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Foreword

From the Editor: The future of managing lipoprotein disorders

For more than 25 years, the National Cholesterol Education Program (NCEP) contributed to reducing illness and death from coronary heart disease in the United States by guiding actions that have reduced the number of Americans with high blood cholesterol (http://www.nhlbi.nih.gov). The program was designed to address both clinical medicine and the related public health issues. The NCEP was initiated and funded in its deliberative meetings by the National Institutes of Health through an office of the National Heart, Blood, and Lung Institute (NHLBI). The various recommendations were developed by panels of experts and then approved by the NCEP. This process provided guidelines on the clinical assessment of common lipoprotein abnormalities, goals for their treatment, and guidance on appropriate therapy to achieve those goals. The content of programs was the responsibility of the NCEP Coordinating Committee, a consortium of 12 government agencies and some 40 major research and voluntary health organizations. This provided representation by health professionals involved in preventing and treating cardiovascular disease at all levels.

The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel) first provided recommendations for clinical management of lipoprotein concentrations in individual patients in 1988.[1] The Adult Treatment Panel (ATP I) guidelines were revised in 1993[2] and again in 2002[3] with further modifications recommended in 2004.[4] These revisions were primarily driven by the availability of new drugs and the results of clinical trials. These trials indicated that further benefit accrued from reductions of apolipoprotein B–containing lipoproteins to concentrations originally believed to be irrelevant to atherosclerosis or even dangerously low. Although only a few of these trials had titration steps or predefined goals of therapy in their design, the message seemed clear that low-density lipoprotein (LDL) cholesterol well below 100 mg/dL led to reductions in major clinical vascular events in the coronary, cerebral, and peripheral vessels. A basic principle of the ATP recommendations has been that the evaluation of the risk status of a patient should determine the goals of therapy. In this way we could expect to maximize the benefit-to-risk ratio. It remains unclear as to how low we may go with blood concentrations of LDL (or all apolipoprotein B–containing lipoproteins) while seeing improved outcomes in patients. This lower limit will most certainly remain a moving target as we continue to develop new drugs, document their safety, and adequately reduce their cost.

In 2011, the European Atherosclerosis Society in conjunction with the European Cardiology Society updated their guidelines.[5] Although taking a similar approach to the NCEP Guidelines, they offered some additional tools for choosing goals of therapy and added new information about clinical trials, as well as risk related to high-density lipoprotein (HDL) cholesterol and lipoprotein a. In 2012, the International Atherosclerosis Society (IAS) recognized that several other countries were creating revisions of their guidelines that were based on new information and that the various innovations and approaches in these guidelines should be reconciled. Accordingly, an International Committee set to work to provide a Position Report on Guidelines. The Committee has representation from many nations by clinical scientists highly experienced in guideline development and their applications in the clinic. The executive summary of the first position paper on guidelines has been submitted by Dr Scott Grundy, the chairperson of this committee and is published in this issue of the *Journal*. The full document explaining the rationale of the changes and innovations suggested for Guideline development will be published in the February issue of the *Journal of Clinical Lipidology*. One of the important proposals is that we should consider "non-HDL cholesterol" as an equally valid alternative target to the measure of LDL cholesterol in all patients. The advantages of using non-HDL cholesterol in treating hypertriglyceridemia seem clear, but the additional value of having a measure that is valid in nonfasting blood provides a strong argument for recommending it for wider use. The rationale for continuing to consider lowering LDL cholesterol further has not come from experiments that used a specific goal in the treated group. Instead, they have come from correlational analyses of the change in vascular events related to the changes in lipoprotein concentrations produced by a given therapy. The data supporting the use of non-HDL cholesterol as a target are derived from

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these same clinical trials that used this type of analysis. This evidence seems at least as strong as that for reducing LDL cholesterol. For appropriate treatment the IAS manuscript describes the basic approach to be the integration of risk assessment, target setting, and goal definition. They are based on all pertinent evidence about the pathogenesis of arteriosclerosis, response to interventions at the tissue level, imaging of human vessels, and from clinical trials. They recognize deductive reasoning and respect expert opinion about issues that are not amenable to direct interventional experimentation while defining questions that need further study.

