Chapter 1

Introduction

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The purpose of this document is to present the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine and Practice Guidelines for utilization of emerging laboratory biomarkers of cardiovascular and stroke risk in a primary prevention setting. The NACB is the American Association for Clinical Chemistry's scientific academy. An important activity of the NACB is to develop laboratory medicine practice guidelines to assist clinical and laboratory practice decisions concerning patients at increased risk for specific diseases.

BACKGROUND

For more than 20 years, heart disease and stroke have been the first and third leading causes of death and major causes of disability in the United States and other developed countries (1). Heart disease and stroke are estimated to be the first and second leading causes of death in the world today and are expected to remain so by the year 2020 (2). Despite significant reduction in all standardized mortality from cardiovascular disease (CVD) over the past 20 years, CVD remains the number one cause of death in the United States, out ranking all cancers by more than 60% (3). More than 70.1 million Americans have some form of CVD (3). Public health priorities for prevention of cardiovascular events and stroke as addressed in Healthy People 2010 are: prevention of risk, detection, and treatment of risk factors; early identification and treatment of heart attacks and stroke; and prevention of recurrent cardiovascular events (4,5). Thus the search for biomarkers that will better recognize patients with coronary disease who could potentially benefit from intensive primary prevention efforts is critically important.

The American Heart Association (6) and the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) (7) have each issued recommendations designed to identify more people who are asymptomatic and clinically apparently free of coronary heart disease (CHD), but at sufficiently high risk for a future coronary event in order to justify more intensive risk reduction efforts. Within these recommendations are specific risk factors, including total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, that are typically used in risk prediction algorithms, such as the Framingham risk score (8), to estimate a global risk assessment for CVD. However, these predictive models based on conventional risk factors are underutilized and have a lower than desired accuracy, thus providing a stimulus to search for new tools to refine CVD risk prediction (9). In recent years, the number of new candidate risk factors that have been proposed as significant predictors of CVD and its complications has grown considerably (Table 1). These biomarkers are termed emerging risk factors because they are associated with an increased risk for CVD, but their causative, independent, and quantitative contributions to CVD are not as well documented as dyslipdemia, high blood pressure, and smoking—major, longest established risk factors (10). An emerging marker may not be emerging in the sense that it is a newly discovered marker, but may be an existing marker for which evidence is only now available for establishing it as effective for independently identifying risk or for monitoring treatment.

While the guidelines issued by the NCEPís ATP III for global risk assessment using the traditional risk factors are based on strong evidence supporting their role in the pathogenesis of CVD, the role for the emerging risk factors in primary prevention is far less clear. Debate has taken place on whether a risk marker must be causally related to disease, or whether clinical utility can be advocated for a marker that might not be causal, but could indicate use of a different course of therapy or management strategy than would otherwise be considered. Additional guidance is needed to help clarify and define the

Table 1. Emerging Risk Factors for Cardiovascular Disease

C-Reactive Protein	Interleukins (eg, IL-6)
Serum amyloid A	Vascular and cellular adhesion molecules
Soluble CD-40 ligand	Leukocyte count
Fibrinogen	Plasminogen activator inhibitor 1
D-dimer	Tissue-plasminogen activator
Factors V, VII, VIII	Small dense LDL
Lipoprotein(a)	Apolipoproteins A1 and B
LDL and HDL subtypes	Oxidized LDL
Homocysteine	Lipoprotein-associated phospholipase A_2
Microalbuminuria	creatinine (glomerular filtration rate)
Cystatin C	Infectious agents
Apo E genotype	Fibrinopeptide A
Remnant lipoproteins	von Willebrand factor antigen

Table 2. American Heart Association/American College of Cardiology Classifications Summary of Indications

I Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

IIa Weight of evidence/opinion is in favor of usefulness/efficacy

IIb Usefulness/efficacy is less well established by evidence/opinion

III Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and insome cases may be harmful

Weight of Evidence

A Data derived from multiple randomized clinical trials that involved large numbers of patients

B Data derived from a limited number of randomized trials that involved small numbers of patients or from careful analyses of nonrandomized studies or observational registries

C Expert consensus was the primary basis for the recommendation

contribution that these emerging risk factors may have in identifying persons at risk for CVD. Benchmarks are needed against which new biomarkers can be evaluated. In evaluating the clinical potential of a new emerging biomarker we should ask; can the biomarker be measured, does the biomarker add information to or improve upon existing tests, and will the biomarker help in patient management (11)? The overall expectation is that a CVD biomarker will enhance the clinician's ability to appropriately manage the patient's disease status.

The NACB convened a multidisciplinary panel of experts to develop recommendations for the clinical utility and laboratory measurement of a selected number of these emerging risk factors for use in primary prevention of CVD and stroke. The selection of risk factors for evaluation and inclusion in this guideline was based on systematic expert consensus of the NACB guideline group after reviewing available evidence and evaluating criteria of clinical usefulness, consistency of epidemiologic data, improved predictive value, independence from other factors, and available analytical methods. The NACB expert panel defined the following risk factors as within the scope of this guideline: lipoprotein subclasses and particle concentration, lipoprotein (a), apolipoproteins A-I and B, C reactive protein, fibrinogen, white blood cell count, homocysteine, brain (B-type) natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT proBNP), and markers of renal function.

The current guidelines for these emerging risk factors have been developed based on the published evidence for their use in primary prevention to predict CVD and stroke risk in non-diseased populations compared to the ATP III recommendations based on the measurement of total cholesterol, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). The scope for these guidelines is primary risk prediction. For this application, it is first necessary to calculate a 10-year predicted risk based on Framingham risk score (8) or other classification which incorporates a lipid profile (total cholesterol, HDL-C, triglycerides, calculated LDL-C, and non-HDL-C).

Specific recommendations in this NACB guideline are based, whenever possible, on relevant published information. For in-depth evaluation of each of the selected biomarkers, we used all available literature from prospective observational studies of initially healthy populations published through February 2005. We did not consider retrospective studies or studies of populations with existing vascular diseases, except in the case of evaluating the use of biomarkers to direct secondary prevention after cardiovascular events (because less data are available in primary prevention settings). The strength of scientific data supporting each recommendation was characterized using the scoring criteria adopted from the American Heart Association/American College of Cardiology, as summarized in Table 2. For each recommendation, the designations I, IIa, IIb, and III describe the indications, and the upper case letters A through C describe the weight of evidence.

The draft guidelines were posted on the NACB website in September 2006 for public comment from individuals, organizations, and other interested parties. The guidelines were also presented at the 27th Arnold O. Beckman Conference in Baltimore, MD, October 2006. Public comments received through these channels were carefully reviewed by the committee and actions were taken to address them.

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