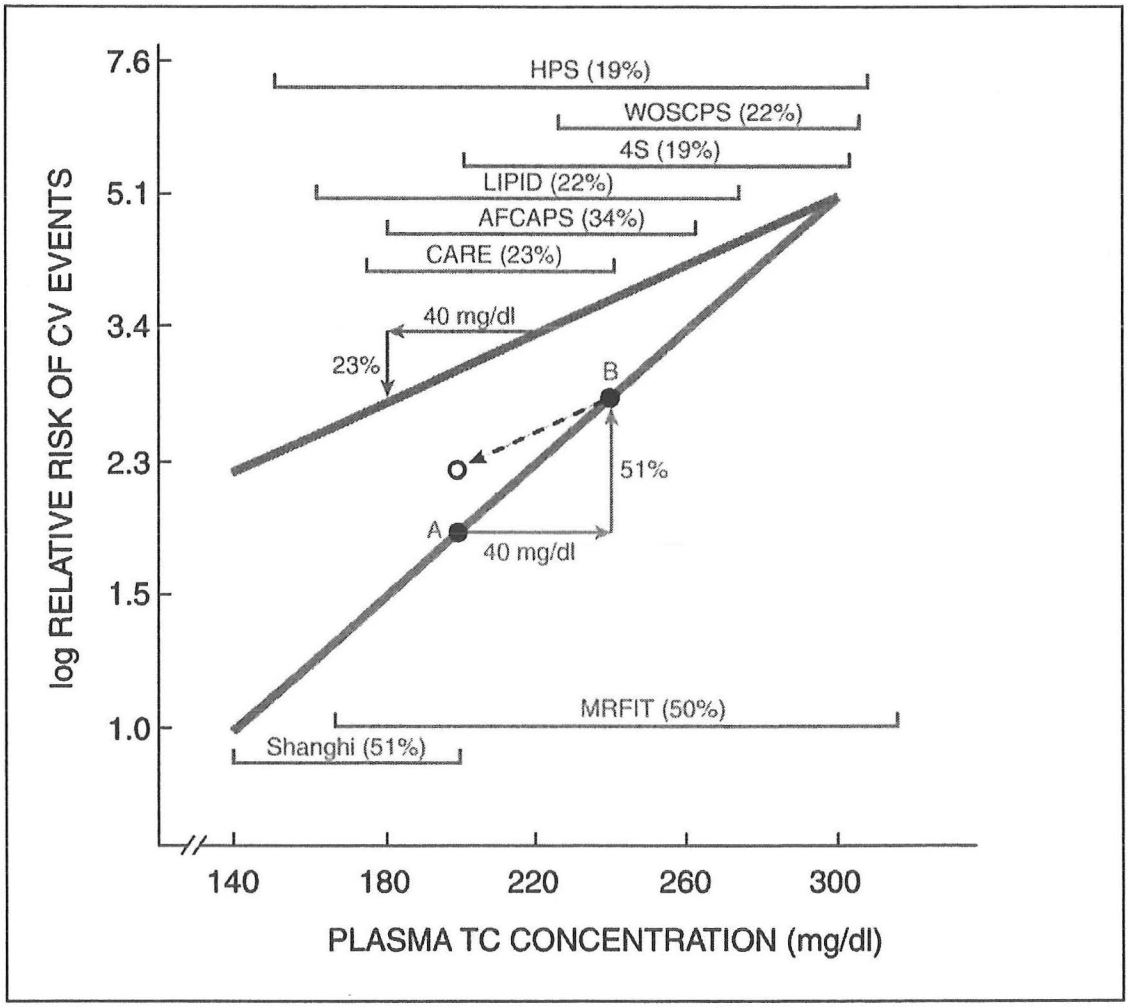

Fig. 7

cardiovascular events has been plotted against the plasma TC concentration. As is apparent, the the MRFIT epidemiological data show that there is approximately a 50% increase in the relative risk of

cardiovascular events for an increase in the plasma TC concentration of 40 mg/dl (1 mmol/l). Remarkably, there are similar, more recent data in urban Chinese who have very low CV event rates and very low plasma TC concentrations. Nevertheless, in this group the slope of this relationship is the same. For example, in the urban Chinese raising the plasma TC concentration from 140 mg/dl to 180 mg/dl increases the relative risk of a cardiac event by about 50%.

The upper curve shows the slope of this relationship derived from the various statin studies in which older individuals (50-65 years) were treated with a statin for approximately 5 years and the rate of reduction in CV events was determined. In the HPS study, which included patients with a very broad range of plasma TC levels, there was a 19% reduction in relatively risk for each 40 mg/dl reduction in the plasma TC concentration. Similar values were found in the other studies and the average for all of these studies was approximately 23%. The importance of these data is illustrated by the two patients labeled A and B. Patient A with a plasma TC concentration of 200 mg/dl has a significant risk of developing a cardiovascular event. On average, patient B with a plasma TC concentration of 240 mg/dl has a 50% higher relative risk. If patient B is an older individual 50-65 years of age and is treated with a statin for 5 years, his/her risk will be reduced approximately 23%. Thus, in order to reduce the risk of a CV event in patient B to the same level seen in patient A, the plasma TC concentration would have had to have been reduced to approximately 160 mg/dl. These epidemiological data are entirely consistent with many other observations that treatment with a statin prevents the formation of new atheroma and may actually reverse unorganized collections of lipid in the arterial wall. Statins do not, however, reverse narrowing of the arterial system brought about by fibrotic and calcified lesions. These data speak very strongly, therefore, for beginning statin therapy at much younger ages.

