Medical Grand Rounds

ELIMINATION OF CORONARY HEART DISEASE:

THE SEQUEL!

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Formulas for Calculating the Theoretical Risk of Developing Coronary Artery Disease in Women

(These calculations do not take into consideration family history, physical activity, fibrinogen levels or LVH.)

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-9	[-9]
35-39	-4	[-4]
40-44	0	[0]
45-49	3	[3]
50-54	6	[6]
55-59	7	[7]
60-64	8	[8]
65-69	8	[8]
70-74	8	[8]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-2
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	2
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-2]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[1]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	5	[5]
35-44	0.91-1.16	2	[2]
45-49	1.17-1.29	1	[1]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-2	[-3]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	-3 [-3] pts				
120-129		0 [0] pts			
130-139			0 [0] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

+ Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	4	[4]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
≤-2	1%	[≤-2]	[1%]
-1	2%	[-1]	[2%]
0	2%	[0]	[2%]
1	2%	[1]	[2%]
2	3%	[2]	[3%]
3	3%	[3]	[3%]
4	4%	[4]	[4%]
5	5%	[5]	[4%]
6	6%	[6]	[5%]
7	7%	[7]	[6%]
8	8%	[8]	[7%]
9	9%	[9]	[8%]
10	11%	[10]	[10%]
11	13%	[11]	[11%]
12	15%	[12]	[13%]
13	17%	[13]	[15%]
14	20%	[14]	[18%]
15	24%	[15]	[20%]
16	27%	[16]	[24%]
≥17	≥32%	[≥17]	[≥27%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	<1%	<1%	<1%
35-39	<1%	<1%	1%
40-44	2%	1%	2%
45-49	5%	2%	3%
50-54	8%	3%	5%
55-59	12%	7%	7%
60-64	12%	8%	8%
65-69	13%	8%	8%
70-74	14%	11%	8%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

CHD score sheet for women using TC or LDL-C categories. Uses age, TC, HDL-C, blood pressure, diabetes, and smoking. Estimates risk for CHD over a period of 10 years based on Framingham experience in women 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC 160 to 199 mg/dL (or LDL 100 to 129 mg/dL), HDL-C of 55 mg/dL in women, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts indicates points.

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Formulas for Calculating the Theoretical Risk of Developing Coronary Artery Disease in Men

(These calculations do not take into consideration family history, physical activity, fibrinogen levels or LVH.)

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-1	[-1]
35-39	0	[0]
40-44	1	[1]
45-49	2	[2]
50-54	3	[3]
55-59	4	[4]
60-64	5	[5]
65-69	6	[6]
70-74	7	[7]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-1	[-2]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	0 [0] pts				
120-129		0 [0] pts			
130-139			1 [1] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
<-3	1%		
-2	2%		
-1	2%	[<-1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥14	≥56%	[≥14]	[≥53%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

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** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

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I. INTRODUCTION

Atherosclerosis is a disease that begins in childhood but becomes clinically manifest largely during and beyond the fifth decade of life. The complications of atherosclerosis, including myocardial infarction and thrombotic stroke, are most common in those human populations that have attained long life expectancies and diets that are rich in triacylglycerol. Since both of these events occurred only during this century, diseases of atherosclerosis are a relatively modern development in human evolution. Over the last 40,000 years, the duration of life expectancy remained remarkably constant at approximately 35-40 years. Only at the beginning of this century when it became possible to control infant and childhood mortality and some infectious diseases did life expectancy begin to increase sharply. By early in the next century it is anticipated that life expectancy will exceed 80 years in many parts of the world, including Japan, many countries in Western Europe, the United States and Canada. However, there are areas of Russia and countries in the former Eastern European bloc where life expectancies are actually decreasing. In many of these countries the incidence of coronary artery disease is dramatically increasing and has been described by some public health officials as an "epidemic." During the past 15 years a new group of pharmaceutical agents has been introduced (collectively referred to as "statins") that markedly reduce circulating plasma cholesterol levels, and these agents have now been shown in a number of major clinical trials to significantly reduce the incidence of atherosclerotic disease including coronary artery disease and thrombotic stroke.

II. IDENTIFICATION OF THOSE INDIVIDUALS WHO ARE AT RISK

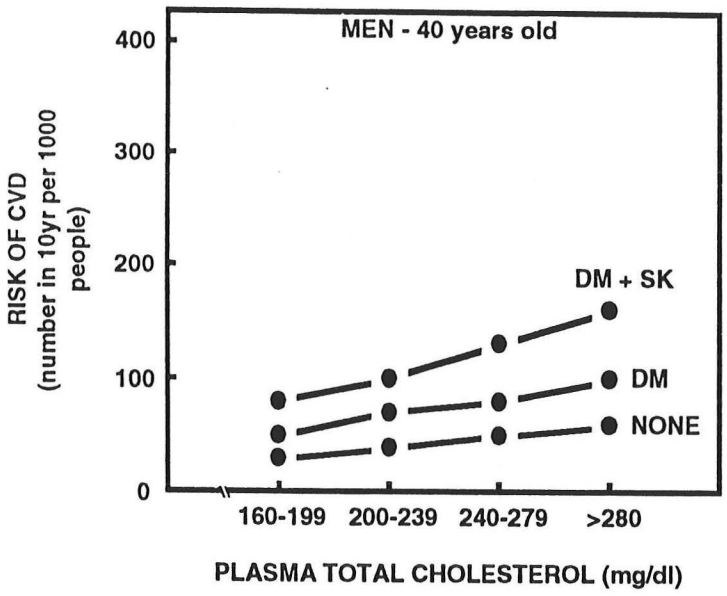
As shown in Fig. 1, 2.3 million Americans will die this year. Approximately 180 individuals will be killed in natural disasters including hurricanes, tornadoes and lightning. Twenty-two thousand individuals will die as the result of homicide and police actions. Thirty-nine thousand will die with AIDS, and 42,000 will die as a result of motor vehicle accidents. In contrast to all of these causes, 740,000 individuals will die from coronary heart disease. Additional significant numbers of individuals will die as the result of other complications of atherosclerosis including individuals who develop strokes, mesenteric vascular infarction and peripheral limb gangrene. Thus, although

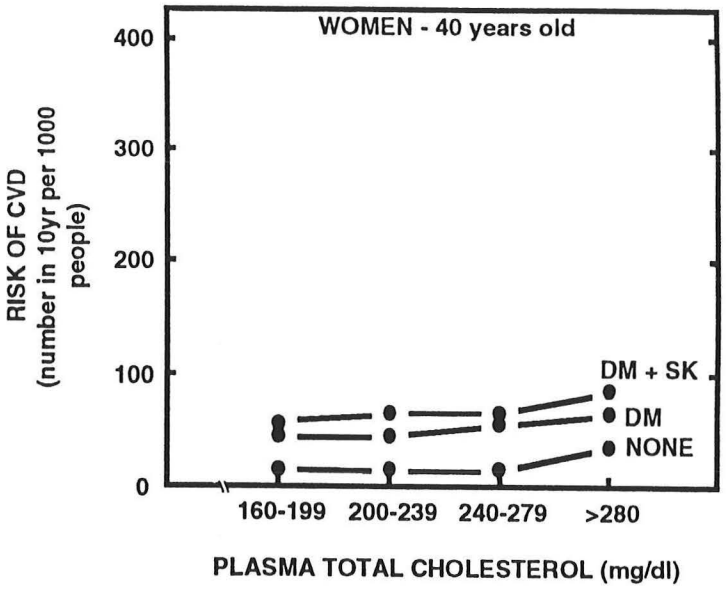
the incidence has been decreasing slowly over the past two decades, atherosclerosis and cardiovascular disease remain one of the leading causes of death in the country.

