VIEWPOINT

Clinical Practice Guidelines for Chronic Cardiovascular Disorders: A Roadmap for the Future

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The World Health Organization lists ischemic heart disease and stroke as the top 2 leading causes of death worldwide in 2011, responsible for 7 million and 6.2 million deaths, respectively.[1] The concept of risk factors for atherosclerotic cardiovascular disease (CVD) was introduced in 1961, based on epidemiologic observations from the Framingham Heart Study. Hypertension and abnormal blood lipid levels were key risk factors shown to be associated with an increased risk of angina pectoris, myocardial infarction, and sudden cardiac death; later, stroke was identified as an important outcome as well, especially in women and racial/ethnic subgroups. Accordingly, clinicians want to provide their patients with the best possible advice with respect to the management of cardiovascular risk, often implementing evidence-based clinical practice guidelines designed to improve health outcomes.

Because management of hypertension and abnormal blood lipid levels continues to be a major focus of clinical investigation and high-profile pharmacologic trials, clinical practice guidelines must be updated periodically. Members of the committee for a clinical practice guideline must evaluate and synthesize the evolving evidence when formulating their recommendations. Sources of evidence have traditionally included randomized clinical trials (RCTs) and epidemiologic observations. When the evidence is not available from the medical literature to answer common clinical questions (eg, should I take aspirin?), expert consensus is often used to guide the development of a recommendation. Various schemes have been introduced to codify recommendations and the strength of the evidence on which they are based, with the goal of developing unimpeachable guidelines with respect to scientific validity and ethical quality. Particular emphasis has been placed on evidence documenting only those interventions that have had an effect on health outcomes. In this Viewpoint, we discuss the challenges imposed by this perspective on evidence when viewed through the interrelated lenses of the biology of the disease process and the results from RCTs to provide reliable signals of an effect on health outcomes.

Biology of Atherosclerotic CVD

Atherosclerotic CVD has a long, silent latency period, with lesions developing over a time horizon measured in decades rather than years. A logical extension of this biological fact is that guideline committees are unlikely to find RCTs that span the continuum from ideal health, development of risk factors (hypertension, elevated cholesterol levels), and the subsequent transition to disease. Consider 3 trial categories as illustrated in the **Figure**. Category A comprises RCTs enrolling study participants presumed to be in ideal health; the follow-up period ends before risk factors develop. Such trials are noninformative regarding outcomes because of the limited sample of the disease continuum examined—despite how critical this time is to the principles of prevention.

Category B enrolls study participants based predominantly on the presence of a risk factor but may include some persons who initially are in ideal health and subsequently develop a risk factor during the course of the trial. Practical concerns (resources, trial fatigue, and inability to maintain adherence to the test regimen) result in category B trials also sampling a limited portion of the continuum, with only a modest number of patients undergoing the transition to disease and experiencing a trial end point. This, too, results in a set of underpowered trials with limited ability to inform guideline committees about how to write recommendations.

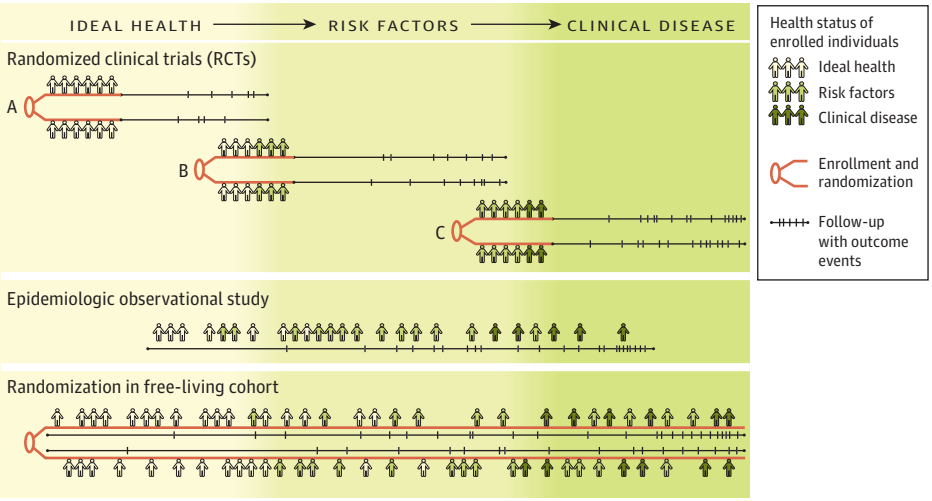
Category C trials enroll study participants later along the disease continuum. Although this improves the likelihood of observing events, the limitation of such an approach is that interventions tested may be applied too late to show any benefit. Also, category C trials impair the ability to ask whether an aggressive approach used at a more proximal point in the continuum (eg, aggressively lowering low-density lipoprotein cholesterol levels or blood pressure decades earlier) would be beneficial.