These data, which indicate that the LDL-C concentration should be well below 100 mg/dl when treating patients for either primary or secondary prevention of CAD have created a major problem for the primary care physician. Most of the statins, as well as other agents used to lower plasma cholesterol levels, are not always powerful enough to lower the LDL-C to these desired levels (Table IV). The response of the pharmaceutical industry to this need for more effective therapy has been two-fold: 1) the companies have obtained permission from the FDA for the use of higher doses of many of the standard

TABLE IV

Drugs Affecting Lipoprotein Metabolism

Drug Class	Lipid/Lipoprotein Effects	Selected Side Effects	Selected Contraindications/Warnings	Outcomes Trial Results
HMG-CoA reductase inhibitors (statins)	LDL ↓ 18%-55% HDL ↑ 5%-15% TG ↓ 7%-30%	Myopathy, ↑ liver enzymes	Active or chronic liver disease Concomitant use of certain drugs	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid sequestrants	LDL ↓ 15%-30% HDL ↑ 3%-5% TG no change or ↑	Gastrointestinal distress, constipation, ↓ absorption of other drugs	Dysbetalipoproteinemia, TG >400 mg/dL TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid	LDL ↓ 5%-25% HDL ↑ 15%-35% TG ↓ 20%-50%	Flushing; hyperglycemia, hyperuricemia (or gout), upper GI distress, hepatotoxicity	Chronic liver disease, severe gout, diabetes, hyperuricemia, peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids	LDL ↓ 5%-20% (may be ↑ in patients with high TG) HDL ↑ 10%-20% TG ↓ 20%-50%	Dyspepsia; gallstones, myopathy, unexplained non-CHD deaths in WHO study	Severe renal, severe hepatic disease	Reduced major coronary events
Plant stanols*	LDL ↓ 10%-20%	Not available	Not available	No outcomes data; over 20 safety/efficacy trials
Plant sterols*	LDL ↓7%-10%	Not available	Not available	Limited clinical trials

Adapted from NCEP ATP III. *JAMA*. 2001;285:2491; *Cater NB. *Prev Cardiol*. 2000;3:127.

statins and, 2) a new group of "super" statins has been developed. In both cases, there has been an increase in the incidence of significant side effects with these drugs and only recently have new data on the pharmacology of these compounds elucidated the reasons for some of the side effects.

VI. THE EFFECT OF INCREASING DOSES OF STATINS

There are a number of different statins available. These include lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin and cerivastatin. The older compounds like lovastatin are derived from fermentation while the newer class of statins such as atorvastatin are fully synthesized. Cerivastatin represents the first of the new generation of "super" statins. Just under half of the market is held by atorvastatin, about one-fourth of the market is occupied by simvastatin

and pravastatin accounts for about 10% of the market. Cerivastatin became available about two years ago, but after one year was withdrawn from the market because of a significant number of deaths due to rhabdomyolysis.

The ability of each of these statins to lower the cholesterol level is shown in Fig. 8. This figure illustrates the effect of the lowest and

