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December 17, 1992

# CHOLESTEROL MANAGEMENT IN ADULTS: CURRENT ISSUES

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Seven years ago the National Heart Lung and Blood Institute (NHLBI) initiated the National Cholesterol Education Program. The purpose of this program is to educate the general public and the medical profession about the dangers of high blood cholesterol. A high level of serum cholesterol is one of three major risk factors for coronary heart disease (CHD) (See Table below). These include cigarette smoking, high blood pressure, and high serum cholesterol. According to the Framingham Heart Study (Stokes et al. 1987), each of these factors accounts for about one-third of all excess deaths from CHD. In the 1960's the dangers of cigarette smoking became well established, and this resulted in the Surgeon Generals report warning the general public. Since then, the smoking habit has declined progressively. In the 1970's the dangers of high blood pressure became widely accepted; and the NHLBI initiated the National High Blood Pressure Education Program. Since then, treatment of hypertension has become routine, and the incidence of stroke has declined markedly; control of hypertension likely has contributed to the nation's decline in CHD rates as well.

## RATIONALE FOR
## CHOLESTEROL EDUCATION PROGRAM

**Risk Factors for CHD***

- **Cigarette smoking - one third**
- **High Blood Pressure - one third**
- **High serum cholesterol - one third**

***Framingham Heart Study**

Finally, in the mid 1980's the NHLBI initiated the National Cholesterol Education program. This program identified low density lipoprotein (LDL) as the major atherogenic lipoprotein, and the primary target of cholesterol management. Certainly the discovery of LDL receptor by Brown and Goldstein (1986) contributed to this decision to focus on LDL. The decision to target LDL in fact is based on several lines of evidence. There is a wealth of epidemiologic data implicating LDL as the primary atherogenic lipoprotein. The Framingham Heart Study (Stokes et al., 1987) and the Seven Country Study (Keys et al. 1970) are two examples. Genetic disorders of LDL metabolism also provide very strong evidence; these include familial hypercholesterolemia, the defect for which was discovered by Brown and Goldstein (1986), and familial defective apo B-100, which was first uncovered by Dr. Gloria Vega in the Center for Human Nutrition (Vega et al. 1986, Innerarity et al. 1990). Studies in laboratory animals, like the Watanabe rabbit and cholesterol-fed primates, point to LDL as an atherogenic lipoprotein. Recent studies at the tissue and cellular level provide details of how LDL produces atherosclerosis (Steinberg et al 1989). And finally, there is growing evidence from clinical trials that LDL lowering reduces risk for CHD. Most noteworthy is the Lipid Research Clinics Coronary Primary Prevention Trial (1984, 1992). Therefore, there is now little doubt that high LDL promotes coronary atherosclerosis and that reducing LDL levels reduces risk for CHD.

The NCEP has adopted two approaches for cholesterol control (See Table below). These include the population approach (Expert Panel 1990) and the high risk approach (Expert Panel 1988). The population approach aims primarily to improve the eating habits of all Americans: to limit intakes of saturated fat and cholesterol, to maintain a desirable body weight, and to promote physical activity. The high-risk approach is based on case findings i.e., to detect and classify patients with high blood cholesterol, primarily high LDL levels. In patients with elevated LDL concentration, it recommends dietary therapy and physical activity, and if necessary, drug therapy.

# NATIONAL CHOLESTEROL EDUCATION PROGRAM

- **Population approach (dietary change)**
- **High-risk approach**
  - **Detection and classification**
  - **Dietary therapy and physical activity**
  - **Drug therapy**

The goals for therapy in patients with hypercholesterolemia were first set forth in 1988 by an expert panel called the Adult Treatment Panel, now known as ATP I (Expert Panel, 1988). These goals are shown in the on the next page. They are not age specific goals. For patients having high serum cholesterol, but less than two CHD risk factors, the LDL-cholesterol goal is less than 160 mg/dl. The CHD risk factors were defined as CHD itself, peripheral vascular disease, smoking, hypertension, diabetes mellitus, low HDL cholesterol, severe obesity, family history of premature CHD, and male sex. For high risk patients, i.e., those with two or more CHD risk factors, the LDL cholesterol goal was set at less than 130 mg/dl.

# GOALS OF THERAPY
# FOR HYPERCHOLESTEROLEMIA

## Adult Treatment Panel I

- **For otherwise low-risk patients**

  **(Less than two CHD risk factors*)**

  **LDL goal = < 160 mg/dl**

- **For high-risk patients**

  **(Two or more CHD risk factors*)**

  **LDL goal = < 130 mg/dl**

*** CHD, PVD, Smoking, HTN, DM, ↓HDL, OB, $FH_x$ of CHD, ♂**

Since 1988, as a result of the NCEP, awareness of the importance of high blood cholesterol has increased enormously. In addition, significant research advances have been made, and new issues have arisen. The time therefore has come to reconsider the recommendations of ATP I, and if necessary, to revise them. Therefore, the NCEP has reconvened the Adult Treatment Panel. In the revision, special attention will be given to the new and pressing issues. These are outlined in the Table below. They include the role of cholesterol management in secondary prevention of CHD, the place of primary prevention (does it reduce total mortality i.e., extend life?) (is it cost effective, i.e., does it cost too much?) the role of cholesterol management in women and the elderly, and what to do about HDL and triglycerides, which were largely ignored in ATP I. Each of the issues can be considered.

