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EDITORIAL

2013 ACC/AHA Guideline: A Guideline for the Population—Without Evidence from the Population

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The release of the *2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults* [1] has elicited much controversy. The new Guideline represents a drastic departure from the previous guidelines, NCEP ATP III[2], and current guidelines in Europe and Canada [2, 3]. Most striking has been the new risk calculator, the focus on statin drugs, and the elimination of LDL-cholesterol (LDL-C) targets for treatment. The Guideline committee addressed pre-specified core questions using evidence from randomized clinical trials (RCT) to identify four patient groups would benefit from statin therapy.

As cardiologists and epidemiologists, we found it bewildering that studies in epidemiology, a discipline that was a cornerstone in establishing plasma lipids as a risk factor for cardiovascular disease (CVD), were not considered in a document that has such far-reaching influence on public health.

Epidemiology is the science of population and observational studies. Epidemiological studies follow large numbers of people to identify factors associated with disease (risk factors), demographics of who gets disease, and ways to prevent and control disease.

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There is no shortage of high-quality cardiovascular epidemiological studies with many sponsored by the National Institutes of Health. The Framingham Heart Study, began enrolling participants in 1948 and reported results in 1961 that established the concept of "risk factors" for cardiovascular disease [4].

Later epidemiological studies expanded on the Framingham model to include older persons (The Cardiovascular Health Study), younger persons (The Coronary Artery Risk Development in Young Adults Study), ethnic and racial groups (The Multi-Ethnic Study of Atherosclerosis), and Blacks (The Jackson Heart Study). However, the ACC/AHA Guideline provides less information for older (> age 75 years), and younger (< age 40 years) persons as well as certain ethnic/racial groups (Hispanics and Asians). According to the authors, "No primary prevention RCT data were available for individuals 21 to 39 years of age and few data were available for individuals > 75 years of age" and add, "Therefore, in adults with LDL-C < 190 who are not otherwise identified in a statin-benefit group . . . clinician knowledge, experience, and skill ("the art of medicine") . . . " should be used in the decision to treat.

The Guideline does not include targets or goals for LDL-C as the committee felt there was no evidence from RCT to support having these as part of a treatment algorithm. Epidemiological studies provide evidence to support the use of goals or targets. This was a focus of the NCEP ATP III guidelines and has been retained in the current European and Canadian Guidelines. In the NCEP ATP III guidelines, targets for LDL-C came from the log-linear relationship between serum cholesterol levels and CHD risk observed in many populations. "LDL-C levels < 100 mg/dL are associated with a very low risk for CHD in populations and were considered "optimal." . . . whereas at levels that are high (160–189 mg/dL) and very high (>/=190 mg/dL) it is markedly accelerated [5].

The 2013 "International Atherosclerosis Society (IAS) Position Paper: Globall Recommendations for the Management of Dyslipidemia also endorsed "optimal" LDL-C levels and state that their position was based on evidence from epidemiology: "Cholesterol-lowering RCTs were not specifically designed to test efficacy at various goals for LDL-C. Epidemiological studies in several populations show that risk for CHD falls progressively to a total cholesterol of approximately 150 mg/dL. This is felt to correspond to an LDL-C of about 100 mg/dL [6].

Unlike the ACC/AHA Guideline, the IAS authors used "three major lines of evidence:" epidemiological studies, genetic studies, and clinical trials. The authors comment on the limitations of RCTs, stating "Clinical trials, especially randomized clinical trials allow testing of single variables, usually drug therapies. This fact has led many guideline panels to give priority to RCT over other lines of evidence. Most RCTs are drug trials. Allowing RCTs to dominate guideline development largely restricts them to drug recommendations; reliable RCTs for lifestyle therapies are few. Drug RCTs moreover have not been carried out in a diversity of populations. Volunteers for RCTs commonly do not reflect the population at large. And finally, RCTs are mostly sponsored by the pharmacological industry. They are designed primarily to obtain regulatory registration, not to answer critical questions in clinical intervention. The IAS panel recognized the enormous fund of useful information provided by RCTs; but it also has placed RCTs in the context of epidemiological and genetic findings" [6].

It is interesting (and foretelling) that Scott M. Grundy, chair of the Panel for NCEP ATP III wrote in 2004: "Because of the success of statin trials, some investigators have suggested that guidelines can be simplified by merely recommending that high-risk patients be treated with the doses of statins used in clinical trials. This suggestion represents an oversimplification that will lead to undertreatment of many patients. It does not take advantage of the strong database supporting the log-linear relationship between LDL-C levels and CHD risk"[7].

The ACC and AHA are planning to have additional documents and updates relating to treatment of cholesterol. Going forward, one hopes that the authors will broaden their definition of "evidence" to include population studies in the preparation of population guidelines.

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