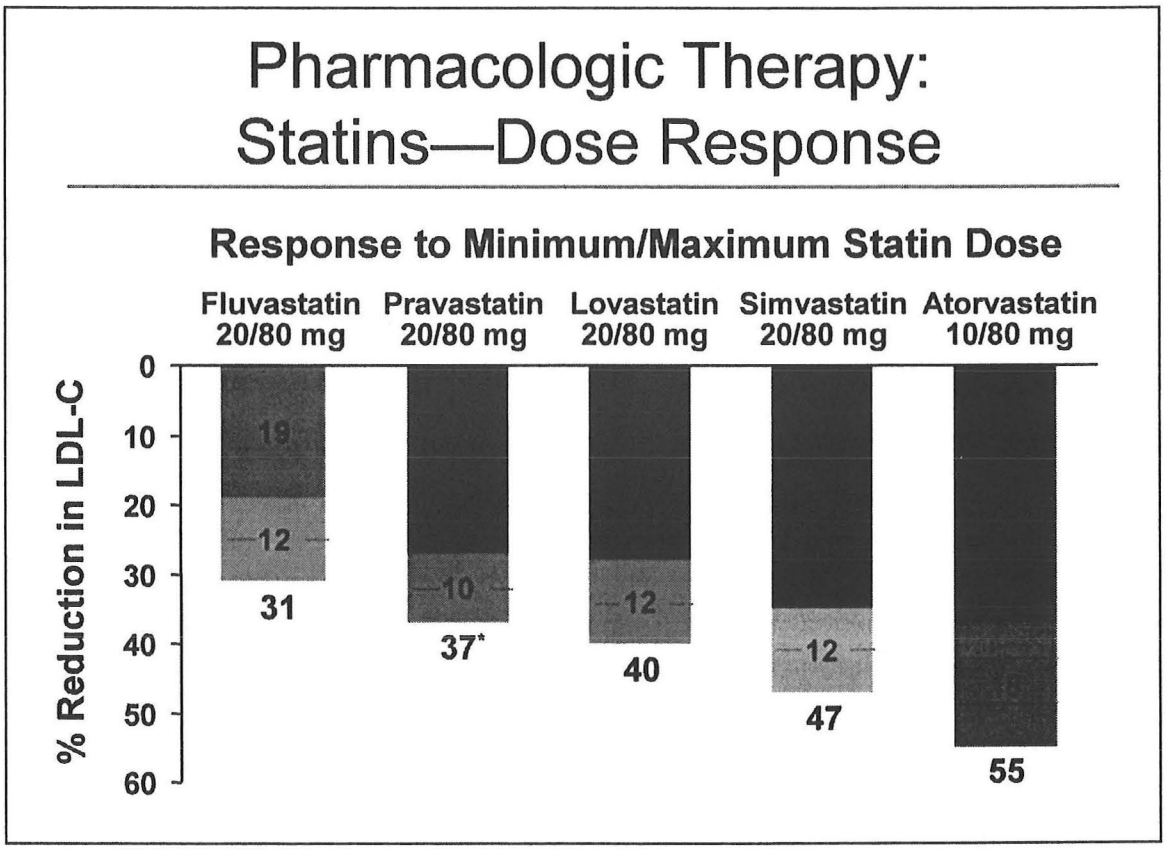

Fig. 8

highest usual dose of each of these statins. As is apparent, the two most effective statins at the lowest permissible dose is simvastatin (20 mg per day) and atorvastatin (10 mg per day). In general, doubling the dose of any of the statins leads to an additional ~6% increase in the level of LDL-C lowering. For example, with atorvastatin, doubling the dose to 20 mg, 40 mg and 80 mg per day increases the effective lowering of LDL-C levels to 43%, 49% and 55%, respectively. These increases, however, are associated with a somewhat higher incidence of abnormalities in liver function tests, elevations of the creatin kinase levels and, most seriously, rhabdomyolysis. Only recently has it become apparent how these higher doses of the statins may interact with other drugs to produce this increased incidence of side effects.

VII. THE PHARMACOLOGY OF THE STATINS

It has been very difficult to get accurate information on the actual incidence of side effects in patients on statins. There is the general impression that liver and muscle toxicity are usually seen in patients who are on very high doses of statins or on statins in combination with a variety of other drugs. It has been difficult, however, to quantitate the incidence of these side effects. In many of the controlled trials, for example, the incidence of liver function test abnormalities is approximately the same in the group of patients on placebo as those on statins. In the 51,110 patients in the controlled statin trials (CARE, LIPID, AFCAPS, 4S, etc.) there were 41 cases with elevated CK levels in the group treated with statins and 35 cases in the placebo group. Similarly, there were 7 cases of rhabdomyolysis in those treated with statin but 5 cases in the placebo groups. Despite the large number of subjects in these trials, therefore, it is difficult to get accurate data on the relatively incidence of these complications. Nevertheless, the impression persists that high doses of statins or statins administered with other drugs have a higher incidence of liver and muscle abnormalities.

Recent publications have provided new insights into the pharmacology of these compounds. Regardless of the structure of a particular statin, all of these compounds have a 7 carbon chain that represents the active site of the drug. This side chain can exist in two forms: the lactone or the open acid form (Fig. 9). Drugs like lovastatin and simvastatin are administered in the lactone form but, within the body, are actively converted to the active statin acid. It is this statin acid that circulates within the blood and is distributed to all of the cells of the body (including the brain) where it partially inhibits the rate of cholesterol synthesis. In the past, it was felt that the statin acid was then metabolized and inactivated primarily using hepatic P450 enzymes. Most of the statins were thought to be metabolized by CYP3A4, an enzyme responsible for the metabolism of a number of other drugs. Fluvostatin is apparently uniquely different in that it is metabolized by CYP2C9. When the first of the "super" statins, cerivastatin, was introduced, it was felt that it would be not only more effective in lowering the plasma LDL-C concentration but would also be safer. This assumption was based on the observation that unlike

the other statins it appeared to be metabolized by two members of the P450 system, CYP3A4 and CYP2C8. It was puzzling, therefore, that cerivastatin was at least 10-fold more toxic than any of the earlier statins in clinical use.

