University of Texas
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Considerations Regarding Treatment of Hypercholesterolemia in the Elderly

Medical Grand Rounds

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I. Introduction

The elderly are among the fastest growing segments of the U. S. population. In 1900, those over age 65 constituted about 4% of the U. S. population (Figure 1). Since then, this group has grown dramatically and by 1990, the elderly will constitute 12-13% of the U. S. population. The U. S. Census Bureau estimates that by 2030, when the total U. S. population is

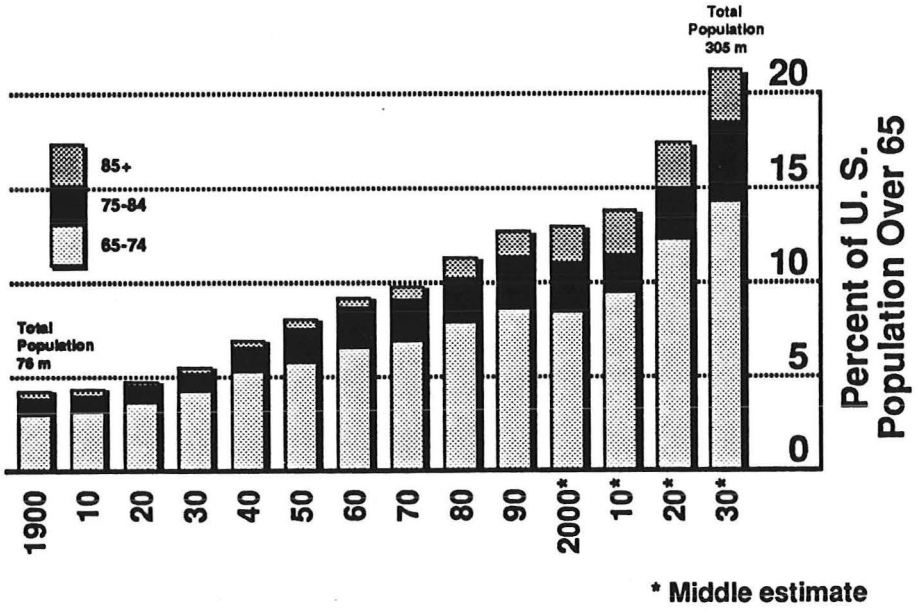


Figure 1. Growth in the elderly population from 1900 through 1990, and projected through the year 2030

estimated to be about 305 million, those over age 65 will constitute slightly more than 20% of the U. S. population (1). It is also projected that women will significantly outnumber men in this age group as time goes by (Figure 2). Health-related issues specifically regarding post-menopausal women therefore become increasingly important.

The average 1985 life expectancy for a 65-year-old U. S. woman was 19.5 years, and for a 65-year-old man, 15.1 years (2). This significant life expectancy beyond age 65 suggests that preventive health care can have a substantial beneficial impact on the health and function of individuals in this population, especially since cardiovascular diseases have become the leading cause of death in the elderly.

The emergence of cardiovascular disease as the leading cause of death in the United States since 1900 is evident from the data in Table 1 (3).

A comparison of the numbers of deaths from all heart disease and specifically from ischemic heart disease by age and sex in the United States for 1986 illustrates the dramatic current impact cardiovascular diseases have on the elderly (Table 2) (4). The absolute numbers of males affected indicate that the hardest hit groups are those in the age range of 45 to 84 years, whereas in women, the number affected increases steadily through 85 years, with the sharpest jump occurring at age 65 and beyond. Thus, although men are traditionally thought to suffer from the ravages of cardiovascular disease, women are also afflicted but the onset of the disease

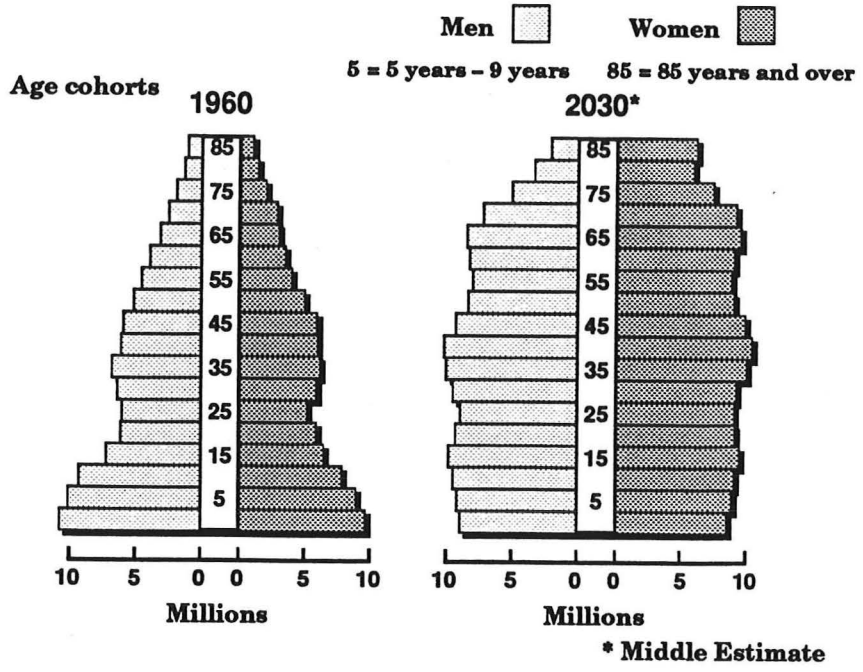


Figure 2. Comparison of men and women in different age groups in the United States in 1960 and projected for the year 2030.

appears to be delayed 10-15 years. The reasons for this delayed clinical appearance of coronary heart disease (CHD) in women have not been clearly defined, but it should be noted that a focus on heart disease in the elderly tends to translate to a focus on heart disease in elderly women.

Table 1. Ten Leading Causes of Death in the United States in 1900 and 1983

	1900		1983	
Rank	Cause of Death	Percent Mortality	Cause of Death	Percent Mortality
1	Pneumonia and influenza	11.8	Heart disease	40.9
2	Tuberculosis	11.3	Cancer	21.9
3	Diarrhea and enteritis	8.3	Cerebrovascular disease	7.7
4	Heart disease	8.0	Accidents	7.1
5	Cerebrovascular disease	6.2	Pneumonia and influenza	7.1
6	Nephritis	5.2	Digestive and liver disease	3.6
7	Accidents	4.2	Endocrine, metabolic, and immune disease	2.3
8	Cancer	3.7	Genitourinary disease	1.6
9	Diphtheria	2.3	Diseases of the nervous system	1.3
10	Meningtitis	2.0	Infections and parasitic disease	1.1

The numbers in Table 2 reflect deaths and give no indication of the morbidity from heart disease in the various age groups. For this reason, the total impact of cardiovascular disease in the elderly is likely to be much

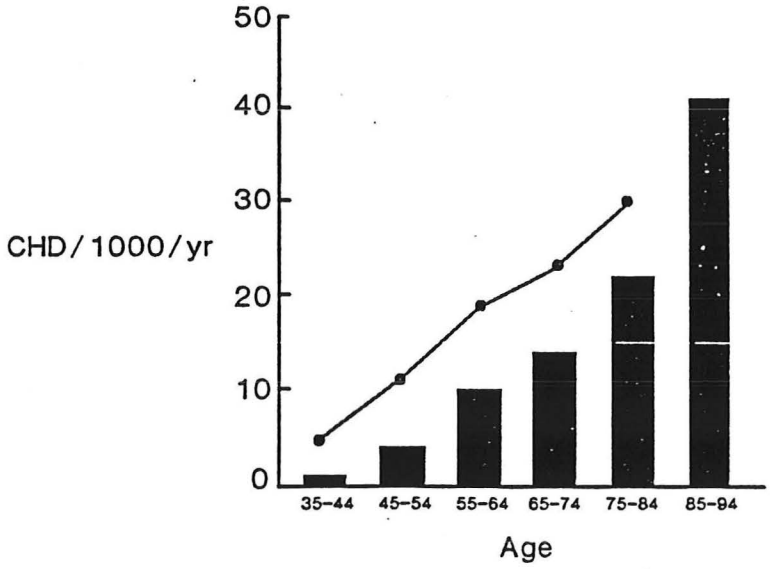
Table 2. Number and Percent Distribution of Heart Disease by Age and Sex, in All Diseases of the Heart and Ischemic Heart Disease in the United States in 1986

	Totals	25-44 years	45-64 years	65-74 years	75-84 years	85 Years and Over
All Diseases of the Heart						
Males	394,003	10,914	93,631	115,664	113,173	60,622
% of Total		(2.8)	(23.8)	(29.4)	(28.7)	(15.4)
Females	365,428	3,845	34,931	68,875	121,654	136,122
% of Total		(1.1)	(9.6)	(18.8)	(33.3)	(37.3)
Ischemic Heart Disease						
Males	282,924	6,804	68,564	81,889	81,259	44,407
% of Total		(2.4)	(24.2)	(28.9)	(28.7)	(15.7)
Females	242,387	1,512	20,771	46,585	84,910	88,610
% of Total		(0.6)	(8.6)	(19.2)	(35.0)	(36.6)

Kapantais et al. National Center for Health Statistics 172, Aug. 24, 1989.

larger. Furthermore, the absolute numbers in this table give no indication of rates of disease in the different age groups. In 1986, the rates for all heart disease ranged from 144.6 per 100,000 persons 45-54 years of age to 7,178.7 per 100,000 persons aged 55 years or older (4). Thus, the "at-risk" group comprises a much larger percentage of the population in the elderly. This trend is reflected in the yearly rate for CHD per 1000 people in the Framingham Study (Figure 3) (5).

Figure 3.



Annual rate of coronary heart disease *(CHD)* in men (indicated by *line*) and women (indicated by *bars*). (From the Framingham Heart Study.)

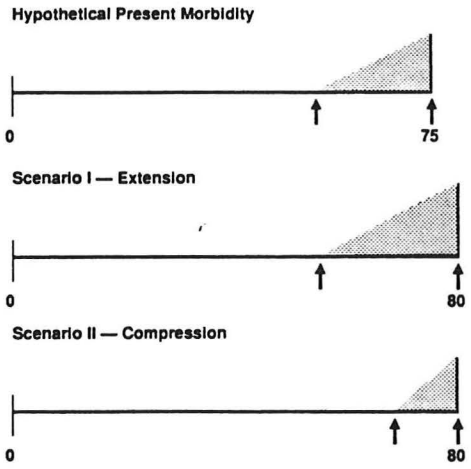
These disease trends are reflected in the consumption of health care dollars by the elderly in the United States. While the elderly currently make up 12% of the U. S. population, they consume one-third of the health care expenditures, a large portion of which is directed to the care of cardiovascular diseases (2). In 1984, $9 billion were spent for cardiovascular procedures in the United States; over one-third of these procedures were performed on elderly patients. More than half of all patients hospitalized for acute myocardial infarction are older than 65 yrs, and there is every reason to expect this fraction to increase in future years (2). In a recent analysis of trends between 1981 and 1985 regarding hospital care for the elderly with diseases of the circulatory system (6), the number of patients 65-74 yrs of age receiving coronary artery bypass surgery rose 203%, while those 75+ years of age rose 313% (Table 3) (6). Thus, the impact of coronary disease is reflected in a greater number of aggressive surgical procedures being performed in the elderly. Since we are increasingly performing surgery to treat symptomatic coronary heart disease, it is fair to ask if we should also be addressing the risk factors known to be associated with the development of coronary atherosclerosis.

