

Impact of the Third Cholesterol Report from the Adult Treatment Panel of the National Cholesterol Education Program on the Clinical Laboratory

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Background: The US National Cholesterol Education Program has recently released the third report of the Adult Treatment Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Incorporating new evidence and more consistent with other international intervention programs, these more complex guidelines will considerably expand indications for treatment. The implications for clinical laboratories are summarized in this report.

Content: LDL-cholesterol (LDL-C) remains the major focus for classification and treatment, whereas diabetes, the presence of multiple risk factors, including the metabolic syndrome, and increased triglycerides (TGs), will now require more intensive management. For screening, a fasting lipoprotein profile is recommended, adding LDL-C and TGs to the previous measurements of total cholesterol and HDL-cholesterol (HDL-C). Lowering the cutpoints defining optimal LDL-C [100 mg/dL (2.58 mmol/L)] and normal TGs [150 mg/dL (1.70 mmol/L)] and raising the cutpoint for low HDL-C to 40 mg/dL (1.03 mmol/L) will select more patients for treatment. A new marker, non-HDL-C, becomes a secondary target in treating high TGs.

Conclusions: Laboratories will need to adjust reporting formats and interpretations and can expect more requests for tests to characterize secondary causes of dyslipidemia, e.g., diabetes, and for the so-called “emerging risk factors”, e.g., lipoprotein(a), homocysteine, and C-reactive protein.

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Clinical laboratories will be affected by the new updated guidelines for prevention and management of high cholesterol in adults, the third Adult Treatment Panel Report (ATP III),⁴ released in May by the National Cholesterol Education Program (NCEP). A summary has been published in *JAMA* (1) and is available on the National Heart, Lung, and Blood Institute website (www.nhlbi.nih.gov) together with a more detailed report (2) and other related resource materials. ATP III recommendations are solidly based on accumulating evidence concerning the contribution of lipoproteins and other risk factors in development of coronary heart disease (CHD) (3) and are more consistent with emerging international consensus (4, 5), for example, in increased emphasis on the risk associated with high triglycerides (TGs) (6). Treatment efforts still focus primarily on treating LDL-cholesterol (LDL-C) but include other important changes, including more effective lifestyle changes and considerable expansion of indications for drug therapy.

The NCEP was organized in 1985 to develop practice guidelines and educate both the general public and the medical community about the need to identify and treat high cholesterol in ameliorating CHD risk. Expert panels were convened to develop recommendations for clinical practice, public health programs, and laboratory measurements. The NCEP expert laboratory panels published recommendations for standardization and analytic performance targets for lipid and lipoprotein measurements. The initial reports summarized the current status and provided recommendations for total cholesterol (TC) analytic performance (7, 8). Three later reports provided

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⁴ Nonstandard abbreviations: ATP, Adult Treatment Panel; NCEP, National Cholesterol Education Program; CHD, coronary heart disease; TG, triglyceride; LDL-C and HDL-C, LDL- and HDL-cholesterol, respectively; TC, total cholesterol; TLC, therapeutic lifestyle change; BQ, β -quantification; CRMLN, Cholesterol Reference Method Laboratory Network; Lp(a), lipoprotein a; and CRP, C-reactive protein.

guidelines for measuring LDL-C (9), HDL-cholesterol (HDL-C) (10), and TGs (11).

The first NCEP clinical report (ATP I) (12), released in 1988, recommended initial screening for TC and focused on primary prevention of CHD in those with increased LDL-C [≥ 160 mg/dL (4.13 mmol/L) or 130–159 mg/dL (3.36–4.11 mmol/L) with two or more risk factors]. [Consistent with the convention followed by the NCEP, units are presented in mg/dL and are followed by (mmol/L)]. In addition, cutpoints for TC, HDL-C, and TGs were defined. ATP II (13), released in 1993, added HDL-C with TC in the initial screen, reflecting a developing consensus that low HDL-C is an important and independent contributor to CHD. In addition, a lower cutpoint for LDL-C [≤ 100 mg/dL (2.58 mmol/L)] was recommended as the treatment goal for patients with established CHD, consistent with a consensus that intensity of treatment should be related to severity of risk.

