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New Noninvasive Modalities in Coronary Angiography - Diagnostic Values of New Biomarkers for Cardiovascular Disease

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1. Introduction

The early identification of susceptibility to adverse cardiovascular outcomes and risk stratification amongst asymptomatic individuals, as well as amongst those with overt disease continues to be one of the major priorities of clinically-orientated research in the field of atherothrombosis (Dotsenko et al., 2008). Conventional cardiovascular risk assessment is based on traditional risk factors such as serum cholesterol concentrations, blood pressure levels, smoking, and diabetes mellitus. However, available data from epidemiological studies indicate that these classic risk factors do not fully explain the distribution of risk in the general population. On the other hand, classic risk scores may provide variable results in different people groups (Blankenberg et al., 2010). Besides, coronary artery disease often occurs in the absence of traditional risk factors (Yilmaz et al., 2007). Therefore, it is becoming increasingly clear that the newer laboratory measures may be useful to refine risk estimates in the general population. The pressing need for the development and clinical implementation of new markers of atherothrombotic disease has fuelled rapidly expanding research into cardiac biomarkers (Dotsenko et al., 2008; Le & Wilson, 2010).

Cardiovascular biomarkers have the potential to augment clinical risk stratification by aiding in screening, diagnosis and assessment of prognosis. However, most current biomarkers have only modest predictive value, and there is a need to identify additional biomarkers from new biological pathways (May & Wang, 2008). Biomarker research is actively developing new testing strategies trying to improve upon current approaches, but it is often unclear how to assess the incremental prognostic information that a new test provides (Wood & Greenland, 2009). Some individual biomarkers such as C-reactive protein (CRP) have demonstrated consistent associations with incident cardiovascular events across multiple studies, but the magnitude of these associations is modest, and only small improvements in discrimination and reclassification are seen. One attractive solution to the limitations of individual biomarkers is to combine nonredundant biomarkers into panels to enhance risk assessment. However, results of studies testing multiple biomarkers for risk prediction in primary prevention populations have not provided a clear picture, with some studies showing qualified promise and others suggesting limited value (de Lemos & Rohatgi, 2010). This chapter provides an overview of the way of biomarker

discovery and selection for cardiovascular disease (CVD) and the practical considerations that are a prerequisite to their clinical use .

2. What is a biomarker and how do we find the best biomarkers for cardiovascular disease?

Biomarkers are one such tool to better identify high-risk individuals, to diagnose disease conditions promptly and accurately, and to effectively prognosticate and treat patients with disease (Dotsenko et al., 2008). The term biomarker (biological marker) was introduced in 1989 as a Medical Subject Heading (MeSH) term and in 2001, a National Institutes of Health (NIH) working group standardized the definition of a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Vasan, 2006). (Table1).

Ambiguity concerning decision limits frustrates clinicians and negatively affects the clinical adoption of a biomarker. At the time of clinical introduction, a new biomarker ideally should have well-characterized decision limits that (a) are pragmatic to apply, (b) have undergone validation in multiple studies, (c) have been evaluated in the relevant population(s) and application(s), and (d) have achieved synergy between available scientific data and regulatory labeling (Morrow & Cook, 2011).

Biological marker (biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.
Risk factor: A risk factor is associated with a disease because it is in the causal pathway leading to the disease.
Risk marker: A risk marker is associated with the disease (statistically) but need not be causally linked; it may be a measure of the disease process itself.
Clinical end point: A characteristic or variable that reflects how a patient feels, functions, or survives.
Intermediate (nonultimate) end point: A true clinical end point (a symptom or measure of function, such as symptoms of angina frequency or exercise tolerance) but not the ultimate end point of the disease, such as survival or the rate of other serious and irreversible morbid events.
Validation of a biomarker (assay or method validation): A process for assessing performance characteristics (ie, sensitivity, specificity, and reproducibility) of a biomarker measurement or an assay technique.
Qualification of a biomarker (clinical validation): The evidentiary process linking a biomarker to disease biology or clinical outcome.
Evaluation of a biomarker: A process of linking biomarkers to outcomes, often with a view to establish surrogate status.
Adapted from Reference : Vasan, (2006).

Table 1. Biomarkers: A basic glossary.

How do we find the best biomarkers for cardiovascular disease? Cardiovascular risk estimation by novel biomarkers needs assessment in disease-free population cohorts, followed up for incident cardiovascular events, assaying the serum and plasma archived at baseline (Blankenberg et al., 2010). Composite end points are often used to increase the number of events in the comparison with persons who do not develop events. Such composite end points might include the development of acute coronary syndrome, cardiac failure, cerebrovascular disease, and intermittent claudication. When possible, it is probably best to focus the research interest on discrete events, such as the occurrence of a first coronary heart disease event (Le & Wilson, 2010); or perhaps research should be done considering the severity of the disease, namely the degree of coronary stenosis evaluated by coronary angiography. Besides, diagnosing coronary artery disease (CAD) in patients at risk can be challenging and typically requires coronary angiography as the gold standard (Rosenberg et al, 2010).