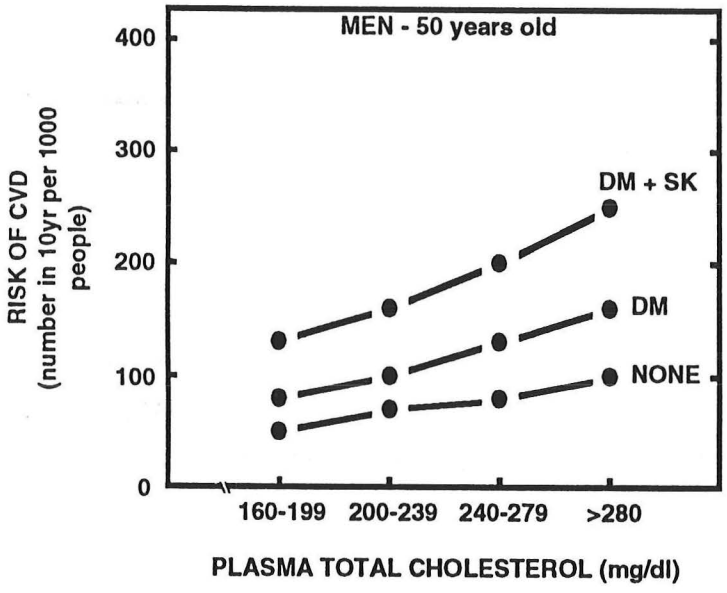
While virtually all of the American population has some degree of atherosclerosis, it is very important to try to identify those subgroups of individuals who are particularly at risk with respect to the development of coronary heart disease (CHD). Fortunately, data from the Framingham Heart Study have recently been reanalyzed, and a new set of equations have been published (see reference XIII-1) that allows one to estimate the relative risk of heart disease based upon a number of variables. In this protocol the means for calculating the theoretical risk of developing CAD in women is shown on page 2 while the formulas for men are given on page 3. These formulas are derived from a statistical analysis of >5,000 men and women followed since approximately 1970. The calculation of the theoretical risk of CAD is based upon a number of variables including age, plasma total cholesterol concentration, the concentration of cholesterol carried in low density lipoprotein (LDL-C), the concentration of cholesterol carried in high density lipoprotein (HDL-C), blood pressure, the presence or absence of diabetes and whether the individual smokes. It should be emphasized that other important risk factors have not been included in these predictive models since complete data were not available in the studies. For example, a family history of premature CHD is not included even though such a history increases risk by approximately 30%. Similarly, factors such as fibrinogen levels, the presence of left ventricular hypertrophy, the level of physical activity and whether or not a woman was on post-menopausal estrogen replacement therapy are not taken into consideration in these calculations. Nevertheless, these formulas do illustrate the relative importance of these different factors in predicting the incidence of CHD in the American population.

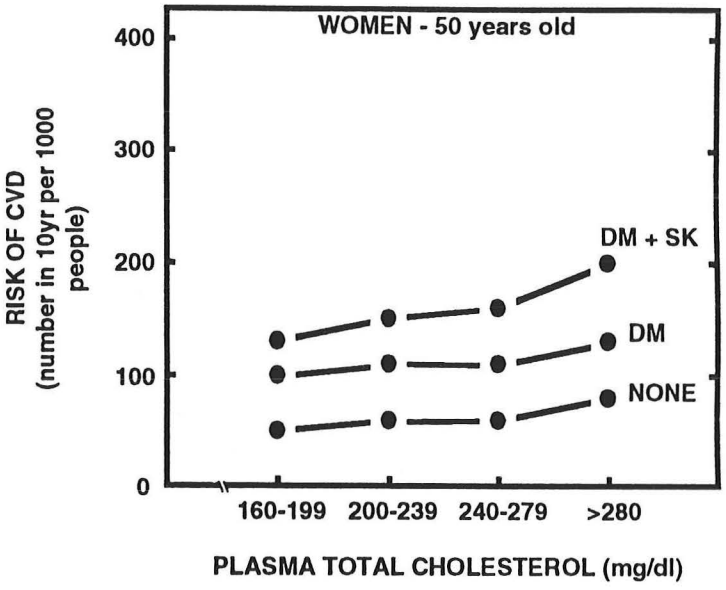
For illustrative purposes the six graphs shown in Table I illustrate the number of individuals that will develop CHD in 10 years per 1000 individuals. This risk is calculated in terms of men and women who are 40, 50 or 60 years of age who have no hypertension and HDL-C concentrations of 45-59 mg/dl but who may have diabetes (DM) and may be smokers (SK). As is apparent in the three left panels, age is a major risk factor in men as is the presence of diabetes and

