Statins for All?

Recent guidelines for cholesterol management proposed by the American College of Cardiology (ACC) and American Heart Association (AHA) recommended statin therapy for most men in their 60s and most women in their 70s. If these guidelines are followed in the United States, most adults will eventually take statins. A companion article in this journal goes a step further by proposing statin initiation for mostly everyone about 10 years earlier. Treatment in ACC/AHA guidelines does not depend on cholesterol levels, for either statin initiation or treatment goals. Selection of patients for statin therapy depends instead on multifactorial risk assessment derived from prospective studies in subgroups of the US population. Because of expansion of statin therapy, the issue of the reliability of risk assessment has come to the fore. Some evidence suggests that the ACC/AHA risk algorithm overestimates risk in many persons; if so, this would lead to statin therapy beyond what was intended. Some investigators favor assessment of risk based on presence or absence of categorical risk factors or higher risk conditions. Others propose selection of individuals for statin therapy grounded in measurement of atherosclerosis burden. Finally, an alternate approach to cholesterol management is to establish cholesterol goals for secondary and primary prevention. Cholesterol levels, and not global risk assessment, here define the intensity of therapy. The use of cholesterol goals allows more flexibility in treatment by taking advantage of lifestyle therapies and various drugs and their doses to attain defined goals. Published by Elsevier Inc. (Am J Cardiol 2014;114:1443−1446)

The American College of Cardiology/American Heart Association (ACC/AHA) recently published guidelines for cholesterol management.[1] They based recommendations on randomized controlled trials (RCTs); from these, they concluded that statin therapy is appropriate for most men >60 years and most women >70 years. In this issue of the *Journal*, Robinson[2] proposes to push back initiation of statins in men and women by approximately a decade. Both these recommendations call for most Americans to sooner or later take statins. In a word, ACC/AHA guidelines and the proposal by Robinson are a bridge between public health recommendations and clinical guidelines. In this editorial, the implications of these recommendations can be examined. Many RCTs have tested statins in patients with preexisting atherosclerotic cardiovascular disease (ASCVD); they document substantial reductions in subsequent vascular events.[1,3,4] The evidence is so strong that statin therapy in patients with ASCVD has become standard of care.

Pros and Cons of Widespread Use of Statins in Primary Prevention

The dramatic reduction in ASCVD risk accompanying statin therapy has led many investigators to believe that statins should be used more widely in primary prevention. Some advocate a "polypill" approach in which statins are started in everyone at age 50 years and are combined with blood pressure−lowering drugs and/or aspirin.[5] Other researchers speculate that statins might be started in most people earlier in life.[6] This concept is based on a genetic condition that results in a lifetime of low levels of low-density lipoproteins (LDLs) and a low prevalence of ASCVD later in life.[7] The ACC/AHA guidelines in contrast espouse a treat-all approach but for those of advancing age. This strategy would be extended by Robinson to include most people a decade earlier, analogous to the polypill approach.[5]

In contrast, there are important questions related to cost, side effects, and burden on the health care system should statins be used in most persons beginning at a certain age. Even if generic statins can be afforded, other potential problems must be considered. One chronic issue is statin intolerance. Although serious side effects are rare, myalgia is a common nuisance and causes many patients to discontinue statins.[8] About 10% of people complain of myalgia or other side effects.[9] Some of these perceived side effects may not be caused by statins, but even so, discussion between physician and patient is required to decide whether to change the dose, switch to another statin, or discontinue altogether. In a word, in the treat-all approach applied in the medical venue, the whole population will become "medicalized." This will cause considerable friction in an already highly burdened health care system.

Who Really Needs Statins in Primary Prevention?

Most national guidelines reserve statins for persons "at risk." The ACC/AHA recommended starting statin therapy when 10-year risk for ASCVD (coronary heart disease [CHD] + stroke) exceeds 7.5%. This differs from a drug treatment threshold of the National Cholesterol Education Program (NCEP),[10] which was a 10-year risk for CHD of

See page 1445 for disclosure information.

0002-9149/14/$ - see front matter Published by Elsevier Inc.