# NEW ISSUES

- **Secondary prevention**
- **Primary prevention**
  - **Total mortality**
  - **Cost effectiveness**
- **Women and the elderly**
- **HDL and triglycerides**

Secondary Prevention

A significant fraction in the overall decline in CHD mortality in the U.S.A. undoubtedly is due to secondary prevention, that is, to prevention in patients with established CHD. Improved treatment of acute myocardial infarction -- thrombolysis, coronary surgery, and anti-arrhythmic drugs-- have contributed as well. But secondary prevention probably has played an even greater role. The major, well-established preventive measures are cardiac rehabilitation, beta-blockers, aspirin, smoking cessation, control of hypertension, and as will be considered here, treatment of cholesterol disorders. The issue is whether treatment of cholesterol disorders will reduce risk for another heart attack and for CHD death, and will decrease total mortality, in patients with established CHD.

There has been a growing number of reported secondary prevention trials of cholesterol lowering. The major trials are listed in the Table below (A Research Committee, 1965, 1968, 1971, Carlson et al. 1988, Coronary Drug Project Research Group, 1975, 1978, Leren, 1966. Trial 1971, Blankenhorn et al. 1987, Brown et al., 1990). They have employed a variety of cholesterol-lowering modalities -- both diet and drugs. Results for individual trials have varied; some have been strongly positive, whereas others have been negative. Individually the results are ambiguous, but when the data of all trials are pooled and subjected to by meta-analysis the results are strongly positive.

## SECONDARY PREVENTION TRIALS

- Coronary Drug Project
- New Castle
- Edinburgh
- Stockholm
- Oslo
- MRC
- CLAS
- FATS
- POSCH

The results of these meta-analyses are summarized in the Table below (Rossouw, et al. 1990). There appears to be two benefits to cholesterol lowering in CHD patients. First, new CHD events were reduced by an average of 25%; and second, total mortality was decreased by 10%. Of importance, the detrimental effects associated with cholesterol reduction were minimal. There was no increase in nonCHD mortality. Thus, the net benefit was positive: total mortality was decreased by reduction of cholesterol levels.

## CORONARY HEART DISEASE

**Benefits of Cholesterol Lowering (CHD patients)**

- 25% reduction in new CHD events
- 10% reduction in CHD mortality

**Detrimental Effects (?)**

- No increase in nonCHD mortality

**Net Benefit**

- Reduction in total mortality

It is probable that revisions of ATP I will emphasize secondary prevention. This implies more aggressive cholesterol management in patients with established CHD. The probable recommendations for cholesterol lowering are presented in the Table below. For low-risk and high-risk patients without CHD, the goals for LDL-cholesterol lowering will remain the same. However, for CHD patients, the goal probably will be lower, i.e., to 100 mg/dl or below.

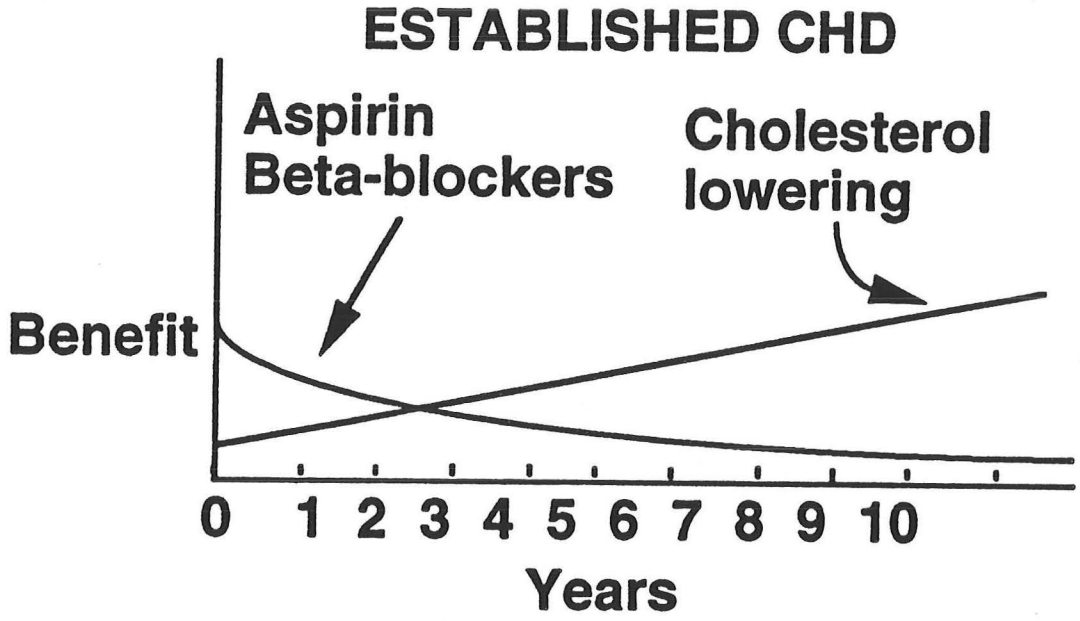
## GOALS FOR LDL CHOLESTEROL

- **Low-risk patients (nonCHD)**
  - **LDL goal < 160 mg/dl**
- **High-risk patients (nonCHD)**
  - **LDL goal < 130 mg/dl**
- **CHD patients**
  - **LDL goal ≤ 100 mg/dl**

