Statin Therapy in Older Persons

Pertinent Issues

HYDROXYMETHYLGLUTARYL COENZYME A reductase inhibitors (statins) are a marvel of modern medicine. They effectively lower serum low-density lipoprotein (LDL) concentrations with a high level of safety. Several large clinical trials document conclusively that statins reduce risk for major coronary events (myocardial infarction and unstable angina) by at least one third.1-5 This risk reduction occurs even for patients with established coronary heart disease (CHD)1-3. In fact, statins have been shown to lower risk for CHD in all subgroups—people with and without established CHD, men and women, persons with and without risk factors including diabetes mellitus, and people with lower as well as higher cholesterol levels. This apparent universal efficacy has led to widespread use of statins in clinical practice.

The prospective study from the Cardiovascular Health Study (CHS)9 described in this issue of the Archives addresses in another way the question of whether statin therapy is associated with a reduction in incident cardiovascular events in older adults. Persons in this study were 65 years and older. A total of 1250 women and 644 men were followed up for an average of 7.3 years. All were free of cardiovascular disease at baseline. For analysis, the subjects were divided into those who were being treated with statins and those not being treated. Follow-up of these subjects revealed that statin use was associated with a significantly reduced incidence of cardiovascular events and all-cause mortality. This apparent benefit was undiminished in persons 74 years and older.

It must be emphasized that this prospective study was not a controlled clinical trial. In such prospective studies, confounding factors can always obscure definitive conclusions. For example, in the CHS,8 persons who were treated with statins may have received better medical care all around. Thus, the better outcome in statin-treated patients may have been due in part to factors other than statin use. Nonetheless, this report can be viewed in light of beneficial effects of statin therapy in controlled clinical trials.1,5,8 The findings are consistent with results of clinical trials; the latter enhance our confidence in the validity of the authors' conclusions.

Without question, the lack of clinical trials that were designed specifically to test efficacy in older persons has been one factor standing in the way of a more forceful recommendation for intensive cholesterol-lowering therapy in this age group. Positive results of subgroup analysis from controlled trials have convinced most authorities that LDL-lowering therapy will reduce risk for major coronary events in older persons. The CHS report9 will further reinforce this perception. The preliminary report of HPS8 indicates that older persons will receive as much risk reduction as in middle age. The latter study seemingly gives final proof of efficacy of LDL-lowering therapy after age 65 years.

In the past, many investigators believed that reducing serum cholesterol levels would not reduce risk for new-onset CHD in older persons.10 This belief was based on results of prospective epidemiological studies that revealed that relative risk for CHD events imparted by serum total cholesterol (and LDL cholesterol) declines with advancing age.10 Studies showed that after age 65, the relative risk due to elevated LDL levels is much lower than in earlier years. Since clinical trials generally have been concordant with prospective epidemiological data,11...
a lack of benefit from LDL lowering might reasonably be expected. On this point it is necessary to distinguish between relative benefit and absolute benefit of therapy. Older persons are clearly at greater absolute risk for coronary morbidity and mortality. A major portion of this higher risk is due to more advanced atherosclerotic disease in older people. Beyond this, however, major coronary events in older persons could have a more diverse etiology than in middle age and thus be less dependent on cholesterol levels. If so, LDL lowering may target less of the totality of CHD causation in older persons than in middle-aged persons. Even so, absolute (attributable) benefit of LDL lowering could be as great or even greater in older persons even if relative risk reduction is lower in this age range.

Thus, CHS results support the increasingly robust evidence from controlled clinical trials for recommending intensive LDL-lowering therapy in older patients with established CHD. Older patients with CHD are doubly at risk for future coronary events, i.e., they have both the advanced atherosclerosis of age combined with demonstrated susceptibility for major coronary events. Thus, LDL lowering undoubtedly should be one therapeutic modality for secondary prevention in older persons with CHD. In this age group, nonetheless, clinical judgment is required for the blending of LDL lowering with other risk-reducing therapy.

The issue of using LDL-lowering drugs for older persons without CHD is more problematic than for patients with CHD. Those without CHD vary widely in risk, and, consequently, some persons will benefit from therapy more than others. Thus, critical issues for primary prevention in older persons are those of risk assessment and patient selection. Some investigators have suggested, perhaps tongue in cheek, that all persons should automatically begin statin therapy at age 65 years. This “modest proposal” is made with the recognition that a major proportion of the older population will eventually develop CHD. An alternate approach, which is more in keeping with current concepts of clinical management of risk, is that LDL-lowering drugs should be reserved for persons who are deemed to be at higher risk. If this approach is accepted as more prudent and more cost-effective, we can address the question of how best to assess risk for future coronary events in older persons without established CHD.