Supported by evidence from continuing research and with more general acceptance of the benefits of aggressively treating dyslipidemias, ATP III has broadened to other important risk contributors, substantially expanding indications for treatment, while providing more tools to improve the management of patients. The presence of diabetes or of multiple risk factors with high (20%) 10-year risk for CHD events are now considered to be CHD “risk equivalents”, requiring aggressive treatment as for established CHD and other types of atherosclerotic disease. A focused life-habit modification program, termed “Therapeutic Lifestyle Changes”, promoted by the acronym TLC, encourages the intensive behavioral changes needed to reduce LDL-C and CHD risk in patients with multiple risk factors, including those with the metabolic syndrome, which is brought into the mainstream.

A change in the initial screening suggests that patients should now begin with a complete fasting lipoprotein panel or profile (TC, LDL-C, and HDL-C together with TGs). Medical decision cutpoints have been modified for LDL-C, HDL-C, and TGs, and a new calculated marker, non-HDL-C is introduced. Obviously, clinical laboratories will not only need to make changes to conform to the new guidelines, but the successful implementation of the guidelines will require that laboratories be able to provide accurate results to the clinician in an appropriate and readily interpreted report format. This report summarizes specific implications of ATP III for the clinical laboratory as well as recommendations for providing reliable lipoprotein measurements.

CHD Risk Equivalents, Multiple Risk Factors, and TLC

ATP III introduces the concepts of CHD risk equivalents and multiple risk factors. Whereas ATP II intensified treatment for patients with CHD and other atherosclerotic diseases, ATP III now defines diabetes and the presence of multiple risk factors conferring a 10-year risk of $\geq 20\%$ as CHD risk equivalents, considered equal in terms of con-

tribution to overall CHD risk and requiring equally aggressive treatment. Enhanced attention to diabetes is justified, because diabetics have a high risk of CHD, similar to that in patients with symptomatic atherosclerotic disease, as well as a high mortality with and after myocardial infarction. For patients presenting with two or more risk factors, the 10-year absolute CHD risk can be estimated from Framingham Point Scores tables provided in convenient formats, including online (<http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>). Risk estimations derive from the Framingham, Massachusetts population, which has been followed for >50 years now, and are based on entry of the patient’s gender, age, TC, HDL-C, blood pressure, and cigarette smoking. TC is used for this estimation rather than LDL-C because its risk relationships are considered more robust in the Framingham data set. For purposes of classifying patients for treatment based on LDL-C, ATP III still considers the major risk factors to be smoking, hypertension, low HDL-C, family history of premature CHD, and advancing age (≥ 45 years for men and ≥ 55 years for women; Table 1).

Lifestyle risk factors, such as overweight/obesity, physical inactivity, and atherogenic diet, are also recognized as important contributors to CHD risk. Appropriately receiving more attention in ATP III is the metabolic syndrome, sometimes termed syndrome X, a complex disorder closely related to type II diabetes and an important contributor to CHD, which is characterized by a constellation of risk factors, including abdominal obesity, increased TGs, increased small and dense LDL particles, decreased HDL-C, hypertension, insulin resistance, and prothrombotic and proinflammatory tendencies.

As indicated above, ATP III will popularize a multifaceted life-habit approach to reducing risk for CHD, designated TLC. This lifestyle therapeutic regimen consists of changes in diet coordinated with weight reduction and increased physical activity. Dietary changes focus on reducing saturated fat consumption to $<7\%$ of total calories and cholesterol to <200 mg/day. For those in whom a diet low in saturated fat and cholesterol is not adequate to achieve the requisite LDL-C goal, use of water-soluble fibers and plant stanols/sterols is also encouraged.

Table 1. Treatment goals for LDL-C and non-HDL-C, in mg/dL (mmol/L).

	LDL-C	Non-HDL-C ^a
CHD and risk equivalents	<100 (2.58)	<130 (3.36)
Multiple (≥ 2) risk factors ^b	<130 (3.36)	<160 (4.13)
0–1 risk factors	<160 (4.13)	<190 (4.91)

^a Non-HDL-C is used as secondary target when the LDL-C goal is achieved and TGs remain ≥ 200 mg/dL (5.17 mmol/L).