Aggressive cholesterol reduction can be carried out in two ways. First, maximal, cholesterol-lowering dietary therapy can be instituted immediately; and second, one can move more rapidly to drug therapy. In some cases, a single drug will be enough, but in others, two drugs may be required. The statin agents and nicotinic acid will be the mainstays of therapy, but bile acid sequestrants and fibric acids also may be used.

How does cholesterol lowering compare to other modalities of secondary prevention? The Figure below compares cholesterol reduction to aspirin and beta-blockers on a theoretical basis. Both aspirin and beta-blockers are thought to have their greatest benefit early on after myocardial infarction. Over the years the benefit may decline. In contrast, risk reduction may be less in the first couple of years, but thereafter it may increase. Thus, the longer a person lives after myocardial infarction, the greater will be the benefit. This has been the pattern observed in primary prevention trials, and it probably will hold true

in secondary prevention as well.




Certainly not all patients with established CHD will be candidates for secondary prevention by cholesterol reduction. In patients with relative contraindications, there is little to gain on a long-term basis by cholesterol reduction, mostly because of poor short-term prognosis. These relative contributions include: (a) marked impairment of heart-pump function (b) severe inoperable 3-vessel disease (c) refactory congestive heart failure (d) advanced chronologic or physiologic age, with a poor overall outlook. (e) previous massive myocardial infarction, and (f) concomitant diseases that carry a high morbidity or mortality. What constitutes CHD that justifies aggressive cholesterol lowering include: (a) previous myocardial infarction (b) anginal pectoris (c) history of coronary artery surgery and (d) history of coronary angioplasty. The finding of coronary atherosclerosis by angiogram alone is not sufficient. It does not convey the high risk imparted by established CHD. But other noncoronary, atherosclerotic diseases carry almost as high a risk for subsequent myocardial infarction as does established CHD. These conditions

include: (a) peripheral arterial disease (b) aortic atherosclerotic disease and (c) symptomatic carotid artery disease. These too justify aggressive cholesterol reduction.

In summary, there will be an enhanced emphasis on secondary prevention by cholesterol reduction. The available clinical trial data are favorable. The therapy will be more aggressive for patients with established CHD. A lower goal for LDL cholesterol, of 100 mg/dl (or less) will be set. And peripheral and carotid arterial disease are CHD risk equivalents when setting goals for LDL reduction.

Primary Prevention

The emphasis on secondary prevention should not detract from primary prevention. Ultimately, the greatest reduction in CHD will come through primary prevention. As indicated before, primary prevention consists of two elements: (a) the population approach and (b) the high-risk strategy. This document will focus on the latter-- the high-risk strategy, but it will pay attention to issues raised in primary prevention. These new issues can be reviewed briefly.

Total Mortality

First let us consider the total mortality issue. In essence this issue is concerned with the question of whether cholesterol reduction extends life. This question can be broken down into three questions.

- Does cholesterol lowering reduce CHD death?
- Does cholesterol lowering increase nonCHD death?
- What is the balance between these two?

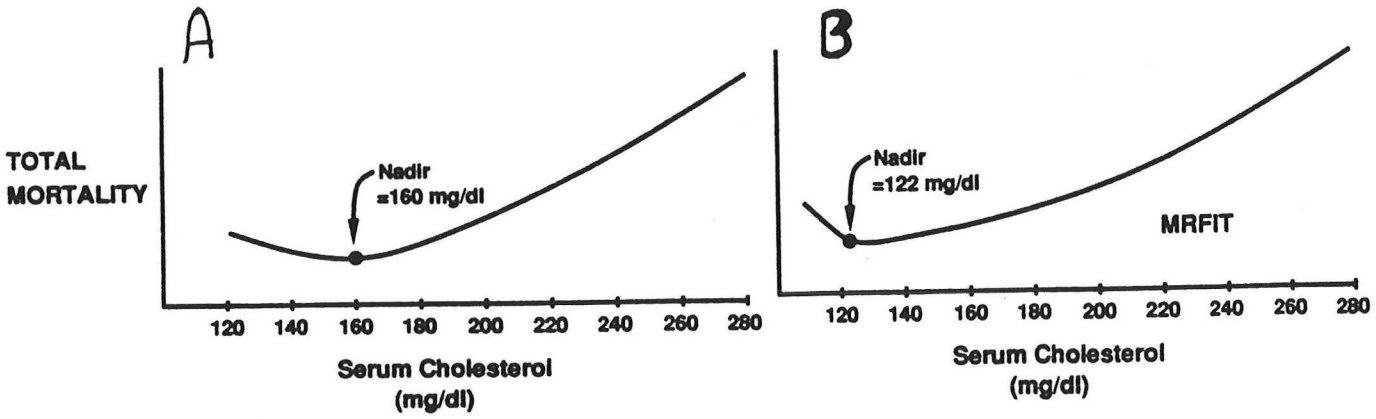
Clinical trials have proven that cholesterol lowering reduces CHD deaths. But what is known about the relation between CHD lowering and nonCHD death?