Table 3. Discharge Rates for Coronary Artery Bypass Surgery in the Elderly in the United States in 1981 and 1985[1,2]

Year	Patient Ages (yrs)		
	65-74	75+	All
1981	146	32	101
1985	296	100	217
1985 as % of 1981	203%	313%	215%

1. Discharge rates are shown per 100,000 persons
2. From Anderson G.M. et al. N. Engl. J. Med. 321:1443-8, 1989.

The elderly consist of a highly heterogeneous group of persons who vary widely in their ability to function physically, behaviorally, cognitively and emotionally. Therefore decisions regarding diagnostic and therapeutic interventions should be based on the physiological age of the patient rather than the chronological age, and on the presence and severity of concomitant disease, mental status and cognitive ability, as well as the patient's expectations from medical care (2). Chronic disease is common in the elderly and is a significant cause of disability (7). Therapy for chronic conditions may not lead to significant prolongation of life but an equally valid therapeutic end-point in the elderly would be compression of morbidity in the time before death such that mobility and independent function are maintained for a significantly longer period before death (Figure 4) (8). This has been variously defined as "adding years to life", extending "active life expectancy", and improving the quality of life. Thus, reducing



Compression of morbidity.

The future of population health is dependent upon relative movement of the two arrows, the first representing the average age of initial onset of disease or infirmity and the second representing average age at death. If the first moves more rapidly than the second, there is compression of morbidity.

Figure 4.

morbidity in the elderly may be just as important or more so than prolongation of life.

The discussion that follows will address the impact of hypercholesterolemia on cardiovascular diseases in the elderly. Consideration will first be given to cholesterol as a predictor of cardiovascular risk in the elderly. The changes in cholesterol with age will be discussed, along with possible physiological alterations that might account for these changes. Evidence that modification of cholesterol is beneficial in humans will then be described. Finally, the emerging concepts of how to evaluate and treat hypercholesterolemia will be described and suggestions will be made with regard to the specific management of hypercholesterolemia in the elderly.

II. Cholesterol as a Predictor of Cardiovascular Risk in the Elderly

The role of cholesterol as a risk factor for cardiovascular disease in the elderly is currently evolving. Until recently, cholesterol was thought to be of little value as a risk factor, especially over the age of 55 years (9). A variety of hypothesis have been put forward to explain this apparent loss of impact of cholesterol as a risk factor in the elderly (10):

- Aging may be associated with changes in the artery wall such that progression of plaque is no longer modulated by plasma cholesterol. Other factors such as plaque rupture and thrombosis, rather than plaque growth, may become more important.

- Other factors in addition to hypercholesterolemia may contribute to the development of atherosclerosis. This is certainly true, but in this specific context, the hypothesis is that hypercholesterolemic individuals "susceptible" to atherosclerosis would die before the age of 50-55 years, while those "resistant" to atherosclerosis despite the hypercholesterolemia would constitute the survivors who live beyond

age 65. This is another way of indicating that not all of the cardiovascular risk factors have been identified.

- The studies indicating that cholesterol loses predictive power with advancing age are often based on one cholesterol measurement coupled with prolonged follow-up. It is possible that individuals with initially low-risk cholesterol levels display a progressive rise in cholesterol to the high risk range but this change would not be detected because of the nature of the study design. Thus, failure to consider temporal changes in cholesterol levels may introduce a bias and error into the analysis of cholesterol and cardiovascular risk, especially in the elderly.

Despite the debate about cholesterol, it is clear that a variety of cardiovascular risk factors do operate in the elderly. These include hypertension, dyslipidemia (high LDL and/or low HDL), impaired glucose tolerance, physical inactivity, left ventricular mass and cigarette smoking (11, 12, 13, 14, 15, 16). The term dyslipidemia has been employed since the impact of the total cholesterol level in predicting risk declines while the value of the LDL-cholesterol and HDL-cholesterol remain powerful predictors (5, 12). In both sexes, triglycerides also serve to predict risk in individuals with low HDL-cholesterol levels (5). Although cholesterol appeared to lose predictive impact in the Framingham study, it was simultaneously noted that the LDL and HDL cholesterol fractions continued to predict risk in persons of either sex aged 49 to 82 years (17). As the Framingham cohort has continued to be followed, it now appears that cholesterol is a modest predictor of risk but it provides less information than the measure of LDL-cholesterol and HDL-cholesterol (5, 18).

To illustrate this loss of impact, one can compare the results of the Multiple Risk Factor Intervention Trial (MRFIT) study in middle aged men (35-57 yrs of age) with individuals from Framingham over age 65 yrs (19, 20). The results are not strictly comparable, but they nevertheless illustrate an important point. In the middle aged men, a rise in cholesterol from about 200 mg/dl to >264 mg/dl was associated with a 4-fold increase in risk (Table 4). However, in subjects over age 65 yrs, a comparable rise in cholesterol was associated with only a 1.5 to 2.3-fold increase in risk (Table 5).

The clinical value of these rate ratios regarding cholesterol and CHD risk can be misleading as the age of the population increases because the background incidence of CHD grows much larger. To deal with this relationship, Malenka and Baron introduced the concept of patient-specific attributable risk (21). Attributable risk (AR) is defined as the difference of two comparable risks, such as the difference in CHD risk between the lowest cholesterol group and the highest cholesterol group in the MRFIT study as a function of age (21). These data are plotted in Figure 5 in comparison with the data for relative risk (RR). They indicate that cholesterol becomes less powerful as a relative risk factor with increasing age (declining RR) but that the background incidence of CHD increases (rising AR). If lowering the plasma cholesterol level actually translates

Table 4. Relative Risk of CHD Death Associated with Serum Cholesterol Levels Among MRFIT Screenees Aged 35-57[1]

Cholesterol Range (mg/dl)	Relative Risk Compared to Lowest Quintile
≤181	1.0
182-202	1.3‡
203-221	1.7‡
222-245	2.2‡
246-263	2.8‡
≥264	4.0‡

‡ $p<0.01$

1. From Martin, M.J. et al. Lancet 2:933-936, 1986.

Table 5. Rate Ratios for Cholesterol as a Cardiovascular Risk Factor as Derived from Multivariate Proportional Hazards Models in Framingham Enrollees Aged 65 or Older[1]

Cholesterol Range (mg/dl)	Relative Risk Compared to Lowest Cholesterol Level		
	Males	Females	Combined
<200	1.0	1.0	1.0
200-239	1.1	1.2	1.1
240 – 90th percentile[2]	1.3	1.4	1.3
≥90th percentile[2]	1.5	2.3	1.8

1. From Harris, T. et al. JAGS 36:1023-8, 1988.
2. The 90th percentile for females = 306; for males = 275.

into lower cardiovascular risk, then an apparent small relative benefit derived from RR may apply to a much larger number of persons in the age group over 65, and overall benefit to the group may become substantial.

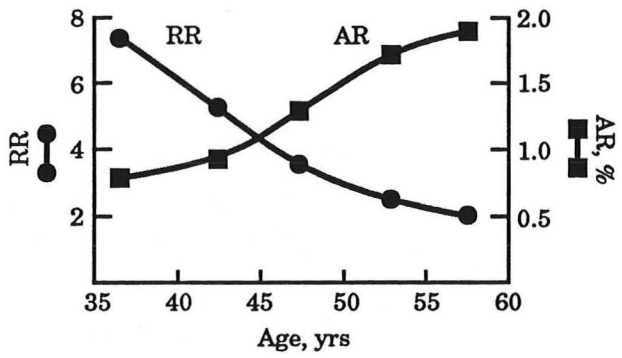
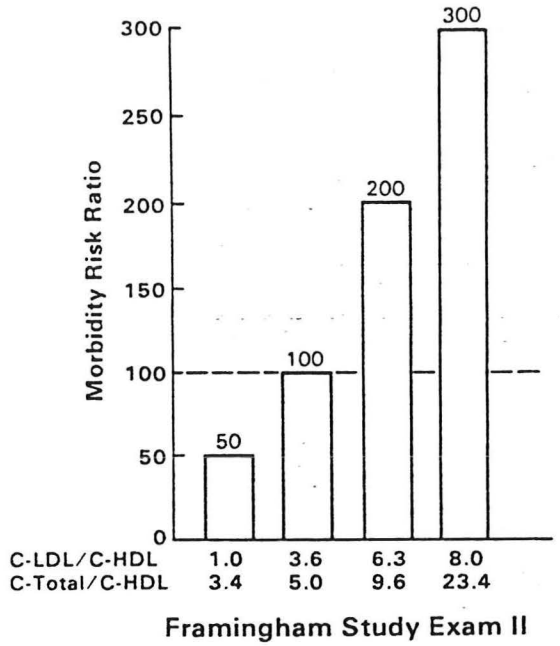


Figure 5. Changes in risk ratio (RR) and attributable risk (AR) with age in men in quintile V (high cholesterol) versus quintile I (lowest cholesterol). From reference 21.

Several investigators, including those from the Framingham study, have recommended the wider use of the total cholesterol/HDL-cholesterol ratio to better define risk in the individual patient. They contend that in younger age groups, the ratio will help to identify patients at high risk because of an apparently desirable total cholesterol but a low HDL-cholesterol level. In addition, the ratio

would help to define elderly persons, especially females, who have high total cholesterols due to elevated HDL-cholesterol levels and therefore are not at increased cardiovascular risk. The morbidity risk ratio for different total cholesterol/HDL-cholesterol ratios is shown in Figure 6 (12).



Four-year risk of coronary heart disease (CHD) according to the ratio of cholesterol lipoprotein fractions.

