Recommendations for Cholesterol Measurement Among the Elderly

The National Heart, Lung, and Blood Institute's National Cholesterol Education Program (NCEP) established an Adult Treatment Panel composed of outside experts that published guidelines in 1988 for the measurement and treatment of hypercholesterolemia (116). NCEP categorized cholesterol levels according to increasing risk of coronary heart disease (CHD). For serum cholesterol, the panel considered measurements under 200 mg/dl as "normal," between 200 and 239 mg/dl as "borderline high," and 240 mg/dl or above as "high." Although it did not provide separate screening guidelines for persons over 65 years old, the panel recommended that all adults over the age of 20 should have their total serum cholesterol measured at least *every* 5 years. The full set of recommendations developed by this group for diagnosing and treating hyperlipidemia are summarized in appendix C.

The conclusions of the Adult Treatment Panel supersede an earlier National Institutes of Health Consensus Conference (114) that concluded, without documentation, that a cholesterol determination during annual physician office visits would be cost-effective for adults.

The American Heart Association (AHA) publishes general guidelines for the prevention of CHD (6,49). Representatives of the A HA participated in NCEP. Like the Adult Treatment Panel, AHA recommends that healthy people should have routine measurement of cholesterol and triglycerides every 5 years until age 60. But for older patients, these tests are considered optional if baseline measurements have been well-established. Like NCEP, AHA categorizes cholesterol levels into normal (<200 mg/dl), borderline high (200 to 239 mg/dl), and high (> 240 mg/dl) categories and recommends that physicians take other risk factors for CHD into account when prescribing treatment for persons whose lipid levels fall outside the normal range.

The U.S. Department of Health and Human Services' Preventive Services Task Force (a group of experts from outside the government) is currently considering screening for hyperlipidemia as well as other conditions. Its recommendations for cholesterol screening are expected to be released in the summer of 1989.

In Canada, a task force convened by the Department of National Health and Welfare to make recommendations on the frequency and content of the periodic health examination considered cholesterol screening in its initial report (20). The Canadian Task Force (CTF) concluded that there was insufficient medical evidence to warrant routine screening of cholesterol or triglycerides. However, this group did suggest that physicians may wish to measure blood lipids for other reasons, such as the presence of other CHD risk factors. CTF has not reevaluated its position since 1979.

Cholesterol Measurement Techniques

The hundreds of assays that have been used to measure cholesterol in blood (90, 108) can be divided into three categories. The first includes multi-stage techniques based on the modified Abell-Kendall method, which is considered the "standard reference method" (2,31). Application of the standard reference method is more demanding than many laboratory procedures, requiring relatively sophisticated facilities and technical skills. The laboratories of the Lipid Research Clinics and others that use this method have made extensive efforts to standardize and improve the quality of testing. These laboratories are thought to supply the most nearly error-free results in clinical use. The test requires a few milliliters of blood, and labora-

tories can generally provide results within 24 to 72 hours of receiving the specimen. These methods are used by the Centers for Disease Control (CDC) and Lipids Research Clinics around the country.

The second kind of assay is based on automated analyzers. This less exacting procedure is used mainly by general clinical laboratories, such as those available in most hospitals and freestanding clinics. Often, the measurement is performed as part of a panel of blood chemistry assays. Inaccuracy in these tests, partly due to variability in technical competence among the thousands of clinical laboratories in the country, is a major concern (1 17). Although the results of these assays may be less reliable than those produced by a reference laboratory, they are convenient because a number of measurements in addition to cholesterol can be performed on the same tube of blood. Results can be available within minutes.

The third kind of assay, a one-step enzymatic method that has recently become available, is particularly convenient for both patients and providers of care. These tests require only a few drops of blood from a finger stick and give results in 3 to 8 minutes. The equipment can be operated in a physician's office, clinic, or community screening site by personnel without a special background in clinical chemistry. These methods have a low per-screening cost (less than $3 in one large-scale community screening program (47)). Preliminary reports, generated under ideal circumstances of operator training and attention to calibration and technique, have found that assays are accurate (18). It is not known whether this level of accuracy will be maintained when the technology is used more widely.

Factors That Influence Cholesterol Measurements

The measured cholesterol level is influenced by long-term or clinically significant biologic factors, transient or insignificant biologic factors, and measurement error. The main determinants of the cholesterol level are genetic characteristics, diet, exercise, and lipid-lowering medications. To the extent that these factors can be altered, the serum cholesterol level may be lowered and the risk of adverse outcome may be influenced.