A useful concept introduced by ATP III to assist in patient selection is that of CHD risk equivalents. According to this concept, persons whose 10-year risk for major CHD events (myocardial infarction + coronary death) is greater than 20% should be managed by the same guidelines as those for patients with established CHD. This is the level of risk for future major coronary events that exists for patients with established CHD. This concept seems particularly useful for the older population. The ATP III identified 3 conditions that qualify as CHD risk equivalents: noncoronary forms of clinical atherosclerotic disease, diabetes, and 10-year risk for CHD greater than 20% by Framingham risk scoring. Each of these conditions can be reviewed briefly as it pertains to older persons.

The detection of noncoronary forms of atherosclerotic disease calls for intensive LDL-lowering therapy. Included on this list are peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease. Peripheral arterial disease is defined by classic clinical syndromes of lower extremity ischemia, demonstration of advanced arterial disease by imaging or blood flow modalities, or by an abnormal ankle-brachial blood pressure index. Carotid artery disease is identified by a history of transient ischemic attacks, strokes of carotid origin, or greater than 50% stenosis of a carotid artery in otherwise asymptomatic patients. (For detailed evidence of predictive power of subclinical atherosclerosis, see the full report of ATP III at: http://www.nhlbi.nih.gov.) Patients with noncoronary forms of atherosclerotic disease are at high risk for major coronary events. They deserve intensive LDL-lowering therapy. The older population is ripe with these forms of vascular disease, and they deserve appropriate clinical attention.

Diabetes also is common among older people. Almost all patients with diabetes have the type 2 form. In general, type 2 diabetes is accompanied by risk for CHD events that approximates that of patients with established CHD. The ATP III sets an LDL cholesterol goal of less than 100 mg/dL (<2.59 mmol/L) for patients with diabetes. Moreover, if such patients have a baseline level of 130 mg/dL or greater (≥3.36 mmol/L), they can be started on an LDL-lowering drug simultaneously with dietary therapy. Once their LDL levels are reduced to the range of 100 to 129 mg/dL (2.59-3.33 mmol/L), several options for therapy are available. Treatment with LDL-lowering drugs and/or dietary therapy can be intensified to achieve the LDL goal of less than 100 mg/dL (<2.59 mmol/L). Alternatively, if the patient has high triglyceride levels or a low high-density lipoprotein level, an alternate drug (fibrate or nicotinic acid) can be added to the regimen. Regardless of lipid risk factors, the non-lipid risk factors should be aggressively modified as well.

The HPS found evidence of benefit of LDL lowering with statin therapy regardless of patients’ baseline LDL cholesterol levels. This benefit presumably extends to persons with diabetes, especially older persons who have multiple metabolic risk factors. Thus, in light of HPS, consideration should be given to initiating statin therapy in older patients with diabetes regardless of their LDL cholesterol levels.

The ATP III further identified a 10-year risk for CHD greater than 20%, as defined by Framingham risk scoring, as a CHD risk equivalent. Although this recommendation extends to the older population, it must be noted that the accuracy of Framingham risk predictions declines with advancing age. According to the Framingham algorithm, advancing age becomes the predominant risk factor affecting risk prediction. In truth, however, age is a surrogate marker for coronary plaque burden, which is the true risk predictor. The fact that plaque burden varies greatly among older individuals accounts for the decline in reliability of Framingham scoring for risk assessment with advancing age.

A possible way out of this dilemma in older persons is to carry out more accurate measures of plaque burden than is provided by chronological age. Carotid artery thickness measured by B-mode sonography has been shown to correlate with coronary plaque burden.
A more accurate estimate of plaque burden can be obtained by measurement of coronary calcium by computed tomography.\textsuperscript{12,13,14} have proposed a technique to substitute coronary plaque burden for age as a risk factor in Framingham risk scoring. Application of this technique may allow for more accurate prediction of risk in older persons. Aggressive LDL-lowering therapy can then be targeted more specifically to higher-risk patients.

In deciding about primary prevention in the elderly population, a distinction between younger elderly and older elderly may be useful. The former can include individuals in the age range of 65 to 74 years. Persons in this age range were included in most of the statin trials. Since many persons in this age group who are at higher risk for CHD are otherwise healthy, use of statin therapy, even in primary prevention, is justifiable. In the older elderly population (≥75 years), statins should be used more cautiously for primary prevention. For example, persons in this older age group often have many of the risk factors for statin-induced myopathy, ie, impaired drug metabolism, multiple drugs, multisystem disease, more women patients of low body weight, and more frequent surgical procedures. Therefore, in older patients, clinical judgment must be used on whether to use statins in the first place, and if so, what dose of the drug to use. A more “conservative” approach seems appropriate even though it must be recognized that some efficacy in CHD risk reduction almost certainly persists. Undoubtedly, though it must be recognized that some efficacy in CHD risk equivalents, especially noncoronary forms of atherosclerotic disease and type 2 diabetes. Although ATP III recommends management of patients according to Framingham risk scoring, the limitations of this scoring in the older population highlight the need for more accurate methods of risk assessment in this age group. Measurements of atherosclerotic plaque burden offer one way to distinguish between higher- and lower-risk persons in the elderly population.

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REFERENCES