Limited data have raised the possibility that cholesterol lowering or low cholesterol itself may have adverse consequences. First, epidemiologic data

raise the possibility that very-low-cholesterol levels are accompanied by increased nonCHD deaths (Jacobs et al. 1992). And second, clinical trial data raise the possibility that cholesterol lowering (especially with drug therapy) can be associated with off setting fatal side effects (Holme, 1990, Muldoon, 1990, Raunskov, 1992, Wyowski and Gross, 1990).

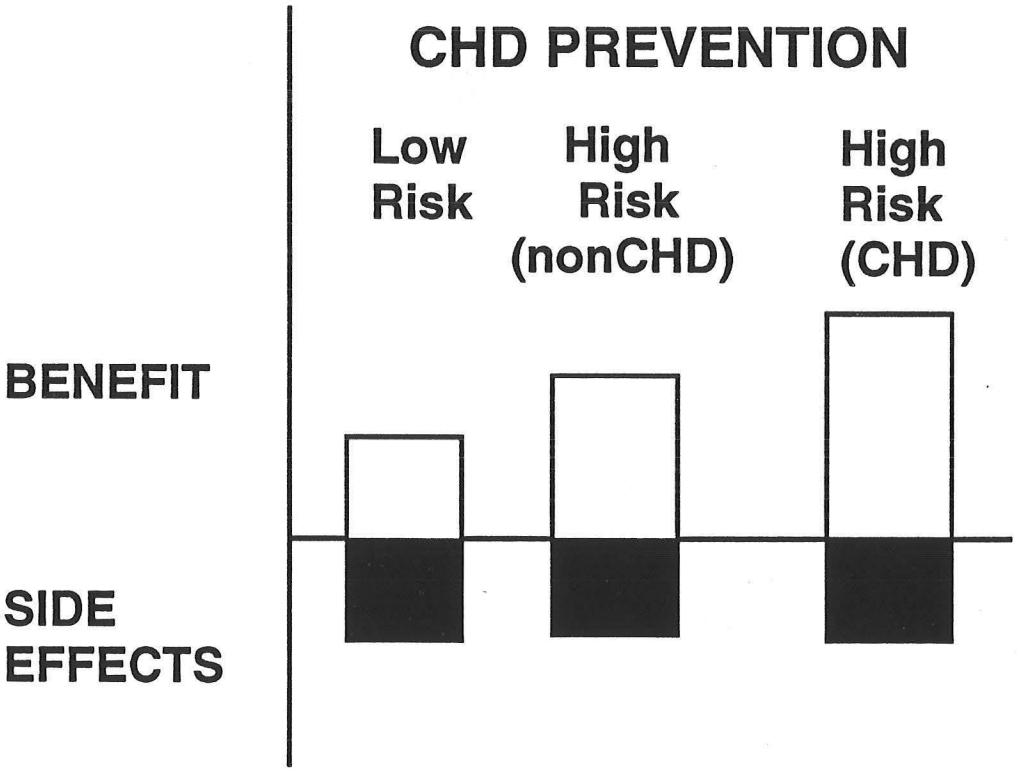
Several conditions have been associated with very low cholesterol levels. It must be emphasized that these are associations. They could be cause and effect, or vice versa, or merely confounding factors. They include: (a) gastrointestinal disorders, particularly cirrhosis of the liver, (b) pulmonary disorders, particularly chronic obstructive pulmonary disease (c) hemorrhagic stroke, (d) some forms of cancer, and (e) various behavioral manifestations, including alcoholism accidents, suicides, and violent behavior. If these conditions are causally related, the mechanisms responsible are by no mean clear. However, a likely possibility is that some of these disorders <u>cause</u> low blood cholesterol, but further research is necessary.

The question to be addressed is what is the nadir of the J-shaped curve relating total cholesterol levels to total mortality. Two possibilities are shown in the Figure. Figure A shows the results from a recent article by Jacobs et al. (1992). These results represent the pooling of a large body data from multiple epidemiologic studies (Jacobs et al, 1992). These data make it appear that the nadir is at 160 mg/dl. However, the analysis included only one category below 160 mg/dl, and the true nadir might be still lower. In fact, a major portion of all patients in this survey came from the MRFIT study (Multiple, 1990). A recent analysis of MRFIT data showed a nadir to be at 122 mg/dl (Neaton et al. 1992) (Figure B). Thus, the increase in deaths due to very low cholesterol levels occurred only when total cholesterol levels fell below 122 mg/dl. This includes only 1% of the population, and it is not a worrisome relationship. The results also suggest that total mortality increases progressively and curvilinearly above 122 mg/dL.




