Workshop IV
Diagnosis, Evaluation, and Treatment: Current Status and Issues

Participants
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Laboratory Measurements of Lipids and Lipoproteins

Background. The status of lipid and lipoprotein measurements in clinical chemistry laboratories throughout the United States was discussed. The major present and future issues concerning laboratory assays were considered.

In January 1988, the first report of the Laboratory Standardization Panel (LSP) of the National Heart, Lung, and Blood Institute (NHLBI) National Cholesterol Education Program (NCEP) was published.† The report summarized the need for precise and accurate serum cholesterol measurements and evaluated their current state of reliability. The report also described the degree to which precise and accurate cholesterol measurements are possible, based on currently available instrumentation, reagents, and methodologies. Also addressed were factors contributing to acceptable laboratory analytic performance and general recommendations for improving this performance, as well as a summary of resources available for implementing a nationwide cholesterol standardization program. With regard to accuracy, the first report of the LSP states that “Bias (deviation from the true value) of cholesterol measurement methods currently in use should not exceed ±5% from the true value and should be no greater than ±3% from true value within 5 years.”

The release of the LSP’s first report heightened the awareness of laboratory, manufacturer, and practitioner communities concerning the need for more reliable cholesterol measurements. A variety of actions have been taken by professional societies and instrument manufacturers to improve the current situation. Recent evidence suggests that there has been a significant improvement in the number of laboratories meeting the accuracy standards established by the LSP.

Desktop analyzers that are commonly used in physicians’ offices or at screening sites were discussed. Although some of these systems can achieve acceptable performance that meets LSP guidelines, some may not, especially in the hands of inexperienced or inadequately trained personnel.

The second LSP report is in the final stage of preparation and is targeted for the manufacturer, the clinical laboratory, and those who use desktop analyzers. Detailed step-by-step guidelines and recommendations for standardizing cholesterol measurement are provided. National resources are described in sufficient detail to allow the user to access the resources, ensuring more reliable cholesterol measurement through the standardization program. This report outlines the technical and organizational elements necessary for overall reliability of cholesterol measurements. In addition, details are provided on preanalytic and analytic issues that affect cholesterol values, such as the biologic effects of age, gender, diurnal variation, long-term intraindividual variation, seasonal variation, and the effects of diet, alcohol, weight changes, exercise, and drugs. Also included are recommendations on posture, method of blood sampling, proper use of anticoagulants, and effects of myocardial infarction, stroke, cardiac catheterization, surgical trauma, and infection, factors known to influence cholesterol values. Details on the development of reference materials for calibration and quality control, issues concerning quality assurance, external surveillance programs, and desktop analyzers are provided.

The workshop participants also discussed the clinical laboratory measurement of serum triglycerides and high density lipoprotein (HDL) cholesterol. It was noted that these assays are distinctly less accurate and precise than those for total cholesterol.
Recommendations. A physician interested in determining the acceptability of a given laboratory for lipid and lipoprotein measurements should ask several questions of the laboratory director: 1) Is the analytic system standardized for accuracy, and is it traceable to the reference method and materials at the Centers for Disease Control? 2) Is accuracy assessed with certified reference materials and with accurate target values from the National Bureau of Standards and the College of American Pathologists? Are the values for precision and accuracy less than or equal to 5%, or even 3%? 3) Have comparison studies been done on patient materials by having specimens analyzed by one of the nine US laboratories in the Reference Method Laboratory Network that have the Abell-Kendall method available? (These laboratories have been standardized to ensure accuracy of cholesterol measurement. See Appendix 1 for the locations of the nine US laboratories.)

With respect to desktop analyzers, the panel recommended that investigators 1) select a system that has documented high precision and accuracy, 2) select a system that is less dependent on the technical background and skills of the operator, 3) select an instrument-reagent system for which the manufacturers provide extensive training of personnel, 4) have a well-designed quality control program similar to that in clinical laboratories, and 5) use the same laboratory safety considerations observed in the clinical laboratory environment and in alternate-site testing.