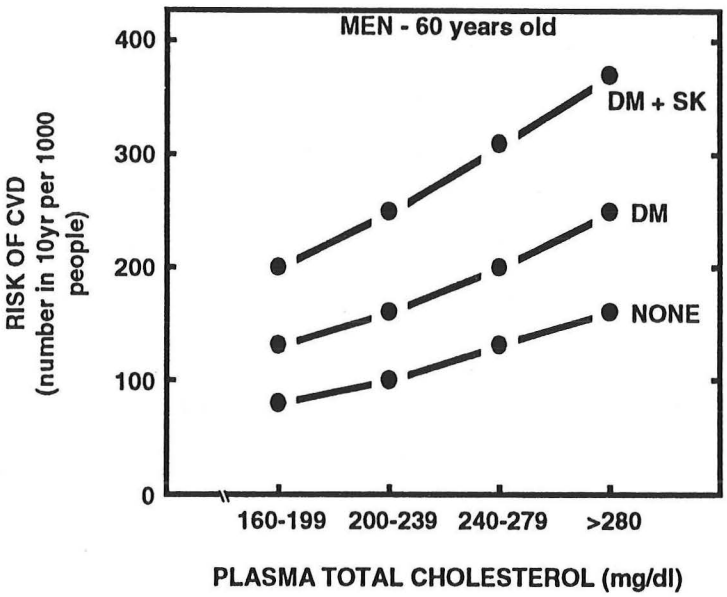
Table I. Risks of CHD in Men and Women

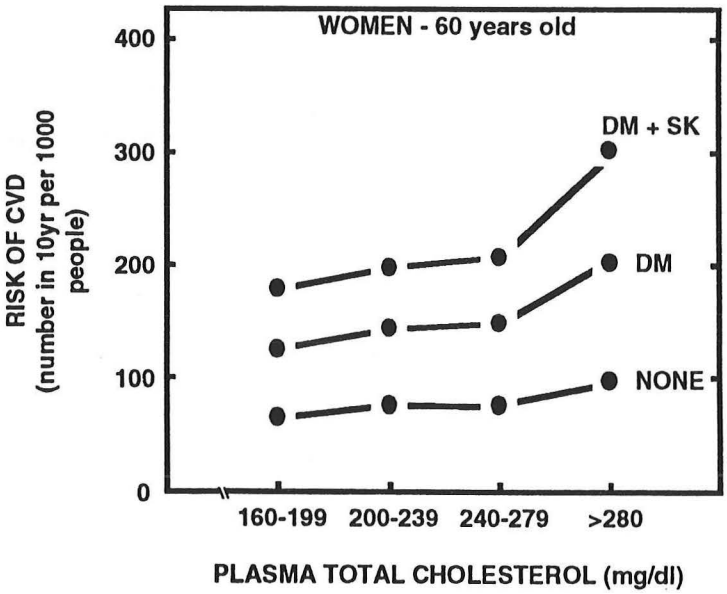












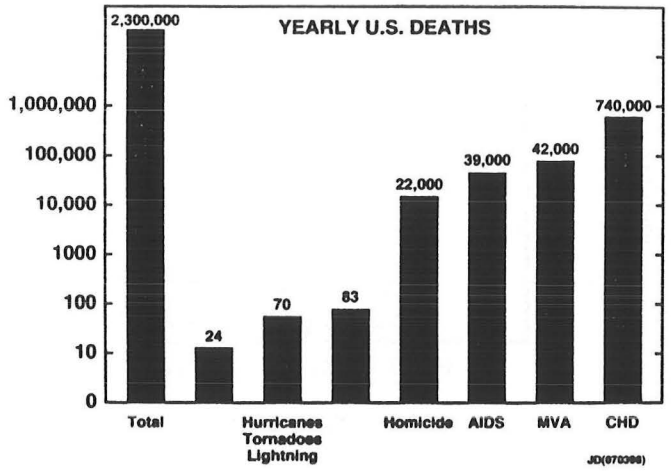


Fig. 1

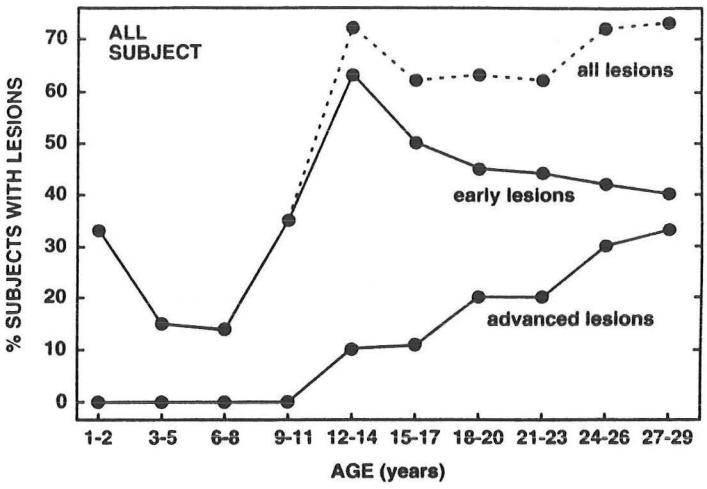


Fig. 2

smoking. The risk of CHD is considerably lower in women at 40 years of age (right panels), but this risk increases considerably after menopause in 50-year-old women. While not illustrated in Table I, it should be emphasized that the presence of a family history of early CHD, hypertension or a very low HDL-C concentration would further elevate the risk at any age, in either men or women. The specific risk in a given individual can be calculated from the formulas given on pages 2 and 3.

III. THE RELATIONSHIP OF THE ATHEROMA TO THE ACUTE EVENT

Atherosclerosis results when the endothelial lining of arteries is exposed for a prolonged period of time to circulating lipoproteins that contain apolipoprotein B. These lipoproteins include low density lipoprotein (LDL), very low density lipoproteins (VLDL) and the remnant particles that are derived from VLDL and chylomicrons. Of this variety of particles, LDL is by far the most important and carries the great majority of cholesterol found in the plasma of humans. The biology of atheroma formation is now relatively well understood and is summarized in several of the references in this protocol. Briefly, however, the apoB containing lipoproteins are apparently taken up across the endothelial lining, recruit monocytes, bring about smooth muscle cell proliferation and cause the accumulation of lipid droplets in the subendothelial region. There is necrosis of cells in this region and deposition of cholesterol crystals that may lead to a soft, mechanically unstable structure that can rupture under the stress of blood flow.

Most acute myocardial infarctions occur in individuals that have minimal to moderate size plaques. The most dangerous atheromatous plaque seems to be the one with a semi-liquid necrotic center. In approximately 75% of acute myocardial infarctions, the cause appears to be disruption of the fibrous cap of the atheroma followed by platelet recruitment and acute thrombosis (see reference II-5). From these very brief considerations it is apparent that control of the incidence of atherosclerotic disease requires information on the natural history of this disease and the causes of the hypercholesterolemia seen in Western civilizations. In addition, it is clear that pharmaceutical agents that successfully prevent CHD must stop the progression of lipid deposition in the atheroma, stabilize the fibrous covering of the plaque and interfere with platelet recruitment and thrombosis.

IV. NATURAL HISTORY OF ATHEROSCLEROSIS

In the past, atherosclerosis was considered to be a disease of the elderly. This concept was clearly proven wrong in the classic studies of Enos et al (reference IV-1) who performed autopsies on 300 American soldiers (average age 22 years) who were killed in the Korean War in 1951-1953. Seventy-seven percent of these young men already had significant coronary artery disease. This observation was confirmed in young men (average age 24 years old) killed in Vietnam where 45% had coronary artery diseases and 26% had more than one coronary vessel involved. Much more detailed studies on the natural history of these lesions became available from detailed investigations of coronary artery morphology in children and young adults who died acutely from trauma (reference IV-4). In these studies the early lesions of sub-endothelial lipid infiltration were seen in approximately 35% of children 1-2 years of age (Fig. 2). These lesions were seen in essentially half of the children by the age of 12-14 years. By the age of 9-11 years, advanced, more raised lesions were evident in the coronary arteries, and these advanced lesions progressively increased over the next two decades. By the age of 30 years, approximately 70% of these individuals had early or advanced coronary atheromatous lesions. Clearly these very detailed studies confirmed the earlier observations in the young men killed during the Korean and Vietnam Wars. Finally, in these children the area of the endothelial lining that was involved in this early lipid deposition was essentially a linear function of the plasma LDL-C concentration between the levels of 40 mg/dl and 140