Perhaps of greater concern is that cholesterol lowering with drugs will lead to side effects that offset the benefit in CHD reduction. There are known and possible side effects of cholesterol lowering drugs. For example, the fibric acids are known to predispose to cholesterol gallstones. And statins sometimes cause hepatotoxicity and myopathy. Some clinical trials have suggested other side effects -- behavioral changes (accidents, suicide, violence) and cancer (Frick et al. 1987, Lipid Research Clinics, 1984, 1992, Oliver et al. 1978, 1980). These latter are very problematic, but almost all drugs have side effects, and it is necessary to use them prudently.

If we put the possibility of side effect of drugs into the total mortality equation, we can estimate the worst case scenario (see Figure on next page). This figure compares benefit versus side effects (in terms of total mortality). For people with only moderately high cholesterol, who are otherwise at low risk, side effects and benefit could balance out. The net effect would be zero -- no reduction in total mortality. There still would be a benefit for nonfatal CHD, which many people would consider a benefit, but not everyone is so soft hearted. The next case (middle) is the high-risk patient without CHD. Since the risk for CHD death is higher, total mortality will be reduced, even in the presence of side effects. The best result will be for patients with established CHD. A reduction in CHD mortality will more than offset any fatal side effects.


CHD PREVENTION
Low Risk
High Risk (nonCHD)
High Risk (CHD)
BENEFIT
SIDE EFFECTS

To summarize, does cholesterol lowering extend life? For patients with established CHD (secondary prevention), cholesterol lowering will almost certainly extend life. For primary prevention, treatment of high risk, older patients probably will extend life. However, treatment of lower risk, younger patients, may produce an uncertain results for total mortality. Only when there is more information about long-term side effects will we be certain about life extension with drugs. The same uncertainty should not exist with use of diet.

## Cost Effectiveness of Cholesterol Lowering

This brings us to the question of cost effectiveness. In other words, how much does it cost to achieve benefit from cholesterol reduction? Even though it costs money when one has a heart attack, it may cost still more to prevent CHD. Nonetheless, it may still be worth the cost, if it isn't too high. In general terms, the greatest benefit-to-cost ratio (cost effectiveness) is found for CHD patients at very high risk. Next comes high-risk patients without established CHD, then borderline high risk patients, and finally, low risk patients.

Estimated costs in dollar terms for cholesterol lowering with drugs are presented in the Figure below (Goldman et al, 1991). For patients with established CHD, money actually is saved. The cost of recurrent CHD events outweighs the costs of drug therapy. For high-risk patients without CHD, it costs about $40,000 to $60,000 per year of life saved. This compares favorable with other therapies, such as treatment of hypertension. However, for low-risk patients the costs can be very high. $100,000 per year of life saved may be a conservative estimate. The cost may be much higher, which is an argument against excessive use of drugs in low-risk patients.

# COST EFFECTIVENESS RATIOS
# (CHOLESTEROL-LOWERING DRUG THERAPY)

## Cost Per Year of Life Saved

- **CHD patients (money saved)**
- **High-risk, nonCHD patients ($40,000-60,000/yr)**
- **Low-risk, nonCHD patients (> $100,000/yr)**

### Primary Prevention in Special Groups

Special consideration must be given to different types of patients in primary prevention. These categories include only patients with elevated LDL cholesterol. The major categories that need to be considered are: (a) premenopausal women (b) young adults men (20-45 years) (c) middle-age men (45-70 years) (d) middle-aged, post-menopausal women (52-70 years) and (e) elderly men and women (over 70 years). Each can be considered briefly.

### Premenopausal Women

Premenopausal women with high cholesterol levels are a special case. As a general rule they are protected from CHD before the menopause. Thus, drug therapy is rarely warranted in premenopausal women except in those with severe hypercholesterolemia (LDL cholesterol > 220 mg/dL) or in those with moderate hypercholesterolemia and multiple risk factors.

### Young Adult Men

This category includes men of ages 20 to 45 years. They develop atherosclerosis more rapidly than women. The approach to this group is open to debate (Hulley, 1992). Several questions must be addressed with respect to drug therapy. First, is long term drug therapy safe in this group? Drug therapy would be required for

many years. Yet no long-term toxicity data are available. The second question is whether it is cost effective. Projections are for a high cost-to-benefit ratio. Some estimates are well over $100,000 per year of life saved (Goldman et al, 1991). The next question is whether drug therapy is necessary? It may be possible to delay drugs until later in life, and the net benefit may be almost as great. Thus, who are the candidates for drug therapy? Basically they are (a) patients with severe hypercholesterolemia or (b) those at high risk from multiple other CHD risk factors.

An approach to drug therapy is shown for young adult men in the Table below. An example is shown for a patient with an LDL-cholesterol level of about 200 mg/dl. According to studies carried out in our laboratory, dietary therapy in hypercholesterolemic men should cause an average reduction of LDL cholesterol of about 20 mg/dl. In addition, if the patients are given a low dose of cholestyramine (8 gm/day) they will get a further reduction of LDL cholesterol levels averaging about 30 mg/dl. The sum (50 mg/dl) will reduce the LDL level to 150 mg/dl, and according to standard risk equations, this should produce a 50% reduction in risk for CHD. In the view of many investigators, this would be an adequate reduction in risk for this age group. Later in life, e.g. after age 45, an HMG CoA reductase inhibitor might be added to the bile acid sequestrant to produce a further decrease in risk.

