SPECIAL ARTICLE

Cholesterol Lowering in the Elderly Population

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The incidence of coronary heart disease (CHD) peaks in the elderly population. In secondary and primary prevention trials, cholesterol-lowering therapy reduces risk for CHD in both older and younger participants. This benefit, therefore, can be extended to the elderly. *Arch Intern Med. 1999;159:1670-1678*

During the past decade, major advances have been made in delineating the role of high serum cholesterol as a risk factor for coronary heart disease (CHD). This progress has expanded along many fronts, including epidemiology, the basic sciences, and clinical trials. The National Cholesterol Education Program (NCEP) has used the opportunity presented by these advances to promote both public health and clinical strategies for reduction of high serum cholesterol levels among Americans. The public's response to the NCEP has been to modify its eating habits to produce a decline in serum cholesterol levels; moreover, the medical profession has increased its frequency of testing for high cholesterol levels and has intensified its treatment of various cholesterol disorders. A new class of cholesterol-lowering drugs, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), has further facilitated the clinical management of high serum cholesterol.

The NCEP's guidelines for detection, evaluation, and management of high serum cholesterol are generally applicable to the entire adult population.[1] Nevertheless, special consideration must be given to certain groups such as the elderly over age 65, who are increasing rapidly in both absolute number of persons and percentage of the population. Since illnesses among the elderly are the highest of any age group, they pose a major challenge for the nation's health care system. Coronary heart disease is the foremost cause of morbidity and mortality in elderly men and women; the incidence and prevalence of CHD are highest in people older than 65 years; and most coronary events occur in this age group.[2]

There is strong evidence that smoking, hypertension, and diabetes mellitus remain major risk factors for CHD in the elderly population.[3] An important question is whether high serum cholesterol also continues to elevate the risk for CHD in older persons. The results of a few prospective epidemiological studies have suggested that an elevated serum cholesterol loses some of its power to predict CHD in older persons. Consequently, the authors of these reports have speculated that the value of measuring and reducing cholesterol levels in older people may be lessened. Since many older people are at high risk for developing CHD or already have established CHD, the value of detection and management of an elevated serum cholesterol for this age group needs to be carefully assessed. The purpose of this article is to review the available evidence related to this issue.

CHOLESTEROL AS A PREDICTOR OF CHD IN THE ELDERLY

Many studies of the relation between serum cholesterol levels and CHD risk have focused on relative risk—the ratio of risk for developing CHD in persons having high cholesterol levels compared with those having low levels. Results of some studies[4-6] suggest that the relative risk for CHD predicted by high serum cholesterol levels decreases markedly in people of advanced age (eg, ≥75-80 years). It is well known that relative risk associated with serum cholesterol levels declines with increasing age over a wide range of years. For example, in the Framingham Heart Study,[7] the CHD risk ratio between high-

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est and lowest quartiles for total cholesterol levels was 2.18 for men 50 years and older compared with 3.58 for men younger than 50 years. This reduction in ratio with aging can be explained by the cumulative nature of coronary atherosclerosis. All aging groups, regardless of serum cholesterol levels, have increasing amounts of coronary atherosclerosis that narrow the differences in risks for clinical CHD between the extremes.

Despite the failure of several studies[4-6] to detect a continued differential between higher and lower cholesterol levels for risk prediction in elderly persons, other prospective studies[8-11] have reported a positive and significant correlation between total cholesterol (or low-density lipoprotein [LDL]–cholesterol) levels and new CHD events (or CHD mortality) in the older age group. Other investigations[12-14] have noted trends for a positive association between serum cholesterol levels and CHD risk, although these trends were not statistically significant. Manolio et al[15] reviewed follow-up data in 25 populations from 22 cohort studies and pooled data across studies to determine pooled risk estimates. The pooled data indicated that total cholesterol and LDL-cholesterol levels were significantly correlated with fatal CHD in both men and women across a broad age range and into older populations (≥65 years). Relative risk nonetheless decreased with increasing age; moreover, the strength and consistency of the relationship were diminished more in older women than in men. Although relative risk may fall substantially in advanced age (≥75-80 years), available data indicate that high serum cholesterol levels still convey an increased risk for future CHD events, at least up to this age. In another recent report,[16] high-density lipoprotein (HDL) cholesterol levels and total cholesterol–HDL-cholesterol ratios retained predictive power, even in patients older than 75 years.

Recently, Frost et al[17] reported findings on serum lipids and incidence of CHD from the Systolic Hypertension in the Elderly Program. This trial included a large number of men and women with a mean age of 72 years at entry. Mean follow-up of patients was 4.5 years. Multivariate regression analysis revealed that levels of total, non–HDL, and LDL-cholesterol were significantly related to CHD incidence. For example, a 40-mg/dL (1.03-mmol/L) higher level of total, non-HDL, or LDL-cholesterol was associated with a 30% to 35% higher event rate for CHD.