A variety of other factors influence the measured cholesterol level (73). Patient posture (reclining, sitting, or standing) and venous stasis (blood pooling in an extremity, which sometimes occurs during blood-drawing when a tourniquet is applied) can change the plasma volume enough to alter reported cholesterol levels by 5 to 12 percent. The cholesterol level increases slightly at ovulation and substantially during pregnancy (75 percent over nonpregnant subjects). Although recent food ingestion, alcohol intake, and exercise are thought not to influence cholesterol, there is some evidence that transient emotional stress may elevate the level. Medications, especially those used to treat high blood pressure, can elevate the cholesterol level (74). Seasonal variation can be responsible for temporary changes (1 10). In the placebo group of the Lipid Research Clinics-Coronary Primary Prevention Trial, which studied men aged 35 to 59 years whose plasma cholesterol levels[1] exceeded 265 mg/dl after a brief trial of diet, the measured cholesterol averaged 7.4 mg/dl higher on December 30 than on June 30 (42). Other studies (reviewed in Hegsted, 1987) have found that even when an individual adheres to a strictly controlled diet, his or her measured cholesterol varies substantially over short periods of time. A number of technical factors can also influence the reported level of cholesterol after the specimen has been collected. The cholesterol level obtained in some assays is affected by hemolysis (mechanical disruption of the blood that can occur when blood is withdrawn from a vein).

---

1 Plasma cholesterol levels are consistently 3 percent lower than serum cholesterol.

The most important source of variability in the reported cholesterol level is, however, the clinical laboratory (1 17). Most of the epidemiologic studies that have contributed to our knowledge of cholesterol as a risk factor used meticulously standardized methods that were periodically tested against a central reference laboratory. Although laboratory error has diminished over the last 40 years, and although NCEP has urged clinical laboratories to redouble their efforts to standardize, measurements remain imprecise (117). Variation in reported cholesterol levels is partially the consequence of the varied methods used to test cholesterol, but substantial variation occurs even among laboratories using the same method. The College of American Pathologists sent a sample specimen whose cholesterol concentration was determined by CDC to be 262.6 mg/dl to 5,000 clinical laboratories. The cholesterol values reported by the surveyed laboratories ranged from 101 to 524 mg/dl (1 17). Current standards established by NCEP call for a coefficient of variation[2] of less than 3 percent. However, recent studies show the coefficient of variation to be at least 6 percent (1 17).

Errors in the cholesterol level may arise from bias in a particular laboratory method, meaning that even when standardized well, the reading will differ repeatedly from the true cholesterol level. A study conducted by Kroll and colleagues (70) compared the performance of the reference standard method to other assays, including the SMAC™ (Technicon Instruments Corp., Tarrytown, NY) and the aca™ (DuPont Co., Medical Products Department, Wilmington DE), the most widely used methods for cholesterol determinations in clinical laboratories. For a true cholesterol value between 170 mg/dl and 260 mg/dl, the aca method had an upward bias of between 4.0 and 4.8 percent, while the SMAC method had a 2.6 percent upward bias,[3] A more recent report showed that one laboratory, with careful attention to standardization and proper performance of the tests, was able to produce highly accurate and precise results using three commonly employed assays for cholesterol (69). The bias and coefficient of variation in each of these tests were less than 3 percent when compared to the standard reference method. Laboratories that do not strictly adhere to quality control measures are unlikely to achieve results as accurate as those of either Kroll or Koch. The physician who orders a serum cholesterol level risks misinterpreting the test result if he or she does not know the laboratory's assay method or if the laboratory fails to standardize properly.

The new one-step enzymatic techniques have not been tested extensively, but they appear to be accurate if well-standardized and properly performed. In preliminary results, collected under near-ideal conditions, three of these methods were evaluated when used by a family medicine physician. The degree of imprecision was less than the *3* percent coefficient of variation recommended by NCEP. However, two of the three methods produced cholesterol values that were 2.5 to 8.1 percent higher than the reference method (18). If not properly standardized, these methods are not likely to perform as accurately in physicians' offices, drug stores, field-screening programs, and other settings.

In order to achieve their goals of biases of 3 percent or less, and coefficients of variation of 3 percent or less for all assays and laboratories, NCEP's Laboratory Standardization Panel has endorsed a campaign to educate physicians and laboratories about the components of accurate and precise measurement methods. In addition, they have encouraged the use of reference serum samples produced by CDC and the National Bureau of

2 The coefficient of variation is the standard deviation of a probability distributions as a percentage of the mean. This statistical allows comparison of variation among distribution with different means.

3 This bias may be due to a "matrix effect" (92). The "matrix" is the environment in which the compound being measured exists. For cholesterol, the matrix is usually serum (11 7).

Standards with which laboratories can test and calibrate their assays. They have also encouraged participation in proficiency testing programs sponsored by the College of American Pathologists and the American Association of Bioanalysts (91,117).

Reliability of HDL and LDL Measurements

Many clinical laboratories can measure the high-density lipoprotein (HDL) cholesterol level directly. However, direct measurement of the low-density lipoprotein (LDL) level requires specialized equipment, so the LDL level is usually calculated from the total cholesterol, HDL cholesterol, and triglyceride levels (37).[4]

When HDL and LDL levels and ratios based on these levels are used for routine screening, they are unlikely to predict CHD risk as accurately as they did in a research setting. In routine clinical use, HDL assays are not as reproducible as serum cholesterol measurements, nor are they standardized as well as the HDL assays used in epidemiologic studies. The calculated LDL suffers from the same flaw because the components of the formula are often inaccurate. In a recent survey of chemistry laboratories *(23),* a standardized specimen whose "true" HDL value (as measured by CDC) was 34.6 mg/dl was sent to a large number of laboratories. Measurements reported by the participants were grouped according to which of eight methods the laboratory used. There was significant variation between the methods and among laboratories using the same method. The mean for each method ranged from 29.0 to 39.4 mg/dl. The method that produced a mean value of 39.4 mg/dl had a standard deviation of 7.9, implying that an HDL level of 34.6 mg/dl would be reported as 47 mg/dl or greater 16 percent of the time, denoting a much lower risk of heart disease than actually exists.