Recommendations and guidelines must be provided for enhancing the accuracy and precision of HDL cholesterol and triglyceride measurements. The need for development of such standardized guidelines and improvement of assay quality is urgent.

Cholesterol Screening

Background. The topic of cholesterol screening was discussed in some detail. The fourth workshop group, while encouraging the use of case finding in a medical setting as the preferred strategy for measuring blood cholesterol in the population, also recognizes that among American Heart Association (AHA) components and many other groups, considerable momentum has developed for the use of public screening as an additional strategy.

Several types of public screening sites (i.e., shopping malls or other community sites, blood banks, school sites, or work sites) may be used. Public screening may have various objectives, including the detection of previously unidentified persons with high blood cholesterol and enhancement of the level of professional and public awareness concerning cholesterol. Screening at work sites may provide a high yield of targeted groups including those who may be unlikely to seek regular medical care (e.g., 20–45-year-old men and those in lower socioeconomic groups). Screening at community sites tends to have high visibility and may be expected to enhance community awareness, but this approach may also yield a less targeted population because it may include those who have previously diagnosed high blood cholesterol and who are monitoring their cholesterol level. Although some interest was expressed for placing greater emphasis on screening in targeted groups, the need for additional research to evaluate this approach was recognized. AHA components should have a clear understanding of the purpose of the screening and its relation to appropriate sites that can maximize community program objectives.

The recently revised AHA-NCEP document, Public Screening Strategies for Measuring Blood Cholesterol in Adults—Issues for Special Concern, was discussed. The issues addressed in this document continue to merit careful consideration in planning cholesterol-screening projects. One of the most urgent issues is the reliability of blood cholesterol measurements. Evidence is available that accurate and precise measurements of blood cholesterol may be achievable with the new desktop instruments but are dependent on consistent adherence to sound laboratory protocols for standardization and quality control, operator training, and sample collection procedures. Individual desktop instruments vary in operator sensitivity. Consequently, instrument selection represents an additional important factor in ensuring reliable measurements.

High Density Lipoproteins in Clinical Management

Background. The appropriate use of HDL cholesterol measurements in clinical practice was discussed and questions were posed: 1) What should be done about HDL in clinical management? 2) Should HDL cholesterol be measured in everyone? 3) How should HDL cholesterol levels be used to guide patient evaluation and treatment? 4) What should be done for patients with low HDL cholesterol (particularly if low density lipoprotein [LDL] cholesterol is not high)? 5) Should HDL cholesterol be a target of therapy?

The evidence relating HDL cholesterol and coronary heart disease was reviewed. The evidence is substantial but distinctly less compelling than that relating LDL cholesterol to atherosclerosis and coronary heart disease. Within-population studies have identified HDL cholesterol as a powerful independent inverse-risk factor for coronary heart disease in most high-risk populations. However, exceptions to this trend have been reported, and between-population studies do not show a clear relation between HDL and coronary heart disease. Unlike the case for LDL, there is no large body of animal research concerning a connection between low HDL and atherosclerosis. The mechanisms by which low HDL might “predispose” to coronary heart disease are unclear. Some investigators have suggested that the HDL level represents a surrogate for a more primary parameter in the causation of atherosclerosis (see Workshop 1). Finally, although some clini-
clinical trial data do suggest a benefit from raising HDL, convincing clinical trial evidence that raising HDL reduces coronary heart disease remains to be obtained (see Workshop I).

Several reasons were discussed for not recommending universal screening for low HDL cholesterol. One concerns technologic limitations in the methods used for HDL cholesterol assay. These methods are not well standardized. It was noted that an uncertainty of a few milligrams per deciliter in HDL cholesterol has little effect on the estimated LDL cholesterol level, but a relatively small error can have a major effect on the clinical interpretation of the HDL cholesterol level. Another reason is the lack of evidence that raising a low HDL cholesterol in a patient without elevated LDL cholesterol would confer clinical benefit (see Workshop I, which recommended measuring HDL cholesterol in all patients with coronary heart disease).