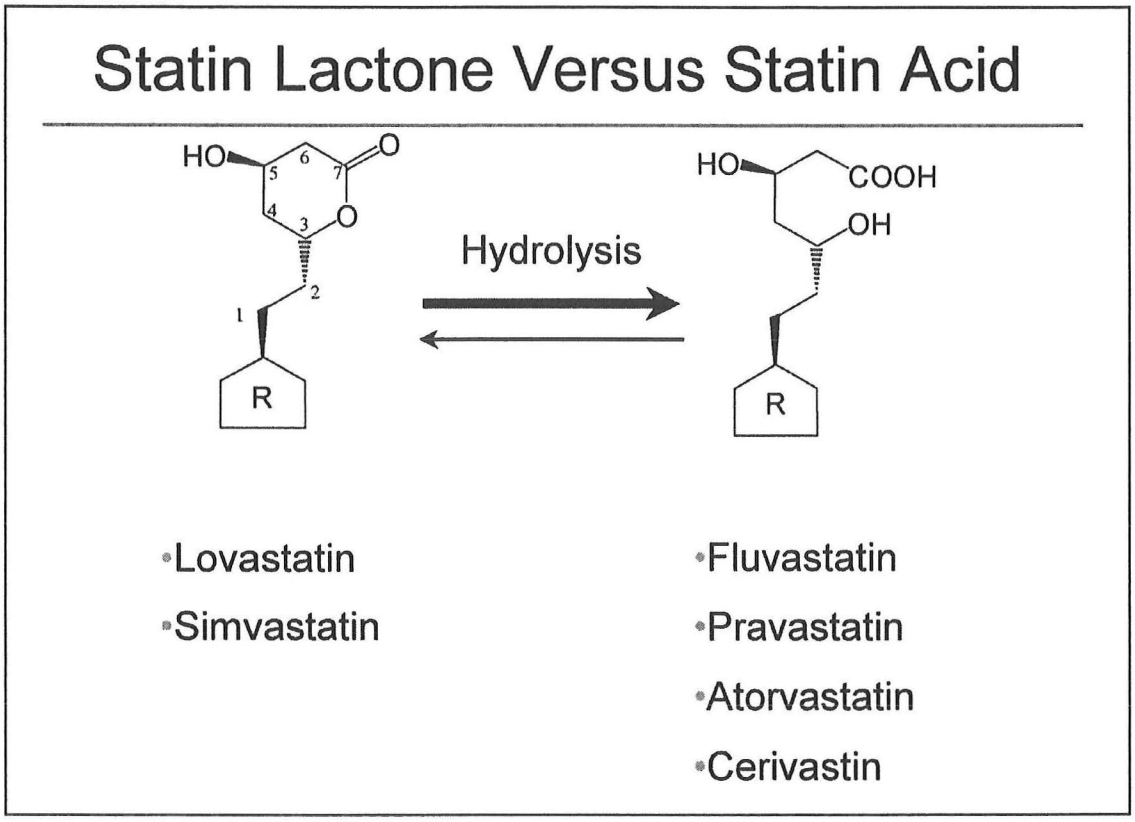

Fig. 9

Recent studies have provided a possible explanation for this finding. As outlined in Fig. 10, it is now believed that the major pathway for the oxidation and degradation of most statins involves the formation of a glucuronide. Apparently, the active statin acid circulating in the blood is glucuronidated within the liver. This glucuronide undergoes spontaneous degradation to the lactone form of the statin and this lactone, in turn, is the preferred substrate for the CYP3A4 system. Thus, any other compound that competes for this glycuronidation reaction could inhibit the degradation of the circulating statin acid. Recent data have shown that other drugs such as fibric acid derivatives are also glucuronidated and when administered with a statin will routinely increase the circulating levels of the statin acid (the area under the curve) administered at the same time. Thus, in patients receiving both cerivastatin and one of the fibrate drugs, the

concentration of the active statin acid was elevated 5- to 10-fold and this, in turn, was associated with a relatively high incidence of rhabdomyolysis. Thus, the incidence of rhabdomyolysis, while rare, is increased when high doses of any statin are used or when the statins are administered with other drugs that may interfere with glucuronidation. Because of the unusually high incidence of rhabdomyolysis with cerivastatin, this drug has been withdrawn from the market.