## CHOLESTEROL-LOWERING DRUGS IN YOUNG ADULT MEN

**LDL Cholesterol = 200 mg/dL**

- **Dietary therapy -20 mg/dl**
- **Low-dose resins -30 mg/dl**
- **Treatment level = 150 mg/dl**
  **(50% risk reduction)**

Middle-Aged Men (45 to 70 years)

With aging, men acquire increased risk for CHD, and for this reason, treatment of elevated cholesterol levels should be more vigorous than for young adult men. Dietary therapy remains the mainstay of therapy in this age group, but consideration for drug therapy can be given with less severe hypercholesterolemia than for younger adults. Suggestions for drug therapy are presented in the Table below. For men with very high LDL-cholesterol levels (190 to 220 mg/dl) should be considered for statin therapy, even if they do not have other CHD risk factors. For those whose LDL-cholesterol levels are in the range of 160 to 190 mg/dl statin therapy also can be considered if the patients have two other risk factors, one of which can be an age over 45 years. On the other hand, if they have LDL-cholesterol levels in this range, but otherwise are devoid of CHD risk factors, dietary therapy should be considered as the primary treatment, but consideration can be given to resin therapy. As indicated above, the combination of diet modification combined with low-dose resin therapy can lower LDL levels by 50 mg/dl, which should be an adequate cholesterol reduction in most patients in this category.

## CHOLESTEROL LOWERING THERAPY IN MIDDLE-AGED MEN

| LDL Chol mg/dl | Other Risk Factors | Therapy |
|---|---|---|
| 190-220 | 0 or + | Statins |
| 160-190 | + + | Statins |
| 160-190 | 0 or + | Diet + Resins(?) |

Post-Menopausal Women (52-70 years)

It must be remembered that CHD is the number one killer of women, and just as many women die from CHD as men (Denke and Grundy 1989). Furthermore, more middle-aged (post-menopausal) women have elevated LDL cholesterol than men (Expert Panel 1988). Therefore, the problem of high LDL cholesterol levels in women presents a challenge for medical management. In this age group, the incidence of CHD is not high because women have a 10 year delay in development of CHD, compared to men. Part of this delay may be related to higher HDL-cholesterol levels in women than in men. On the other hand, they undoubtedly are developing coronary atherosclerosis that will produce CHD later in life.

There are three possible ways to treat hypercholesterolemia in post-menopausal women. These are (a) dietary therapy, (b) estrogen replacement therapy, and (c) cholesterol lowering drugs. Certainly dietary therapy should be employed first, and in many women it may be sufficient. Estrogen replacement therapy has several potential advantages (Bush, 1991, Lobo, 1991, Knopp, 1988). Estrogens lower LDL levels and raise HDL levels. According to prospective studies, estrogen therapy reduces risk for CHD, but it should be pointed out that this has not been confirmed in controlled clinical trials. Also, there are potential side effects of estrogen therapy (e.g. increased risk for uterine cancer and possibly increased risk for breast cancer) which must be taken into consideration when deciding to start a postmenopausal woman on estrogen replacement therapy. An alternative strategy to postmenopausal women with high cholesterol levels is to employ cholesterol-lowering drugs, most commonly HMG CoA reductase inhibitors. Recent studies suggest that low doses of these drugs are effective in reducing LDL-cholesterol levels in these patients (Grundy et al. unpublished data).

A general approach to the treatment of hypercholesterolemia in post-menopausal women is outlined in the Table below. Those who have LDL cholesterol levels exceeding 220 mg/dl on dietary therapy almost certainly should receive cholesterol lowering drugs. Those who have levels in the range of 190 to 220 mg/dl on dietary treatment and who have other risk factors or low HDL-cholesterol levels likewise should get drug treatment. On the other hand, levels in this same range in patients who have high HDL-cholesterol levels or those without

other risk factors should preferentially be treated with estrogen replacement therapy, and only if reductions are not satisfactory should drug therapy even be considered. If the LDL-cholesterol level is in the range of 160 to 190 mg/dl, estrogen replacement therapy should be considered, but the physician should be conservative about use of drug therapy.