The relative risk ratio does not adequately predict the magnitude of CHD that is related to elevated serum cholesterol in the elderly because it does not take into account the high frequency of CHD in this age group. A more appropriate estimate appears to be attributable risk, an estimate of the difference in absolute risk between cohorts having high and low cholesterol levels; it reveals the impact of high cholesterol levels on the absolute incidence at a given age. As opposed to relative risk, attributable risk accompanying a high cholesterol level increases with age.[18] In other words, an elevated serum cholesterol produces a greater number of acute coronary events in the elderly population than in a middle-aged or younger population. Because of the great burden of coronary atherosclerosis in the elderly, the absolute, short-term (eg, 10-year) risk for CHD is highest in this age group. Because of the high attributable risk in the elderly, the danger accompanying an elevated serum cholesterol is likewise high in this age group. Consequently, reducing cholesterol concentrations from high to low could well produce a greater overall reduction in new CHD events in older people than in middle-aged people, who generally have a lower absolute risk.

CHD IN THE ELDERLY

There is no evidence that coronary artery disease is fundamentally different in older persons than in younger ones. Atherosclerosis continues to progress into the elderly years, and older people have much more coronary atherosclerosis than middle-aged people.[19] Nonetheless, the rates of atherogenesis vary greatly and depend on the presence or absence of risk factors.[19,20] Thus, by the later years of life, the total burden of coronary atherosclerosis differs substantially among individuals. Still, total amounts of atherosclerosis are not the whole story; new concepts are emerging on the development of clinical CHD. Two forms of clinical CHD must be distinguished, namely, chronic angina pectoris and acute coronary events (eg, unstable angina and acute myocardial infarction). Chronic angina pectoris appears to be largely the result of progressive obstruction of the coronary arteries, leading to insufficient coronary blood flow with exercise. Acute coronary events result from instability and/or rupture of the atherosclerotic plaque that precipitates a thrombosis and leads to acute coronary obstruction.[21-23] Unquestionably, both angina pectoris and acute coronary events contribute to clinical CHD in the elderly. A substantial portion of the elderly population carries some form of clinical CHD, and this portion requires intervention to retard progression of their disease. Most elderly patients do not have clinically manifest CHD, but even so, they are at high risk. Two thirds to three quarters of people older than 65 years have either clinical CHD or subclinical atherosclerotic disease.[24] Thus, risk reduction in these patients should have a high priority. These efforts are conveniently divided into secondary and primary prevention.

SECONDARY PREVENTION IN THE ELDERLY

Concept of Secondary Prevention

A considerable opportunity exists for reducing recurrent morbidity and prolonging the lives of patients with established CHD. This opportunity is especially welcome for older persons in whom the prevalence of CHD is high. The literature supporting the benefit of a variety of therapeutic modalities—life-habit changes, medication, and cardiovascular surgery—has expanded greatly in the past decade. For example, procedural intervention on established CHD—coronary artery surgery and coronary angioplasty—can improve the quality of life and, in some catego-

ries of patients, prolong life. The same is true for a growing list of medications, eg, aspirin, β-adrenergic blocking agents (β-blockers), and angiotensin-converting enzyme inhibitors. Changes in life habits, including smoking cessation and increased physical activity, additionally improve the prognosis in patients with established CHD. A large body of data supports the use of these modalities in patients with clinically manifest CHD. Their use in such patients is called secondary prevention. Moreover, there is a wide acceptance of their applicability to older persons with CHD. Even surgery and other invasive procedures on the coronary arteries can be carried out successfully in very old patients. The question addressed herein is whether cholesterol-lowering therapy provides added benefit when included in a regimen of secondary prevention. To examine this question, evidence from secondary prevention trials can be reviewed.

Secondary Prevention Clinical Trials

Meta-analysis of Early Trials. Between the mid-1960s and 1990, a series of secondary prevention trials were carried out using several different therapeutic regimens, including cholesterol-lowering diets and drugs. In general, the degree of serum cholesterol lowering was only moderate, averaging about 10%. In most of these trials, a trend toward a reduction in recurrent CHD events was observed, but only in some of the trials was the reduction statistically significant. Thus, when the results of each trial were examined separately, trends were not definitive but were suggestive. A more distinct beneficial outcome emerged, however, when data from all trials were pooled and analyzed as a single set (meta-analysis).[25] A larger number of patients were examined in the aggregate, which removed some of the limitations of individual trials. Meta-analysis revealed that recurrent CHD events and CHD mortality were significantly reduced by cholesterol-lowering therapy, with a strong trend toward a reduction in total mortality. The magnitudes of the decrease in subsequent morbidity and mortality were similar to that observed by meta-analysis of secondary prevention in trials with aspirin therapy. The results of the meta-analysis of secondary prevention trials of cholesterol lowering influenced the second Adult Treatment Panel (ATP II)[1] of NCEP to place greater emphasis on cholesterol-lowering intervention in patients with established CHD.