^b Risk factors: smoking, hypertension $\geq 140/90$ mmHg, low HDL-C [<40 mg/dL (<1.03 mmol/L)], premature (males <55 years; females <65 years) CHD in first-degree relative, age (men ≥ 45 years and women ≥ 55 years).

Many patients will also require treatment with cholesterol-lowering drugs, which have shown to be highly effective in reducing CHD risk. Because the drugs tend to be expensive, they are generally prescribed in primary prevention for higher risk patients and after efforts to treat dyslipidemias by modifying diet and other lifestyle factors have been unsuccessful. In secondary prevention, the risk-benefit considerations favor more aggressive drug use. Important from the laboratory perspective, every patient hospitalized for an acute coronary event or a coronary procedure should have a lipid panel within 24 h of admission and appropriate therapy initiated. The statin drugs have been highly beneficial in reducing risk of a subsequent event; some specialists prescribe a statin for every such patient before discharge.

Screening with Fasting Lipid Profile

ATP II recommended measurement of TC and HDL-C in the initial screen, which did not require fasting, followed by a fasting lipoprotein profile only in those at increased risk. Consistent with the enhanced emphasis on LDL as well as on TGs, ATP III begins with the fasting complete profile or lipid panel to determine TC, LDL-C, HDL-C, and TGs, recommended for all adults at least every 5 years. Should the patient not be fasting, the TGs and calculated LDL-C are not considered valid; in this case, a fasting profile should be done if TC is ≥ 200 mg/dL (5.17 mmol/L) or HDL is < 40 mg/dL (1.03 mmol/L). The new recommendations could be expected to increase the number of profiles performed, although in practice many physicians and laboratories have previously used profiles for screening. Note that after an acute coronary event, the lipid profile must be performed within 24 h to be valid; otherwise the results can be compromised by changes in lipoprotein composition or concentration (14). Beyond 24 h, an increased LDL-C nevertheless requires LDL-lowering treatment.

Changes in LDL-C Cutpoints

ATP III introduces changes in the medical decision cutpoints, generally such that more patients will require follow-up, mandating changes in laboratory reporting and interpretations. For LDL-C, < 100 mg/dL (2.58 mmol/L) is now considered optimal for all adults, adding a new risk category with a total of five classification categories (Table 2). Lowering the optimal value for all adults is consistent with recent intervention studies demonstrating efficacy of cholesterol lowering even in pa-

tients with only moderately increased values (15). However, the relevant cutpoints and the treatment goals remain the same as in ATP II (Table 2), although more patients will now qualify.

To streamline laboratory reports, the NCEP has informally suggested that rather than listing all five categories, patients might be categorized based on the three treatment targets: 100, 130, and 160 mg/dL (2.58, 3.36, and 4.13 mmol/L). Patients at highest risk, with CHD or equivalent risk, are considered increased with LDL-C ≥ 100 mg/dL (2.58 mmol/L) and require treatment to bring values below the cutpoint, patients with two or more risk factors are treated to bring LDL-C to < 130 mg/dL (3.36 mmol/L), and all others to < 160 mg/dL (4.13 mmol/L). Recommendations for laboratory reporting published after the release of ATP II are still relevant, although the three, rather than only two, interpretation categories might be more appropriate for LDL-C (16). In addition, to compensate for variability in the measurements, both from biologic sources, generally the greater contributor, and from analytic sources, treatment decisions should be based on the mean of at least two measurements taken at least 1 week apart (9). Cutpoints for TC, monitored as a surrogate for LDL-C in previous guidelines, were not changed in ATP III. Desirable TC remains < 200 mg/dL (5.17 mmol/L), borderline is 200–239 mg/dL (5.17–6.18 mmol/L), and high is ≥ 240 mg/dL (6.20 mmol/L).

Recommendations for Measuring LDL-C

Including LDL-C in the initial screen reflects awareness of new capabilities for determining this analyte, although the Executive Summary does not give any specific recommendations for measurement. Many lipid specialists will likely continue to rely on β -quantification (BQ), a robust but tedious method that is the basis for the LDL-C reference method. BQ requires highly specialized ultracentrifugation, considered impractical for general use (9). Calculation by the Friedewald formula has become by default the most common routine approach, although calculation is precluded when TG concentrations are > 400 mg/dL (4.52 mmol/L) or when chylomicrons or dysbetalipoproteinemia is present (9). Calculated LDL-C has been shown to be reasonably reliable for TGs < 200 mg/dL (2.26 mmol/L) and marginal, but considered acceptable up to 400 mg/dL (4.52 mmol/L).