## CHOLESTEROL LOWERING IN POST-MENOPAUSAL WOMEN

| LDL Cholesterol | Other Risk Factors | | HDL Cholesterol | Therapy |
|---|---|---|---|---|
| > 220 mg/dl | – | | – | Drugs |
| 190-220 | + + | or | ↓ | Drugs |
| 190-220 | 0 | or | ↑ | Estrogens |
| 160-190 | ± | | ± | Estrogens |

Elderly Patients (over 70 years)

CHD is the number one killer of Americans and most CHD deaths occur in the elderly population (i.e., over age 65). In the elderly, CHD is an equal killer of men and women. Although the average age of death from CHD is about 10 years older in women than in men, CHD is a major health problem in older women as well. The significance of the problem of CHD in the elderly population can be considered in several ways. From social, family, and to some extent, personal points of view, premature CHD (i.e. CHD before age 65) has more adverse consequences than CHD in the elderly. On the other hand, CHD in the elderly also is a major problem: it is just as costly financially and the financial burden of CHD in older people typically falls on society as a whole; in the aggregate the costs are enormous. Although clinical CHD in the American population has "declined" significantly in the last two decades, it must be noted that this

decline is "age adjusted". In other words, the total incidence of CHD has declined little; instead, the age of onset of CHD has been delayed. Absolute rates of CHD in the elderly have decreased little, and actually may be increasing.

Age is the foremost risk factor in the elderly. However, the other classical risk factors for CHD--cigarette smoking, hypertension, high serum cholesterol, and diabetes mellitus--appear to raise risk for CHD in older people as well as in young and middle-aged adults. The relation of serum cholesterol to CHD in the elderly is a subject of particular interest. For many years it was believed that high cholesterol levels loose their power to predict CHD in older people (Gordon, 1977). More recent studies however reveal that total cholesterol and LDL cholesterol levels are positively correlated with risk for CHD, whereas HDL-cholesterol levels are inversely correlated (Castelli et al. 1986). Still, there is no question that the risk ratio for total cholesterol declines with age; this is the ratio of risk at higher versus lower cholesterol levels. The rise in risk ratio with age was earlier interpreted to mean that serum cholesterol levels are of lesser significance in elderly people. On the other hand, the <u>total number</u> of people developing CHD increases markedly with age, and the total number increases more in those having higher cholesterol levels than in those with lover levels. The difference in risk between these two groups is called the attributable risk, and this type of risk rises with age (Malenka and Baron, 1988) Thus, over a given period of time, higher cholesterol levels adverse affect many more older individuals than they do at younger ages. The increase in attributable risk with age holds for both high LDL-cholesterol and low HDL-cholesterol levels, and it provides a strong rationale for active intervention to lower cholesterol levels in older people.

The best way to prevent CHD in the elderly is to inhibit the development of coronary atherosclerosis early in life. Atherosclerosis is a life-long process, beginning in the teens, and progressing throughout life (McGill, 1968). The goal of prevention is to slow the rate of atherogenesis. The reason that CHD is so common in elderly people is because so much atherosclerosis has accumulated in the coronary arteries throughout life. CHD prevention thus should start in adolescence and be continued thereafter for the rest of one's life. For the vast

majority of people, this means appropriate eating habits, regular exercise, prevention of obesity and avoidance of cigarette smoking. If these measures were to be followed by the general population, premature CHD (before age 65) would become a rarity and the incidence of CHD in the elderly would be greatly reduced. But it is not too late to begin prevention later in life. Several clinical trials suggest that interruption of atherogenesis at anytime delays onset of CHD from that time forth. Apparently there is "no point of no return" beyond which preventive measures have no value. For example the Systolic Hypertension in the Elderly Program (SHEP Research Group, 1991) revealed that treatment of systolic hypertension in older people reduces the incidence of both stroke and CHD. No such clinical-trial data exist for cholesterol lowering in the elderly, but it is reasonable to extrapolate from previous trials in middle-aged people (Lipid Research Clinics, 1984). Although we cannot predict with certainty the magnitude of benefit that will occur through primary prevention by cholesterol lowering in the elderly, the probability of some degree of benefit is extremely high.

Further the greatest benefit in risk reduction is likely to accrue to those older people who do not have CHD but who are at high risk for CHD. In other words, among older people, preventive measures should prevent more heart attacks in those who are at high risk than in those otherwise at low risk. Higher risk may be conveyed by hypertension, cigarette smoking, diabetes mellitus, and low HDL cholesterol. Therefore, as a general principle, cholesterol-lowering drug therapy should be reserved mainly for patients who are deemed to be in the high-risk category. Individuals without risk factors preferably will receive dietary therapy for cholesterol-lowering; this form of therapy is less expensive and carries a lower risk.

An important consideration for primary prevention of CHD in older patients is that of competing risk (Denke and Grundy, 1990). This consideration holds primarily for efforts to lower cholesterol levels. This consideration holds primarily for efforts to lower cholesterol levels. The intensity of preventive therapy should depend on the patient's overall health status and prognosis for future health. If the patient has a poor quality of life or a limited-life expectancy, intensive preventive measures are not warranted. Competing risks can be of two types: cardiovascular and noncardiovascular. For example, chronic

congestive heart failure usually carries a relatively poor prognosis, and aggressive cholesterol-lowering drug therapy in patients with this condition generally would inappropriate. In addition, if an older patient has metastatic cancer, chronic lung disease, advanced osteoporosis, or dementia, attempts to lower cholesterol levels do not make sense.

