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CHOLESTEROL MEASUREMENT

Variability in Methods and Test Results

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Madam Chairman and Members of the Subcommittee:

It is a pleasure to share with you the results of a recent study in which we examined how cholesterol is measured in different laboratory settings and assessed what is known about the accuracy of different measurement techniques. My statement is based upon our study's report, entitled Cholesterol Measurement: Test Accuracy and Factors That Influence Cholesterol Levels, which is being issued today.

This work is one of three studies that the former Subcommittee on Investigations and Oversight asked us to conduct on the National Cholesterol Education Program (NCEP). The National Institutes of Health (NIH) established NCEP in 1985 to encourage Americans to lower their high blood cholesterol levels with the objective of reducing coronary heart disease. In one of the other studies, we are reviewing the findings of the clinical trials that have been used to support NCEP, and in the third, we plan to look into how NCEP has influenced the health and food industries.

Let me begin by briefly highlighting the key results of our cholesterol measurement study. In conducting this work, we synthesized a large body of relevant scientific literature and interviewed measurement experts who work in government agencies, private industry, universities, and clinical laboratories.

We found that instrument measurement error and day-to-day variations from biological and behavioral factors make it highly unlikely that individuals can "know" their cholesterol levels based on a single measurement. Because of such variation, cholesterol levels should be viewed in terms of ranges rather than as absolute fixed numbers. Individuals and physicians need to be aware of cholesterol measurement variability, and any decisions to classify patients and initiate treatment should be based on the average of multiple measurements as well as on an assessment of other risk factors, as recommended by NCEP's guidelines. This is particularly important when measured cholesterol levels are close to the cutpoints that differentiate risk categories and may lead to recommendations for treatment with drugs.

Although much progress has been made in developing better testing methods and materials in recent years, cholesterol continues to be difficult to measure with accuracy and consistency across the broad range of instruments and settings in which it is analyzed. Studies show that under controlled conditions, particularly research, clinical, and hospital laboratories, measurement is reasonably accurate. Considerably less is known, though, about the performance of cholesterol measurement in other settings, such as physicians' office laboratories and public health screenings, where many people are

routinely tested. Since no overall evaluation of different instruments and laboratories has been conducted, it is impossible to know whether the accuracy goals established for cholesterol measurement have been met.

Furthermore, even if a laboratory is able to provide reasonably accurate test results, biological factors such as diet, exercise, and illness cause an individual's cholesterol level to vary. Some individuals' cholesterol levels can vary dramatically over time while others' remain relatively constant. Although some biological variation can be minimized if individuals maintain their weight and diet for a modest period prior to measurement, many other factors cannot be controlled for and reduced.

Before turning to any further discussion of our findings, let me first provide some background information on cholesterol and the NCEP guidelines.

BACKGROUND

Coronary heart disease is a leading cause of death for Americans, accounting for about half a million deaths per year. Further, about 1.25 million Americans suffer heart attacks each year. The American Heart Association estimates that total costs associated with coronary heart disease amount to about $55 billion per year. Because of the large numbers of people affected and the large costs involved, efforts have focused on prevention.

Within the federal government's effort to address the problem of heart disease, NIH has established several education programs to inform the public about different risk factors associated with heart disease and to provide guidelines for reducing risks that can be modified. The major factors that influence a person's chance (or risk) of getting coronary heart disease include high blood pressure, cigarette smoking, high blood cholesterol, diabetes, age (45 years or older for men; 55 years or older for women), family history of early heart disease, physical inactivity, and obesity.

Accumulated scientific evidence has shown that individuals with higher levels of blood cholesterol have a greater risk of coronary heart disease. Certain amounts of cholesterol, however, are essential to the body, helping form cell membranes and some hormones. Cholesterol is manufactured by the body (mostly in the liver) and derived from the diet (in foods containing cholesterol as well as those that are high in certain saturated fats).

Cholesterol is transported through the blood by carriers called lipoproteins. Of the several different kinds of

lipoproteins, two are of major importance: low-density lipoprotein (LDL) and high-density lipoprotein (HDL). LDL cholesterol, which contains about 60 to 70 percent of the total cholesterol, is often referred to as the "bad" cholesterol because too much of it can cause a buildup of plaque in the arteries that can block the flow of blood and subsequently result in a heart attack. HDL cholesterol is believed to help remove excess cholesterol from the blood and prevent the buildup of plaque and is thus referred to as the "good" cholesterol. A higher level of LDL cholesterol is associated with a higher risk of heart disease, whereas a higher level of HDL cholesterol is associated with a lower risk of heart disease. LDL and HDL cholesterol levels, however, are considered independent risk factors with different determinants.

NCEP Treatment and Measurement Guidelines

NCEP emphasizes two parallel approaches to (1) identify and treat individuals who are particularly at high risk and (2) get the entire population to reduce its cholesterol by encouraging people to "know their cholesterol number" and modify their diet. NCEP convened expert panels and published adult treatment guidelines in 1988 and 1993, covering the classification of cholesterol, patient evaluation, and dietary and drug treatments.