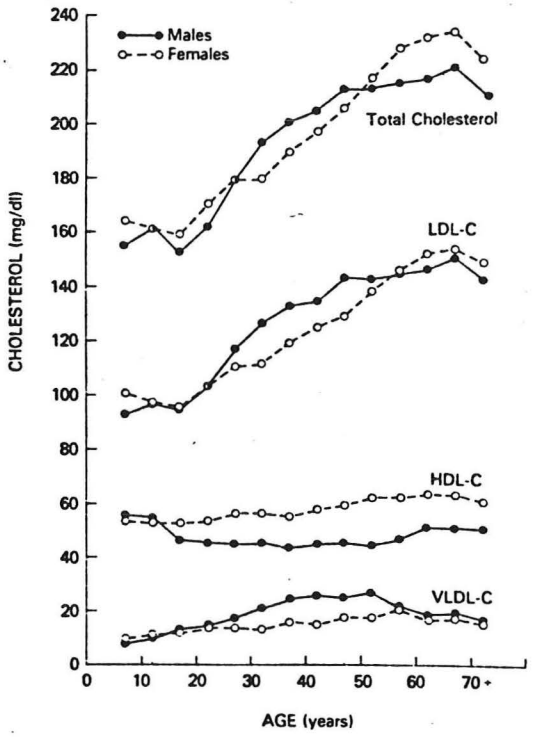
Figure 6.

There is no uniform agreement about the use of this ratio and the National Cholesterol Education Program (NCEP) advisory panel has recommended that it not be used. The NCEP panel points out that measures to raise the HDL-cholesterol level have not clearly been related to reduced risk for CHD, and that no biological mechanisms to explain the apparent protective effect of HDL against CHD have emerged (22, 23). This question should be resolved with further research. Meanwhile, it is reasonable to obtain a fasting total cholesterol and HDL-cholesterol in selected elderly patients to better define risk, provided that any abnormal results are confirmed by repeat measurements (22), since the precision and reproducibility of the HDL-cholesterol measurement are still not adequate in many laboratories.

III. Changes in Cholesterol Metabolism with Age

The total plasma cholesterol level increases with age in most industrialized countries (Figure 7) (24). In the United States, the rise is progressive in both sexes over age 20 years. In men, the rate of rise slows after age 45-50 and the cholesterol declines over age 70, presumably because hypercholesterolemic subjects have died from cardiovascular disease. In women, the cholesterol level continues to rise into the 7th decade of life. Between the ages of 50 and 70 yrs, mean total cholesterol levels in women exceed those in men (12, 24). The data in Figure 7 indicate that this rise in total cholesterol is due largely to an increase in LDL-cholesterol. Since LDL-cholesterol is directly related to cardiovascular risk, it is apparent that one factor contributing to the rising risk of cardiovascular disease with increasing age is the progressive increase in LDL-cholesterol.

HDL-cholesterol remains relatively stable throughout life in females but in males, the HDL-cholesterol drops at about the time of puberty, and



. Mean plasma total cholesterol, LDL-C, HDL-C and VLDL-C by 10-year age groups for 3581 males and 3426 females. LRC Prevalence Study, Visit 2 random sample.

Figure 7.

the mean levels remains consistently lower than in females thereafter (Figure 6). The reason for this drop in HDL in males has been attributed to a testosterone effect rather than to a lack of estrogen effect, because a reduction of estrogen production after menopause is not associated with a substantial drop in HDL levels in women (Figure 7).

There are no major alterations in lipid and lipoprotein metabolism associated with aging. However, several subtle changes occur that could contribute to atherosclerosis over one or more decades. A figure describing plasma lipoprotein metabolism is shown in Figure 8. Dietary cholesterol (exogenous) is absorbed via the intestine in the form of chylomicrons which traverse the intestinal lymphatics to enter the plasma via the thoracic lymph duct. Upon entering plasma, the chylomicrons deliver triglyceride to peripheral tissues where lipoprotein lipase, located on capillary endothelial cells, hydrolyzes the triglyceride. The resultant free fatty acids are taken into tissues for oxidation or for storage and later use. Limited results indicate that older subjects (40-72 yrs, n=10) have reduced lipoprotein lipase activity and delayed clearance of both chylomicrons and VLDL particles following a fat meal, as compared to young subjects (19-28 yrs, n=16) (Figure 9, middle panel) (25). This delay results in higher peak concentrations and higher sustained concentrations of post-prandial triglyceride-rich lipoprotein particles. There are some data to suggest that such post-prandial hyperlipidemia may be atherogenic, but very little experimental data in humans exist regarding this important question. If this delayed clearance of triglyceride-rich particles does contribute to atheroma formation, then a low fat, low total cholesterol diet would be prescribed to reduce the formation of these particles by the gastrointestinal tract.

Endogenous cholesterol transport begins with the secretion of very low density lipoprotein (VLDL) from the liver (Figure 8). The VLDL particles also deliver triglycerides to peripheral tissues where the fatty acids are released through the action of lipoprotein lipase. The resultant intermediate density lipoprotein particles (IDL) may either be taken up

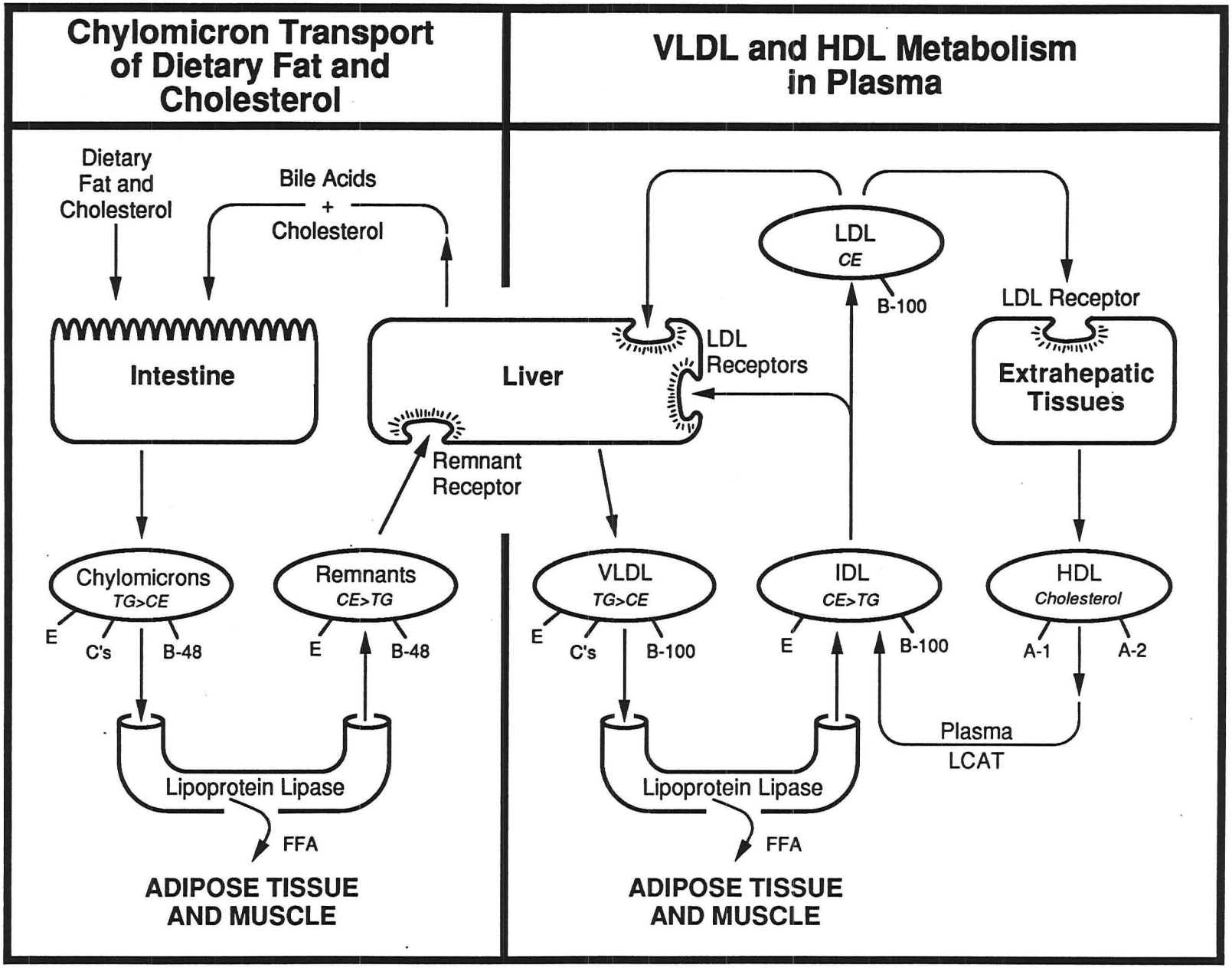
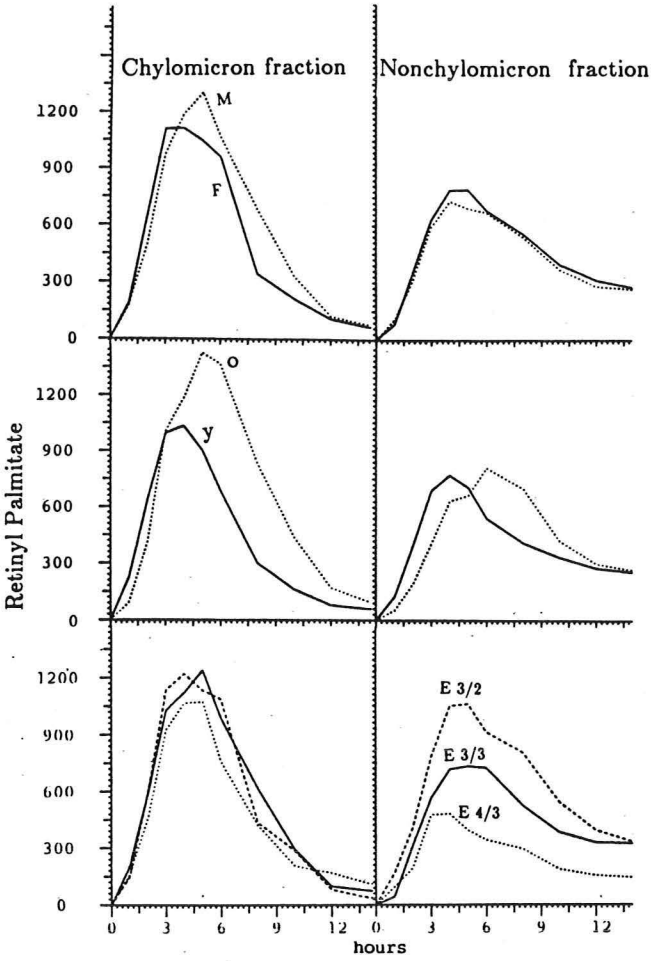