We have been expecting a report of the Adult Treatment Panel IV (ATP IV) In June of this year, the plan for the development of the new NHLBI-driven guidelines was revealed to be a collaboration between the American College of Cardiology, the American Heart Association, and the NHLBI.[6] These were to be based on an evidentiary review performed by panels appointed by the director of the NHLBI. Separate panels had been and are continuing to develop reviews of pertinent data for cholesterol management, risk assessment, diabetes management, high blood pressure management, and management of obesity. Apparently, the documents were originally to be provided to voluntary health organizations for the conversion to clinical guidelines. However, in October, the publication of 2 articles in the *Journal of the American College of Cardiology* revealed more details about this new approach to clinical guideline development. In the first article, the NHLBI informs that it has now adopted a new policy of developing evidentiary reviews but is no longer to be directly responsible in the development of guidelines.[7] Guidelines would be the purview of other organizations. In the second article, more details of the guideline development phase were described.[8]

As stated in the first of these publications:

> *It is noteworthy that the IOM [Institute of Medicine] issued 2 separate reports, on writing of systematic reviews[9] and 1 on development of guidelines.[10] The 2 activities are related, require careful intersection and coordination, but nonetheless, are distinct. In some respects, this distinction reflects the composition and charges of the 2 committees that Secretary Richardson appointed back in 1972. This important delineation between the writing of systematic reviews and the construction of clinical practice guidelines has been articulated by others. For example, Clifton Gaus, an administrator of the Agency for Health Care Policy and Research from 1994 to 1997, recalls that when he consulted stakeholders, ''Almost unanimously they said, We dont use your guidelines per se, but the synthesis of science you base them on is invaluable to us in writing our own guidelines ''.*[11]

The NHLBI is cognizant of the clear distinction between the processes underlying the performance of systematic reviews and the creation of practice guidelines. Both NHLBAC working groups facilitated our evaluation of the existing landscape and evolving best practices to define the best approach for the NHLBI to fulfill its leadership role in health education for the public. Accordingly, we plan to refocus our health education agenda on our core mission of knowledge generation and synthesis by supporting and producing rigorous systematic reviews that can then be used by other collaborating organizations to generate guideline products that serve the public interest. The NHLBI has decided that the 5 pending cardiovascular guideline products will be published as evidentiary reviews, and that the Institute will subsequently collaborate with other organizations to prepare and issue the related clinical practice guidelines.

We enthusiastically embrace this public service leadership role in promoting health education by taking responsibility for generating the systematic review data set and evidence syntheses that other organizations will use to develop cardiovascular guidelines. Although the detailed elements of the new NHLBI model remain to be further refined, the overall framework is well aligned with the IOM approach, and our implementation plan will be governed by 6 operating principles:

1. *Before taking on new evidence syntheses, the NHLBI will consult closely with external stakeholders to identify high-priority needs with compelling relevance to the NHLBI mission and the health of the nation.*
2. *Once those needs are identified, the NHLBI will work with external stakeholders to determine which critical questions are most crucial for their ability to generate guidelines that are reliable, robust, credible, relatively easy to implement, and likely to promote significant improvements in public health.*
3. *In supporting and generating evidence syntheses, the NHLBI will pay careful attention to the evolving standards on systematic reviews promulgated by the IOM and other credible sources.*[9]
4. *In enabling partner organizations to generate their own guideline products, the NHLBI will continue to abide by the highest standards for developing trustworthy clinical practice guidelines and will continue to adapt as best practices and the landscape of stakeholders evolve.*[10]
5. *The NHLBI will implement a process for internal evaluation and continuous improvement in line with our commitment to results-based accountability and stewardship of public resources.*[12]
6. *The syntheses will identify evidence gaps, which can guide research investments in areas of importance to public health.*

This seemed a welcome approach with the NHLBI to provide updated material from clinical trials performed in the period from 2004 through 2009. This could then stimulate a further evolution of the successful programs sustained and growing over the years by the NCEP. The clinical arena has matured and become increasingly adept at using these guidelines. Many organizations such as the American Diabetes Association, the Kidney Foundation, and agencies in other countries have adapted them to their own clinical systems and special problems. Although it was