The variability in measured HDL levels is reflected in the coefficient of variation of the test results obtained by different laboratories. The coefficient of variation for the serum HDL among laboratories using the same method ranged from 11.1 to 20.0 percent. The striking variation in reported HDL levels indicates that routine HDL assays are imprecise, and are unlikely to predict risk as well as the meticulously standardized HDL assays used in epidemiologic studies.

Costs of Lipoprotein Measurement

The costs of lipoprotein testing depend on the method used and the combination of tests performed. Although the incremental costs of performing these tests are not easily determined, the charges reported to third-party payers provide a useful estimate of the likely costs of implementing a testing program. Table *3* summarizes the average allowed charges for lipoprotein determination procedures reported by two payers and a community-based screening program. Of the two payers, Blue Shield of California reports somewhat higher charges than the national Medicare program. The community-based screening program in Rochester, New York used an analyzer representative of the fingerstick method (the Retroflon™ manufactured by Boehringer-Mannheim). This equipment costs $5,000 for the analyzer and $1.10 per reagent strip. The organizers of the screening program estimated the costs to be $2.78 per determination (47).

---

4 The "Friedewald formula" for calculating the LDL level is:

LDL = total cholesterol - HDL cholesterol - triglycerides/5.

This formula is considered accurate when the triglyceride level does not exceed 400 mg/dl. A triglyceride level of 400 mg/dl is very uncommon in the general population, so this formula can usually be applied. The 95th percentile for serum triglyceride levels in American men and women is well below 400 mg/dl at all ages, at least 6 years and above (75).

Table 3--- Selected Charges for Lipoprotein Measurement

	Blue Shield California[a]	Medicare[b]	community screening program[c]
Total cholesterol	$14.26	$6.35	$2.78
Lipoprotein cholesterol fractionation (by calculation formula)	23.80	15.80	NA
Complete lipid profile (HDL, cholesterol, and triglycerides)	39.06	NA	NA

[a] Blue Shield average allowed charges (R. Schaffarzick, Blue Shield of California, personal communication, November 1988).

[b] Medicare average allowed charges (M. Newton, Health Care Financing Administration, Baltimore, MD, personal communication, October 1988).

[c] Estimated cost of cholesterol determination in community screening program using the Retroflon™ fingerstick method (P. Greenland, J.C. Levenkron, M.G. Radley et al., "Feasibility of Large-Scale Cholesterol Screening: Experience With a Portable Capillary-Blood Testing Device," Am. J. Pub. Health 77:73-75, 1987).

ABBREVIATIONS: HDL = high-density lipoprotein; NA = not applicable.

SOURCE: Office of Technology Assessment, 1989.

Followup Testing

Followup testing for hypercholesterolemia can include repeating the cholesterol determination and performing assays for lipoprotein fractions and triglycerides. Although apolipoprotein determinations may eventually prove to be an important component of the followup testing for individuals found to have hypercholesterolemia, these tests are experimental at this time.

NCEP recommends that all subjects with an initial cholesterol of 200 mg/dl or greater have one or two repeat determinations. If the average of the two readings remains over 240 mg/dl, lipoprotein analysis is advised. The recommended threshold for lipoprotein analysis is 200 mg/dl in subjects with known CHD or two risk factors (including male sex). Further treatment advice is based on the calculated LDL-cholesterol level.

Importance of the Locale of Testing

A successful screening program depends upon characteristics of the test procedure, the population screened, and the efficacy of treatment. All of these may vary with the setting for testing. The most obvious problem for cholesterol is accurate testing procedures. Because most current methods require careful calibration, extra precautions must be taken to assure valid reporting when assays are performed away from a highly standardized clinical laboratory. Although newer fingerstick methods show promise for making accurate cholesterol assays available in the field, they have not yet been validated.

The completeness of followup testing is likely to vary with the locale of the original cholesterol test. An individual who is screened as part of a mass screening program or in a nonmedical setting will almost always need to go to another site for followup testing. This may deter some Medicare recipients from obtaining further tests. Similarly, when a cholesterol test is ordered or performed in a doctor's office or hospital clinic, it will be simpler to institute treatment than if screening is performed elsewhere.

Finally, the place where testing is performed may influence the feasibility of reimbursement under the Medicare program. A cholesterol measurement obtained as part of a battery of tests, in a physician's office or a hospital, could be reimbursed like other covered services under Medicare Part A or Part B. It is likely that the administrative costs would be large relative to the size of the reimbursement if cholesterol was measured as a single test, without any associated services. Consequently, while screening in shopping centers and drug stores might be inexpensive, reimbursement by Medicare or any other third-party payer is likely to be impractical.

5 A lipoprotein test that analyzes their protein composition.