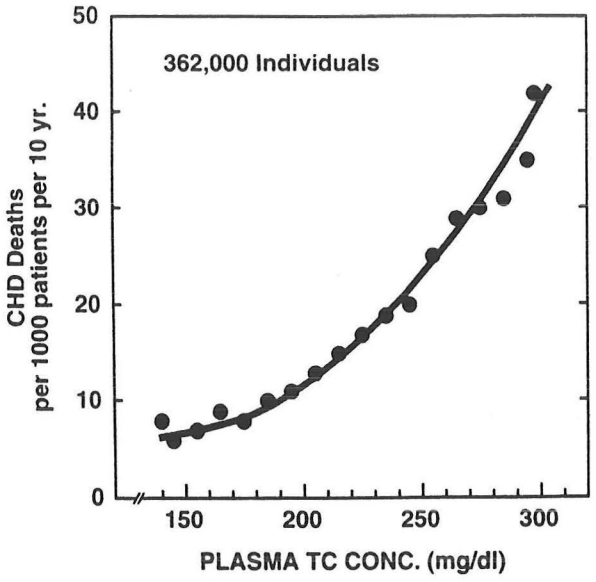


Fig. 3

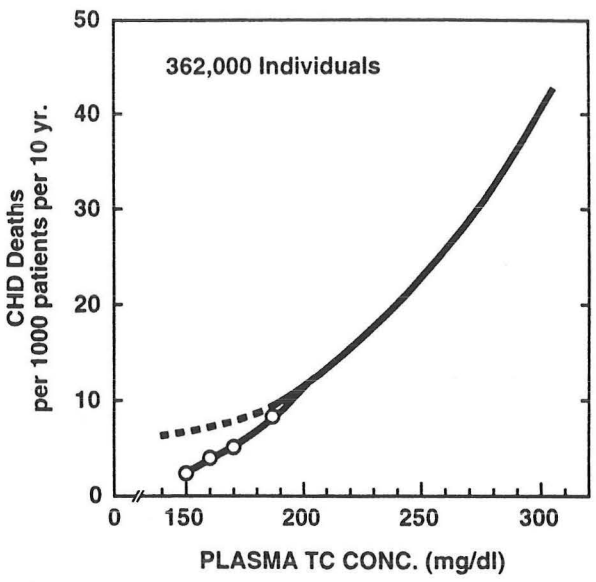


Fig. 4

mg/dl. Clearly, atherosclerosis is a disease that begins in infancy and childhood, that progresses throughout middle age and that becomes clinically evident in the fifth, sixth and seventh decades of life.

V. WHAT IS A "NORMAL" PLASMA CHOLESTEROL CONCENTRATION?

There is little doubt that the development these atherosclerotic lesions is very dependent upon the concentration of apoB-containing lipoproteins, in general, and LDL-C concentration, in particular. As shown in Fig. 3, for example, there is a clear relationship between death due to CHD and the plasma total cholesterol concentration between approximately 150-300 mg/dl. These early data suggested that there might be a "threshold" at about 200 mg/dl below which the relationship between the plasma cholesterol concentration and cardiovascular disease became less obvious. However, a much more recent study investigated this relationship in urban Chinese, a group of individuals who traditionally have very low plasma cholesterol levels and incidence of atherosclerotic disease. These studies unequivocally showed that there was no "threshold" effect and that the relative risk of CHD continued to decrease linearly as the mean total plasma cholesterol concentration was reduced from about 180 to 140 mg/dl. The absolute incidence of CHD deaths in this urban Chinese group is replotted in Fig. 4. Clearly there is essentially a linear relationship between the incidence of CHD deaths in a population and the plasma total cholesterol concentration. These data predict that at a plasma total cholesterol concentration of <150 mg/dl, there would

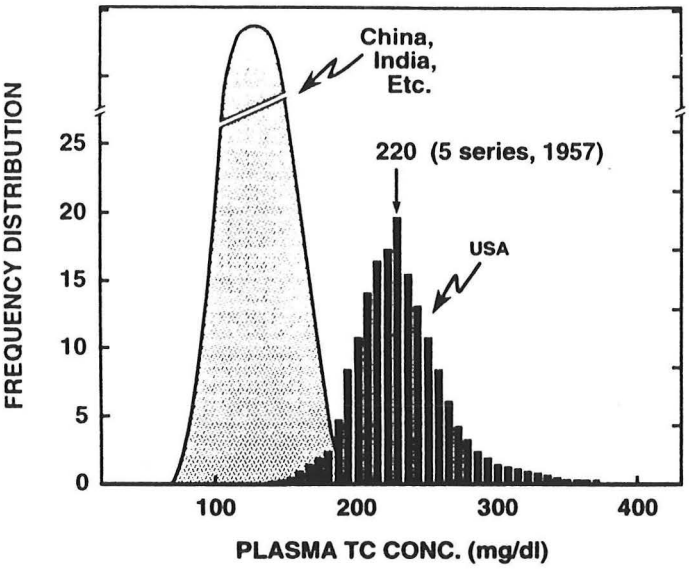


Fig. 5

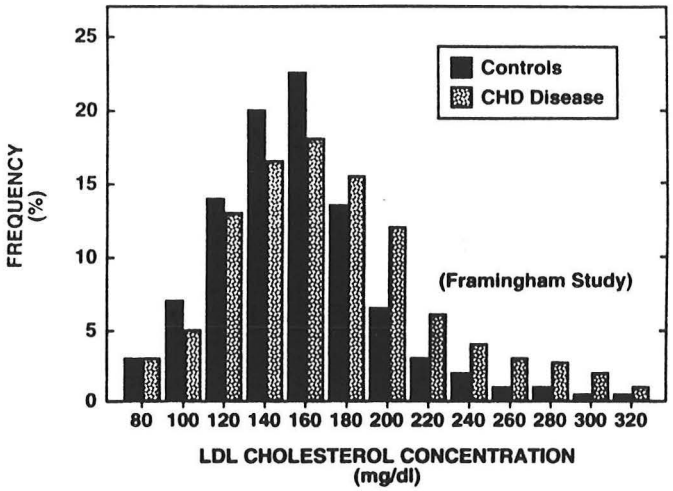


Fig. 6

be no coronary artery disease. This finding is consistent with earlier publications that in populations like the Tarahumara and Yandapu-enga that traditionally have plasma cholesterol levels in the range of 150 mg/dl (LDL-C ~70-80 mg/dl) also have essentially no coronary artery disease. Thus it is now clear that most Americans (and Europeans) have plasma cholesterol levels that are very much higher than the rest of the world and these elevated plasma cholesterol levels are associated with a high incidence of coronary artery disease. This difference is emphasized in Fig. 5 which shows the frequency distribution of the plasma cholesterol concentration in the USA relative to the distribution in other major populations such as the Chinese. The data in Fig. 6 show the frequency distribution of the LDL concentration and the frequency distribution of clinical CHD disease. Thus, several major conclusions can be drawn from these data. 1) 90% of Americans have plasma total cholesterol concentrations that are greater than 180 mg/dl. 2) CHD essentially does not occur in populations with plasma total cholesterol concentrations below 180 mg/dl. 3) In the United States, virtually all CHD disease occurs in patients with a plasma total cholesterol concentration >180 mg/dl (LDL-C concentration > 80 mg/dl).