Angiographic Trials. Since 1990, the results of several angiographic trials designed to test the effects of cholesterol-lowering therapy on progression and regression of atherosclerotic lesions have been reported.[21] Most of these trials used therapies that produced marked reductions in cholesterol levels. In several of the trials, statin drugs were employed. The duration of many trials, however, was relatively short, often only 2 or 3 years. Angiographic results varied somewhat, but on the whole, the findings followed a consistent pattern. Angiography revealed that cholesterol-lowering therapy, compared with placebo, usually slowed the progression of coronary lesions and, in some instances, induced regression of a few lesions. Despite these positive findings, the changes in lesion size were relatively small, and most lesions were unchanged. In these trials, clinical events were also recorded, and in most, a striking result was obtained. In the treatment groups, new coronary events (eg, unstable angina and acute myocardial infarction) were markedly reduced.[21]

The finding that the observed reduction in clinical events greatly exceeded that which would be expected from the degree of apparent lesion modification raises the question of mechanism. Cholesterol lowering has a greater effect on coronary lesions than is revealed by angiography. One interpretation of this finding is that coronary lesions prone to plaque rupture are stabilized by cholesterol-lowering therapy. This postulate accords with newer concepts of how lipid-enriched lesions contribute to plaque rupture.[21-23] Unstable angina and acute myocardial infarction typically result from plaque rupture that initiates a superimposed thrombosis. Pathologic studies indicate that plaque rupture most often occurs at the margins of atherosclerotic plaques, where lipid-rich areas are covered by a thin fibrous cap. These fatty regions are thought to be filled with activated macrophages and foam cells that release enzymes and cytokines that digest the thin fibrous covering and rupture the surface. Lowering of atherogenic lipoproteins may reduce the "inflammatory" component of susceptible lesions and thus stabilize them. Moreover, cholesterol-lowering therapy may also protect coronary artery endothelium and, in this way, increase the stability of vulnerable lesions.[26,27] Angiographic trials strongly support the concept that cholesterol-lowering therapy, regardless of the exact mechanism, protects against acute coronary events more than would be predicted from changes in observable lesion sizes. These trials provide further support for the value of therapeutic lowering of cholesterol levels for secondary prevention.

Recent Statin Trials. Three large secondary prevention trials using statin agents have been carried out: the Scandinavian Simvastatin Survival Study (4S),[28] Cholesterol and Recurrent Events (CARE) trial,[29] and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.[30] In the 4S trial,[28] simvastatin therapy in patients with hypercholesterolemia and established CHD reduced total mortality by 30%. It further markedly reduced coronary end points: total deaths due to coronary events decreased by 42%; coronary procedures (coronary artery surgery and angioplasty) declined by 37%; and major coronary events decreased by 34%. The number of nonhemorrhagic strokes was decreased significantly on statin therapy.[28] The reduction in coronary end points was similar in different subgroups: men vs women, patients with higher initial cholesterol levels vs those with lower levels, and older vs younger patients. Patients older than 65 years taking simvastatin, compared with placebo, showed significantly fewer total deaths and major coronary events; these reductions paralleled those in patients younger than 65

years.[31] This consistency of results for different clinical end points and across different subgroups supports the efficacy of statins for reducing new events in patients with established CHD.

Another major finding of the 4S trial[28] was the lack of significant adverse effects from simvastatin therapy. Patients receiving it manifested no increase in noncoronary mortality (rates of death from cancer, trauma, suicide, or other specific causes) compared with the control group. This finding underscores the safety of cholesterol lowering; for the duration of the trial, patients taking simvastatin remained free of serious adverse effects.

In the CARE trial,[29] patients with CHD and average cholesterol levels were treated with pravastatin or placebo. Pravastatin therapy significantly reduced definite nonfatal myocardial infarction and coronary death by 24%, and reduced coronary revascularization procedures by 27%. The CARE trial did not have enough statistical power to test for a reduction in total mortality. However, there was no significant increase in noncardiovascular mortality or major nonfatal adverse effects. The only negative aspect of this trial was that rates of incident breast cancer were higher in women receiving pravastatin therapy than in those receiving placebo. This trend was not observed in other trials using statins, particularly the larger LIPID trial.[30] Despite the numerical increase in breast cancer, women receiving pravastatin had more than an offsetting benefit in CHD risk reduction. More important, CARE demonstrated that patients with CHD need not have high serum cholesterol levels to achieve risk reduction from statin therapy. Older patients in CARE appeared to benefit as much as younger ones from pravastatin therapy.[32] Finally, the LIPID trial[30] showed similar results to those of CARE,[29] but in addition, in LIPID,[30] there was a reduction in total mortality in patients treated with pravastatin. In this trial,[30] the benefits of drug therapy extended to the subgroup of patients older than 65 years.