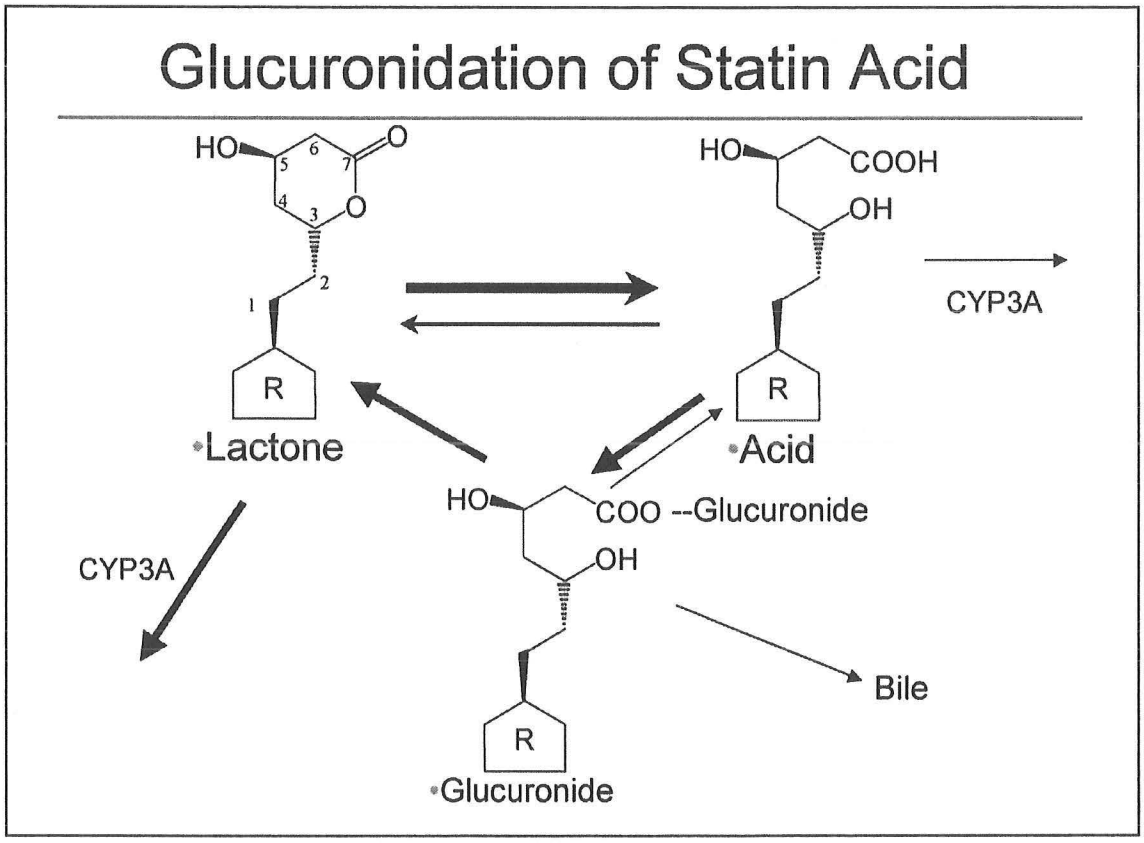

Fig. 10

VII. DRUGS INTERACTING WITH THE STATINS

Based on what is now known about the degradation of statin acids, it is clear that other drugs that are metabolized by the CYP3A4 system or that involve glucuronidation can lead to prolonged elevations of the active form of the statins in the plasma and a

somewhat elevated incidence of complications such as myositis and rhabdomyolysis. Based on event reports to the FDA, in 601 cases of rhabdomyolysis associated with statin administration, there was often co-administration of a second pharmaceutical agent. These agents included fibrates (80), cyclosporin (51), macrolide antibiotics (42), azole antifungal agents (12), antidepressants (6), protease inhibitors, calcium channel blockers, digitalis, and warfarin. It should be emphasized that in a small percentage of cases (percentage unknown), rhabdomyolysis has been reported in patients on statins alone at relatively low doses. Presumably these cases represent patients who have polymorphisms in the degradative pathways that prevent them from rapidly detoxifying the active statin acid.

In summary, as a group, the statins are relatively safe drugs that have a very low incidence of serious side effects. Significant liver function abnormalities occur in approximately 1 in 500 or 1,000 patients. Generally, this is considered to be a benign side effect that disappears with cessation of the drug. The incidence of myositis and rhabdomyolysis is much less common and probably occurs as a rate of about 1 in 10,000 patients. Most of these cases will have been on high doses of statins or will have been placed on a statin in combination with a second drug that interferes with degradation. Very rarely, rhabdomyolysis can occur in patients on low doses of a statin administered alone.

VIII. A NEW CLASS OF DRUGS FOR LOWERING LDL-C CONCENTRATIONS

There is clearly a need for new pharmaceutical agents that can lower the plasma LDL-C level to values that would significantly lower the incidence of CAD (Fig. 6). While using higher doses of the existing statins or, possibly, with the introduction of "super" statins, this need for more powerful agents can be partially met. However, as just outlined, these manipulations are associated with a higher rate of complications, particularly myositis and rhabdomyolysis. Fortunately, a new class of drugs is about to be introduced that act through a different mechanism and so complement the effects of statins in lowering the plasma LDL-C level.

In general, statins act by partially inhibiting cholesterol synthesis in the liver and various extrahepatic compartments (including the brain). Since all of this newly synthesized cholesterol must eventually pass through the hepatocyte, the liver senses a "deficit" in cholesterol, less sterol is secreted into the plasma in very low density lipoproteins, and there is an increase in LDL receptor activity. Consequently, the steady-state concentration of LDL-C in the plasma diminishes. Essentially, the same series of events can be initiated by any pharmaceutical agent that increases the excretion of sterol from the liver. Cholesterol is excreted from the body either as cholesterol itself or after conversion to bile acids. Both cholesterol and bile acids that reach the intestinal lumen are partially reabsorbed. Pharmaceutical agents that interfer with this enterohepatic circulation will cause an excessive excretion of sterols in the feces, the liver will again sense a deficit, and the LDL-C concentration will decrease.