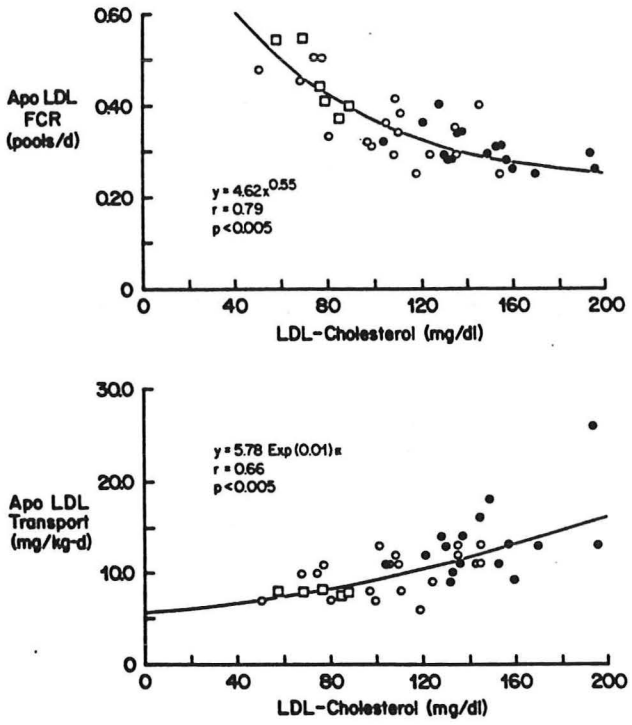
Figure 8. Lipoprotein Metabolism in Plasma.
Exogenous (dietary) cholesterol is transported in the chylomicron pathway. Endogenous cholesterol (originating from the liver from remnant uptake or *de novo* synthesis) is transported in the VLDL → LDL pathway. Modified from Goldstein, J.L. et al. N. Engl. J. Med. 309:288-96, 1983.



Effect of sex, age, and apolipoprotein E polymorphism on chylomicron and nonchylomicron RP concentration curves (in micrograms per liter) in normal subjects. The upper panel shows RP responses of males (· · · · ·) (n = 14) and females (=) (n = 13). The middle panel compares older (· · · · ·) (n = 10) to younger (——) (n = 16) subjects. The lower panel shows RP responses of subjects with apo E3/2 (– – –) (n = 9), apo E3/3 (——) (n = 10), and apo E4/3, E4/4 (· · · · ·) (n = 8) phenotypes. For each group, the levels at each time point were averaged.

Figure 9.

directly via LDL receptors on the liver or converted to LDL particles, which then serve to deliver cholesterol to tissues throughout the body via the LDL receptor pathway (26). LDL receptor activity *in vivo* plays an important role in regulating plasma LDL metabolism and steady state levels (26). When LDL receptor activity is increased, IDL clearance from plasma is accelerated and less is converted to LDL, so that LDL production declines. In addition, the rate of LDL catabolism is increased, and both effects (↓ production, ↑ catabolism) lead to reduced steady state plasma LDL levels. Exactly the reverse occurs when LDL receptor activity is depressed or genetically deficient (26). Mahley et al (1981) noted that hepatic LDL receptor activity was decreased with increasing age in the dog (27). When LDL catabolism was evaluated in a group of human subjects varying in age from 22 to 60 yrs, there was a decrease in the fractional rate of catabolism (FCR) of LDL with increasing age and the change was associated with an increasing LDL-cholesterol concentration and increasing rates of production of apoLDL (apoLDL transport) (Figure 10) (28). These data suggested that LDL receptor activity did diminish with age. However, when LDL receptor activity was measured on circulating lymphocytes isolated from patients of widely varying age, there was no evidence for an age effect on the maximal expression of LDL receptor activity in these cells (29). It was proposed that the apparent decline in LDL receptor activity noted with age was actually related to dietary fat consumption (26). As more dietary fat was consumed, the increased production of chylomicrons would lead to enhanced delivery of cholesterol to the liver as dietary fat. As hepatic stores of cholesterol increased, the hepatocytes would express fewer LDL receptors and plasma



Correlations between plasma LDL-C concentrations and fractional clearance rates (FCRs) and transport rates of apoLDL. □ = young adults studied previously;[7] ○ = young men in this study; ● = middle-aged men.

Figure 10.

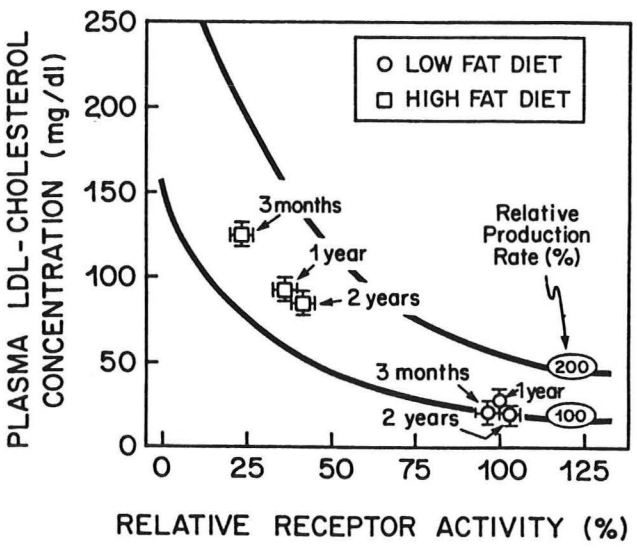
LDL-cholesterol levels would increase. Experimental evidence for such an effect in the male hamster model has been presented by Spady and Dietschy (Figure 11) (30). Their results indicate that when hamsters are maintained on a low fat diet, LDL receptor activity is not altered in animals ranging in age from 3 months to 2 years. However, when the animals are fed a high fat diet, LDL receptor activity is suppressed and plasma LDL-cholesterol levels rise (Figure 11). The magnitude of this response in the different age groups is similar, indicating that older animals are not more susceptible to this effect than younger animals.

There are limited data to suggest that tissue pools of cholesterol expand in human subjects with increasing age from 35 to 61 years (31). If this effect is confirmed, it could partially explain the progressive decline in LDL receptor expression that appears to occur with increasing age. It should be stressed that this apparent decline in LDL receptor expression *in vivo* is not irreversible but rather reflects regulation of receptors. When certain cholesterol-lowering medications are given, or when low cholesterol, low total fat diets are consumed, LDL receptor expression *in vivo* appears to increase.

No effects of age on HDL metabolism have been published.

From a review of the information just presented, it should be evident that a low cholesterol, low total fat diet would theoretically be helpful in reducing post-prandial hypertriglyceridemia and would also promote enhanced *in vivo* expression of the LDL receptor. Both changes would be expected to reduce long-term cardiovascular risk. However, these concepts have not been rigorously tested in the elderly.

Recent results indicate that the post-menopausal use of estrogens is associated with a significant reduction in subsequent cardiovascular risk. One of the most detailed reports to appear related to the study of 2270 white women, aged 40-69 years at baseline, who were followed an average of 8.5 years in the Lipid Research Clinics Program (32). The age-specific and age adjusted cardiovascular disease death rates for estrogen users and



The effect of aging on the plasma LDL-cholesterol concentration in the hamster. This diagram illustrates how the plasma cholesterol concentration changes under circumstances where there has been an alteration in either receptor-dependent LDL-cholesterol transport out of the plasma (horizontal axis) or a change in the rate of LDL-cholesterol production. The two solid curves show the manner in which the plasma LDL-cholesterol concentration would be expected to change if there were an alteration in total body receptor-dependent transport activity ($^{*}J^{m}$) under circumstances where the production rate (J_r) was either normal or twice normal. In this diagram the normal values for $^{*}J^{m}$ (7,560 μg/hr per kg) and J_r (1,650 μg/hr per kg) have been set at 100% of relative activity. The experimental values found in the animal groups of different ages are superimposed on these curves.

Figure 11.

nonusers are shown in Table 6 (32). The risk ratio for the estrogen users compared to nonusers was 0.34. Multivariable adjustment for possible confounding factors such as age, blood pressure and cigarette smoking increased the estimated risk ratio to only 0.37. Despite this low incidence of cardiovascular risk in estrogen users, it was noted that the prevalence of cardiovascular disease at baseline was slightly higher in this group (12%) than in nonusers (10%). The estrogen users had a mean LDL-cholesterol level slightly lower than users (145 mg/dl vs 156 mg/dl) and slightly higher mean HDL-cholesterol levels (66.7 mg/dl vs 57.1 mg/dl in nonusers) (32). The authors concluded that the apparent protective effect of estrogens was mediated "substantially" through increased HDL-cholesterol levels. These results are in agreement with other studies in various groups of post-menopausal women (for review, see the article by R.H. Knopp) (33).

A more recent report described a slight decrease in HDL-cholesterol and a slight increase in LDL-cholesterol with natural menopause in women who do not receive estrogen replacement. In contrast, women who proceed through the menopause and receive estrogen replacement show no change in plasma LDL and HDL levels, but develop mild hypertriglyceridemia. These results suggest that the natural menopause has slight but unfavorable results on plasma lipoprotein levels that can be prevented by estrogen replacement (34). Whether these mild changes account for the apparent reduction in cardiovascular risk in post-menopausal estrogen users is unknown.

Cummings, et al have attempted to calculate the risk of various problems that are known to affect post-menopausal women in an attempt to estimate the potential risk/benefit ratio of post-menopausal hormone therapy (35). Their calculations are shown in Table 7. The authors suggest that <u>if</u> hormone replacement therapy reduced cardiovascular risk by as little as 10%, this benefit would still substantially offset a 5-fold increase in risk of death from endometrial cancer or a 2-fold increase in death from

Table 6. Age-Specific and Age-Adjusted[1] Cardiovascular Disease Death Rates (per 10,000) by Estrogen Use at Visit 2

Age at Risk	Estrogen Use	
	Nonuser (n=1677)	User (n=593)
40-49	0.0 (0/3315)*	0.0 (0/710)
50-59	16.2 (9/5549)	4.5 (1/2245)
60-69	39.1 (16/4097)	11.8 (2/1701)
70-79	150.8 (19/1260)	61.7 (3/486)
Crude Rate	30.9 (44/14221)	11.7 (6/5142)
Age-Adjusted Rate	38.1	13.1
RR	0.34	
95% CL	(0.12-0.81)	

1. Rates adjusted by the indirect method using the 1976 U.W. white female cardiovascular disease mortality rates (ICD 390-448) as the standard.
* Number of deaths/number of person-years of follow-up.
From reference 32.

breast cancer. Thus, an analysis of risk/benefit regarding hormone replacement therapy in menopausal and post-menopausal women really focuses primarily on its potential benefit in reducing subsequent cardiovascular risk. However, it is important to remember that no prospective therapeutic trials of estrogen replacement therapy on the risk of coronary heart disease in post-menopausal women have been conducted. Thus, estrogen replacement cannot be recommended for this purpose at the present time. It is also not clear if the beneficial effects of estrogens described above will be evident in the future if a progestin is added with estrogen in a cyclical fashion (33, 36).