There is now wide agreement that an elevated LDL-cholesterol is the primary target of lipid-lowering therapy in secondary prevention. ATP II[1] recommends an LDL-cholesterol goal in secondary prevention of 100 mg/dL (≤2.59 mmol/L) or less. Considered as a whole, the total evidence from epidemiological studies and angiographic and clinical trials appears to be consistent with this goal.[33-35] To achieve an LDL-cholesterol of100 mg/dL (≤2.59 mmol/L) or less, most patients with established CHD will require cholesterol-lowering drugs. In elderly patients with CHD, clinical judgment is required as to whether and when to intensify drug therapy when an elevated–LDL cholesterol has already been reduced to the range of 100 to 129 mg/dL (2.59 to 3.34 mmol/L). At the very least, most CHD patients with a baseline LDL-cholesterol ≥130 mg/dL (≥3.36 mmol/L) will require cholesterol-lowering drugs to achieve the goal of therapy.[36]

Secondary Prevention in Elderly Patients

The largest segment of the population having established CHD are those older than 65 years.[2] This is true for men and women. The 4S, CARE, and LIPID trials revealed efficacy from cholesterol lowering in women and men; consequently, neither sex should be excluded from considerations of secondary prevention. Since older and younger patients benefited similarly from cholesterol reduction in 4S,[28,31] CARE,[29,32] and LIPID,[30] the overall findings can be extended to the elderly population.

The recent clinical trial data strongly justify including cholesterol-lowering therapy in a secondary prevention regimen in "younger elderly" (eg, 65-75 years). Special consideration, however, must be given to the issue of secondary prevention in the "older elderly" (eg, >75 years). Who among older elderly patients with established CHD are appropriate candidates for aggressive cholesterol-lowering therapy? Elderly people differ markedly in their functional age. At one extreme are vigorous, independent, physiologically robust persons in their 80s or even 90s who are as fit and resilient as much younger people. On the other hand, some elderly patients have multisystem disease and limited reserves. Clinical judgment must therefore dominate treatment decisions in the elderly. If a patient has other serious illnesses that impart a poor prognosis for quality or duration of life, withholding aggressive cholesterol management may be prudent. On the other hand, if a patient older than 75 years with CHD is otherwise in relatively good health, cholesterol-lowering therapy can be given serious consideration. This is true even if the patient has advanced atherosclerotic disease or a history of compensated congestive heart failure. Of course, if a patient has advanced cardiovascular disease and carries a poor prognosis for survival, cholesterol-lowering therapy may not be beneficial. To date, no clinical trial data are available to define which subgroups of the old elderly with CHD will benefit from aggressive cholesterol management. Thus, decisions must be based on the older patient's overall health status. However, it appears unwarranted to withhold cholesterol-lowering therapy solely on the basis of age.

Cost-effectiveness of Secondary Prevention

Medical and surgical managements of CHD in the elderly make up a major component of the nation's health care costs—a heavy burden on Medicare and other payment systems. Cholesterol lowering in elderly patients with established CHD offers the opportunity to achieve great benefit with little added cost. In the 4S, CARE, and LIPID trials, reducing cholesterol levels provided substantial reductions in the need for coronary artery surgery and coronary angioplasty. Various analyses[1,32,37-39] reveal that aggressive reduction in serum cholesterol levels in patients with established CHD reduces both morbidity and mortality at low cost.

PRIMARY PREVENTION IN THE ELDERLY

Since the majority of first CHD events occur after 65 years of age, primary prevention in the elderly is a topic of great importance. The NCEP emphasizes that the optimal approach to prevention of CHD in the elderly is lifetime prevention,[40] with the goal of reducing the total burden of coronary atherosclerosis

in the population. To sustain lifetime preventive efforts, older persons should be encouraged to follow healthy eating habits, exercise regularly, and eliminate excess body weight, which will improve health besides reducing an elevated serum cholesterol level. For example, exercise and weight control will promote the control of blood pressure and help prevent the development of type 2 diabetes. Emphasis on healthy life habits is particularly important in elderly patients who are projected to have more years of quality life. Many elderly people are highly motivated to prevent CHD through changes in life habits; they should be encouraged to do so.

In addition, the detection of high serum cholesterol levels in an elderly patient triggers the need for specific medical intervention to achieve modification of eating habits, appropriate physical activity, and weight control. For patients without manifest CHD, life-habit interventions should take precedence over drug treatment. Nonetheless, some patients deemed to be at particularly high risk may be candidates for drug therapy. Although the benefit of cholesterol lowering for primary prevention in the elderly population has not been firmly established through clinical trials that specifically target this age group, a reasonable extrapolation of evidence provides a rational guide to cholesterol lowering in elderly individuals. The high attributable risk in elderly patients warrants an effort in primary prevention, especially when a high serum cholesterol level is combined with other CHD risk factors. Moreover, mounting evidence of the benefits of cholesterol-lowering therapy in both middle-aged and older populations provides a rationale for including the elderly population in primary prevention efforts. Primary prevention trials of cholesterol reduction underlying this evidence can be reviewed briefly.