VI. WHY MOST OF THE U.S. POPULATION IS HYPERCHOLESTEROLEMIC

A considerable amount of new information is now available concerning the regulation of plasma cholesterol levels and, particularly, the concentration of LDL-C levels. The steady-state concentration of LDL-C is determined primarily by

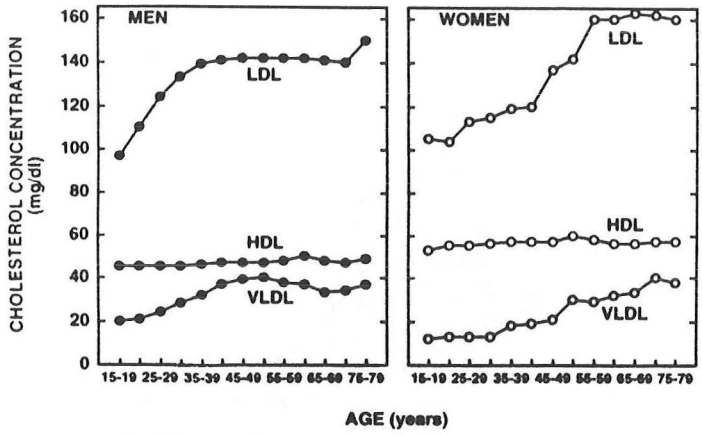


Fig. 7

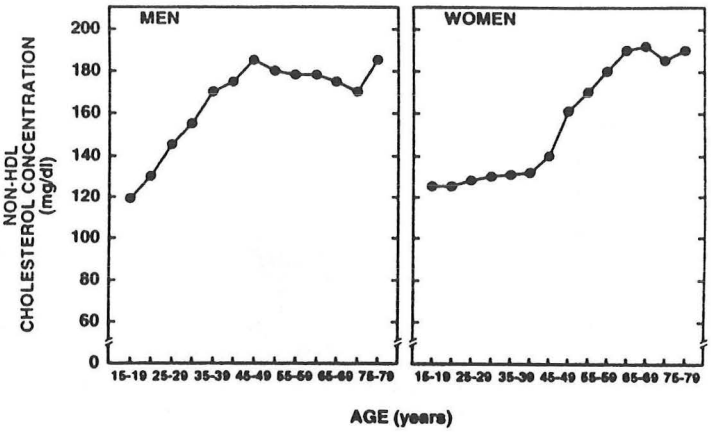


Fig. 8

the rate at which LDL-C is formed from VLDL (the LDL-C production rate). The level of LDL receptors in the liver also plays a role in determining this steady state. In the primate, in general, and in the human, in particular, the concentration of LDL-C is essentially a linear function of the LDL-C production rate. When small amounts of cholesterol are added to the diet (in humans this is typically 300-500 mg/day) there is a small increase in the LDL-C production rate and a small suppression of LDL receptor activity. Consequently there is a small increase in the plasma LDL-C level. However, when large quantities of triacylglycerol are added to the diet (typically 100 g in humans) there is a much greater increase in the LDL-C production rate and greater suppression of LDL receptor activity. As a consequence, there is a very marked rise in the plasma LDL-C concentration. For example, in the newborn human infant the plasma LDL-C concentration is approximately 25 mg/dl. The nursing infant, however, receives a very large amount of cholesterol and triacylglycerol in mother's milk, and the plasma LDL-C concentration promptly rises to about 90 mg/dl. As the young child is weaned to the typical American diet where approximately 40% of calories is derived from lipid, the plasma LDL-C continues to rise slowly throughout life. Thus, such data suggest that the high plasma cholesterol concentrations seen in Americans are purely environmental. This conclusion is supported by a number of other observations. Immigrants to the United States who come from areas where the plasma cholesterol is typically low have

significant increases in their plasma cholesterol levels as they are assimilated into the American culture. When the Tarahumara, who typically derive 75% of their calories from carbohydrates and have plasma LDL-C concentrations of ~70 mg/dl, are placed on American diets, within two weeks they raise their LDL-C concentrations 40%. Finally, in American cities like San Antonio, individuals of three different racial groups (Caucasoid, Negroid and Amerind) all have essentially the same high plasma cholesterol levels, and all have the same incidence of coronary artery disease. Thus, there seems to be little genetic influence on the mean plasma cholesterol levels of any ethnic groups: rather, these levels are primarily determined by the American diet.

As a consequence of this diet which generally is excessive with respect to caloric intake and, particularly, triacylglycerol intake, there is a progressive rise in the apoB-containing lipoprotein fractions throughout life. These changes are illustrated in Figs. 7 and 8. In both men and women, the concentration of HDL-C remains relatively constant throughout life (Fig. 7). However, there is an age-dependent increase in both LDL and VLDL concentrations in men and an abrupt increase in these fractions in women at menopause. As a consequence, the concentration of cholesterol in the atherogenic non-HDL lipoprotein fractions (Fig. 8) rise from ~120 mg/dl to over 180 mg/dl in older individuals. This rise is gradual in men but more abrupt in women at the time of menopause. It should again be emphasized that the concentration of non-HDL cholesterol in most of the rest of the world is <120 mg/dl.

VII. CONTROL OF PLASMA LDL-C CONCENTRATIONS

Much is now known about the regulation of the concentration of LDL-C in the steady state, and it is recognized that it is the interaction of dietary cholesterol and dietary triacylglycerol that are the major determinants of these steady-state levels. The liver synthesizes the VLDL particle and the function of this particle is apparently to move triacylglycerol from the liver to the peripheral sites of utilization. However, the remnants of the VLDL particle, and the LDL that is also formed from this structure, are removed from the plasma primarily by LDL receptors that are located on the liver. Thus, in theory, the LDL-C concentration of the plasma would be elevated by events which caused an increase in the rate of cholesterol secretion from the liver in VLDL and/or any event which reduced the

activity of LDL receptors in the liver. In most non-Western populations there is relatively little cholesterol and triacylglycerol in the diet. As a consequence, the average LDL-C concentration is in the range of 70-80 mg/dl. When small amounts of cholesterol are added to the diet, this sterol is delivered to the liver carried in chylomicrons. There it interacts with an enzyme, ACAT, and becomes distributed between a pool of unesterified cholesterol and a pool of cholesteryl esters. As the pool of unesterified cholesterol is expanded, formation of the transcriptionally active form of sterol regulatory element binding protein (SREBP) is suppressed and less LDL receptor is formed. In addition, an increased amount of cholesteryl ester is incorporated into the VLDL and transported out of the liver. As a consequence of these two events, there is a small increase in the LDL-C level. When triacylglycerol is added to such diets both of these processes may be markedly enhanced. First, long-chain, saturated fatty acids significantly enhance the effect of dietary cholesterol in suppressing LDL receptor activity in the liver. Secondly, the long chain, unsaturated fatty acids markedly increase the level of cholesteryl ester formation in the liver and this, in turn, markedly increases the outflow of cholesteryl esters in VLDL. Thus, because the combination of cholesterol and triacylglycerol in the diet markedly increases the rate of LDL-C production and suppresses the levels of hepatic LDL receptors, the steady-state concentration of LDL-C progressively increases (as, for example, seen in the Tarahumara people put on a Western diet). On such diets the plasma cholesterol level progressively rises as illustrated by the curves in Figs. 7 and 8. It should be emphasized that these increases are seen in all racial groups introduced to the typical American diet.