The NCEP expert laboratory panel recommended development of alternative direct methods (9), but until recently such methods were either unreliable or tedious, requiring pretreatment. Only recently has a new generation of homogeneous assays, modeled on those that have become standard for HDL-C, offered the capability for direct and fully automated measurement of LDL-C. The limited evaluations to date show promise, but are still insufficient to support more than a supplemental role for the homogeneous assays. A recent review (17) of LDL-C methods concluded that, based on technical considerations, homogeneous assays can at present be recom-

Table 2. LDL-C medical decision values, in mg/dL (mmol/L).

Optimal	< 100 (2.58)
Near optimal	100–129 (2.58–3.33)
Borderline high	130–159 (3.36–4.11)
High	160–189 (4.13–4.88)
Very high	≥ 190 (≥ 4.91)

mended only for those specimens with TGs >400 mg/dL (4.52 mmol/L), but not for general replacement of calculation until the direct assays are clearly demonstrated to be more accurate and capable of providing better classification of patients.

Even when the homogeneous methods are fully optimized and validated, an important factor in the choice between calculation and direct measurement by a homogeneous assay will be cost. At present the homogeneous methods are still relatively expensive, with reagent costs for a single direct assay approximately the same as those for the combined measurement of TC, HDL-C, and TGs, from which LDL-C can be calculated. Thus, if the physician wants the other markers in addition to LDL-C, then calculation is overall more economic. However, should the physician need only the LDL-C, which might be the case for some patients with only increased LDL-C determined by the initial profile, then the two approaches are approximately equivalent in cost.

On the other hand, direct measurement might actually be encouraged by a proposed change in reimbursement policy; this year, the US Center for Medicaid and Medicaid Services (formerly the Health Care Financing Administration) released a draft policy decreasing the number of reimbursed lipid panels from four to one in the first year, with a compensating increase in the number of ancillary individual tests to six in the first year. Under the proposed change, reimbursement could be made for any combination of TC, HDL-C, LDL-C, or TGs up to a total of six tests. This policy change, unless revised after the comment period, is expected to go into effect during the year 2002. Should these changes be implemented, practice would likely favor the direct LDL-C assay over calculation with the lipoprotein panel regardless of technical considerations.

In any case, more extensive evaluation studies are needed of the promising new homogeneous assays for LDL-C before they can be confidently recommended to replace calculation. The various homogeneous assays must still be validated in comparison with the reference method (BQ), not only on typical specimens, but also on a broad cross-section, including unusual specimens, to determine their agreement and identify the specimen characteristics that give discrepant results. The homogeneous assays and the Friedewald calculation need to be compared using accurate BQ as the standard to determine their relative concordance in classification of a range of representative patient specimens. Moreover, the homogeneous assays must be validated for reliably tracking of the effects of treatment.

Changes in TG Cutpoints

The cutpoint defining normal for TGs was lowered in the ATP III report to 150 mg/dL (1.70 mmol/L) from 200 mg/dL (2.26 mmol/L) in ATP II, and the upper cutpoint was lowered to 500 from 1000 mg/dL (5.65 from 11.30 mmol/L). ATP III still includes four categories of risk for TGs, however, as defined by the new lowered cutpoints

Table 3. TG medical decision values, in mg/dL (mmol/L).

