What Works and in Whom?

A Simple, Easily Applied, Evidence-Based Approach to Guidelines for Statin Therapy

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At the behest of the National Heart, Lung, and Blood Institute, guideline committees have worked over the past 3 years to produce a simple set of recommendations to assist practicing physicians in the task of reducing the population burden of heart attack and stroke. Commendably, those guidelines will be unique in that for the first time they are required to be fully evidence-based and will rely solely on published data that have withstood peer review. Most importantly, those guidelines will rely whenever possible on data from randomized clinical trials that evaluate hard clinical outcomes rather than surrogate end points. This latter step is important and a formal recognition that quality of care and the prevention of heart disease have entered an era where untested hypotheses take a back seat to proven preventive strategies.

When framed clinically, there are 2 fundamental questions an evidence-based guideline must address. First, are there therapies or interventions that have been proven to have a net clinical benefit for our patients? If so, in which patients do such data clearly apply?

Regrettably, few fields of medicine have robust clinical trials that can be used to address these 2 simple questions. Most preventive cardiologists agree that diet, exercise, and smoking cessation are crucial components of any practice recommendation, yet formal trial evidence demonstrating such effects is sparse.

In some arenas, however, we are blessed with abundant data from multiple large-scale randomized, double-blind, placebo-controlled trials in which a trial-based guideline approach of "what works?" and "in whom?" is easily applied. One such area is the use of statin therapy for the primary and secondary prevention of cardiovascular disease.

With regard to secondary prevention, we have clear evidence from multiple major trials that statins are effective in reducing clinical outcomes across a broad spectrum of individuals with clinically evident atherosclerotic disease.[1] With regard to primary prevention, we have additional clear randomized trial evidence that statins reduce vascular event rates among those who meet core trial entry criterion. For example, we know with certainty that statins are effective in primary prevention among those who meet the West of Scotland Coronary Prevention Study (WOSCOPS) core entry criterion of elevated low-density lipoprotein cholesterol.[2] Similarly, we know with certainty that statins are effective in primary prevention among those who meet the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) core entry criterion of reduced high-density lipoprotein cholesterol.[3] Thus, applying the simple 2-question rule of "what works?" and "in whom?" to statin use, a simple, evidence-based approach based on completed randomized trials and their respective trial entry criteria would be as follows: (1) Statin therapy should be used as an adjunct to diet, exercise, and smoking cessation for all individuals with a history of myocardial infarction, stroke, or clearly established atherosclerosis (secondary prevention); (2) among middle-aged and older men and women (for example, men >50 years and women >60 years), statin therapy can be considered for use as an adjunct to diet, exercise, and smoking cessation for those who meet the major entry criteria for published primary prevention trials (for example, those with low-density lipoprotein cholesterol >130 mg/dL or a total cholesterol:high-density lipoprotein cholesterol ratio >5; primary prevention); and (3) for patients not meeting this criterion, physicians may consider issues such as multiple risk factors, unique lipid abnormalities, insulin resistance, or a family history of premature coronary disease when making decisions for individual patients in primary prevention. For some of these patients, referral to lipid or atherosclerosis specialists may be useful for consideration of secondary testing and potential use of alternative lipid-lowering therapies.

Although easily remembered and thus easily applied, it is crucial to recognize what is not being advocating in this simple, trial-based approach to the prevention of heart attack and stroke.

First, this is a recommendation for physicians to specifically use statin therapy, not a recommendation to use lipid-lowering therapies in general. This formulation avoids the confusion of prior recommendations that have often led to use of second-line nonstatin agents where proof of effectiveness for outcome reduction is unavailable.

Second, the proposed formulation does not endorse or describe specific low-density lipoprotein cholesterol treatment targets because these have neither been formally tested nor proven an effective method to improve compliance or adherence. Rather than focusing on a given level of low-density lipoprotein cholesterol reduction, physicians better serve patients by emphasizing the importance of compliance and long-term adherence. If new agents develop evidence of event reduction

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This article was handled independently by Guest Editor Eric R. Bates, MD. The Editors had no role in the evaluation of the article or the decision about its acceptance.

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(*Circ Cardiovasc Qual Outcomes*. 2012;5:592-593.)