There is a limit, however, to the effectiveness of both statins and agents that interfere with the enterohepatic circulation of cholesterol or bile acids. As illustrated in Fig. 11, for example, when agents that

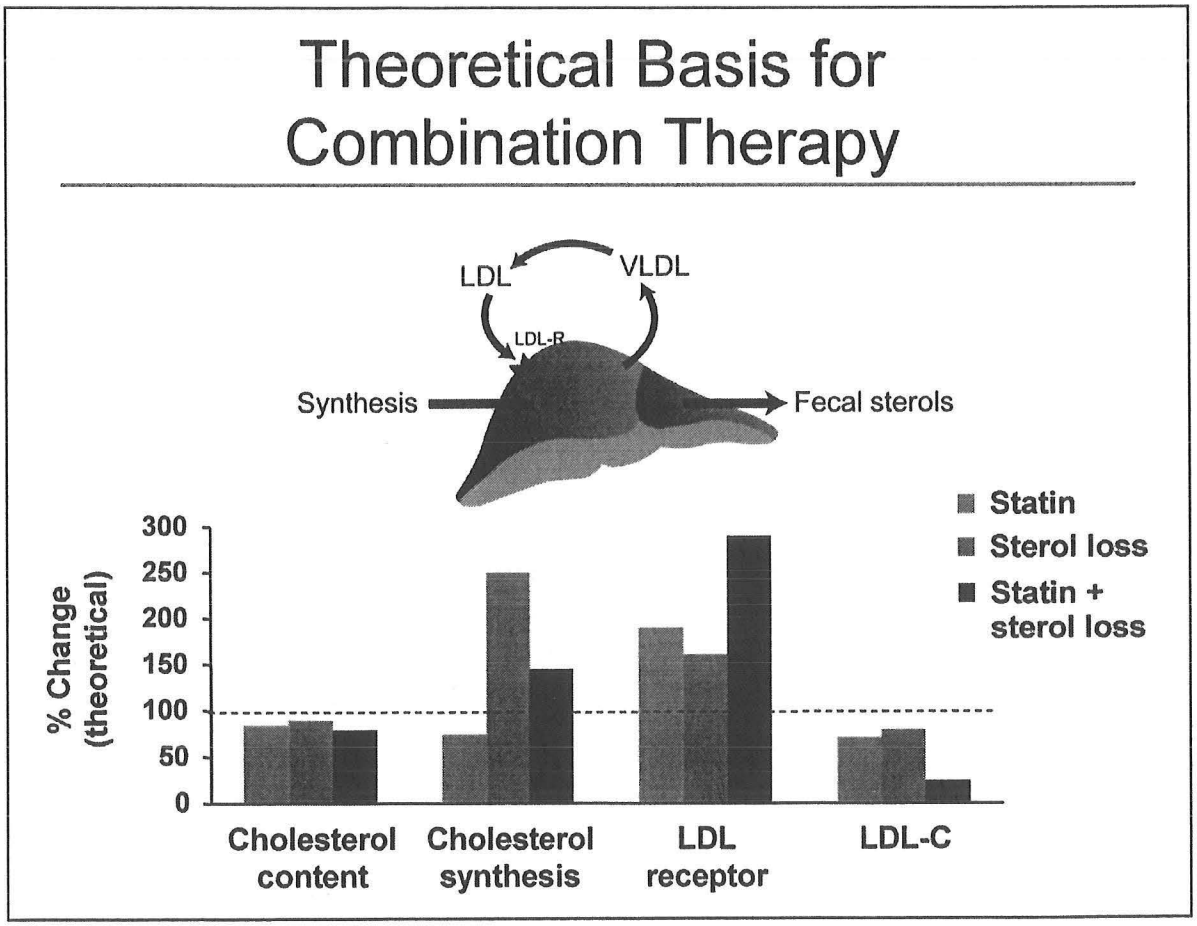

Fig. 11

block cholesterol or bile acid reabsorption are given to a patient, there is a modest reduction in the plasma LDL-C concentration. The effectiveness of such agents, however, is limited because the liver immediately responds to excessive sterol loss from the body with a marked increase in cholesterol synthesis. In theory, however, if this adaptive response in hepatic cholesterol synthesis was partially blunted by the simultaneous administration of a statin, the effect on the plasma cholesterol concentration might be much greater. Indeed, using older agents, it has clearly been demonstrated in both experimental animals and in humans that such combined therapy is much more effective in inducing a greater net negative balance of sterol across the liver and a proportionately greater reduction in the circulating LDL-C concentration.