Epidemiologic observations offer the advantage of sampling a larger cohort of individuals; certain methodological approaches may provide insights over a longer portion of the disease continuum. Of concern, however, is the potential for bias and confounding that might mislead guideline committee members. For example, observational studies suggested a net benefit for hormone therapy in postmenopausal women. However, the comprehensive picture of risks and benefits based on factors such as type of hormone therapy, age, and time since onset of menopause became more apparent as data from RCTs became available.[2]

Ability of RCTs to Provide Reliable Signals of Effects on Health Outcomes

Because RCTs are less subject to bias and confounding, they are considered the preferred source for evidence reviews. It is important to critically assess the ability of a set of RCTs to provide reliable signals of an effect of an intervention on health outcomes. Features of trial design that influence the number of events observed include the definition of events, the duration of follow-up, and the sample size. Patient factors (age, comorbid conditions, position along the disease-process continuum) and aspects of the test intervention (potency of treatment, dose, drug interactions) also influence the relative difference in events in the treatment groups of the RCT. Thus, the critical issue is not that randomization was used but rather the adequacy of the number of events observed in the various treatment groups.

Figure. Different Methods for Acquiring Evidence in Relation to the Biologic Continuum of Disease



The biologic continuum of disease progresses from ideal health through the development of risk factors (eg, hypertension, hypercholesterolemia) and the transition to disease (eg, atherosclerosis) with development of outcome events (eg, myocardial infarction, stroke). Three categories (A, B, C) of RCTs illustrate the available evidence reviewed by committees for clinical practice guidelines. In epidemiologic observational studies, patients enter the study cohort at different stages along the continuum and vary in the duration they are at risk for an outcome event. The proposed solution to the limitations of the current evidence base is to embed randomized trials in large free-living cohorts of patients who enter the trial and are randomized at different stages throughout the biologic continuum. See text.

Roadmap for the Future

Given the effect of CVD not only on health but also the economic well-being of society, it is imperative that guideline committees consider the optimum evidence base from which clinical practice recommendations can be formulated. As an interim solution, while maintaining the focus on RCTs, guideline committees should have greater latitude in assessing the totality of the available evidence—including epidemiologic observations, meta-analyses, and biologic insights. For example, a synthesis of data from multiple RCTs showed a direct and near-linear relationship between the amount of lowering of systolic blood pressure with drugs and the likelihood of a CVD event.[3] Similar pooled RCT data are available showing a linear relationship between the absolute reduction in levels of low-density lipoprotein cholesterol with a statin and the proportional reduction in CVD events.[4] No single RCT has the sample size, power, and duration of follow-up to provide such insights.

A more satisfactory approach would be to embed randomization in a large, free-living cohort of persons that spans the entire life spectrum shown in the Figure. This would allow testing of interventions at various stages of the disease process and provide sufficient power to reliably assess treatments. Randomization would minimize bias and confounding. Such an approach, which would have been difficult to implement in the past, can now be undertaken efficiently if the new and emerging technologies available today are used. For example, an option for randomization can be included in electronic medical records, which become the case report form for an RCT.[5] The US Food and Drug Administration has released a guidance document on how such electronic sources of data can be used in clinical investigations.[6] Another novel approach is that used in the Health eHeart Study, which is using the Internet and mobile technology to enroll a large (1 million adults) decentralized cohort. Data from surveys, mobile apps, sensors, electronic health information, and biospecimens will be correlated with CVD outcomes.

Rather than continue with a silo approach in which RCTs are constructed to answer a small, focused set of questions, a systems approach to structuring recommendations is necessary to ensure that interconnected data at the genomic, molecular, cellular, organ, and whole-body levels are considered. This will require novel bioinformatics approaches and adaptive designs of RCTs during the exploratory phase of therapeutic development, with a seamless transition to the confirmatory phase. The large, free-living cohort proposed at the bottom of the Figure offers the type of platform needed to accomplish these goals.

By assembling the evidence base in a fashion that accords with the biology of chronic CVD, a more precise, personalized approach to medicine can be achieved. Members of guideline committees in the future will have the information they need to guide clinicians on how to offer personalized estimates of the benefits and risks of primordial, primary, and secondary prevention. The roadmap outlined will require significant social and cultural changes, including support for the infrastructure needed to develop and maintain the databases from free-living cohorts, education of patients and clinicians about their importance, and innovations in regulatory science to accelerate translation of new evidence into practice.

ARTICLE INFORMATION

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported serving as the current president-elect and president of the American Heart Association (AHA). The AHA has a strategic scientific collaboration but no financial relationship with the Health eHeart Study.

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