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org

DOI: 10.1161/CIRCOUTCOMES.112.966556

beyond that achievable with background statin therapy, updated guidelines can be developed to address these important advances appropriately.

Third, the approach outlined does not endorse imaging tests as a method to target statin therapy. This is appropriate because no prospective trial indicates efficacy for an imaging-based strategy. Using simple biomarkers rather than imaging ensures that the locus of control for prevention remains with the primary care physician rather than being transferred to imaging specialists and avoids the expense and radiation associated with some imaging modalities. If appropriately designed randomized trials based on carotid intimal medial thickness, coronary artery calcium scanning, or other imaging modalities are conducted and demonstrate use, then updated guidelines can and should be developed to address these important advances as well.

Fourth, this approach deviates from past recommendations by eliminating the need to compute a global risk score before therapeutic intervention. There are many reasons to favor this approach. First, no global risk algorithm including the Framingham Risk Score has ever been used as a formal enrollment criterion for statin trials, so continued reliance on this approach violates basic evidence-based principles. Second, the main argument voiced in the past for using a global risk score to estimate absolute risk was to limit prescription to those most likely to benefit and to minimize drug expenditures. However, with markedly reduced costs of generic statin therapy and far larger databases available for both safety and efficacy, such approaches are largely outdated, particularly as the notions of "lower," "intermediate," and "higher" risk neither reflect our biological understanding of statin mechanisms nor incorporate our emerging concepts of lifetime risk. Age, however, is by far the greatest predictor of absolute risk in all risk prediction algorithms. Thus, by retaining age, this formulation de facto includes a crucial determinant of absolute risk without burdening the physician user with a formal computation. This is not a trivial issue because community-based physicians have long demonstrated their reluctance to use any global risk tool in daily practice. Finally, we must recognize that it would be a violation of principles if those writing guidelines were to create and present to the prevention community a de novo risk score without undergoing the full peer review and external validation procedures demanded for all other parts of the guideline process. Such an approach would represent the kind of "behind the doors" practice that a transparent guideline process must explicitly avoid.

Attention should be paid to the specific language chosen for these recommendations. In secondary prevention, it is stated that "statin therapy should be used as an adjunct to diet, exercise, and smoking cessation" because trial data clearly indicate that in the absence of a formal contraindication, all such individuals should be treated.

By contrast, in primary prevention, it is stated that "statin therapy can be considered for use as an adjunct to diet exercise and smoking cessation" to recognize that a spectrum of risk and benefit exists, that net use is less compelling in primary as compared with secondary prevention, and thus that controversy remains in some settings. As noted, the use of suggested age criteria (men >50 years, women >60 years as examples) is incorporated to approximate trial evidence and to de facto limit prescription to those with higher absolute risk without requiring computation. Although physicians may elect to start treatment earlier for some individuals and later for others, those in middle age or older are the group best supported by current evidence. If new studies indicate clear benefits from therapy begun at younger age, such data can be incorporated into future practice guidelines.

Finally, the simple 3-part formulation outlined here recognizes that individual patients may present with unique lipid profiles, a clustering of multiple risk factors, or with a significant history of premature coronary disease, groups that may not have been explicitly enrolled in statin trials with adequate power to define a net treatment benefit. It further recognizes that special situations exist and that specific therapies not tested in large trials may nonetheless benefit individual patients. For these reasons, this formulation notes that these issues can be considered in decision-making and also suggests referral to lipid or atherosclerosis specialists for secondary evaluation and perhaps additional therapy when unique clinical situations arise.

The approach advocated here including its reliance on trial evidence (to know what works) and on trial entry criteria (to know in whom) has strong precedent and is the basis for the 2009 Canadian Cardiovascular Society guidelines for the diagnosis, treatment, and prevention of cardiovascular disease.[4] Statin guidelines based on trial enrollment criteria and trial outcomes are protected against claims of bias and thus are likely to result in increased application and clinical consensus.

Disclosures

Dr Ridker receives investigator-initiated research funds from AstraZeneca and Novartis; has served as a consultant for Merck, ISIS, Genzyme, and Vascular Biogenics; and is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Seimens and AstraZeneca.

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