IV. Evidence That Cholesterol Reduction in Human is Beneficial

Although a positive relationship between cholesterol and coronary heart disease has been recognized for decades, only recently has it been shown that cholesterol reduction translates into reduced cardiovascular risk. Most of the therapeutic trials have been conducted in middle-aged men because this group was most susceptible to premature heart disease. Extensive therapeutic trials in women and in the elderly have not been

conducted and any recommendations regarding treatment in these groups of patients must be inferred from the data in men and the known pathophysiology of atherosclerosis.

Table 7. Lifetime Risks of Death Due to Selected Conditions for 50-Year-Old White Post-Menopausal Women[1]

Condition	Lifetime Risk (%)
Coronary Heart Disease	31.0
Hip Fracture	2.8
Breast Cancer	2.8
Endometrial Cancer	0.7

1. From Cummings, S.R., et al. Arch. Int. Med. 149:2445-8, 1989.

The results of several of the major trials are described below and a summary of the recent large scale trials involving lipid-altering medications are summarized in Table 8.

1. The Oslo Study Diet-Smoking Trial (37) was conducted in 1232 healthy normotensive men aged 40-49 yrs who were at high risk for developing CHD. Men were enrolled in the study if they had serum cholesterol levels of 290-380 mg/dl; coronary risk scores, based on cholesterol levels, smoking habits and blood pressure, in the upper quartile of distribution; and systolic blood pressure below 150 mm Hg. The intervention group (n=604) were given lipid lowering diets and were counselled to stop smoking. The control group (n=628) received routine care. Over the 5 year trial period, the mean serum cholesterol and triglyceride dropped 13% and 20%, respectively, in the intervention group versus the control group. Mean tobacco consumption declined 45% or more in the intervention group but only 25% of these subjects discontinued smoking versus 17% in the controls. At the end of the study, the incidence of fatal and non-fatal myocardial infarction were 47% lower in the intervention group versus the controls. A more detailed statistical analysis suggested that the reduction in CHD incidence in the intervention group correlated more with the reduction of cholesterol and less with the reduction in smoking (37).

2. The Lipid Research Clinics - Coronary Primary Prevention Trial (LRC-CPPT) involved 3,806 asymptomatic men age 35-59 years with plasma cholesterol levels ≥265 mg/dl (Table 8). They were randomly allocated into two groups, one of which received diet plus placebo, while the other received diet plus cholestyramine 24 g/day (38)(39). The mean duration of follow-up was 7.4 years. The total and LDL-cholesterol levels decreased 8% and 12%, respectively, relative to the placebo group. These changes were associated with a 19% reduction in

Table 8. Summary of Large Scale Clinical Trials to Prevent Coronary Heart Disease in High Risk Populations

Trial (references)	Study Group	Duration (years)	Treatment	Response of Lipids to Therapy (mean values, mg/dL)	Outcome
LRC-CPPT[1]	3806 asymptomatic men, cholesterol >265 mg/dL	7	cholestyramine (24 g/day) (n = 1906); placebo (n = 1900)	Cholesterol (start→7th year) Total (280→257) LDL[3] (205→175 HDL[3] (44→47) Triglycerides (156→183)	19% reduction in risk of definite CHD death and/or definite non-fatal myocardial infarction.
Coronary Drug Project	8341 men with CHD[2], age 30-64 years	6.2	estrogen, dextrothyroxine, clofibrate or niacin	For niacin (3 g/day) (baseline→year 1) Cholesterol (253→227) Triglycerides (6.4→4.7 mEq/L)	119 men in niacin group had 11% less all-cause mortality and 12% less CHD death than placebo group at 15-year follow-up.
Helsinki Heart Study	4081 asymptomatic men, age 40-55 years with non-HDL cholesterol >200 mg/dL	5	gemfibrozil (1.2 g/day)	Cholesterol (baseline→ ≥25 months) Total (270→247) LDL (189→174) HDL (47→51) Triglycerides (175→115)	Cholesterol ↓ 8.5%; cardiac end-points ↓ 34%; no change in all-cause mortality.

1. LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial.
2. CHD, Coronary Heart Disease; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein.
3. Modified from reference 41.

the incidence of coronary heart disease, including both fatal and non-fatal coronary events. Other indicators of coronary heart disease, including a positive exercise tolerance test, angina and the need for coronary bypass surgery were reduced by 25, 20 and 21%, respectively (38, 39).

3. The Helsinki Heart Study involved 4,081 asymptomatic men age 40-55 years with non-HDL cholesterol levels >200 mg/dl. They were randomly allocated to receive either placebo or gemfibrozil at a dose of 600 mg twice daily. Over the 5 year observation period, gemfibrozil treatment decreased the total cholesterol by 8%, the LDL-cholesterol by 8-9%, and the triglycerides by 38%. The HDL-cholesterol rose by 10%. Cardiac endpoints were decreased by 34% but total mortality was not affected by this drug treatment (40).

These large scale prospective trials showed a benefit from cholesterol reduction on long-term cardiovascular risk in middle-aged men with high risk cholesterol levels at the start of therapy. In general, for every 1% drop in the cholesterol level, the risk was reduced by 2% in this high-risk group of subjects. It was also noted that the benefits of therapy usually became evident after the second year of treatment, which tends to dispel the notion that treatment of hypercholesterolemia takes many years to show clinical benefit. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) and the Helsinki Heart Study did not demonstrate a reduction in total mortality but the trials were considered inadequate to show such an effect (41). However, a reduction in all-cause mortality as well as CHD mortality was observed in the Coronary Drug Project which was extended to 15 years of follow-up (42).

Special mention must be made of the Stockholm Ischaemic Heart Disease Trial (43). This was a secondary prevention trial in survivors of myocardial infarction below age 70 yrs. About 20% of the subjects were female. The control group (n = 276) received only diet therapy; the treatment group received diet therapy to which was added clofibrate (1 g b.i.d.) and niacin (up to 1 g t.i.d.). The mean cholesterol and triglyceride levels in the treatment group at baseline did not differ from controls and were 252 and 208 mg/dl, respectively. During the trial, which ran for 5 years, serum cholesterol dropped 13%, triglycerides dropped 19%, total (all cause) mortality dropped 26%, total mortality in those over 60 yrs of age dropped 28% and total ischemic heart disease mortality dropped 36%. The study was not blinded and data in the women were not analyzed apart from the total results.

These Stockholm trial results, while limited and somewhat flawed, suggest that treatment of high risk patients at least between ages 60-70 years, may be beneficial. It should be noted that clofibrate would no longer be used for such studies because of the apparent toxic effects associated with its use in the World Health Organization Trial (41).

The average degree of cholesterol reduction in these trials was clinically modest and the question persisted as to whether more aggressive cholesterol reduction would result in a more convincing reduction in risk.

Two studies have addressed this point and both have used coronary angiography to evaluate the effects of cholesterol reduction on coronary atheroma evolution.

The Cholesterol Lowering Atherosclerosis Study (CLAS) involved 162 men, aged 40-59 years, with moderate hypercholesterolemia, coronary artery disease, and coronary bypass grafts (44). All participants discontinued cigarettes and were prescribed a low cholesterol, low saturated fat diet. They were randomized into a placebo group and a group receiving therapy with colestipol and nicotinic acid. The dose of medication was adjusted to lower the total cholesterol at least 15%. Coronary angiograms were performed at baseline and again after 2 years of treatment.

The results of the lipid-lowering therapy are listed below in Table 9. This sustained reduction in total and LDL-cholesterol levels, plus an associated rise in the HDL-cholesterol induced largely by nicotinic acid therapy, was associated with evidence for regression of atherosclerosis, as summarized in Table 10 and Table 11.

Table 9. Mean Baseline and On-Trial Fasting Lipid Levels in the CLAS Trial[1]

Lipid or Lipoprotein	Drug Treatment[2]		Placebo	
	Baseline	On-Trial	Baseline	On-Trial
	mg/dl		mg/dl	
Total Cholesterol	246	180	243	232
Triglyceride	151	110	154	141
LDL-Cholesterol	171	97	169	160
HDL-Cholesterol	45	61	44	44

1. Blankenhorn, D.H. et al. JAMA 257:3233-3240, 1987.
2. Colestipol 30 g/day, Niacin 3-12 g/day.

Table 10. Effects of CLAS Treatment on Progression and Regression of Atherosclerosis at Two Years of Therapy[1]

Parameter	Treatment[2] (n = 80)	Control (n = 82)
	% of Subjects	
Regression of Lesions	16.2*	2.4
No Change in Lesions	45.0	36.6
Progression of Lesions	38.8	61

1. Blankenhorn, D.H. et al. JAMA 257:3233-40, 1987.
2. Colestipol 30 g/day; Niacin 3-12 g/day as required.

* $p<0.002$

Table 11. Effects of CLAS Treatment on Atherosclerotic Progression in Native and Grafted Coronary Vessels at Two Years of Therapy[1]

Parameter in Native or Grafted Vessels	Treatment[2] (n = 80)	Control (n = 82)
	% of Subjects	
Native Vessels:		
• New Lesions	10	22*
• Average No. of Lesions Showing Progression Per Subject	1.0	1.4*
Grafted Vessels:		
• New Lesions	18	30*
• Adverse Atherosclerotic Changes	24	39*

1. Blankenhorn, D.H. et al. JAMA 257:3233-40, 1987.
2. Colestipol 30 g/day; Niacin 3-12 g/day as required.

* $p<0.03$

This study provided information on several important clinical issues. First, atheromas in the coronary circulation could be reduced in patients by lowering total and LDL-cholesterol, and probably by raising HDL-cholesterol. Second, substantial progression of atherosclerosis occurred in native and grafted vessels over a 2-year period in male patients with total cholesterol levels often considered alright by clinicians (Table 11). Third, despite treatment, some progression of atherosclerosis continued. These results have been extended to 4 years of observation in 103 of the subjects and the benefit of aggressive lipid-lowering therapy continues to accrue (45).