Normal	<150 (1.70)
Borderline high	150–199 (1.70–2.25)
High	200–499 (2.26–5.64)
Very high	≥500 (5.65)

(Table 3). This change is especially relevant considering that ATP II had previously lowered the upper limit of normal from 400 mg/dL (4.52 mmol/L) in ATP I, the changes signaling increasing acceptance in the US that TG-rich lipoproteins are indeed an independent risk factor for CHD, requiring treatment. In many cases, increased TGs indicate the presence of the metabolic syndrome, which requires intensified lifestyle intervention with weight reduction and increased physical activity. The two lower risk categories, 150 and 200 mg/dL (1.70 and 2.26 mmol/L) are especially closely spaced and, considering the large biologic variation, will require increased emphasis on accuracy and standardization of TG measurements for reliable classification of patients. In fact, assuming an analytic imprecision (CV) of 5% with a not-unusual bias of 5% and a representative biologic variation (CV) of 22.4%, we calculate that even averaging five serial specimens would be insufficient to reliably classify a patient with a true TG concentration between 150 and 200 mg/dL (1.70 and 2.26 mmol/L) as borderline high with 95% confidence. On the basis of the average of the recommended two serial specimens, correct classification to the normal group would be limited to true concentrations <120 mg/dL (1.36 mmol/L) and correct classification to the high group would be limited to true concentrations >264 mg/dL (2.98 mmol/L). With these diagnostic limitations in mind, it is mandatory that fasting specimens (at least 9 h but preferably up to 12 h) be taken, and treatment decisions must be made based on averaging multiple measurements taken at intervals of at least 1 week (11). Although 1000 mg/dL (11.30 mmol/L) is no longer a cutpoint for TGs, physicians should be aware that values higher than this may be associated with pancreatitis, which requires immediate medical attention.

Introduction of Non-HDL-C

Increased attention to high TGs will bring the US more in line with other international guidelines (18). The emphasis on treatment of even moderately increased TGs acknowledges that TG-rich lipoproteins, especially their partially degraded remnant particles, are highly atherogenic. Because the remnants are found primarily in the VLDL fraction, VLDL-cholesterol is considered a surrogate for monitoring treatment. To facilitate monitoring, ATP III invokes use of a new secondary target for therapy, the non-HDL-C, which essentially combines all apolipoprotein B-containing lipoproteins in the LDL and VLDL fractions, most of which are considered to some degree atherogenic. Non-HDL-C should be monitored as a secondary target when the primary treatment goal for

LDL-C has been achieved but TGs remain high, ≥ 200 mg/dL (2.26 mmol/L). For patients with borderline high TGs, between 150 and 199 mg/dL (1.70 and 2.25 mmol/L), ATP III recommends primarily TLCs, obviating the need to calculate non-HDL-C. Calculation of non-HDL-C focuses attention on the cholesterol in the atherogenic LDL and VLDL fractions rather than on the increased TGs, which is regardless a marker for increased CHD risk, and pragmatically sidesteps the well-known limitations in the Friedewald estimation of LDL-C with increasing TGs; when TGs are increased, one can simply measure TC and HDL-C and by difference report the non-HDL-C. ATP III recommends cutpoints for non-HDL-C (Table 1) as those for LDL-C plus 30 mg/dL (0.78 mmol/L), which is approximately equivalent to the amount of VLDL-cholesterol at the lower TG cutpoint, i.e., 150 mg/dL (1.70 mmol/L) divided by 5 (in mmol/L divided by 2.17).

With regard to laboratory reporting and interpretations, certainly the lower cutpoint defining normal TGs should be lowered to <150 mg/dL (1.70 mmol/L), which will shift many patients into a higher risk category. On the basis of population distributions from the Lipid Research Clinics study, $\sim 30\%$ of middle-aged adults will exceed the new 150 mg/dL (1.70 mmol/L) cutpoint, whereas only $\sim 15\%$ exceeded the ATP II cutpoint of 200 mg/dL (2.26 mmol/L) (19). The new non-HDL-C might also be included on laboratory report forms as a calculated value whenever TC and HDL-C are measured. Even better, the laboratory could report non-HDL-C as a reflex value only for those patients with TGs >200 mg/dL (2.26 mmol/L). A reflex decision to report the calculated non-HDL-C value based on whether the patient has also achieved the requisite LDL-C goal will be possible only if the laboratory has access to the relevant heart disease and risk factor status. On the other hand, the laboratory might choose to not include the non-HDL-C calculation on the report form, leaving the calculation to the physician. However, in this case, the laboratory would perform a useful service by at least informing physicians regarding the appropriate use and method for calculating the non-HDL-C. It is also possible that physicians might actually request a non-HDL-C determination, in which case the laboratory would need to measure TC and HDL-C and provide the calculated value. Experience and continuing evaluation of clinical usefulness will likely guide appropriate implementation of this new marker in general practice.

