In November 2013, the American Heart Association (AHA)/American College of Cardiology (ACC) released a new Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Recommendations were made for several groups of patients. This perspective will focus only on the recommendation for those with no history of atherosclerotic cardiovascular disease (ASCVD) but with a 10-year ASCVD risk of ≥7.5% and a low-density lipoprotein (LDL) cholesterol level of 70 to 189 mg/dL and who are between the ages of 40 to 75 years. The guideline recommends such individuals receive moderate-intensity statin therapy to reduce LDL cholesterol between 30% and 49%.

The guideline specifies that the 10-year risk of ASCVD, defined as nonfatal myocardial infarction (MI), coronary heart disease death, and nonfatal and fatal stroke, be calculated using the pooled cohort equations. The pooled cohort equations represent a new algorithm for estimating 10-year risks of the same atherosclerotic events using the new guidelines without a prior period for external scientific evaluation. In fact, the algorithm has already been loaded from http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp.

Let’s look at 2 implications of this new risk algorithm. For example, the algorithm asks for sex, age, race (white versus African American), total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, hypertension treatment (Y versus N), diabetes mellitus (Y versus N), and smoking (Y versus N). Patient information is entered and the 10-year risk calculated, and a comparison is made to an individual of the same sex, age, and race with ideal values for total cholesterol (170), high-density lipoprotein cholesterol (50), systolic blood pressure (110), and without hypertension treatment, diabetes mellitus, or smoking. The algorithm indicates that, even with ideal lipid and blood pressure levels and without hypertension treatment, diabetes mellitus, or smoking, white men exceed the 7.5% 10-year risk threshold at age 63, African American men at age 66, white women at age 71, and African American women at 70. This means that every healthy, low-risk individual above these age cutoffs would be recommended for statin therapy. I am troubled by making age such a primary determinant of statin use. The guideline report admits that “few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD.” Moreover, there is a suggestion that statin adverse events are more common in this population. This creates a rather awkward situation in which perfectly healthy people in the fastest growing segment of the population (≥265 years of age) are recommended statin therapy for the rest of their lives with the unsubstantiated hope that the net effect will not be harmful.

The risk algorithm does not include LDL cholesterol, but from the ideal values for total cholesterol (170) and high-density lipoprotein cholesterol (50) and assuming triglycerides of 100, ideal LDL cholesterol can be calculated to be 100. Now, what if a 63-year-old white man with ideal values except for elevated LDL cholesterol of 167 was treated with moderate-intensity statin therapy and his LDL cholesterol lowered by 40% to 100? The algorithm predicts the 10-year risk of developing ASCVD would fall from 9.7% to 7.5%. This is a relative risk (RR) reduction of 23%. Treating 1000 similar individuals for 10 years would result in 22 fewer nonfatal MIs or coronary heart disease deaths, or nonfatal or fatal strokes. If the algorithm overestimates risk as indicated in the Ridker and Cook analysis, the benefit would be more like 9 to 13 fewer nonfatal MIs or coronary heart disease deaths, or nonfatal or fatal strokes. Thus, whether following the algorithm or
the Ridker and Cook correction, the number needed to treat during a 10-year period is in the range of 50 to 100, which does not make a persuasive argument for statin therapy in this low-risk population.

Let us now move to the larger question of whether or not it is justified to prescribe moderate-intensity statin therapy for individuals with no history of ASCVD with a baseline 10-year risk of ASCVD of ≥7.5% and LDL cholesterol of 70 to 189 mg/dL. This decision requires carefully weighing the benefits and risks of statin therapy. Many meta-analyses have been published summarizing the results of randomized control trials (RCTs) of statins in primary prevention. In these meta-analyses, the RR for total mortality has varied between 0.85 and 0.95, with the 95% confidence interval (CI) indicating significance (upper bounds of the CI are between 0.94 and 1.01). The exact definition of major cardiovascular events has varied among the meta-analyses, generally including fatal and nonfatal MI. For major cardiovascular events, the RR has varied from 0.70 to 0.77, with the 95% CI indicating significance (upper bounds of the CI are between 0.80 and 0.95).

Unfortunately, many of the RCT data sets relied on for these analyses are not purely primary prevention and contain ≥10% of individuals with ASCVD at baseline. In addition, none of the meta-analyses except for the one by the Cholesterol Treatment Trialists Collaborators (CTTC) had the information to determine the baseline risk of those who went on to experience events during the course of the various trials. Thus, although they are generally helpful, only a single meta-analysis directly deals with the AHA/ACC guideline on individuals with no history of ASCVD and with a baseline 10-year risk for ASCVD of ≥7.5% and LDL cholesterol of 70 to 189 mg/dL.

The CTTC meta-analysis had access to the individual participant data from 22 trials of statins versus placebo and 5 trials of high- versus low-dose statins, allowing categorization of the baseline risk for those without ASCVD at entry into the various trials. They identified subjects without vascular disease at baseline and separated them into categories of 5-year major vascular event risk (defined as nonfatal MI or coronary death, any stroke, or coronary revascularization procedure) of <5%, 5% to 10%, 10% to 20%, 20% to 30%, and >30% and estimated the RR per 1.0 mmol/L LDL cholesterol reduction on statin therapy for each category. The RR for these categories was 0.61 (99% CI, 0.45–0.81), 0.66 (99% CI, 0.57–0.77), 0.82 (99% CI, 0.72–0.93), 0.81 (99% CI, 0.65–1.01), and 0.83 (99% CI, 0.58–1.18), respectively, and overall 0.75 (95% CI, 0.70–0.80). The corresponding numbers for any vascular death in each category were 0.80 (99% CI, 0.43–1.47), 0.75 (99% CI, 0.55–1.04), 0.84 (99% CI, 0.67–1.05), 0.97 (99% CI, 0.72–1.32), and 0.88 (99% CI, 0.59–1.33), respectively, and overall 0.85 (95% CI, 0.77–0.95). Thus the major vascular event RR for the first 2 categories of risk was significantly reduced by statins. However, the vascular death RR was not significantly reduced in these categories.

