Developing and assessing cardiovascular biomarkers

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Atherosclerosis is a slow process that over time can lead to fatal events. Early identification and prediction of future risk can allow for preventive strategies to be instituted. There is an increasing interest in utilizing novel biomarkers in cardiovascular disease screening and management. These novel biomarkers may help in cardiovascular disease risk assessment and treatment monitoring, and some may be treatment targets. To be useful for risk prediction, novel biomarkers need to show a significant association with cardiovascular disease events and bring additional value in risk stratification when added to known risk prediction models. Biomarkers used for treatment monitoring need to show that they can serve as good surrogates of cardiovascular disease status. In this article, we present 3 biomarkers that are currently approved by the U.S. Food and Drug Administration for use in cardiovascular disease management and risk assessment: C-reactive protein, lipoprotein-associated phospholipase A2, and myeloperoxidase. Other new biomarkers have also been shown recently to help in cardiovascular disease risk prediction and management. In this article, we will review 2 of these new biomarkers: cardiac troponin T measured by a highly sensitive assay and brain natriuretic peptide. (Translational Research 2012;159:265–276)

Abbreviations: ACC = American College of Cardiology; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; AHA = American Heart Association; AUC = area under the curve; BNP = brain natriuretic peptide; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CAPTURE = c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina; CARE = Cholesterol and Recurrent Events trial; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HOPE = Heart Outcomes Prevention Evaluation; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; IDI = integrated discrimination improvement; JUPITER = Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; Lp-PLA2 = lipoprotein-associated phospholipase A2; LDL-C = low-density lipoprotein cholesterol; MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease; MPO = myeloperoxidase; MI = myocardial infarction; NT-proBNP = N-terminal pro–brain natriuretic peptide; NRI = net reclassification index; OR = odds ratio; PEACE = Prevention of Events With Angiotensin-Converting Enzyme Inhibition; RR = relative risk; USPTF = U.S. Preventive Task Force; WOSCOPS = West of Scotland Coronary Prevention Study

Atherosclerosis is a slow process that after decades of silent progression may lead to fatal events such as myocardial infarction (MI) and stroke, which are the first and third causes of death worldwide. Clinical tools to enhance the ability to identify the patients at risk for cardiovascular disease (CVD) events are therefore needed. Biomarkers are one such tool that might improve identification of high-risk patients for CVD events and help guide treatment. Biomarkers such as cholesterol and blood pressure have helped in cardiovascular risk assessment and management for a long time. Lately new biomarkers are being studied as potential aids in CVD management and prevention.[1] In the first part of this article, we will discuss

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a few critical steps that are required in identifying new biomarkers for CVD risk assessment and management. Then, we will review the most important available data on 3 biomarkers approved by the U.S. Food and Drug Administration as well as 2 new biomarkers that have been recently shown to be associated with CVD and might have potential value in risk assessment and management of this disease.

DEFINITION AND CHARACTERISTICS OF BIOMARKERS

A biomarker is a substance that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention. Biomarkers may have value in improving global CVD risk assessment and monitoring response to therapy or as targets for therapy.[2] The desirable characteristics of a biomarker differ with their intended use.[3] For screening biomarkers, features such as high sensitivity, specificity, and predictive values, large likelihood ratios, and low costs are important.[4] For biomarkers monitoring the response to therapy, features such as narrow intra-individual variation and association with disease outcome are critical.[5]

Identifying new biomarkers for cardiovascular disease (CVD) risk prediction. Biomarkers for CVD risk assessment can be used to assess the short-term outcomes of acute illnesses such as MI or to guide preventive therapies in adults with CVD risk factors. The most common study design used to examine such biomarkers is usually a prospective cohort study on a representative at-risk population.[6] The statistical association between the outcome of interest and the potential biomarker is usually tested with logistic regression, Cox proportional hazards models, or parametric survival models.[7] After an association between the biomarker and the outcome is established, one should evaluate whether the biomarker provides incremental improvement in risk prediction beyond that provided by models that use traditional risk factors, by assessing the calibration and discrimination of the new model.

The calibration compares the observed and predicted probabilities when a biomarker is added to a risk score. Goodness-of-fit tests such as Hosmer-Lemeshow and Grønnesby-Borgan may also be used to assess calibration.[8] Once the additive value of a biomarker in risk prediction has been shown, the final phase of evaluation is assessment of whether the use of the risk marker in clinical management improves clinical outcomes with a randomized trial.[7]

Discrimination refers to the ability to classify patients when the disease state is known by other means. The most common tests used to assess discrimination are area under the curve (AUC), also known as c-statistic, and the receiver operating characteristic (ROC). The values of these tests range from 0.5 to 1, and the c-statistic for models predicting 10-year risk of CVD in a healthy population is often in the range of 0.75 to 0.85.[9] Two other measures used for discrimination are the net reclassification index (NRI) and the integrated discrimination improvement (IDI). The NRI compares the proportions of cases vs controls moving up or down in clinical risk categories, and the IDI compares the sensitivity and specificity of the 2 models.

Developing new biomarkers for monitoring treatment of CVD. To use biomarkers to assess the efficacy of a therapy, the biomarker must demonstrate not only an association with CVD but also a change in response to the therapy under investigation. In addition, this change should be a good surrogate for the clinical outcome of interest. For example, biomarkers used as surrogates for CVD are useful only if the changes that are seen in the biomarker as a result of a certain therapy reflect a change in a meaningful clinical endpoint (eg, MI or stroke). Measurement of the biomarker should also be reproducible and standardized. The definitive validation of a biomarker to be used in evaluation of therapy includes demonstration that the change due to therapeutic intervention independently predicts benefit and that a clear correlation exists between change in the biomarker and change in risk for the outcome. The study design to test the efficacy of a therapeutic agent should involve a control therapy with a known clinically effective drug and a documented or plausible effect on the chosen biomarker. The clinically meaningful effect should be paired with the minimum change associated with the control therapy.[4,10]

As the biomarker industry continues to expand rapidly, concurrent advances in physician training are required so that clinicians can order tests appropriately and interpret them correctly. In the next section of the article, we will review the most important data on 5 biomarkers that may have value in the management of CVD. Of the multitude of available biomarkers, we will present the 3 FDA-approved biomarkers: C-reactive protein (CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and myeloperoxidase (MPO). We will also review 2 of the most promising biomarkers that are currently approved for other indications: cardiac troponin T (cTnT) measured by a highly sensitive assay and brain natriuretic peptide (BNP).

C-REACTIVE PROTEIN (CRP)

CRP is a nonspecific inflammatory marker that has now been extensively studied in CVD. It is a member of the pentraxin family of innate immune response proteins.[11] CRP is postulated to have a role in atherosclerosis, as it