Changes in HDL-C Cutpoints

For HDL-C, the cutpoint below which patients are considered to be at increased risk, thus adding a risk factor for classification based on LDL-C, was increased from 35 to 40 mg/dL (from 0.90 to 1.03 mmol/L). On the basis of population distributions from NHANES III, $\sim 40\%$ of adult males and 15% of females will now be included in the high-risk category vs 15% of males and 5% of females with the previous HDL-C cutpoint (13). An HDL-C value ≥ 60 mg/dL (1.55 mmol/L) is still considered a negative

risk factor, subtracting one from the total number of risk factors. A low HDL-C is the most common lipid abnormality observed in men with CHD (20) and can be associated with other risk factors, such as high TGs and diabetes as well as overweight/obesity, physical inactivity, smoking, diet, and certain drugs. Therapeutic regimens for low HDL-C are not as well established as for increased LDL-C, but are nevertheless considered appropriate. More research in the future will likely focus on appropriate treatment for low HDL-C.

Some have advocated the use of ratios, combining HDL-C with either TC or LDL-C to obtain a single number defining risk. Although evidence from epidemiologic studies supports the predictive value of the ratios, the ATP II report, although acknowledging their utility, recommended focusing on the individual lipoproteins in relation to their respective cutpoints. The ATP III Executive Summary (1) does not specifically address the issue of ratios, but panel members have indicated that the position regarding use of ratios has not changed, which will be explained in the full report (2).

Reporting of Results

After release of the ATP II guidelines, efforts were made to improve and standardize the format for reporting lipoprotein results to clinicians (16). The intention was to reinforce the criteria for diagnosing and managing the treatment of hypercholesterolemia and assure the use of appropriate cutpoints for interpretation. In addition to reporting the actual laboratory results, the relevant CHD risk factors, various lipoprotein cutpoints, work-up for the diagnosis of hypercholesterolemia, and LDL-C therapeutic goals were included in the recommended report format. A survey taken in the mid-1990s suggested that the NCEP guidelines and cutpoints had not been widely adopted by clinical laboratories (16). The recommendations accompanying the survey results are generally still pertinent and appropriate as a guide for incorporating the new ATP III guidelines into the report other than the changes in cutpoints noted above. However, the ATP III changes in risk classification will present even greater challenges. For example, determining a patient's 10-year CHD risk will require information not usually available to the clinical laboratory, such as blood pressure and smoking habits. An alternative is to simply include for the physician, who has the needed clinical information, a link to the risk calculator on the NCEP web page (<http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>).

Need for Accuracy and Standardization in Measurement

The need for accurate and precise measurement of TC, HDL-C, LDL-C, and TGs will continue to be highly important in achieving appropriate classification of patients according to the cutpoints and treatment strategies outlined in ATP III. The recommendations by the NCEP Expert Laboratory Standardization Panels for acceptable performance in TC, HDL-C, LDL-C, and TG measurement

Table 4. NCEP recommendations for acceptable analytic performance.

	CV, %	Bias, %	Total error, %
TC	3	3	9
LDL-C	4	4	12
HDL-C	SD \leq 1.7 mg/L at $<$ 420 mg/L CV \leq 4% at \geq 420 mg/L	5	13
TGs	5	5	15

(Table 4) are still pertinent with the new features of ATP III. The accepted accuracy targets for TC, HDL-C, LDL-C, and TG measurements remain the reference methods maintained by the CDC. The medical decision points recommended by ATP III are based on studies that were standardized by CDC; thus, proper classification of risk based on these medical decision points requires results that are standardized and traceable to the CDC reference methods. To help clinical laboratories produce the needed reliable results that are traceable to this accuracy base, CDC maintains the Cholesterol Reference Method Laboratory Network (CRMLN) to assist diagnostics manufacturers in validating appropriate calibration of their lipid/lipoprotein assays (21). The CRMLN certifies the performance of diagnostic products for TC, HDL-C, LDL-C, and TGs through comparisons with the reference methods, using fresh patient samples. Clinical laboratories should use only diagnostic assay systems that have been certified by the CRMLN as meeting the NCEP criteria for acceptable performance. A list of the assay systems currently certified as well as instructions for performing the comparison studies can be found online at www.aacc.org/standards/cdc/cholesterolinfo.stm. Clinical laboratories can also verify the accuracy of their results by performing a fresh sample comparison directly with a CRMLN laboratory or by participating in a reliable proficiency-testing program that uses fresh or fresh-frozen patient samples with target values assigned by the reference methods.