The CTTC interpreted their results as follows: “in individuals with 5-year risk of major vascular events <10%, each 1 mmol/L reduction in LDL cholesterol produced an absolute reduction in major vascular events of ≈11 per 1000 for 5 years.” It seems that the CTTC database has not been made available to the interested scientific community. Because this is the only meta-analysis that directly deals with primary prevention in low-risk individuals, this is a serious cautionary note. For example, the CTTC results are expressed in terms of RR per 1.0 mmol/L LDL cholesterol reduction, whereas others might want to count actual events and the type of events in statin- versus placebo-treated individuals, especially in certain subgroups.

In considering the justification of prescribing moderate-intensity statin therapy for individuals with no history of ASCVD, let us now turn to the risks. Statin therapy has been associated with muscle problems, cognitive impairment, type 2 diabetes mellitus, and liver damage. The most common side effects are muscle related (statin-associated myopathy [SAM]). Although not originally appreciated by the academic medical community, there is a major discrepancy in the incidence of SAM in subjects undergoing RCTs and patients seen in a clinical setting. In the former group, the incidence reported is at most a few percent, whereas in the latter the estimated incidence is 10% to 15%. This discrepancy is mainly because of 2 factors. First, subjects undergoing RCTs are a select group that largely excludes older subjects and, in some studies, women; 2 groups reported to have a higher frequency of statin adverse events. Also, patients who consume significant amounts of alcohol, who have multiple comorbidities, and who are on several medications are generally excluded from RCTs, whereas in clinical practice such individuals might be prescribed statins. Moreover, trial volunteers would tend not to be those with a previous history of SAM, and trials would tend to exclude those with a previous history of SAM.

The second factor is that RCTs have focused on the 2 most serious manifestations of SAM, rhabdomyolysis, and myositis (>10-fold elevation of creatine phosphokinase). However, the SAM spectrum is much broader and includes widespread or localized muscle pain, muscle heaviness stiffness or cramps, weakness or loss of strength during exertion, and tendonitis. Although all of these symptoms can arise without a >10-fold elevation of creatine phosphokinase (or any other biochemical marker), they do affect quality of life.

Too few studies have made a serious attempt to document the muscle problems associated with statin therapy. The best in this regard is the Prediction of Muscular Risk in Observational Conditions study, which was a country-wide observational survey of SAM in patients receiving high-dose statin treatment in general practice in France. In total, 7924
hyperlipidemic patients aged 18 to 75 years who were seen in regular outpatient visits with their general practitioners were entered in the study. Patients were included if they had been prescribed high-dose statin treatment (fluvastatin, 80 mg; atorvastatin, 40 or 80 mg; pravastatin, 40 mg; or simvastatin, 40 or 80 mg) for ≥3 months before the study. Patients were also included if their regimen had been adjusted (statin withdrawal or dose reduction) within the previous 3 months because of muscular pain.” A questionnaire was completed by the physician in the presence of the patient including demographic data, lifestyle, personal and family medical history, and current cardiovascular treatment status. “If muscular symptoms were reported, a second questionnaire was also completed, providing information about the type, location, duration, possible causes, and management of the symptoms.” There were 832 patients with muscle symptoms (10.5%). Of those, 28% experienced minor disruption of daily life, 26% experienced interference with major exertion, 38% experienced interference with moderate exertion, and 4% had major disruption of daily life causing them to be bedridden or to stop work.

For many years, physicians and lipid specialists chose to ignore SAM. This refusal to acknowledge the problem was frustrating for the affected patients and has probably contributed to the low statin therapy adherence rates documented in both primary and secondary prevention efforts. Improved communication and frank acknowledgment of SAM will probably improve the situation. Articles are now appearing in the literature arguing that SAM can be managed and most patients restored to some type of statin-based regimen (different statin, lower dose, and altered dosing regimen). Although this is a good trend, it still must be debated whether or not it is worth persisting with statin therapy for the relatively small absolute benefits to be garnered in low-risk individuals.

Finally, in an especially apt discussion of the current situation, the Cochrane Collaboration, a group generally regarded as providing a gold standard for meta-analysis, state in their 2013 article “Several issues remain to be considered before widespread use of statins could be recommended in people at low risk. These include (1) the feasibility and desirability of having to treat the majority of people over the age of 50 with a statin, (2) the cost-effectiveness of such a strategy using a conventional healthcare delivery system, (3) diversion of attention from achieving coverage in people at high risk of events, (4) use of alternative public health strategies to lower blood cholesterol, (5) the views of patients on life-long drug therapy, and (6) limited evidence on less serious but nonetheless potentially important adverse effects and quality of life.”

In summary, from my perspective the guideline committee’s recommendation for primary prevention in low-risk individuals has placed too much weight on an unproven risk algorithm, an unusual statistical analysis by a group whose database has not been made available to the interested scientific community, and drug company-sponsored RCTs that have not thoroughly evaluated risks in populations more relevant to practice situations, especially the elderly. By narrowly focusing on rather modest absolute event rate reductions proven by complex statistical methods, I feel the guideline committee did not adequately consider the broader health and societal issues, as outlined in the previous paragraph, of placing such a large fraction of the population on statins.

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