VIII. TREATMENT OF HYPERCHOLESTEROLEMIA IN THE AMERICAN POPULATION

Since the high plasma cholesterol levels seen in Americans almost certainly are a result of the dietary environment, it seems reasonable to assume that one could reduce the plasma cholesterol to acceptable values by adjustment of the diet. Unfortunately, this has proved nearly impossible to accomplish since most Americans are unwilling to reduce the dietary fat levels down to those values typically seen in the Tarahumara Indians or rural Chinese. This failure of diet therapy to significantly reduce plasma cholesterol levels has been

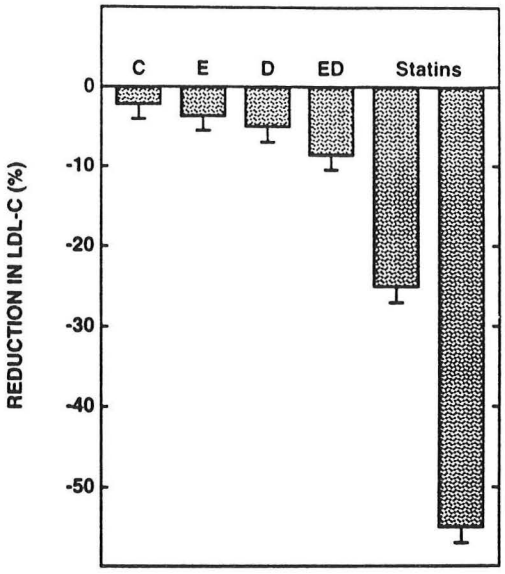


Fig. 9

documented in several recent large studies and was also seen in a major study just published in the New England Journal of Medicine. The results of this study are outlined in Fig. 9. Both men and postmenopausal women were given intense personal instruction in diet control and systematic exercise. Despite this level of personal attention, which is beyond what any individual patient would expect in the American health care system, there was only about a 7% reduction in the calories acquired from fat. As a consequence (Fig. 9), the exercise (E) and diet (D) treatments decreased the plasma LDL-C concentration only 1-3% below the control group. The combination of exercise plus diet (ED) reduced the LDL-C only 9-12%. Given the fact that the mean LDL-C cholesterol concentrations in these patients was 156-161 mg/dl, this degree of reduction is wholly inadequate. However, as also shown in Fig. 9, treatment of patients with inhibitors of the rate limiting step in cholesterol synthesis (statins) can easily achieve reductions in the circulating LDL-C concentration of 25% to over 50%. Since this degree of lowering is required to bring the circulating cholesterol level into the range where the incidence of CHD is markedly reduced, it is apparent that the use of these pharmaceutical agents is critically important in patients at risk for coronary artery disease.

It is not entirely clear how these compounds actually achieve their effects. These agents inhibit HMG-CoA reductase, the rate limiting step in cholesterol synthesis. When given as a single dose to experimental animals, they inhibit cholesterol synthesis in the liver and a number of other organs. Since less

cholesterol is delivered to or synthesized in the liver, this organ apparently responds by increasing the level of LDL receptors. In addition, there may be a simultaneous reduction in the concentration of hepatic cholesteryl esters which, in turn, also causes a reduction in the secretion of these sterols in VLDL. The net effect of these two events, therefore, is that the steady-state concentration of LDL-C is significantly reduced. However, in the face of prolonged treatment with these drugs, there appears to be little reversal of the atherosclerotic plaque. In many studies it has now been shown that treatment with statins prevents further thickening of the arterial wall and further occlusion of the luminal diameter. There is little, if any, increase in luminal diameter, however. Experimental data in animals does indicate that there is reduction in the number of inflammatory cells in the atheroma, thickening of the fibrous cap on the plaque and a reduction in the tendency of platelets to aggregate. Thus, when these agents reduce the circulating LDL-C levels, the atheroma stops growing and, in some studies, may minimally shrink. More importantly, however, inflammation in the atheroma is significantly reduced, the fibrous cap becomes thicker and, presumably, the atheroma becomes more stable. This series of events has been used to explain the significant reduction in clinical events even at periods of less than one year of treatment.

These compounds generally have been found to be very safe but have manifested two types of toxicity. One percent or less of patients taking these drugs may develop elevated liver function tests. Most pharmaceutical companies suggest periodic performance of liver function tests, therefore. More seriously, these compounds have rarely been associated with rhabdomyolysis. Apparently this may occur when a particular statin is administered along with another agent that acts as an inhibitor of P450 CYP3A4. As summarized in Table II these compounds should not be administered at the same time as the statins. Finally, the HMG CoA reductase inhibitors should not be administered to the pregnant or nursing woman and probably should not be administered to young women who could potentially become pregnant. The fetus and newborn are critically dependent upon cholesterol synthesis for the development of the central nervous system and these compounds are, therefore, contraindicated.

Table II. Agents that May Interfere with the Metabolism of Statins

ANTIBIOTICS	clarithromycin‡	erythromycin‡	metronidazole
ANTIFUNGALS	ketoconazole‡	itraconazole*‡	miconazole
PROTEASE INHIBITORS	indinavir	ritonavir	nelfinavir
CALCIUM CHANNEL BLOCKERS	mibefradil*‡		
IMMUNOSUPPRESENT	cyclosporin A‡		
H2 BLOCKERS	cimetidine		
FOOD	grapefruit	grapefruit juice	
ANTIDEPRESSANTS	fluoxetine	fluvoxamine	

*Co-administration contraindicated with HMG CoA reductase inhibitors predominantly metabolized by the CYP3A4 pathway (ie: loastatin, simvastatin).
‡Cases of rhabdomyolysis have been reported with either simvastatin or lovastatin.
(From Daniel T. Stein, M.D., Director, Parkland Hospital Lipid Clinic)

IX. OVERVIEW OF THE MAJOR TRIALS INVOLVING STATINS TO REDUCE CHD

Approximately 20 years ago, the early versions of the statins became available and it was apparent that these drugs were well tolerated, had a low incidence of significant side effects and markedly lowered the circulating plasma total cholesterol and LDL-C concentrations. Since that time many trials have been carried out to evaluate the effectiveness of these compounds in lowering total death rates, preventing clinical manifestations of atherosclerosis and altering the rate of development of atherosclerotic plaques. Prior to this time there had been at least two dozen earlier studies of this type using treatments such as diets, bile acid sequestrants and fibric acid derivatives (summarized in reference VII-D1). In general, these studies showed a favorable result and suggested that for each 1% reduction in plasma cholesterol levels there was approximately a 2% reduction in the risk of developing CHD. However, these various forms of therapy were so ineffective that they seldom lowered the plasma cholesterol level more than 10%. In addition, some of the pharmaceutical agents that were used were potentially toxic. Finally, because of the minimal lowering of the plasma cholesterol that was achieved, the results were inconsistent and most physicians remained skeptical that this was, in fact, an effective form of therapy.