Primary Prevention Trials

Earlier primary prevention trials were carried out in middle-aged people, whereas more recent trials have increasingly included patients older than 60 years at entry. One limitation of earlier primary prevention trials was that the agents used produced only moderate reductions in serum cholesterol levels. For example, drugs used in the World Health Organization clofibrate trial,[41] the Lipid Research Clinics cholestyramine trial,[42,43] and the Helsinki gemfibrozil trial[44] all produced an approximately 10% decrease in total cholesterol levels. Despite such modest reductions in serum cholesterol levels, these therapies yielded substantial reductions in acute coronary events compared with controls. Taken together, the findings from these trials support the concept that a 1% lowering of cholesterol levels reduces CHD risk by approximately 2% in middle-aged people (*the 1%/2% rule*). Meta-analysis of primary prevention trials yields a similar level of benefit from cholesterol lowering.[45,46]

The results of a major primary prevention trial—the West of Scotland Coronary Prevention Study (WOSCOPS)—were published in 1995.[47] This multicenter trial randomized high-risk men with hypercholesterolemia to pravastatin therapy or placebo. Pravastatin reduced total cholesterol by 20% and LDL–cholesterol by 26%. Pravastatin therapy reduced major coronary events by 31% compared with placebo, and similar reductions were observed for coronary procedures and coronary mortality. Of particular interest, no increase in noncardiovascular mortality was observed; consequently, all-cause mortality was reduced by 22%. Older patients in WOSCOPS had similar reductions in CHD rates as younger patients. Cost analysis of WOSCOPS indicated that statin therapy in high-risk patients with hypercholesterolemia is relatively cost-effective.[48]

Recently, another primary prevention trial, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[49] compared the effects of lovastatin with placebo on the frequency of first major coronary events (unstable angina, myocardial infarction, or sudden CHD death) in 5608 men and 997 women. Lovastatin therapy reduced LDL-cholesterol levels by 25%. After 5.2 years of treatment, lovastatin therapy decreased major coronary events by about 37%, with corresponding reductions noted in other coronary end points. Mean age at entry was 57.5 years in men and 62.5 years in women; 22% of all patients were older than 65 years. Older patients responded similarly to younger patients in risk reduction with lovastatin therapy. Thus, AFCAPS/TexCAPS supports the concept that cholesterol-lowering therapy is efficacious for primary prevention in older patients.

Whether the degree of risk reduction observed in primary prevention trials in middle-aged people would be of the same magnitude in older people remains unclear, because the trials have not specifically targeted patients older than 65 years. Several lines of evidence, however, support extrapolation to older people:

- Similarity of the pathobiologic process
- Epidemiological data—high cholesterol confers a high attributable risk in the elderly
- Angiographic trials—even advanced disease responds to cholesterol lowering with risk reduction, so it is not "too late" in the elderly
- Recent statin trials—older subgroups of patients in these trials responded favorably

The 1%/2% rule relating cholesterol lowering to risk reduction observed in middle-aged patients may not apply strictly to older populations. Since the relative risk imparted by high vs low serum cholesterol levels declines with age, the 1%/2% rule may be attenuated. This attenuation appears to be a characteristic of high-risk populations, such as middle-aged patients with hypercholesterolemia and patients with CHD. In WOSCOPS,[46] a high-risk primary prevention trial, a 1% cholesterol lowering gave a 1.5% decrease in new CHD events. Comparable results were noted in the 4S trial,[28] a secondary prevention trial. Thus, a similar attenuation of the 1%/2% rule may well hold in high-risk, elderly patients. In WOSCOPS[47] and 4S,[28] the attenuation in relative benefit in high-risk patients, however, was offset by a striking reduction in cholesterol levels achieved with statin therapy. A similar risk reduction should occur with statin treatment in elderly patients, comparable to that observed in

high-risk populations.[28,29,31,47] In addition, because of the high attributable risk in older persons,[16] a greater number of acute coronary events should be prevented with statin therapy in this group than in middle-aged persons.

One long-standing concern about the use of drugs for primary prevention has been a failure to observe a significant reduction in total mortality in clinical trials.[41-44] In retrospect, this failure was the inevitable result of experimental design. Earlier trials were designed to detect benefit in CHD incidence (chiefly, nonfatal myocardial infarction) and, because of the relatively small size and short duration of these trials, the chances of detecting a reduction in total mortality were correspondingly small. Some investigators have attempted to enhance the resolving power by pooling data from several trials. Such meta-analysis of earlier primary prevention trials failed to document a decrease in total mortality; in fact, an increase in non-CHD mortality was noted in the combined data from various drug therapies. This aggregate increase in deaths was made up of small and nonsignificant increases in various types of death: cancers and other diseases of liver, biliary tract, and intestine in one trial and accidents, suicide, and homicide in others. Several questions can be raised about any interpretation of meta-analyses as they pertain to an increase in non-CHD mortality: whether data from one trial using a drug with adverse effects can obscure the favorable effects of another, safer drug; whether a significant increase in total deaths has any biological meaning when it derives from multiple types of death—none of which alone are significantly increased in individual trials; and whether a plausible mechanism can account for a diversity of fatal adverse effects.