These results were confirmed and extended recently by investigators at the University of Washington (46). This Seattle study is called the Familial Atherosclerosis Treatment Study (FATS) and included 103 men, ≤62 yrs of age, with atherosclerosis, a family history of premature cardiovascular events, and with plasma apolipoprotein B ≥125 mg/dl. The group was divided into thirds and all were prescribed a low total fat, low cholesterol diet. One group received colestipol (30 g/day) plus placebo and constituted the control group. Another group received colestipol plus niacin (4 g/day), and a third group received colestipol plus lovastatin (40 mg/day). The men had coronary angiograms at baseline and after two and one-half years of treatment. The effects of treatment on plasma lipoprotein levels (expressed as percent change) are listed in Table 12. The results of these treatments on cardiovascular events and on regression of coronary atherosclerosis are summarized in Table 13. Both lovastatin and niacin, when combined with colestipol produced substantial reductions in LDL-cholesterol levels. Both combinations also raised HDL-cholesterol, but niacin produced the greater

Figure 12. Familial Atherosclerosis Treatment Study (FATS)

Effect of Niacin or Lovastatin, Combined with Colestipol, on Plasma Lipoprotein Levels in Men ≤ 62 Yrs with Elevated Plasma Apolipoprotein B Levels and Coronary Artery Disease[1]

Treatment[2]	N	% Change Over 2.5 Years	
		LDL	HDL
Colestipol	37	- 9	3
Colestipol + Lovastatin	34	- 48**	14**
Colestipol + Niacin	32	- 34**	41**

Versus Colestipol: * p< 0.05; ** p < 0.006

1. BG Brown et al. Circulation 80(suppl II):II-266 (1989).
2. Doses: Colestipol 30 g/day; Lovastatin 40 mg/day; Niacin 4 g/day.

Figure 13. Familial Atherosclerosis Treatment Study (FATS)

Effect of Niacin or Lovastatin, Combined with Colestipol, on Premature Cardiovascular Events and Regression of Coronary Atherosclerosis in Men ≤ 62 Yrs with Elevated Plasma Apolipoprotein B Levels and Coronary Artery Disease[1]

Treatment[2]	N	Cardiovascular Events[3]	Stenosis Change %	Patients With Only	
				Progression	Regression
Colestipol	37	11	+ 1.7 ± 3	16	4
Colestipol + Lovastatin	34	3*	- 0.3 ± 4*	10	13*
Colestipol + Niacin	32	1**	- 0.9 ± 4**	9	15**

Versus Colestipol: * p< 0.05; ** p < 0.006

1. BG Brown et al. Circulation 80(suppl II):II-266 (1989).
2. Doses: Colestipol 30 g/day; Lovastatin 40 mg/day; Niacin 4 g/day.
3. Includes death, proven myocardial infarction or newly refractory ischemic symptoms requiring bypass surgery or angioplasty.

change (Table 12). Cardiovascular events were significantly reduced in both combined treatment groups. Progression of plaque was reduced and there was significant regression of lesions in both combined treatment groups (Table 13).

The results from the CLAS and FATS studies are very encouraging. They clearly demonstrate reversibility of plaque in males when aggressive cholesterol reduction is maintained for as little as 2-2 1/2 years. Both suggest but do not prove that elevation of HDL-cholesterol may also be beneficial. They also demonstrate that progression of lesions also occurs despite aggressive plasma lipid reduction. Perhaps more regression and less progression will occur if treatment is continued for longer periods of time. Although the age groups extend to slightly beyond age 60 years, these results cannot be extrapolated unequivocally to the elderly.

Despite a paucity of data regarding plaque reversal in the elderly, there is reason to believe that reversal might take place, or at least that arrest of the process can occur. First, there are no data to suggest that atherosclerosis in the elderly is anything other than a continuation of the disease process that occurs in early and middle age (47, 48). Based on autopsy studies, the effect on the artery wall in a particular person depends on the genetically determined response to the type and intensity of risk factors, as well as the duration of exposure to those risk factors (49). None of these data indicate that the fundamental atherosclerotic process differs in the elderly. In the plaque-reversal process, lipid deposition in foam cells is the first to undergo reversal, whereas extracellular cholesterol crystals are mobilized very slowly (50). It is unclear if any significant removal of fibrous connective tissue deposits in the plaque occurs (51). The large lumenal space-occupying lesions consisting of foam cells are therefore most readily reversible. Apart from reversal, a reduction of plasma lipid levels appears to slow the rate of deposition of debris in the plaque areas and thereby appears to retard the growth of many lesions.

A more direct clue that the atherosclerotic process may be altered in the elderly comes from a study of mortality rates from coronary heart disease in the United States between 1968 and 1975 (52). As shown in Table 14, there has been a steady decline in coronary heart disease death in the United States over this time period (actually, the decline has continued through the early 1980's). The decline occurred in both sexes, in both whites and nonwhites, and in all age groups, including the elderly. These results indicate that the older age groups can benefit from risk factor modification, although it must be pointed out that the reasons for this decline have not been conclusively related only to risk factor reduction (53).

V. A General Definition of Hypercholesterolemia, and Guidelines for Evaluation and Treatment of Hypercholesterolemia in Adults

The large scale clinical trials described in section IV, combined with information from regression studies in animal experiments, clinical studies in genetic forms of hypercholesterolemia and the outcome of

Table 14. Percent Change, Age-Specific Mortality Rates, Coronary Heart Disease, United States 1968-1975[1]

Sex-Color Group	Age Group (Years)			
	35-44	45-54	55-64	65-74
White Males	– 23	– 17	– 18	– 19
White Females	– 22	– 16	– 19	– 25
Nonwhite Males	– 29	– 21	– 24	– 33
Nonwhite Females	– 44	– 32	– 30	– 37

1. From Cooper, R. et al. J. Chron. Dis. 31:709-20, 1978.

epidemiological studies (eg. Framingham) generated compelling arguments for the more aggressive detection and treatment of hypercholesterolemia in adults. The National Cholesterol Education Program (NCEP) was launched and one of the first major reports it developed was entitled "Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults"(54). This report presented a series of guidelines for clinicians to assist in the management of hypercholesterolemia. They contain several unique features related to clinical practice:

- They stratify patients by plasma cholesterol levels into 3 groups: desirable, borderline high risk, and high risk. Precise numbers are given to define these cholesterol ranges based on the epidemological information from the Multiple Risk Factor Intervention Trial (MRFIT), which included observations on 360,000 men ages 35-59 years in the United States.

- The risk status of patients is initially assessed with total cholesterol levels, and then refined by the use of LDL-cholesterol levels.

- Patients with low HDL-cholesterol levels (≤35 mg/dl on repeat measurements) are considered at high risk, but those with higher HDL-cholesterol levels (ie. >55 mg/dl) receive no "credit" for the reduction of cardiovascular risk imparted by the high HDL-cholesterol level.

- The risk status of a patient is affected by the presence of other cardiovascular risk factors, one of which is the male sex. Thus the guidelines are applied more conservatively to females.

- The rise in cholesterol with age is considered abnormal. Therefore the cut-points for plasma cholesterol are not age-adjusted.

- In addition to providing precise cut-points for initially stratifying patients, the guidelines recommend therapeutic goals that vary

depending on the presence of other risk factors or the presence of cardiovascular disease in the individual patient.

- Diet is the mainstay of treatment. If therapeutic goals are not achieved with diet therapy alone, then drug therapy is considered. However, to prevent the overuse of drugs in the asymptomatic patients with no risk factors other than hypercholesterolemia, the LDL-cholesterol level for initiation of drug treatment is recommended to be 190 mg/dl (very high risk category). However, if a patient has CHD, peripheral vascular disease or 2 other risk factors, the threshold for initiating drug treatment is lowered to 160 mg/dl.

- The report acknowledges a paucity of data regarding the effectiveness of treating hypercholesterolemia in the elderly. It recommends considering treatment in high risk patients, based on the clinical judgement of the attending physician. Thus the decision to treat or not to treat is based on the physiological age of the patient rather than the chronological age.

The stratification of patients over the age of 20 years based on the total cholesterol is listed in Table 15. The stratification of patients based on the LDL-cholesterol is presented in Table 16. A flow diagram outlining the

Table 15. National Cholesterol Education Program Recomendations for Initial Stratification and Follow-up of Adults Based on the Total Cholesterol Level: Considerations are Based on the Presence or Absence of Coronary Heart Disease and Other Cardiovascular Risk Factors

Initial Finding	Follow-up
<200 mg/dL	Repeat total cholesterol within 5 years
200-239 mg/dL	
• without CHD[1] or 2 other CHD risk factors[2]	Dietary Information and recheck annually
• with CHD[1] or 2 other CHD risk factors[2]	Lipoprotein analysis[3]; then take further action based on LDL-cholesterol level.
≥240 mg/dL	

1. CHD = Coronary Heart Disease.
2. Risk factors include male gender; family history of premature CHD; cigarette smoking; hypertension; reduced HDL-cholesterol level; diabetes mellitus; severe obesity; definite cerebrovascular or peripheral vascular disease.
3. LDL-cholesterol is calculated with the following equation using data from fasting plasma specimens:
   LDL-cholesterol = Total cholesterol — HDL-cholesterol — (Triglyceride/5)
   but the formula loses accuracy when the triglyceride level exceeds 400 mg/dl.

decision plan for evaluation and treatment of hypercholesterolemia in adults is shown in Figures 12 and 13.

These guidelines provide a framework for the clinician in evaluating patients with hypercholesterolemia. They should not be considered rules for clinical practice; they are not to supersede the application of sound clinical judgement and the individualization of therapy.

Table 16. National Cholesterol Education Program Guidelines for Treatment of Hypercholesterolemia Based on the LDL-Cholesterol Level

Initial level (mg/dL)	Suggested Treatment	Minimal goal of therapy (mg/dL)
• Without CHD[2] or other cardiovascular risk factors[2]		
≥160	diet	<160
≥190	diet and drug treatment[1]	<160
• With CHD[2] or 2 other cardiovascular risk factors[2]		
≥130	diet	<130
≥160	diet and drug treatment[1]	<130

1. Drug treatment should not be automatically initiated but is considered if diet therapy does not achieve desired therapeutic goals.
2. Abbreviations and risk factors are as in Table 15.