Table III. Major Trials Using Statins To Reduce CHD Events in Normal (Primary) Individuals and in Patients (Secondary) with Establish 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

With the advent of the statins, however, one could reasonably expect at least a 20% decrease in the plasma cholesterol level and so a number of major clinical trials were initiated. The five largest and most important of these trials are summarized in Table III. These trials are divided into two groups: those that were undertaken in patients who already had obvious clinical coronary artery disease (secondary prevention) and those individuals who had not yet manifest clinical disease (primary prevention). The first of these studies was directed at patients in the highest risk group who already had an MI or angina and who also had very high plasma cholesterol concentrations. The 4,444 patients entered into the Scandinavian Simvastatin Survival Study (4S) had plasma total cholesterol concentrations of 209-313 mg/dl (mean ± 2 SD) and LDL-C levels of 163-213 mg/dl (Fig. 10). More recently, another secondary prevention trial (CARE) was reported and is important because these individuals, who also had coronary artery disease, had essentially "normal" (by the old criteria) levels of total cholesterol (175-243 mg/dl) and LDL-C (109-169 mg/dl). A third major secondary prevention trial has now been completed (LIPID) but the final data have not yet been published. This trial is very important, however, in that it is very large (approximately 9,000 patients), contains the largest number of women of any of

these trials (17%) and includes individuals with plasma total cholesterol levels (162-274 mg/dl) and LDL-C concentrations (96-204 mg/dl) that bridge the entire range of serum lipid levels seen in typical Western populations.

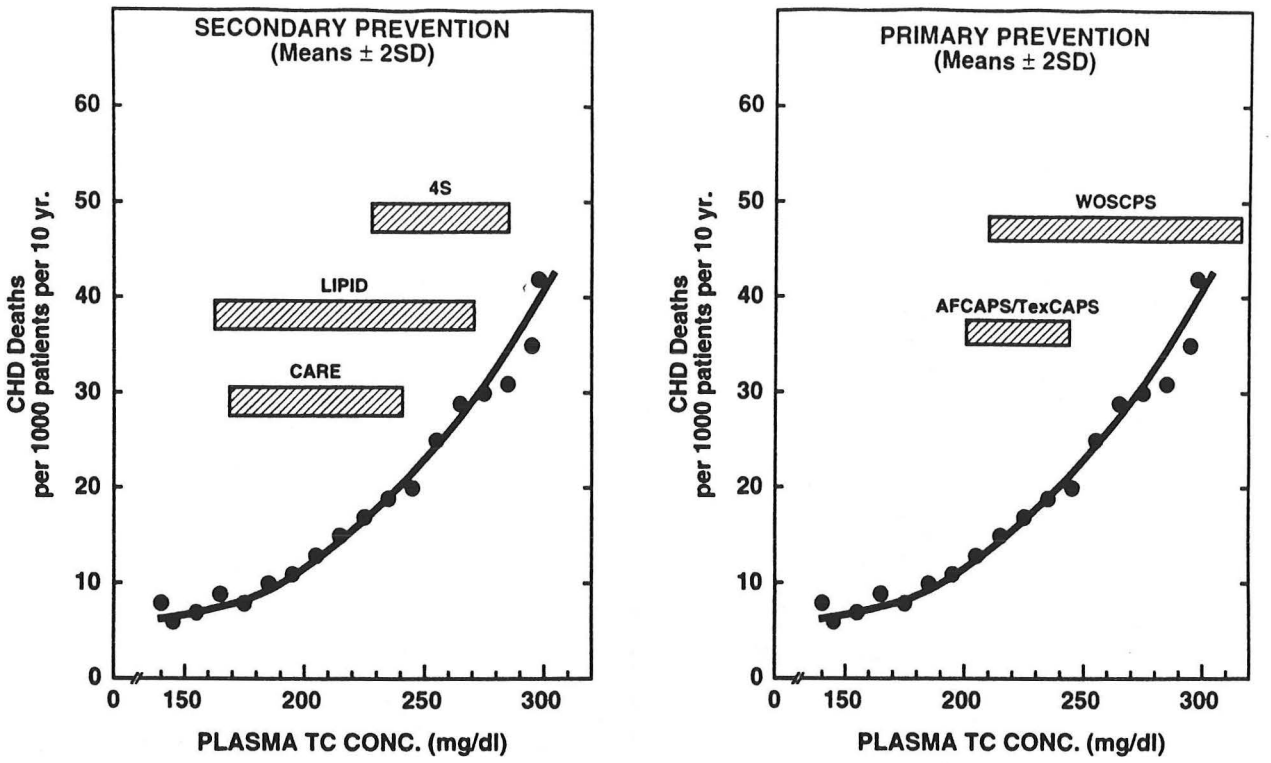


Fig. 10

Equally important, two large studies have now been completed which evaluate primary prevention of CHD using statins, and these two studies include nearly 13,000 individuals. The first of these dealt with populations that were recognized as being very hypercholesterolemic (by the old criteria). The West of Scotland Study (WOSCPS) included approximately 6,600 men with elevated plasma total cholesterol concentrations (226-318 mg/dl) and LDL-C levels (158-226 mg/dl) (Fig. 10). Very recently, a similar study was published from Texas (AFCAPS/TexCAPS) that was carried out in approximately 6,600 subjects that had normal (by the old criteria) total cholesterol concentrations (180-263 mg/dl) and LDL-C levels (116-184 mg/dl). This study evaluated whether reduction of the plasma cholesterol level in a group of individuals with "normal" serum cholesterol concentrations significantly reduced the onset of CHD. In addition, this study contains a significant number of women and a number of individuals

who were diabetic and elderly. Thus, in summary, these five major clinical trials carried out in nearly 31,000 subjects have evaluated whether lowering the plasma cholesterol from nearly 300 mg/dl to 150 mg/dl prevents the initial episode of clinical CHD or prevents additional coronary events in patients who already have clinical atherosclerotic disease.