Any concerns about the dangers of statin therapy in primary prevention were largely alleviated by WOSCOPS[47] and AFCAPS/TexCAPS.[49] These trials gave no evidence of significant adverse effects from statin therapy over periods of 5 years. With statin therapy, there were no increases in deaths from noncardiovascular causes, cancer, or violence. In WOSCOPS,[47] as a result of a significant decrease in cardiovascular deaths, statin therapy reduced total (all-cause) mortality. Thus, concerns about the dangers of cholesterol-lowering therapy from previous meta-analysis did not materialize in these statin trials, particularly WOSCOPS[47]—the first primary prevention trial with the power to test all-cause mortality.

Because any drug may have adverse effects and because of cost considerations, the NCEP recommends that drug therapy be used cautiously in young adults having high blood cholesterol but who are otherwise at low risk.[1] Such persons will have to be treated for many years to achieve a benefit in CHD risk reduction. In addition, the chances of adverse effects resulting from long-term therapy may be increased. In contrast, as absolute risk increases with age, the benefit-risk ratio from drug therapy should also rise. In older patients, many years of drug therapy will not be required to produce a benefit. Thus, high-risk, elderly patients should be suitable candidates for cholesterol-lowering drugs in primary prevention, provided they are appropriately selected and the drugs are used prudently.

Although 4S, CARE, and LIPID[28-30] were secondary prevention trials, they also have implications for use of statins in primary prevention. These trials showed that statins are much more effective agents for cholesterol lowering than drugs used previously in primary prevention trials. Further, statins possess the ability to reduce risk for CHD commensurate with their ability to lower serum cholesterol levels. In accord with WOSCOPS[47] and AFCAPS/TexCAPS,[49] no major adverse effects occurred during the course of these other statin trials, implying that statins are safe for use in elderly populations. The 4S, CARE, and LIPID trials[28-30] further demonstrate that aggressive cholesterol-lowering therapy can markedly reduce fatal and nonfatal coronary events in patients with advanced atherosclerotic disease. In this way, many elderly persons without CHD resemble middle-aged persons with CHD. Thus, in high-risk elderly patients without CHD, cholesterol-lowering therapy should produce an absolute benefit similar to that in younger patients with CHD. As with CHD patients, therefore, judicious use of cholesterol-lowering therapy in high-risk, elderly patients has the potential to effect a substantial reduction in morbidity and health care costs.

Cholesterol Testing in the Elderly

The NCEP recommends that total cholesterol should be measured at least once every 5 years in all adults 20 years of age and older. In addition, HDL-cholesterol should be measured if accurate results are available. ATP II[1] puts increased emphasis on HDL cholesterol because of growing evidence of its importance as a risk factor for CHD. A recent report[16] indicates that the total cholesterol–HDL-cholesterol ratio retains its power to predict new CHD events even into advanced age. Thus, combining HDL cholesterol with total cholesterol (or LDL-cholesterol) may help identify high-risk, older patients for cholesterol-lowering therapy. In other words, an older patient with a high-risk LDL–cholesterol (≥160 mg/dL [≥4.14 mmol/L]) and a low HDL cholesterol (<35 mg/dL [<0.90 mmol/L]) would be a good candidate for drug therapy if life-habit changes do not produce sufficient cholesterol lowering.

The preferred setting for cholesterol measurement is the medical examination that also obtains other information about CHD risk factors such as age, sex, family history, cigarette smoking, high blood pressure, diabetes mellitus, obesity, and physical activity. Details of cholesterol testing, including LDL-cholesterol measurement, are outlined in the ATP II report. This report details initial classification based on serum total cholesterol and HDL cholesterol, subsequent classification based on LDL-cholesterol levels, clinical evaluation to exclude secondary causes of dyslipidemia, and family testing.

Garber and Browner,[50] writing for the American College of Physicians, recently proposed that cholesterol testing in the elderly population is not warranted. This recommendation appeared to be based mainly on epidemiological evi-

dence of an age-related decline in relative risk associated with high cholesterol levels. In contrast, ATP II[1] placed increased emphasis on cholesterol management in the elderly. Of course, aggressiveness of cholesterol testing and treatment must be tempered by clinical judgment. Priority should be given to the younger elderly, denoted by both age and function. Testing may not be necessary for elderly patients who have other serious medical conditions and thus are poor candidates for cholesterol-lowering therapy. If an elderly patient is considered a potential candidate for cholesterol-lowering treatment—dietary or drug treatment—then cholesterol testing (including lipoproteins) should be performed. Moreover, finding a high serum cholesterol level in an elderly patient should alert the physician to the possibility that a first-degree relative, including middle-aged offspring, may have an elevated serum cholesterol.