For primary prevention of CHD through lipid management the major target of therapy is elevated LDL cholesterol (Expert Panel, 1988). As noted before, the CHD risk attributable to high LDL levels increases with age, and this fact justifies therapy in otherwise good candidates. The first line of cholesterol-lowering therapy is dietary adjustment. If a diet that is low in cholesterol and saturated fatty acids is substituted for a typical American diet, LDL-cholesterol levels fall by an average of about 10%. From the results of previous clinical trials (Lipid Research Clinic, 1984), we can speculate that a 10% LDL lowering will reduce the risk for CHD by about 20%, even if therapy is instituted later in life. According to the National Cholesterol Education Program (Expert Panel, 1988), dietary therapy should be instituted if a patient has a high-risk LDL cholesterol (greater than 160 mg/dl) in the absence of other CHD risk factors, or if a patient has a borderline-high-risk LDL cholesterol (130 to 159 mg/dl) in the presence of CHD risk factors. These guidelines can be applied to elderly patients provided these patients meet the general criteria for therapy considered above.

If the decision is made to start an elderly patient on dietary therapy it may be wise to seek the assistance of a dietitian. Sometimes the nutritional adequacy of the diets of older people is marginal, and care must be taken to make certain that dietary modification does not lead to malnutrition. This does not mean that older people with elevated cholesterol levels are not good candidates for cholesterol lowering diets, but rather that the instructions about dietary change must be as clear as possible and patients must be monitored carefully. Avoidance in extremes of dietary intakes in older patients appears to be prudent. Some older people have fallen into the habit of eating too much relative to their caloric expenditure and hence they have become obese; in these patients, weight reduction should be an important part of dietary therapy. Others may be consuming too much alcohol, and they should be encouraged to reduce alcohol

intake beside modifying the contents of their diets.

Drug therapy for treatment of hypercholesterolemia in older people should be reserved for those considered to be at high risk for CHD and who otherwise are generally healthy. The "younger" elderly (i.e. 65 to 70) are better candidates for drug therapy than are older persons. Several years are required before the benefit of drug therapy becomes apparent, and the later therapy is initiated the less time there will be for a favorable effect. In general, men may be better candidates for drug therapy than women because women tend to develop CHD later in life than men. The different cholesterol-lowering drugs have not been tested adequately in elderly populations. Bile acids sequestrants are effective but inconvenient to take; they also tend to produce constipation which already is a problem for many older people. Nicotinic acid has several side effects that may be poorly tolerated by the elderly; its action to raise plasma glucose and uric acid may be particularly disadvantageous for this population. Fibric acids currently have little role except in patients with severe hypertriglyceridemia. The most promising agents are the statins; they have a powerful LDL-lowering effect and are generally well tolerated by older people.

Low HDL and Hypertriglyceridemia

There is growing evidence that a low HDL cholesterol level is accompanied by increased risk for CHD. This evidence is based on epidemiologic studies, genetic forms of low HDL, data in experimental animals, and to some extent, clinical trial data (Grundy et al 1989). The available data justify classifying low HDL cholesterol as a risk factor for CHD, measuring HDL levels in risk assessment, and under certain circumstances, attempting to raise HDL levels to reduce CHD risk. In all patients with low HDL-cholesterol levels, nonpharmacologic approaches to raising these levels can be recommended. These include smoking cessation, weight reduction in overweight patients, and increased physical activity. Avoiding the use of drugs that lower HDL levels (e.g. beta-blockers) may be appropriate in certain patients. In addition, if a patient with low HDL cholesterol is to receive drug therapy for elevated LDL cholesterol, the preferable drug may be one that raises HDL as well (e.g. nicotinic acid). Drug

therapy for "isolated" low HDL cholesterol probably should be reserved for patients with established CHD or those deemed to be at very high risk because of other CHD risk factors, especially a family history of premature CHD.

Elevated serum triglycerides are positively correlated with risk for CHD in univariant analysis, but they lose some or most of their ability to predict CHD in multivariant analysis, i.e., when other lipid risk factors are added to the model. The link between triglycerides and CHD appears to be complex, and it may be explained by the effects of high triglycerides to lower HDL levels, produce unusually atherogenic forms of LDL, or to promote coronary thrombosis (Grundy and Vega 1992). In addition, elevated triglycerides often reflect an increase in triglyceride-rich, remnant lipoproteins that have atherogenic potential. In this document, triglyceride levels are classified as normal (>200 mg/dL), borderline-high (200-400 mg/dL), high (400-1000 mg/dL), and very high (>1000 mg/dL). Patients with borderline-high and high triglycerides may have accompanying dyslipidemias that increase risk for CHD (e.g. familial combined hyperlipidemia and diabetic dyslipidemia). Those with triglyceride levels in excess of 1000 mg/dL are at increased risk for acute pancreatitis. Nonpharmacologic therapy (weight reduction in overweight patients, alcohol restriction, and increased physical activity) is recommended for all patients with elevated triglycerides. When triglycerides are elevated in association with "atherogenic" dyslipidemias (e.g. familial combined hyperlipidemia), drug therapy may be indicated; the choice of drug preferably is one that effectively lowers triglycerides (e.g. nicotinic acid). Drug therapy (nicotinic acid or fibric acids) generally is indicated in patients with very high triglycerides to prevent acute pancreatitis.

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