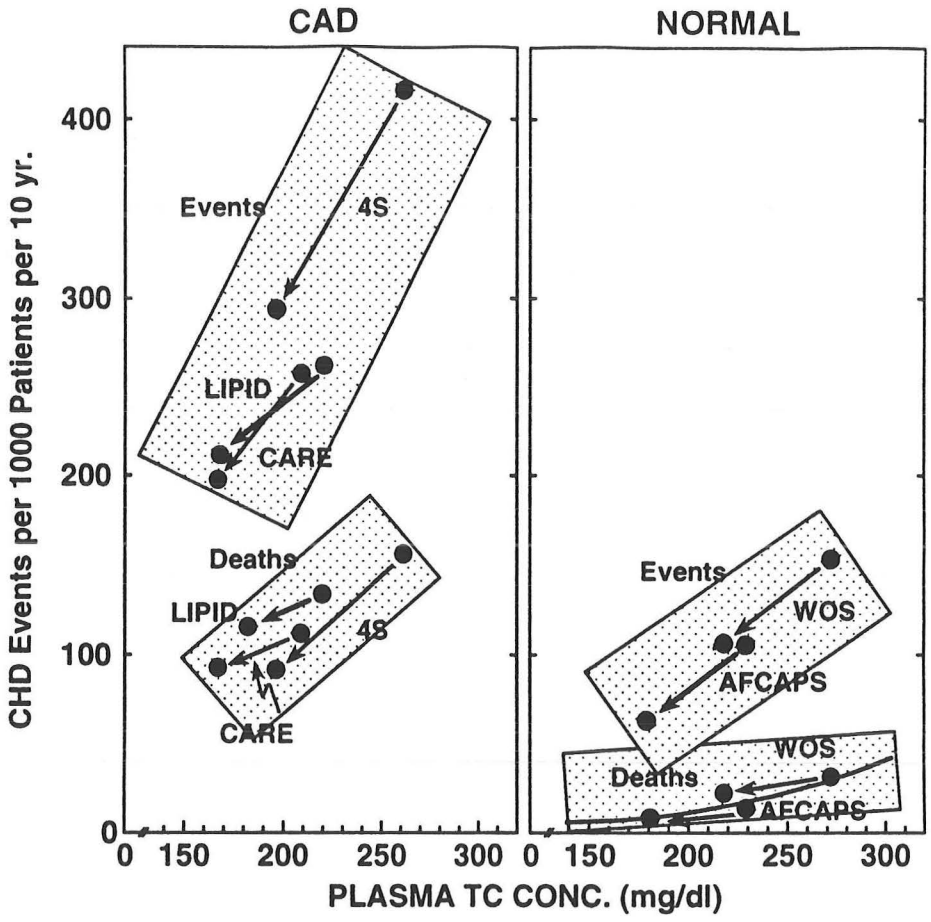


Fig. 11

An overview of all of these studies is shown in Fig. 11. In this and subsequent figures, the data from each of the studies have been recalculated and are presented as the number of individuals who develop a cardiac event (MI, angina, sudden death) or who die as a result of CHD per 1,000 subjects over a 10-year period. The left panel shows those studies carried out in patients who already had established coronary artery disease while the right panel shows the primary prevention trials carried out in normal individuals. The mean values are shown for the control and treated group in each study, and these two mean

values are connected by the arrows. The shaded box simply collects data from each study relevant to "events" and "deaths." Three general observations can be made concerning the data presented in this figure. First, in all groups there is essentially a linear relationship between reduction in the plasma total cholesterol concentration and the onset of cardiovascular events or death. Second, the occurrence of a new cardiovascular event is approximately 3-4 times more likely in those individuals who have already had clinical coronary artery disease (left panel) as in those individuals who had not yet manifest CHD (right panel). Third, the rate of cardiovascular death is 8-10 times higher in the subjects who already had CAD as in those who were part of the primary prevention trials.

X. THE SPECIFIC SECONDARY PREVENTION TRIALS

Table IV outlines the major findings in the three secondary prevention trials. The 4S study treated patients with CAD who had high LDL-C concentrations (mean -188 mg/dl). Treatment resulted in a 35% decrease in the LDL-C concentration, 30% reduction in cardiovascular events and 41% reduction in cardiovascular deaths. These patients had an average age of 60 years and were treated for approximately 5.4 years. Subgroup analysis showed similar effects in men and women and in both sexes over the age of 60. Notably, the incidence of death and nonfatal MI's decreased by 26% in the first two years and by 46% thereafter. The number of cerebrovascular events was also reduced by approximately 35%. When applied to the United States, treatment with this statin over the 5.4 years of the trial brought about a reduction in the hospitalization cost per patient of $3,872 and effectively reduced the cost of the statin medication by 88% to only 28 cents per day. The second study of this type (CARE) investigated a similar group of patients with established CAD except that these individuals had plasma total and LDL-C concentrations that were essentially in the "normal" range (Table IV). These patients averaged about 50 years of age and were treated for 5 years. The TC concentration was reduced only 20%, but this resulted in a 24% reduction in new CV events and a 19% reduction in CV deaths. There was also a reduction in the need for bypass surgery and coronary angioplasty, and there was a reduction in the incidence of stroke of 31%. These reductions were greater in women than in men and greater in individuals with the higher pre-treatment levels of LDL-C. This study suggested that there was no reduction in

Table IV. Secondary Prevention Trials

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)

Table V. Primary Prevention Trials

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)

the risk of coronary events in patients with pre-treatment levels of LDL-C below 125 mg/dl. The results from the largest of these secondary prevention trials (LIPID) are not yet published. However, this is a very important study since it contained approximately 9,000 patients, 17% of whom were women, and the pre-treatment LDL-C levels included the entire range commonly seen in Western populations (96-204 mg/dl). These individuals averaged only an 18% reduction in their TC concentration and had a 22-23% reduction in CV events and CV deaths. The effects apparently were seen in all age groups and were similar in women compared to men. Importantly, there appeared to be no threshold effect: the reduction in risk was similar in patients that fell into the upper, middle and lower third of values for the pre-treatment LDL-C concentration. This study, therefore, contradicted the result reported in CARE. There was virtually no toxicity associated with intake of the statin, there was no difference in the incidence of cancer, and the cost per life saved equalled approximately $30,000.

XI. THE SPECIFIC PRIMARY PREVENTION TRIALS

The two major primary prevention trials carried out in nearly 13,000 subjects cover the entire range of plasma cholesterol levels seen in Western populations and the results of these studies are summarized in Table V. The West of Scotland (WOSCPS) study was undertaken in men with an average age of 55 years and treatment occurred over 4.9 years. These individuals were all hypercholesterolemic and treatment with these statins lowered the TC concentration 20% and the LDL-C level 26%. This was associated with a 27-30% reduction in CV events and CV deaths. These positive effects were observed after only 6 months of drug therapy. The favorable result was similar in subjects with initial LDL-C concentrations above or below the median. Similarly, the reduction in risk was about the same in individuals above 55 years compared to individuals younger than this age. It was also similar regardless of smoking status. Finally, the reduction in risk was seen in individuals with no other risk factors as well as in those with multiple risk factors. As with the other studies, the risk of death from any cause was significantly reduced by treatment with the statins. The final primary prevention study has just been published (AFCAPS/TexCAPS) and was carried out in approximately 5,600 men and 1,000 women with plasma cholesterol levels that were in the "normal" or even low range for the U.S. After an average of

5.2 years of treatment the TC concentration was reduced 19%, from 228 to 184 mg/dl. This resulted in a decrease in CV events of 37% and a decrease in deaths of 32%. Risk reduction was evident across all LDL-C tertiles with no threshold to the beneficial effect. The effects were similar in men and women and in older and younger members of the treated groups. There was no difference between the treated and placebo groups with respect to liver function abnormalities or increases in CK levels.

XII. SUMMARY OF ALL TRIALS

In summary, these trials in nearly 31,000 patients have unequivocally demonstrated the beneficial effects of lowering the plasma cholesterol levels by the administration of statins. These effects are approximately the same in men versus women, older individuals versus younger individuals, smokers versus nonsmokers, diabetics versus nondiabetics, hypertensives versus non hypertensives and in individuals with "high" versus "normal" plasma cholesterol levels. Finally, where data were collected, there was a consistent beneficial effect in the reduction of strokes.

XIII. RECOMMENDATIONS

The results of these trials are so uniform and unequivocal that it is clear that one can significantly reduce the risk of primary or secondary atherosclerotic events by substantially reducing the circulating LDL-C concentration. Clearly, it would be desirable to have a total plasma cholesterol concentration of <200 mg/dl, an LDL-C level of <80 mg/dl and a non-HDL-C concentration of <110 mg/dl. In a very small percent of the population this can be achieved with diet management and, perhaps, exercise. In the remainder of the population further guidelines will have to be developed to identify those groups that are particularly at risk (Table I) and society, in general, and managed health care organizations, in particular, will have to make a judgment about what level of risk is acceptable and above which drug therapy should be initiated. Current guidelines effectively identify a large number of individuals who have above average risks for development of coronary artery disease, and these individuals clearly should be vigorously treated to lower their circulating cholesterol concentrations.

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