Unfortunately, in the past, only a limited number of agents have been available to interfer with the enterohepatic circulation of sterols. Older agents such as cholestyramine, and newer compounds such as colestipol and colesevelam, can effectively block the reabsorptiion of bile acids. The combination of these sequestrants with statins results in a greater reduction in the plasma cholesterol concentration. The newest agents to block cholesterol enterohepatic circulation have included dietary stanol esters and sterol esters. Unfortunately, all of these various substances must be given in very large quantities (grams per day) to effectively interfere with either bile acids or cholesterol absorption. Attempts to specifically block cholesterol absorption across the intestinal epithelial cell have largely failed. For example, compounds have been developed that interfere with the formation of the chylomicron (MTP inhibitors) or block the esterification of cholesterol to cholesteryl ester (ACAT inhibitors). Unfortunately, none of these inhibititors has been successfully developed into an acceptable pharmaceutical agent.

This situation changed with the identification of a new compound that apparently blocks the uptake of lumenal cholesterol into the intestinal epithelial cell. Presumably, it acts on some type of sterol transporter, but this transporter has not yet been identified. The structure of this compound, ezetimibe, is shown in Fig. 12. This molecule has a relatively simple chemical structure that can undergo glucuronidation within the body. Both the parent compound and the glucuronide are active in blocking cholesterol absorption.

Ezetimibe has a rather unique enterohepatic circulation. When the parent compound is administered to an animal or human, the

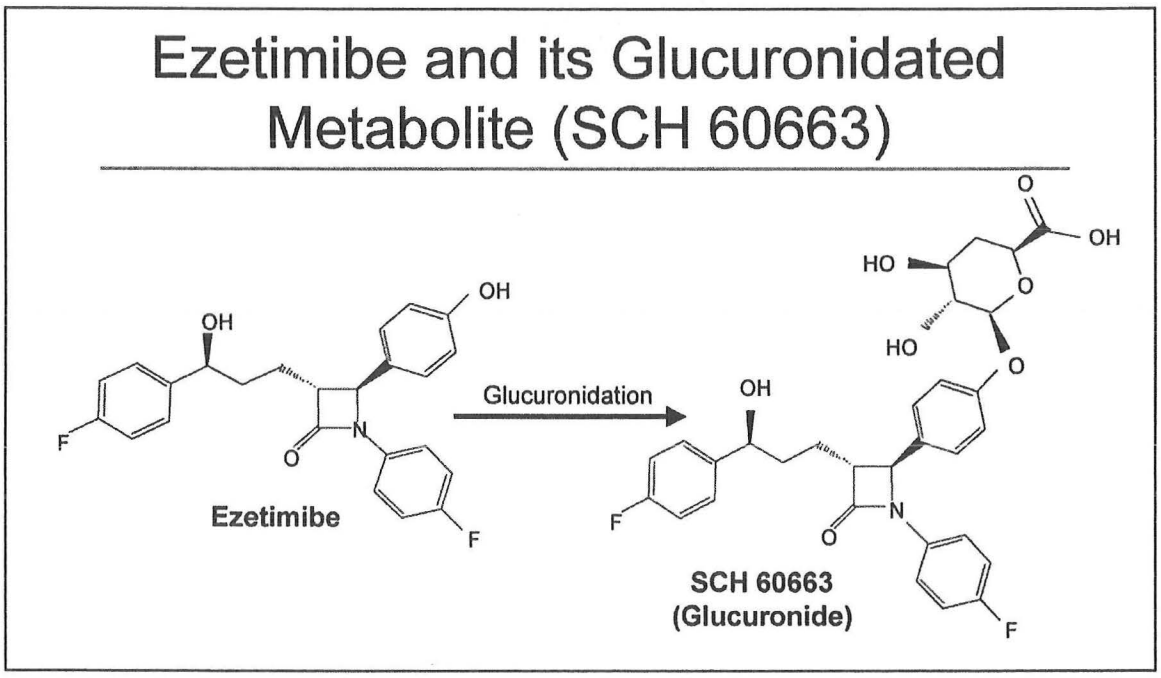

Fig. 12

ezetimibe binds to the brush border of the intestinal epithelial cell and partially blocks the uptake of cholesterol from the intestinal lumen. Part of this pharmaceutical agent is itself absorbed into the intestinal cell and glucuronidated. The ezetimibe glucuronide is then carried to the liver and immediately re-excreted into the bile where it binds again to the intestinal brush border. The ezetimibe-glucuronide is 3-4 times more potent in blocking cholesterol uptake than is the parent compound. Because of this unique pharmacology, the doses required for blocking sterol absorption are very low (5-20 mg/day), the half life for the effectiveness of the drug is very long (about 24 hours), and the exposure of the body to the active drug is very limited (only the intestine, liver and kidney). As a result of these characteristics, a single dose of 10 mg of ezetimibe apparently is effective for 24 hours and is associated with virtually no toxicity.

There appears to also be no interaction between ezetimibe and statins. As has been outlined above, when a statin is administered with a drug such as a fibrate, the concentration of the active statin acid is increased and its turnover is prolonged (the area under the curve). However, when a statin is administered with ezetimibe, there is no change in the area under the curve. This is apparently true because statins are glucuronidated in the liver while ezetimibe is glucuronidated in the intestinal epithelial cell.