These guidelines emphasize classification and treatment decisions based on a person's risk status, which is defined by cholesterol levels (including total, HDL, and LDL cholesterol) in conjunction with other key coronary heart disease risk factors. The guidelines recommend that all adults have their total cholesterol measured at least once every 5 years and that HDL cholesterol be measured at the same time. Individuals with high cholesterol and existing symptoms of coronary heart disease or at least two other heart disease risk factors are candidates for more intensive treatment.

NCEP classifies total cholesterol into three distinct levels: desirable (below 200 mg/dL), borderline high (200 to 239 mg/dL), and high (equal to or above 240 mg/dL). In addition, an HDL cholesterol level of less than 35 mg/dL is considered low and a contributing risk factor for coronary heart disease. Individuals without evidence of existing coronary heart disease are recommended to have a follow-up lipoprotein analysis if they have one of the following characteristics: (1) high total cholesterol, (2) borderline-high cholesterol and low HDL cholesterol, or (3) borderline-high cholesterol, higher HDL cholesterol, but two or more risk factors. Lipoprotein analysis includes measurement of fasting levels of total cholesterol, HDL cholesterol, and triglycerides and the calculation of LDL cholesterol.

NCEP also classifies LDL cholesterol into three levels: desirable (less than 130 mg/dL), borderline high risk (130 to 159 mg/dL), and high risk (equal to or greater than 160 mg/dL). Decisions for beginning diet or drug treatment are based on these LDL levels in combination with other evident risk factors. Thus, candidates for diet therapy without existing symptoms of coronary heart disease include those with high LDL cholesterol (160 mg/dL or more) or those with borderline-high LDL cholesterol (130-159 mg/dL) plus two or more risk factors. NCEP recommends diet therapy as a first line of treatment for most individuals, with drugs to follow if the diet is ineffective at lowering LDL cholesterol. Individuals usually must maintain long-term treatment in order to keep their cholesterol at reduced levels.

Although national data indicate that cholesterol levels for the U.S. population have declined since the early 1960's, the average total serum cholesterol for adults is currently about 205 mg/dL (within NCEP's borderline-high category). Women tend to have lower total and LDL cholesterol levels than men up to the age of menopause, at which time they increase to levels slightly above those of men. Compared to men, women also appear to have higher HDL cholesterol levels. It is estimated that 29 percent of American adults--52 million people--are candidates for dietary therapy. Of this group, it is estimated that 12.7 million have cholesterol levels sufficiently elevated that they might be candidates for drug therapy.

For a widespread cholesterol-lowering campaign to be effective, it is important that individuals and physicians be able to obtain accurate test results. NCEP convened a panel of experts in 1988 who concluded that considerable inaccuracy in cholesterol testing existed in the United States. They and a subsequent panel in 1990 made recommendations about how cholesterol measurement could be standardized and improved.

Recognizing the problem of measurement variability, NCEP has recommended that two separate cholesterol measurements be averaged together to assess an individual's level, with a further test to be conducted if the first two varied substantially. They also established the goal that by 1992 a single total cholesterol measurement should be accurate within ±8.9 percent. NCEP has not previously issued goals for HDL and LDL cholesterol measurement, but such goals are expected to be issued shortly. The Health Care Financing Administration (HCFA) has also established testing requirements for total cholesterol (±10 percent) and HDL cholesterol (±30 percent).

With this background, we can now turn to some of our study findings.

PRINCIPAL FINDINGS

Measurement Methods and Analyzers

Currently, 45 manufacturers have as many as 160 device systems on the market that use different technologies and chemical formulations to conduct cholesterol tests in different settings. Cholesterol is commonly tested in clinical, research, hospital, and physician office laboratories as well as in mass screenings such as public health fairs. Although over 150,000 U.S. laboratories that conduct medical tests have registered with HCFA, under implementation of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), no national data are available on the number of laboratories that do cholesterol tests or the number of tests that are done each year.

Of the different cholesterol components, total cholesterol is the best understood and documented. HDL and LDL cholesterol, which have been given greater emphasis under the NCEP guidelines, are more difficult to measure. Officials we interviewed from the Centers for Disease Control and Prevention (CDC) pointed out that considerable scientific work remains before HDL measurement is as well understood as total cholesterol currently is. Direct measurement methods for LDL cholesterol have not generally been available in most cholesterol test settings, although such a method has recently been marketed. In practice, LDL cholesterol has usually been calculated from measurements of total cholesterol, HDL cholesterol, and triglycerides. Because measuring LDL cholesterol relies on the accuracy of these other measurements, potential measurement error can be greatly compounded.

Measurement Accuracy

A process to assess and improve cholesterol measurement was established under the National Reference System for Cholesterol. Rather than require that all laboratories use the same devices and test methods, emphasis is directed toward having test results consistent with accepted accuracy standards. CDC and the National Institute of Standards and Technology have developed reference methods as well as processed reference materials that device manufacturers and clinical laboratories can use to assess cholesterol measurement accuracy. As part of this system, CDC supports a network of nine reference laboratories in the United States. A laboratory can gauge its accuracy and standardize its measurements by splitting samples with a CDC network laboratory and comparing results. Participation in the network, however, has been relatively low according to CDC officials. In 1992, for example, 167 laboratories applied for a certificate of traceability to the CDC standards, and 79 percent passed.

