INTRODUCTION

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Kevin F. Foley PhD, MT *is the* ***Focus: Cardiovascular Risk Assessment*** *guest editor.*

There is no area of laboratory medicine that requires more interpretive knowledge than cardiovascular risk assessment. The clinical laboratory has moved far from the days when triglycerides, total cholesterol, HDL and a calculated LDL were the only laboratory tests that could be used to assess the cardiovascular risk for patients. In this series we will look at four different topics in cardiovascular laboratory medicine.

One can think of cardiovascular laboratory medicine as having two arms; tests used to assess cardiovascular risk, and tests used to assess myocardial infarct. Of course these two arms overlap significantly in that myocardial infarct is a major cardiovascular event for which we want to gauge risk. Measuring markers such as CK-MB or troponins allows us to confirm or rule out myocardial infarction. In contrast, risk markers are a tool we can use to assess a person's risk for cardiac morbidity or mortality. When considering markers for myocardial infarct, most laboratorians know that CK-MB and troponin can provide valuable diagnostic and sometimes even prognostic information. But is it time to phase-out CK-MB testing given the performance and demonstrated superiority of troponin testing? In this series we review the use of troponin and CK-MB in contemporary laboratory practice.

This journal also discusses the value and supporting data for genetic assessment of patients at risk for coronary artery disease. Clinical laboratorians are no doubt aware that a genetic component exists when predicting cardiovascular risk. The linkages, specific genes and utility of genetic testing with regard to cardiovascular disease is particularly timely for those in laboratory medicine given the increasing role that molecular diagnosis has on the clinical laboratory and the increasing overlap between genetic and conventional clinical chemistry testing. Given the multiple variables that can influence or contribute to cardiovascular disease, gene association studies aimed at identifying genetic risk factors can be difficult to design and interpret. The following article on genetic markers of coronary artery disease (CAD) attempts to review some recent findings in light of these challenges.

A biomarker that can be used predict the risk of a future cardiovascular event would be a powerful tool for any physician given the global prevalence of heart

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disease and atherosclerosis. There are dozens of cardiovascular risk markers which can, to various degrees, indicate cardiovascular pathology. In 2009 the National Academy of Clinical Biochemistry released practice guidelines for cardiovascular risk markers[1]. This expert panel evaluated clinical data associated with the risk markers listed in Table 1. Although there are many more putative risk markers than appear on this list, the list reflects those risk markers that have been most studied.

As of now, only high sensitivity C-reactive protein (hsCRP) has been endorsed by the NACB as meeting all the risk marker requirements needed for routine clinical practice[1]. In this series we discuss another of the markers on this list: B-natriuretic peptide (BNP). BNP measurement has been available since 1997 and is found on most clinical chemistry laboratory testing menus. The value of BNP as a marker for heart failure is a current topic of debate and the clinical utility of this marker is discussed in this series[2]

Vitamin D testing volumes are increasing dramatically in clinical laboratories due to our increasing knowledge of the ubiquitous role that this vitamin/hormone appears to have in overall health. Studies showing that vitamin-D levels correlate with the prevention of osteoporosis, and measure risk for developing cancer, autoimmune disease and type 1 diabetes are plentiful[3]. In addition to these diseases, studies are now revealing that cardiovascular diseases may be associated, to varying degrees, with vitamin-D deficiency. Our series summarizes some of these recent findings in the context of cardiovascular risk.

Although well-validated, sensitive and specific cardiovascular risk markers are valuable, risk can also be assessed without using novel cardiovascular risk biomarkers. The Framingham risk score is a proven tool used to gauge cardiovascular risk. Although the Framingham Heart Study has validated various clinical factors for several cardiovascular disease outcomes, general cardiovascular risk can be calculated based on a patient's age, gender, total cholesterol, HDL, systolic blood pressure and a person's diabetic and smoking status. This calculated score will predict the likelihood of an adverse cardiac event in the subsequent ten years.

Given this easy to use and well-validated risk formula, an obvious question to ask is 'why do we need additional cardiovascular risk markers?' The reason is multifold. It is possible that different populations of patients will have different patterns of risk markers which may correlate to different pathologies. For example, Lp(a) is an independent marker for cardiovascular disease yet in African American populations Lp(a) values tend to be as much as three times higher than those found in Caucasians.[4] Thus one marker does not always work to the same degree in all populations. Further, risk prediction is a statistic, not a certain prognosis. Therefore with each new risk marker there is the potential that we can increase the predictive power of our risk estimates. Perhaps a biomarker exists which can strongly predict a cardiovascular event in the next year or month rather than in the next ten years.

It is also likely that multiple risk markers, when used together can provide additional information to predict risk and guide therapy. For example, a recent study by Dai et al. showed that for major adverse cardiac events, elevated CRP had an odds ratio of 2.4 whereas elevated NT-proBNP carried an odds ratio of 5.2[5]. When both risk markers were used, an odds ratio of 7.04 was found[5]. So despite the fact that traditional risk factors such as LDL, blood pressure and total cholesterol are cheap and readily assessed, we can likely increase our detection of cardiac pathologies and risk when we employ additional cardiovascular risk markers. Their application is most justified for those patients with intermediate risk: 10–20% chance of an event in the next 10 years as measured by the Framingham risk score. Finally, many patients present with a major adverse cardiovascular event with no previous history of cardiovascular disease and lipid levels within the normal ranges recommended by the National Cholesterol Education Program. A risk marker that could be used to screen these patients so that effective

intervention could be initiated early on, would be invaluable.

The landmark JUPITER study (The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) provides an example of how a novel cardiovascular risk marker can function.[6] In this trial, individuals with low LDL cholesterol but elevated C-reactive-protein (CRP) levels were given rosuvastatin (Crestor), a cholesterol-lowering statin. The study found that this treatment significantly reduced the chances of nonfatal myocardial infarct, nonfatal stroke, hospitalization for unstable angina, revascularization, and confirmed death from cardiovascular causes. The treatment group had a risk reduction of 44% compared with placebo-treated individuals. This decrease was large enough to justify halting the study so that all patients could benefit from the treatment. This trial demonstrates that even in patients with normal LDL levels, cardiovascular risk may be present and can be reduced with conventional statin treatment.

Studies such as this validate the use of cardiovascular risk markers, in this case, hsCRP; and show that such markers can drive changes in the standard of care to achieve better outcomes. Because of data such as these from the JUPITER study, the NACB practice guidelines support the use of hsCRP as a proven and validated biomarker for risk assessment in primary prevention. Although hsCRP is the only novel risk marker currently endorsed by the NACB, other biomarkers may provide significant predictive power, warranting future studies.

An overview of the leading novel cardiovascular risk markers (Table 1) is not within the scope of this series. However we have endeavored to touch on several important areas in cardiovascular lab medicine: myocardial infarct markers, genetic testing, BNP (a risk marker and marker for heart failure) and the potential influence of Vitamin-D.

Table 1. Cardiovascular Risk Markers

- Apolipoprotein A1
- Apolipoprotein B
- high sensitivity C-reactive protein (hsCRP)
- Fibrinogen
- White blood cell count
- Homocysteine
- B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP)
- Lipoprotein (a)
- Lipoprotein subclasses and particle concentration

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