VI. Special Considerations and Recommendations Regarding the Application of NCEP Adult Guidelines for the Diagnosis and Treatment of Hypercholesterolemia to the Elderly Population

When the NCEP adult guidelines are applied to the U. S. population between the ages of 20 and 74 years, 24-25% of males and 24-29% of females are hypercholesterolemic as defined by a plasma cholesterol level ≥240 mg/dl (Table 17) (54). However, when the ages are subdivided by decades, the prevalence of hypercholesterolemia increases sharply in the older age groups, as would be expected, given the progressive rise in cholesterol with age described previously. Thus, by age 55 years, 37% of white men, 35% of black men, 41% of white women and 41% of black women have total cholesterol levels ≥240 mg/dl. By age 65, the prevalence is even greater in women, but declines slightly in men (Table 17). Based on these figures, about 40 million Americans between the ages of 20 and 59 years are

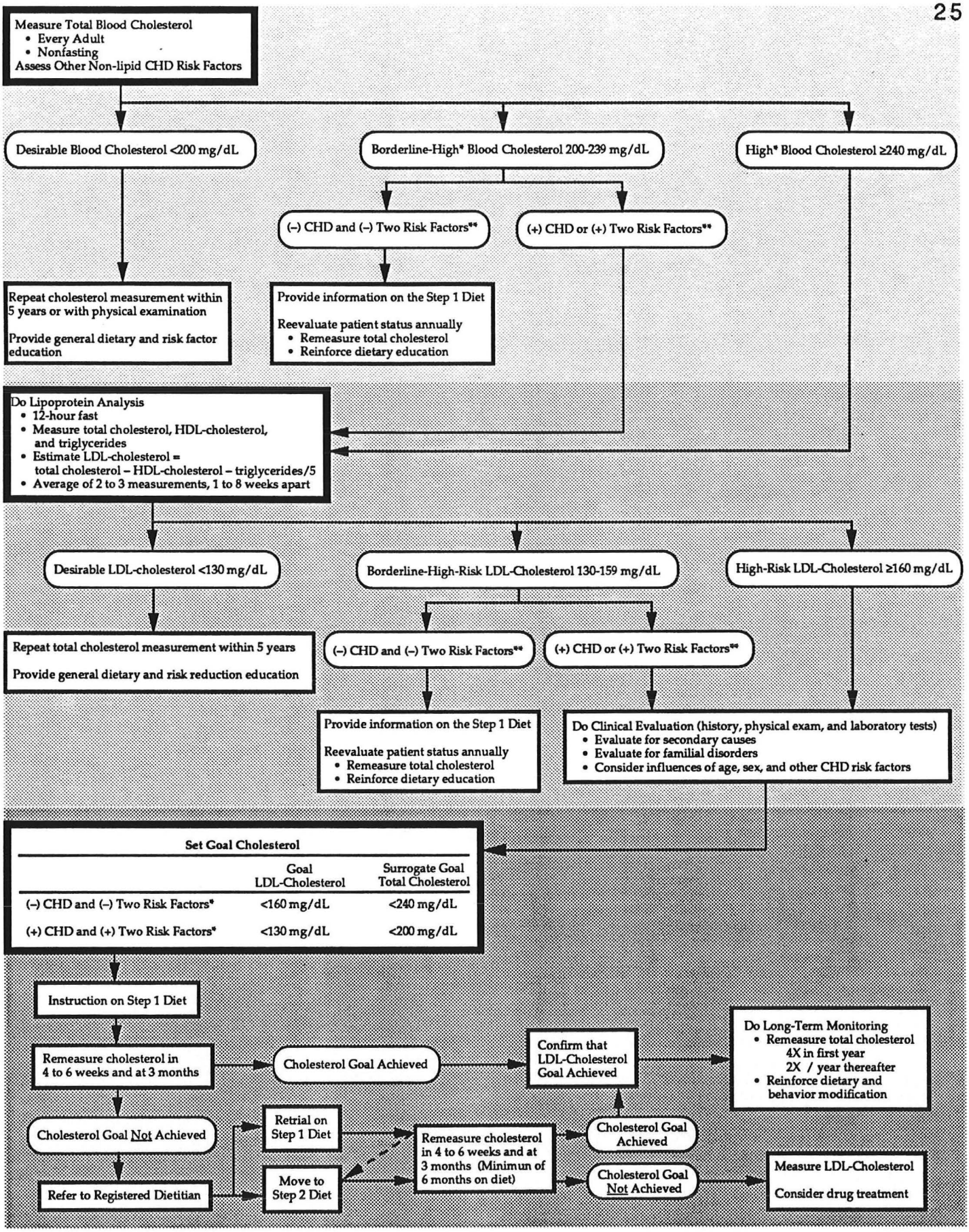


Figure 12. Decision Plan for Evaluation and Treatment of Hypercholesterolemia.

(*) indicates the result must be confirmed by repeat measurement; (**) indicates one risk factor can be the male sex. Modified from reference 54.

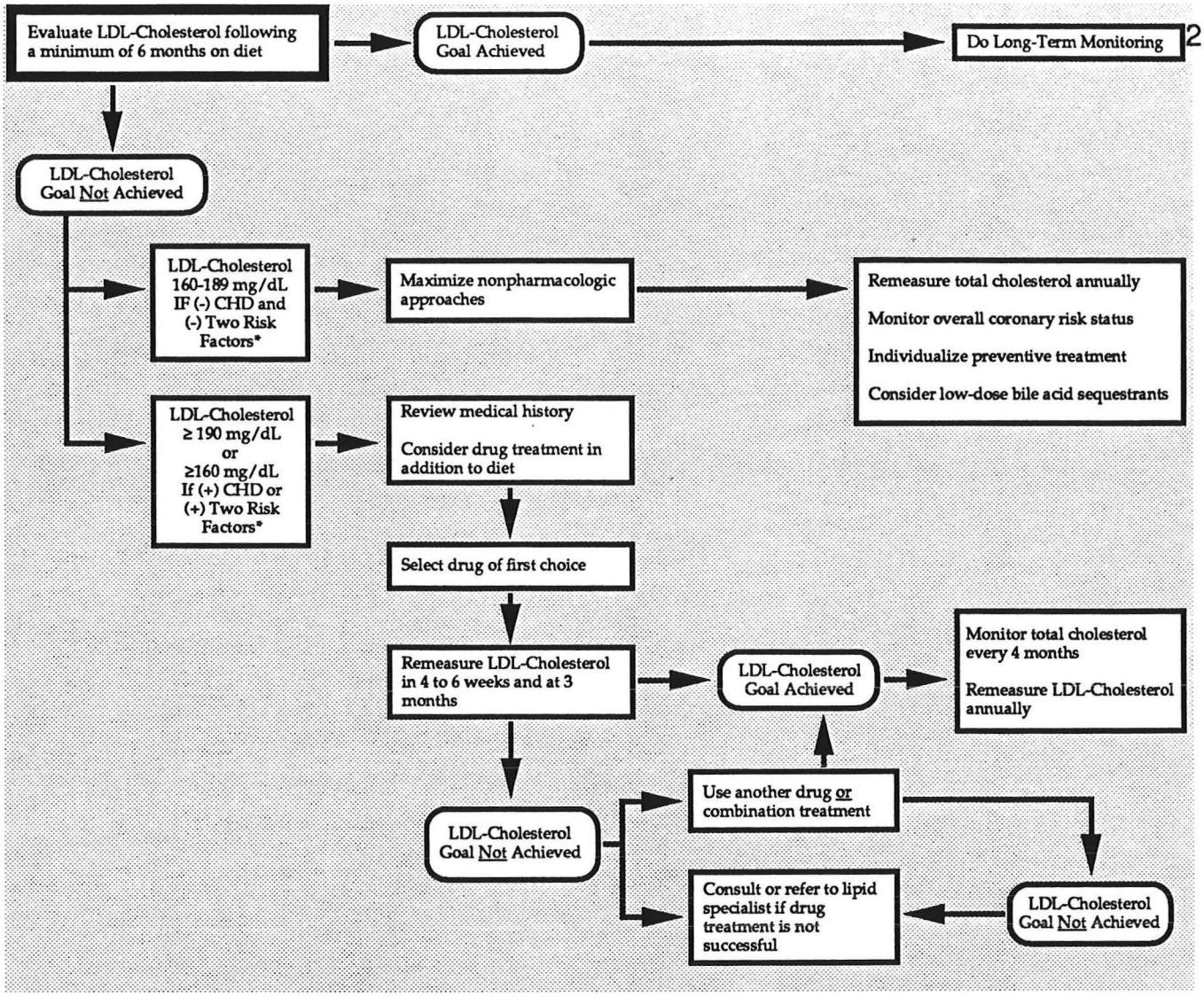


Figure 13. Step-Wise Approach to Drug Treatment of Hypercholesterolemia Based on National Cholesterol Education Program Guidelines.
(*) indicates one risk factor can be the male sex. From reference 54.

Table 17. U.S. Prevalence of High Blood Cholesterol* by Age, Race, and Sex (Percent of Each Population)

	Men		Women	
Age, yr	White	Black	White	Black
20-74	25.0	23.9	29.2	23.7
20-24	6.1	2.9	6.5	7.0
25-34	15.0	19.3	12.4	8.7
35-44	27.9	24.5	21.1	16.9
45-54	36.5	40.3	40.6	40.7
55-64	37.3	35.3	53.7	46.5
65-74	32.4	27.2	52.1	48.4

* Serum concentration of cholesterol ≥240 mg/dl.

candidates for medical advice and intervention, and 24 million Americans aged 60 years and older are candidates (55).

A literal application of the NCEP guidelines would have a dramatic economic impact on the health care market. Furthermore, as already noted, medical interventions would be undertaken in a large elderly group of "patients" without sufficient data to determine if these interventions were of any benefit. For this discussion the term elderly will apply to individuals over the age 65 yrs. Some authors use the term "elderly" to describe the group between the ages of 60 or 65 and 75 years, and use the term "old age" for those over age 75 years. With regard to the current topic there are not sufficient data in the entire age group to warrant differentiating between the "elderly" and the "old".

1. Clinical Considerations in Treating Hypercholesterolemia in the Elderly. I recommend treatment of hypercholesterolemia in the appropriately selected elderly patient, especially those in the range of 60-75 years where life expectancy is considerable. First, for any given set of risk factors, onset of clinically apparent atherosclerosis varies in different patients. Progression of atherosclerosis can be halted and regression can be induced in hypercholesterolemic patients when the hypercholesterolemia is controlled. Optimal LDL-cholesterol levels are not established but are probably less than 130 mg/dl, and perhaps less than 100 mg/dl (see results of the CLAS study). Atherosclerosis appears to represent a continuum or spectrum of pathology rather than a distinctly different disease in the elderly as compared to the middle aged. Evidence is clear that cardiovascular risk factors continue to exert an adverse effect in the elderly. Although the total cholesterol appears to lose power as a risk predictor in the elderly, the lipoprotein fractions retain this power and thereby implicate dyslipidemia in the atherogenic process.

2. Patient Selection: As already noted, the average life expectancy at age 65 years ranges from 15 to 19 years (2). Patients in this age range who enjoy relatively good health, function well behaviorally and emotionally, and retain good cognitive function should be candidates for testing and possible therapy because of their good "physiological" or "biological" age. Testing and evaluation should not be undertaken unless the patient has an interest and motivation for cardiovascular risk factor modification. Since benefit from therapy of hypercholesterolemia may occur in as little as two years, starting therapy in a high risk patient at age 60 or even later may be worthwhile if morbidity is delayed. If members of this age group are considered candidates for coronary artery bypass graft surgery, then it seems reasonable to also undertake appropriate treatment to control for cardiovascular risk factors that cause the problem (56).