Table 1
Major risk factors for ASCVD and higher risk conditions

Major risk factors
Cigarette smoking
Hypertension
Hypercholesterolemia
Higher risk conditions
Diabetes mellitus
Metabolic syndrome and/or high C-reactive protein
Chronic kidney disease

10%. The NCEP used Framingham risk scoring. The difference is substantial because ACC/AHA included stroke and CHD under ASCVD. The ACC/AHA−estimated risk of 7.5% for ASCVD corresponds roughly to a 10-year risk for CHD of 5%. This relatively low-risk cut point means that most men become statin eligible in their early 60s and women in their early 70s. Robinson proposes reducing the risk threshold for ASCVD to 5% (threshold for CHD of about 3%). As the treatment threshold is lowered, at some point, it intersects with the population-targeted polypill concept.

How Reliable Is a Quantitative Risk Algorithm?

The ACC/AHA[11] developed a new risk algorithm using 5 large prospective studies, 2 of which included Framingham. It includes CHD and stroke (hard ASCVD). It incorporates the following risk factors: age, smoking, blood pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and diabetes. This approach, also used by NCEP, has its limitations. For example, various populations differ in their susceptibility to CHD and stroke, which depends on their baseline characteristics. In Southern Europe, the baseline risk is about 1/2 that of Northern Europe[12]; and the latter in turn is about 1/2 of that reported in the United States.[13] Baseline risk is relatively high in India but low in China and Japan.[14] However, even in the United States, different subgroups of the population vary in underlying risk.[15]

There are other problems with risk algorithms besides population baseline risk. Population-based algorithms impose population average risk on individuals, but there are no average individuals. Moreover, single measurements of risk estimated by the ACC/AHA algorithm surely are not a reliable indicator of an individual's lifetime risk. Measurements of lipids and blood pressure vary from day to day; hence, single measurements often do not equate to average levels. Moreover, if risk factors are treated, long-term risk will no longer be the same as originally predicted. If a person stops smoking, risk related to smoking falls to near baseline within about 3 years. Treatment of hypertension will modify the predicted risk. These changes may be clinically significant in otherwise low-risk patients.

A particularly unreliable risk factor is age, which counts heavily in risk estimation using the ACC/AHA algorithm. Population risk increases with age because of increasing atherosclerotic burden. However, the rate of atherogenesis varies greatly from one person to another. Thus, assigning a single risk number to everyone at a given age will misrepresent risk in most persons, who will have more or less atherosclerosis than the mean. The older a person becomes, the more unreliable will be age as an indicator of atherosclerosis burden. Yet in ACC/AHA guidelines, most older persons are prescribed statins based on their age alone. Of course, if the risk threshold for treatment is set low enough, defects in global risk assessment become immaterial. Virtually everyone is treated. This apparently has been the approach taken by the ACC/AHA.

Should Statin Therapy Be More Directly Linked to Nonlipid Risk Factors?

ACC/AHA guidelines, which make treatment decisions on population-derived risk algorithms, cannot candidly be called an RCT-based guideline. The risk threshold chosen for initiation of statins depends on expert opinion. Clinical trials generally do not recruit or stratify research subjects by risk algorithms; instead, they mostly have recruited according to risk factor category. For this reason, Ridker and Wilson[16] suggested selection of patients for statin therapy based on particular risk factors.

Risk factors or risk conditions that could be used to invoke statin therapy are listed in Table 1. Therapeutic decisions can be made on the presence or absence of these conditions. Moreover, each has a lifestyle component that deserves intervention, especially when they occur earlier in adulthood. However, if they persist unabated until later middle age or into older years, concomitant statin therapy can be justified for each. RCTs confirm risk reduction with statin treatment for all these conditions. One advantage of making therapeutic decisions on each person's risk factor pattern is that they individualize risk status, and this approach requires physician involvement and clinical judgment.

Just how much weight to give to average levels (or borderline elevations) of cholesterol and blood pressure in otherwise low-risk persons is uncertain. Many people with borderline elevations will have metabolic syndrome, which can justify starting a statin. Framingham data suggest that otherwise low-risk people with borderline elevations of only cholesterol or blood pressure have a relatively low ASCVD up to age 80 years.[17]

Is Atherosclerosis Imaging Helpful?

Another method for risk assessment is atherosclerosis imaging. This has the advantage of determining an individual's atherosclerosis burden, which itself is a strong predictor of ASCVD events. The preferred method is coronary artery calcium (CAC). Several recent studies link CAC scores to absolute risk.[18] In these studies, a CAC score of 0 to 100 Agatston units confers a low risk for ASCVD.