The workshop participants affirmed the NCEP guidelines that LDL cholesterol should be the primary target of therapy. It was proposed that a knowledge of HDL cholesterol level is useful in clinical care, since such knowledge helps the physician to decide how aggressive the therapeutic approach to lowering LDL cholesterol should be. Thus, a patient with a lower HDL might be considered for drug therapy at a somewhat lower LDL level than that of a corresponding patient with a higher HDL level. The HDL cholesterol level may also be useful in helping to select the best drug for a given patient.

The workshop participants also supported the NCEP guidelines in discouraging use of a ratio including HDL cholesterol such as total:HDL cholesterol as an index for clinical care.

**Recommendations.** Workshop participants made several recommendations: 1) More research is needed on the mechanisms responsible for the inverse association between HDL and coronary heart disease. 2) Improvements in HDL assay are needed; tests are needed that can be widely used in clinical chemistry laboratories and that give highly accurate and precise values. 3) Further information is needed on the potential value of HDL-related parameters (e.g., apolipoprotein [apo] A-I) other than HDL cholesterol to estimate coronary risk and to guide clinical care (see Workshop I discussion of HDL subfractions). 4) Better and more specific methods of raising HDL levels are needed. These methods can include new pharmacologic agents. 5) Ultimately, a clinical trial that examines the possible benefit of raising low HDL levels will be desirable if a suitable intervention and a suitable target population can be identified. 6) AHA educational programs should emphasize the importance of using LDL cholesterol as the key index in clinical care of cholesterol and coronary risk. Physicians should be taught the NCEP guidelines and be advised of the use of HDL assays in clinical care.

Finally, it was noted that these current guidelines and considerations about HDL might well change as further information becomes available.

**Apolipoproteins**

Workshop participants discussed "What is the evidence and future potential for the use of apolipoproteins to assess coronary heart disease risk?"

**Background and scientific evidence.** Provocative evidence has accumulated from case-control studies linking disordered levels of apolipoproteins with increased coronary heart disease risk. First, 24 of 27 studies have shown decreased levels of apo A-I in cases compared with controls. Second, six of 14 studies have shown decreased levels of apo A-II in cases compared with controls. Third, 11 of 12 studies have shown increased levels of apo B in cases compared with controls.

Several investigators have also obtained data suggesting that there are patients who do not have elevated levels of LDL cholesterol but who do have high levels of apo B. These patients appear to have smaller LDL molecules in their plasma and an increased risk of coronary heart disease. Nevertheless, several critical kinds of evidence about apolipoproteins are lacking. In particular, evidence is needed that can be obtained by prospective epidemiologic studies with large-scale cohorts and by intervention studies. In addition, standardized methods for measuring apolipoproteins are not yet available.

**Conclusions and recommendations.** 1) There is a need for more research on apolipoproteins, especially large-scale epidemiologic studies and intervention studies that make direct comparisons between the efficacy of apolipoproteins and that of HDL cholesterol and LDL cholesterol as estimators of coronary heart disease risk. 2) There is a pressing need to develop standardized methods for measuring apolipoproteins for immediate research purposes and, in the longer run, for future clinical applications (see Workshop I). 3) Efforts to fill the gaps in apolipoprotein research and to standardize the measurement methods should be made as quickly as possible. 4) At this time, the routine use of apolipoprotein measurements in clinical practice is not appropriate, given the limitations of current knowledge. 5) In the future, it is unlikely that apolipoproteins will play a role as part of the initial screen for lipid risk factors for coronary heart disease. However, apolipoproteins could become part of a more sophisticated estimate of coronary heart disease risk after the initial screen.

**Appendix 1**

**National Reference System for Cholesterol: National Reference Method Laboratory Network Participating Laboratories**

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* CDC-NHLBI standardized reference method laboratories.
** Reference method laboratories to be standardized.

Reference

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