Laboratories can also participate in proficiency testing programs such as those conducted by the College of American Pathologists (CAP) and the American Association of Bioanalysts. In these programs, participating laboratories receive, analyze, and compare results with processed reference materials that have an assigned target value for cholesterol. CAP, the largest such testing program, has 12,000 subscribers that use its service to evaluate several different clinical chemistry tests. In addition, under the CLIA implementation, HCFA has recently begun conducting laboratory inspections to assess quality control procedures and test results on all medical equipment, including cholesterol testing.

Survey data from CAP indicate that interlaboratory measurement variability (the extent to which test values varied from one laboratory to the next) for total cholesterol has improved over the past 40 years, declining from about 24 to 6 percent. Furthermore, several large collaborative studies of selected clinical laboratories have found that accuracy was good when testing was evaluated with patients' specimens. Measurement error problems occurred, however, when accuracy was evaluated using processed reference materials. Because such materials behave differently from fresh patient samples, they can produce different test results on many types of devices. Since such materials are an important component of proficiency testing programs, problems with them will hamper both standardization and government monitoring efforts.

Studies of portable desk-top analyzers, such as those used in physician offices and public health screenings, indicate that many of these devices can provide fairly accurate measurements when they are operated properly under controlled conditions. Studies, however, have also documented that several devices did not meet the established goals for accuracy, and incorrectly overestimated or underestimated from 17 to nearly 50 percent of patient samples, based on the NCEP risk categories.

Factors That Influence Cholesterol Levels

Although cholesterol testing methods and devices may be able to measure a sample of cholesterol accurately and reliably, a single test result does not reflect how an individual's cholesterol level can vary over time. Some variation in an individual's cholesterol level is normal and to be expected because of biological factors. It has been estimated that such factors may account for up to 65 percent of the total variation in an individual's reported cholesterol measurement. A recent synthesis of several studies found that biological variation in individuals averaged 6.1 percent for total cholesterol, 7.4 percent for HDL cholesterol, and 9.5 percent for LDL cholesterol.

Biological factors stem from behavioral influences such as diet, exercise, and alcohol consumption as well as from clinical factors such as illness, medications, and pregnancy. With diet, for example, changes in the consumption of foods high in saturated fats and cholesterol can raise or lower blood cholesterol levels, although individuals tend to respond quite differently to changes in diet. Similarly, exercise can alter cholesterol levels and cause measurement variability, depending on the volume, intensity, and type of exercise undertaken. Studies have also shown that total and LDL cholesterol levels within individuals tend to vary by season, being slightly higher in winter than summer.

In addition to biological factors, differences in the way blood specimens are collected and handled can lead to different results. Recent studies, for example, have reported that capillary (finger-stick) samples are more variable than venous samples, and researchers have called for more standardized capillary collection procedures. This finding is important because capillary specimens are taken in screening settings and are used in recently marketed home test kits. The knowledge and training of technicians who take and prepare blood specimens for analysis can also contribute to measurement variability. For example, the length of time an individual is sitting or standing before being tested has been demonstrated to influence cholesterol levels. In addition, the proper storage of specimens is important to avoid changes in the composition of the blood serum and to ensure accurate measurement results.

Potential Effect of Inaccurate Measurements

The total error associated with both instrument and biological variability can be considerable. If, for example, the total error for a single measurement of total cholesterol is assumed to be about 16 percent (which is equivalent to the sum of the NCEP goal for instrument variability plus the average biological variability derived from a synthesis of existing studies), then a value of 240 mg/dL could be expected to range from 201 to 279 mg/dL. Similarly, a single measurement of HDL cholesterol with a known value of 35 mg/dL could range from 24 to 46 mg/dL based on combined analytical and biological variability. Multiple measurements narrow the variability; however, some variability cannot be reduced since many factors that affect cholesterol measurement cannot be controlled.

Having accurate cholesterol measurements is important, given the central role that cholesterol cutpoints have in classifying, evaluating, and treating individuals deemed at risk of coronary heart disease. Although the NCEP guidelines acknowledge the issue of measurement variability and stress the need for multiple measurements, important consequences can result from measurement

error. Some physicians may not consider measurement errors and may base their decisions on only a single measurement that may incorrectly characterize an individual's cholesterol level. In a worst-case scenario, two types of diagnostic errors could occur: (1) a false-positive error could result in the treatment of individuals with drugs who in fact had desirable cholesterol levels or (2) a false-negative error could incorrectly reassure an individual that his or her cholesterol level was desirable. The potential for misclassification would be greatest for those whose measurements are near the high-risk cutpoint.

Continuing efforts are needed to improve the accuracy of cholesterol measurements so that medical decisions to initiate and continue treatment to lower elevated cholesterol can be both effective and efficient. To minimize potential misclassification problems, it is also important to ensure that physicians are knowledgeable about measurement variability and the need to conduct multiple tests before initiating treatment.

Madam Chairman, this concludes my prepared statement. I would be happy to address any questions that you or members of the Subcommittee may have at this time.

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