   Patients with genetic forms of hypercholesterolemia associated with premature atherosclerosis (eg. Familial Hypercholesterolemia,

Familial Combined Hyperlipidemia, Polygenic Hypercholesterolemia) should be treated if their overall health status warrants.

3. Therapy of Hypercholesterolemia in the Elderly.

A. *General Therapy*. An overall assessment of non-lipid cardiovascular risk factors should be made and appropriate measures taken to control any that are modifiable (Table 18). Beneficial results in the elderly with therapy of hypertension (57) and the cessation of smoking (58) have been reported. In the treatment of hypertension, drugs that do not exert a harmful effect on plasma lipid levels should be selected whenever possible (eg. ACE inhibitors, calcium channel blockers) (59, 60).

Table 18. Major Cardiovascular Risk Factors Other than Cholesterol and LDL-Cholesterol to Consider in the Evaluation and Treatment of Hypercholesterolemia*

Male sex.
Family history of premature coronary heart disease: a myocardial infarction or sudden death before age 55 years in a parent or sibling.
Cigarette smoking: currently smokes more than ten cigarettes per day.
Hypertension.
Low HDL-cholesterol level: below 35 mg/dL and confirmed by repeated measurement.
Diabetes mellitus.
History of definite cerebrovascular or occlusive peripheral vascular disease.
Severe obesity (≥30% over weight).

* From reference 54.

B. *Diet Therapy*. Conservative therapy with diet is the mainstay of treatment in all adults with hypercholesterolemia. Dietary cholesterol and saturated fats suppress LDL receptor activity *in vivo*, and obesity stimulates VLDL overproduction, leading often to concomitant LDL overproduction. Thus, therapeutic diets are adjusted to achieve or maintain ideal body weight, and they are restricted in saturated fats and cholesterol. The NCEP dietary guidelines are listed in Table 19. In general, dietary therapy is initiated with the Step-One diet and if the appropriate cholesterol goal is not achieved in 3 months, the more restrictive Step-Two diet is prescribed. However, severe dietary restrictions are not recommended in the elderly (54). Therefore, dietary restriction of saturated fat and cholesterol should not exceed that recommended in the Step-One diet. Appropriate follow-up after initiating diet therapy is outlined in Figure 12. The response to diet is evaluated with regular follow-up at 6-8 weeks, and again at 3-4 months. If

the cholesterol goal is achieved as defined in Figure 12, regular follow-up 2-3 times each year with a total cholesterol measurement is adequate. If the cholesterol goal is not approximated and the patient remains at high risk, therapy with medication should be considered.

Table 19. Dietary Guidelines for Therapy of Hypercholesterolemia Using a Two-Step Diet*

	Recommended Intake	
Dietary Constituent	Step-One Diet	Step-Two Diet
Total fat	Less than 30% of total calories	Less than 30% of total calories
Saturated fatty acids	Less than 10% of total calories	Less than 7% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories	Up to 10% of total calories
Monounsaturated fatty acids	10-15% of total calories	10-15% of total calories
Carbohydrates	50-60% of total calories	50-60% of total calories
Protein	10-20% of total calories	10-20% of total calories
Cholesterol	<300 mg/d	<200 mg/d
Total calories	To achieve and maintain desirable body weight	To achieve and maintain desirable body weight

* From reference 54.

C. Drug Treatment for Hypercholesterolemia in the Elderly. Drug therapy for hypercholesterolemia should be reserved for those high-risk elderly patients who are functional and who are highly motivated to control their hypercholesterolemia as part of an overall risk factor modification program. The major drugs used in the therapy of hypercholesterolemia are listed in Table 20 (54, 61, 62). Since the metabolism of and reactions to drugs may be altered in the elderly, it is prudent to start with the lowest therapeutic doses and make upward adjustments carefully while monitoring regularly for both unwanted side effects and an appropriate therapeutic response (63, 64). The NCEP guidelines for initiating drug therapy and appropriate follow-up are outlined in figure 13.

Suggested doses for cholesterol-lowering medications in the elderly and some additional precautions are listed below:

1. **Cholestyramine**: 8-16 g/day in 2 daily doses.

2. **Colestipol**: 10-20 g/day in 2 daily doses.

The above two bile acid sequestrants frequently cause constipation, which can be especially troubling in the elderly patient. Increasing free water intake by 12-24 oz per day is one solution, as is the addition of a fiber laxative such as metamucil. Metamucil alone has mild cholesterol-lowering properties and

might be considered as initial therapy at a dose of 3.4 g t.i.d. in more mildly affected patients (65, 66).

Bile acid sequestrants may bind to other medications and render them therapeutically ineffective. Other medications must be given one hour before or up to 4 hours after the bile acid sequestrant dose is taken. In elderly patients taking other medications, it may not be possible to establish an appropriate medication schedule while attempting to use a bile acid sequestrant; they are best avoided in more medically complex patients.

Table 20. Summary of Major Drugs for Treatment of Hypercholesterolemia*

Drugs	Reduce CHD§ Risk	Long Term Safety	LDL-Cholesterol Lowering (percent)	Special Percautions
Cholestyramine, Colestipol	Yes	Yes	15-30	Alters absorption of other drugs; may increase triglyceride levels.
Nicotinic Acid	Yes	Yes	15-30	Hyperuricemia, hyperglycemia, liver function abnormalities, cutaneous flushing.
Lovastatin	Yes‡	Unknown	25-40	Abnormal liver function; myositis.
Gemfibrozil	Yes	Yes	5-15	May increase LDL in hyper-triglyceridemic patients; lithogenic bile.
Probucol	Unknown	Unknown	10-15	Lowers HDL-cholesterol, but significance of this is not known; may prolong QT interval.

* Modified form reference 54.
§ CHD = Coronary Heart Disease.
‡ In combination with colestipol

3. **Nicotinic acid**: 1 g t.i.d. with meals. Start with a dose of 100 mg t.i.d. and build up over time. Avoid sustained-release preparations which cause more GI side-effects. Requires considerable patient education because of frequent side-effects. Aspirin (325 mg) may decrease incidence of flushing. It may induce hypotension in patients taking antihypertensive medications because of its vasodilatory effects. Its side effects may be less troublesome if lower doses are combined with small doses of a bile acid sequestrant (eg. Cholestyramine 4 g b.i.d.).

4. **Gemfibrozil**: 600 mg b.i.d.; useful for hypertriglyceridemia and for combined hyperlipidemia when HDL-cholesterol is low. Generally well tolerated.

5. **Lovastatin**: 20 to 80 mg/day, with meals, taken b.i.d. when a dose greater than 20 mg/day is used. Often, therapy with 20 mg/day is sufficient. Single dose therapy is taken with the evening meal. Risk of myopathy is increased when lovastatin is used with any of the following: erythromycin, cyclosporine, nicotinic acid, gemfibrozil. Lovastatin inhibits cholesterol biosynthesis *in vivo* to lower cholesterol levels. Insomnia has been reported in a few patients; if this side-effect is suspected with single dose therapy taken in the evening, the dose should be administered in the morning. Short-term studies in the elderly with simvastatin, a close relative of lovastatin, have shown it to be well tolerated and highly effective in a dose dependent manner, reducing total cholesterol up to 35% and LDL-cholesterol up to 49% in patients ranging in age from 60-82 years (67). However, long-term experience with these drugs in the elderly is not available.

6. **Probucol**: 500 mg b.i.d. with meals. Lowers HDL-cholesterol. Antioxidant properties may make it an antiatherosclerotic drug despite its relatively limited cholesterol-lowering abilities. Its role in the treatment of hypercholesterolemia is still not clearly established but therapeutic trials to define its use are currently in progress.

7. Combined drug treatment in hypercholesterolemia may have several advantages, as listed in Table 21. The most useful combinations are those pairing lovastatin or nicotinic acid (niacin) with a bile acid sequestrant. These combinations should be considered in particulary high risk patients such as those with familial hypercholesterolemia. In general, however, drug therapy in the elderly should be kept as simple as possible.

D. Individualize Therapy. The NCEP guidelines can be applied appropriately if clinical judgement is used to assess the general health, personal interest and cardiovascular risk of the individual patient.

E. Ethical and Cost Considerations. Time does not permit a detailed discussion of these important topics. The ethical considerations in restricting therapy on the basis of age are discussed in references 68, 69, and 70. Issues of cost are discussed in reference 71. However, there are some significant shortcomings to these cost projections that are described briefly in reference 10.

F. Benefits of Therapy. There are no clinical trials available in the elderly to help in evaluating the benefits of therapy for hypercholesterolemia.

Table 21. Advantages of Combined Drug Treatment in Hypercholesterolemia Unresponsive to Diet Alone

- **Greater Cholesterol Reduction in Severe Cases.**
- **Demonstrated Benefit in Halting Coronary Plaque Progression – CLAS, FATS.**
- **Demonstrated Benefit in Promoting Coronary Plaque Regression – CLAS, FATS.**
- **May Decrease Side-Effects of Single Drug Therapy if Doses Can Be Reduced.**
- **May Be Less Costly in Some Instances.**

Gordon and Rifkind (10) used data from the Framingham Heart Study and the MRFIT study to calculate the potential benefit of reducing cholesterol from 285 to 200 mg/dl in various age groups. Their calculations are summarized in Table 22. This analysis re-emphasized a point made earlier regarding relative risk versus

Table 22. Potential Benefit of Reducing Cholesterol from 285 to 200 mg/dl

Age Group (yrs)	Decrease in CHD Risk* (%)	"Preventable" CHD Deaths†		"Preventable" CHD Cases‡	
		Men	Women	Men	Women
35–44	77.4	1.8	0.7	11.8	3.2
45–54	61.8	6.3	0.9	23.4	6.0
55–64	46.3	8.7	1.8	26.0	10.2
65–74	33.1	9.5	3.8	20.4	10.6
75–84	22.9	12.7	6.5	20.4	12.3

* Calculated from exponential decay extrapolation in Figure 2 for midpoint of age range.
† Per 1,000 patients per year. Estimated by applying calculated age-specific percent decrease in CHD risk to age- and sex-specific CHD mortality rates in the Framingham Heart Study.[5]
‡ Per 1,000 patients per year, estimated as above. Totals include cases of myocardial infarction, coronary insufficiency and angina pectoris in subjects without prior CHD manifestations, and all CHD deaths.
CHD = coronary heart disease.

attributable risk (Figure 5). Because of the high baseline level of CHD in the elderly, cholesterol reduction does not dramatically decrease risk in the individual elderly patient. However, this modest risk reduction applied to a large number of persons at risk results in a substantial increase in preventable CHD deaths and CHD cases in both men and women (Table 22). Although definitive answers are not available, considerable circumstantial evidence indicates that the elderly are likely to benefit from cardiovascular risk factor modification and should not be denied cholesterol-lowering therapy simply on the basis of their chronological age.

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