Impact of ATP III on the Clinical Laboratory Workload

The formal shift to the lipoprotein panel for screening will likely increase the total number of tests performed by the clinical laboratory, although the specific numbers are uncertain because in many cases this practice has already been adopted. Clearly the changes in treatment criteria will substantially increase the number of patients requiring follow-up. For example, the number of patients qualifying for drug treatment, mainly by one of the statin drugs, is expected to nearly triple (2). The NCEP estimates that 36 million adults in the US will now qualify for drug treatment and 65 million for the TLC intervention. This comprises 18% and 33% of all adults for drug and TLC treatment, respectively. By comparison, the previous ATP II guidelines selected \sim 13 million adults for drug treatment and 52 million for dietary intervention.

Role of the Laboratory in Providing Testing for Emerging Markers

Although the ATP III Executive Summary did not make specific recommendations regarding measuring emerging biochemical risk markers of CHD, they recognized that CHD risk is influenced by lipoprotein(a) [Lp(a)], homocysteine, high fasting glucose, and prothrombotic and proinflammatory markers. Measurement of Lp(a) and homocysteine is not currently recommended in the general population for the purpose of assessing coronary risk, but is appropriate in certain patients, such as those with increased family risk of CHD. Recent findings from American and European prospective epidemiologic studies have consistently shown that C-reactive protein (CRP), a proinflammatory acute-phase reactant, is a strong and independent predictor of future coronary events in apparently healthy men and women (22). Furthermore, CRP seems to identify individuals with normal LDL-C concentrations who are at increased risk for future coronary events and can be useful in targeting persons with normal lipid values who could benefit from statin treatment.

Currently the measurements of these novel markers are not very widely performed in clinical laboratories. However, it is likely that the determination of at least some of them will increase as more compelling data regarding their clinical utility become available. Therefore, laboratories must be capable of reliably measuring these markers, and their standardization is essential before they make the transition from the medical research environment to routine clinical practice. The IFCC has identified a secondary reference material suitable for most commercially available Lp(a) assays, a major step toward standardization. The National Heart, Lung, and Blood Institute (NHLBI) will sponsor a workshop on Lp(a) standardization in late 2002. In addition, the CDC has recently embarked on a project to standardize commercial methods for CRP. Phase I of this project, aimed to identify an acceptable secondary reference material, is scheduled for Fall 2001. In addition, the IFCC has formed a working group to develop a plan to standardize homocysteine measurements.

In conclusion, the ATP III guidelines introduce major changes that can be expected to impact clinical laboratories as follows:

- Modification of cutpoints for LDL-C, HDL-C, and TGs, introduction of non-HDL-C, and incorporation of the Framingham Point Scores to calculate CHD risk will require changes in the reporting format
- The lowered and more closely spaced cutpoints will emphasize the need for accuracy and require increased efforts to standardize lipoprotein measurements
- The requirement for a fasting lipoprotein profile at initial screening and the substantial increase in the number of patients treated by drugs or lifestyle changes will substantially increase laboratory testing

- Testing for “emerging risk factors” and secondary dyslipidemias is likely to increase

The primary objective continues to be ameliorating the morbidity and mortality associated with deadly CHD. Now the rising epidemic of diabetes and the metabolic syndrome will be better addressed as well. Laboratorians have an important role to play in successful adoption of the new guidelines. Appropriate changes will need to be made in laboratory routine practices and in reporting formats. Even more attention to accuracy and standardization of the measurements will be required to achieve reliable patient classifications. Last but not least, full implementation of these important new guidelines will require education of physicians and other medical professionals as well as the general public, an effort clinical laboratories can support through their various channels of communication.

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