Control of Other Risk Factors

Other CHD risk factors retain much of their predictive power in the elderly. Many older patients have isolated systolic hypertension. Elevated systolic and diastolic blood pressures in elderly persons enhance their risk for CHD and stroke, and a major clinical trial[51] revealed that treatment of systolic hypertension reduces these risks. Blood pressure lowering in most older patients is therefore indicated. Cigarette smoking also remains a potent risk factor in the elderly, and prospective studies[52] demonstrate that smoking cessation reduces CHD risk, even at relatively advanced ages. Finally, type 2 diabetes often makes its initial appearance in older persons and contributes importantly to cardiovascular disease. Because these other risk factors predispose to CHD and underlie several other morbid conditions, they should receive priority in risk management, but not preclude treatment of high serum cholesterol levels in the elderly population.

Selection of Patients for Therapy

ATP II[1] emphasizes that persons should not be excluded from cholesterol management solely on the basis of age. Although clinical trial data in the elderly population are limited, a large body of circumstantial evidence indicates a probable benefit from primary prevention in high-risk individuals. The relatively high absolute (short-term) risk in older persons increases the likelihood for a favorable benefit-risk ratio. Two factors to consider in selecting patients for therapy are overall prognosis and risk status. Regarding the former, patients expected to have relatively prolonged and healthy lives certainly deserve attention to serum cholesterol levels. On the other hand, patients with multisystem disease and marginal physiologic reserves should receive more attention to function than to prevention. Patients with debilitating conditions (eg, malignant neoplasms, dementia, stroke, severe osteoporosis, or chronic lung disease) and limited life expectancy are poor candidates for cholesterol-lowering therapy. Physicians are trained to exercise clinical judgment that balances competing factors, and clinical experience combined with common sense usually will lead to a rational and appropriate decision. At the same time, since the benefits of cholesterol-lowering therapy are becoming increasingly apparent, it behooves the physician to not overlook an opportunity to reduce morbidity and improve the quality of life by relatively simple means. Older patients are increasingly aware of the potential benefits of cholesterol-lowering therapy; the physician, therefore, must be sensitive to their desires and motivations, as long as they are not misplaced.

If an older patient is found to be a good candidate for cholesterol-lowering therapy, consideration must be given to appropriate treatment. The **Table** outlines a general approach to cholesterol-lowering therapy in primary prevention for older patients, keeping in mind dietary therapy, weight control, and increased physical activity as the primary modes of cholesterol management. Drug therapy is reserved for high-risk patients; dietary therapy will be needed, regardless of whether drug therapy is used. Risk status of the patient is determined not only by LDL-cholesterol levels but also by the presence or absence of other CHD risk factors (ie, cigarette smoking, hypertension, diabetes mellitus, and low HDL-cholesterol levels). Moreover, in older people, subclinical evidence of advanced atherosclerotic or cardiovascular disease may suggest the need for drug therapy.[24,53,54] Examples of presymptomatic disease include a decreased ankle-brachial blood pressure,[54] electrocardiographic evidence of left ventricular hypertrophy,[3] or a positive Rose questionnaire result for angina. Several investigations also suggest that increased carotid intimal medial thickness[55,56] or high scores of coronary calcium[57,58] reflect increased risk for CHD and may justify use of cholesterol-lowering drugs. If LDL-cholesterol levels are in the range of 130-159 mg/dL (3.36 to 4.11 mmol/L) and other risk factors or evidence of subclinical atherosclerotic disease are present, dietary therapy should be maximized to reduce LDL-cholesterol levels to below 130 mg/dL (3.36 mmol/L). Cholesterol-lowering drugs are generally not necessary if the LDL-cholesterol is in the range of 130 to 159 mg/dL (3.36 to 4.11 mmol/L), unless there is evidence of clinical atherosclerotic disease. An exception may be the older patient with type 2 diabetes in whom an LDL-cholesterol goal of ≤100 mg/dL (≤2.59 mmol/L) may be indicated.[1,59] If LDL-cholesterol levels are between 160 and 189 mg/dL (4.14 and 4.89 mmol/L), drug therapy can be considered if multiple risk factors or subclinical atherosclerotic disease are present. If LDL-cholesterol levels are ≥190 mg/dL (≥4.91 mmol/L) in any patient, drug therapy likewise may be indicated, after maximal dietary modification, regardless of other risk factors.