When administered alone ezetimibe results in an 18-20% reduction in the circulating plasma cholesterol concentration. This same 18-20% reduction is added on top of the effect of a statin when these two compounds are administered together. This effect is seen in

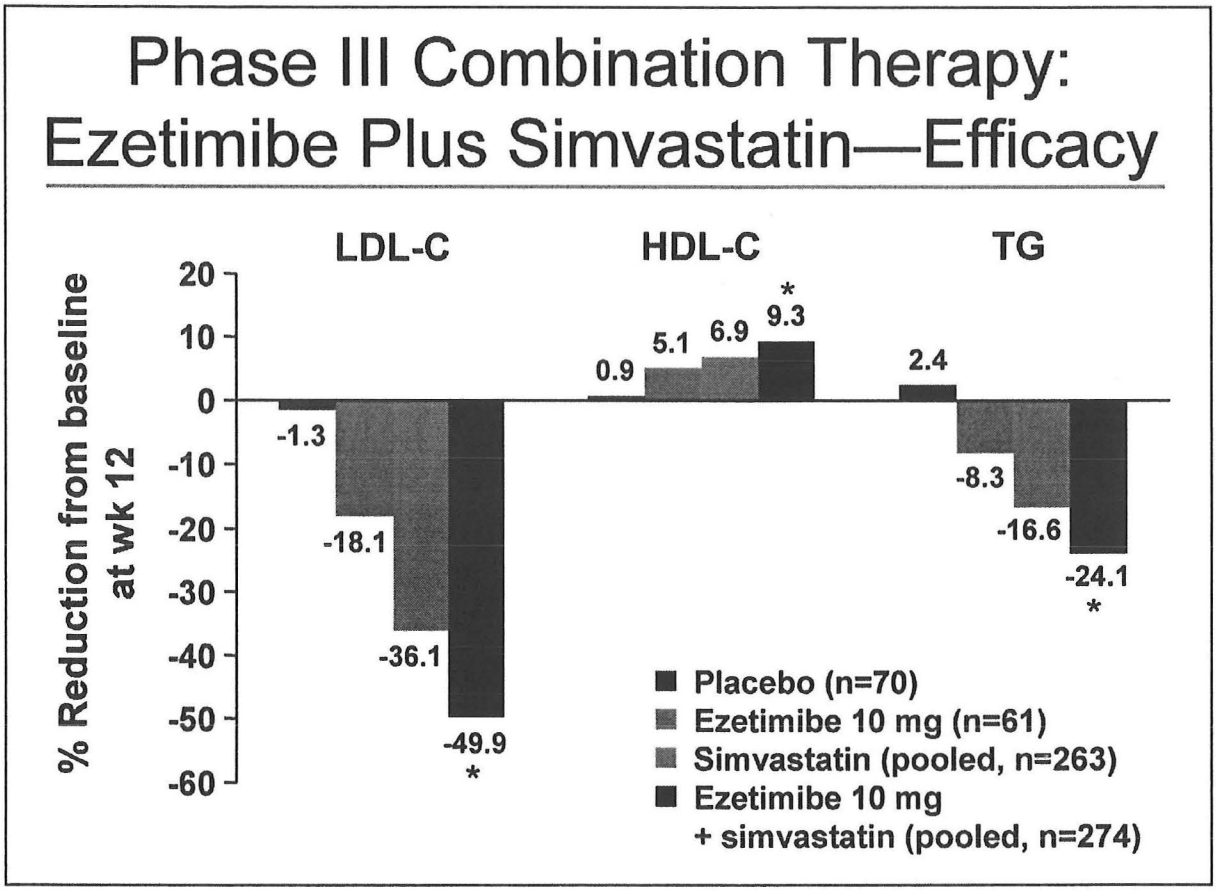

Fig. 13

Fig. 13 where a low dose of simvastatin resulted in a 35% reduction in the LDL-C level while the combination of simvastatin and ezetimibe resulted in a 50% reduction in the serum cholesterol concentration. This additive effect is seen when ezetimibe is given in conjunction with any of the commonly used statins.

Thus, the usefulness of this new class of compounds seems to be that it will add an additional 18-20% reduction in the plasma LDL-C concentration when added to any dose of a statin and, in addition, this extra effectiveness is gained without an apparent increase in toxicity. Thus, for example, the use of a combination of a low dose of statin and a low dose of ezetimibe can routinely give 50% reductions in the plasma LDL-C with no increase in side effects.

It should be emphasized that this new class of compounds has not yet been approved by the FDA, but approval is anticipated within the next few months. While ezetimibe appears to be free of serious side effects, this new compound has been given to only a few thousand patients for a few years. Exactly how this drug will be administered and how it will be formulated in combination with statins remains to be worked out by the pharmaceutical company and the FDA. Nevertheless, ezetimibe represents a very interesting new class of compounds for the lowering of plasma cholesterol levels that, in conjunction with statins, may provide the physician with additional help in lowering the LDL-C levels down to desired levels.

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