Special Consideration for Primary Prevention in Elderly Women

Coronary heart disease in elderly women is a health issue of national proportions. It is the leading cause of death in women older than 65 years; in fact, just as many women as men die of CHD.[60] It has received less attention in women because their age at onset tends to be later; there is less premature CHD in women. In older women, however, CHD is a major health problem, and its prevention de-

Therapeutic Considerations for Primary Prevention in Elderly Patients

Low-Density Lipoprotein Cholesterol Level, mg/dL (mmol/L)	Risk Factors*	Therapeutic Considerations†
130-159 (3.36-4.11)	0-1	Life-habit changes indicated
	≥2	Intensify life-habit changes; special considerations for drug therapy‡
160-189 (4.14-4.89)	0-1	Intensify life-habit changes
	≥2	Consider adding drug therapy
≥190 (≥4.91)	±§	Consider adding drug therapy to life-habit changes

**Risk factors include cigarette smoking, hypertension, low high-density lipoprotein cholesterol level, advancing age (≥45 years in men and ≥55 years in women or postmenopausal), and diabetes mellitus.*

†Life-habit changes include Step I diet, weight control, and regular exercise. Intensify life-habit changes includes Step II diet, medically supervised weight reduction, and exercise program.

‡Some authorities consider cholesterol-lowering drug therapy if a patient has diabetes mellitus plus other risk factors. Drug therapy also may be appropriate if the patient is considered at very high risk from multiple risk factors or from subclinical atherosclerosis.

§± indicates with or without risk factors.

serves high priority. Most authorities agree that other CHD risk factors—cigarette smoking, hypertension, and diabetes mellitus—should be effectively treated in elderly women. Less attention has been given to elevated cholesterol in women, and some investigators argue that high serum cholesterol is not a major risk factor in elderly women. The issues behind this argument need to be examined.

Some epidemiological studies[61] suggest that serum cholesterol levels carry less predictive power for CHD in women than in men. Others,[62] however, indicate that high cholesterol levels are predictive of CHD in postmenopausal women. There is little doubt that LDL is an atherogenic lipoprotein in women. Genetic forms of high LDL-cholesterol can cause premature CHD in women; their coronary arteries are, therefore, not immune to the atherogenic potential of LDL. On the other hand, atherogenesis in many postmenopausal women may be retarded by the presence of a high HDL-cholesterol level (≥60 mg/dL [≥1.55 mmol/L]), which ATP II[1] counts as a protective factor that should lessen the aggressiveness of cholesterol-lowering therapy; about one third of postmenopausal women have a high serum HDL cholesterol.

ATP II[1] recommends the same guidelines be used for management of high serum cholesterol in elderly women and men. This similarity in guidelines extends to dietary therapy, weight control, and physical activity, as well as drug therapy. However, according to ATP II,[1] postmenopausal women with high cholesterol levels may be considered for estrogen replacement therapy as an alternative to cholesterol-lowering drugs; this probably should be reconsidered in light of the recent results of the Heart and Estrogen/progestin Replacement Study (HERS).[63] Previously, prospective observational studies[1] in postmenopausal women strongly suggested that estrogen replacement therapy would reduce the risk for CHD and osteoporosis, as well as lower LDL-cholesterol levels.[64] HERS was a randomized, placebo-controlled trial to test whether conjugated equine estrogen (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) would reduce the occurrence of nonfatal myocardial infarction or CHD death in postmenopausal women with established CHD. In HERS,[63] estrogen (plus progesterone) therapy did not reduce overall CHD events, but it did increase the rate of thrombotic events and gallbladder disease. This negative finding, together with the positive results of recent statin trials that included women,[28-30] suggest that cholesterol-lowering drugs should be used instead of estrogens by high-risk women in whom drug therapy is considered necessary to lower CHD risk.

CONCLUSIONS

The NCEP emphasizes the need to include the elderly population in clinical management of high serum cholesterol. This age group carries the highest risk for CHD and the highest burden of atherosclerotic disease. Although clinical trials of cholesterol-lowering therapy have not specifically targeted older persons, growing evidence of several types supports the inclusion of the elderly in cholesterol management. Epidemiological data point to an increase in attributable risk that offsets a decline in relative risk from high cholesterol levels. Recent clinical trials of statin therapy indicate similar benefit in older and younger patients. Because of the similar pathobiologic process of coronary atherogenesis in middle-aged and older patients, extrapolation of clinical trial data from the middle-aged patient to the elderly patient seems warranted. Aggressive cholesterol lowering in older patients with established atherosclerotic disease seems fully justified, as does selection of high-risk patients without clinically manifest atherosclerotic disease for cholesterol-lowering therapy. The first line of primary prevention is dietary therapy, regular physical activity, and weight control; drug therapy can also be considered for patients at highest risk. Clinical trials that primarily recruit elderly patients are currently under way and should provide more specific data on the relative benefits of cholesterol-lowering therapy in elderly populations.

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