When a new biomarker X is evaluated, it is important to remember that the question of interest is not whether X is a better predictor of disease than a previously known biomarker Y. Rather, the pertinent question is whether X improves the predictive accuracy of the best available model (representing the standard of care for that disease) that incorporates several known predictors of disease including Y. Thus, the relative added values of new biomarkers is best evaluated by estimating the increment to the c statistic compared with that from a model that incorporates other previously known predictors (Vasan, 2006). The c statistic, or area under the receiver operating characteristic (ROC) curve, achieved popularity in diagnostic testing, in which the test characteristics of sensitivity and specificity are relevant to discriminating diseased versus nondiseased patients (Cook, 2007).

Although it is generally believed that new biomarkers should add to the c statistic to be useful, there are exceptions to this rule. Novel biomarkers (eg, homocysteine) that are not incremental to known risk factors may be measured in select clinical situations such as in the following: asymptomatic individuals without obviously elevated conventional risk factors but with very strong family history of vascular disease; patients with premature vascular disease but no obvious risk factors; and patients with aggressive recurrent vascular disease in the face of well-controlled levels of conventional risk factors (Vasan, 2006).

Most of the cardiovascular biomarker studies that test the utility of a large number of laboratory tests are hypothesis-generating in nature, and validation of the results is important. Several validations of a new biomarker may be needed to demonstrate that the new test provides information that could help predict risk in the population or in specific subgroups of the population. When the usefulness of a new test for predicting disease is assessed, it is important to bear in mind whether the test adds or replaces information concerning risk or prognosis for a specific clinical or subclinical outcome. The test must also be reproducible, be standardized, have a high diagnostic sensitivity and specificity, and have a high predictive value (Le & Wilson, 2010).

3. What are the new biomarkers for CVD?

In recent years, a number of new candidate risk factors or markers have been proposed as significant predictors of atherosclerosis and its complications (Table 2) (Hackam & Anand, 2003). In a contemporary publication of the MONICA (Monitoring of Trends and Determinants of Cardiovascular Disease) investigators, Blankenberg and colleagues evaluated the potential contribution of 30 novel biomarkers to the 10-year cardiovascular

disease risk in 2 population cohorts (Blankenberg et al., 2010). These biomarkers were part of the MORGAM (MONICA, Risk, Genetics, Archiving, and Monograph) Biomarker Project (Evans et al., 2005) and were representative of 9 distinct metabolic processes linked to atherosclerosis. They include (a) lipid-related biomarkers, (b) renal function markers, (c) metabolic markers representing glucose and obesity pathways, (d) markers of vascular function and neurohumoral activity, (e) inflammation markers, (f) markers of oxidative stress and antioxidants, (g) coagulation markers, (h) angiogenesis markers, and (i) necrosis markers; classified similar to the risk factors in Table 2 (Blankenberg et al., 2010).

In recent years, the importance of inflammation and increased reactive oxygen species (ROS) for the pathogenesis of atherosclerosis is well recognized (Kaneto et al, 2010; Mayer, 2000; Tabit et al, 2010). Consequently, “non-traditional factors” such as high-sensitive C-reactive protein (hs-CRP), total homocysteine (t-Hcy), as well as oxidative stress, have been proposed as risk factors for the development and progression of atherosclerosis and atherothrombotic cardiovascular disease (Djoussé et al, 2001; Eren et al, 2002; Lee et al, 2003; Pence et al, 2003). Therefore, this chapter will focus on total-homocystein, hs-CRP and the underlying oxidative stress mechanism of CVD or atherosclerosis.

Inflammatory Markers	Lipid-Related Factors
C-reactive protein Interleukins (eg, IL-6) Serum amyloid A Vascular and cellular adhesion molecules Soluble CD40 ligand Leukocyte count	Small dense low-density lipoprotein (LDL) Lipoprotein(a) Remnant lipoproteins Apolipoproteins A1 and B High-density lipoprotein subtypes Oxidized LDL
Hemostasis/Thrombosis Markers	Other Factors
Fibrinogen von Willebrand factor antigen Plasminogen activator inhibitor 1 (PAI-1) Tissue-plasminogen activator Factors V, VII, and VIII D-dimer Fibrinopeptide A Prothrombin fragment 1+2	Homocysteine Lipoprotein-associated phospholipase A(2) Microalbuminuria Insulin resistance PAI-1 genotype Angiotensin-converting enzyme genotype ApoE genotype Infectious agents: Cytomegalovirus, Chlamydia pneumonia, Helicobacter pylori, Herpes simplex virus Psychosocial factors
Platelet-Related Factors	
Platelet aggregation Platelet activity Platelet size and volume	

Table 2. Novel risk factors for atherosclerotic vascular disease (Hackam & Anand, 2003).

4. Diagnostic values of homocysteine, C-reactive protein and bilirubin for coronary artery disease.

C-reactive protein (CRP) is a circulating acute-phase reactant that is increased many-fold during the inflammatory response to tissue injury or infection (Pepys & Baltz, 1983). This protein has received substantial attention in recent years as a promising biological predictor of atherosclerotic disease (Pearson et al., 2003). On the other hand, it has been postulated that mild to moderate elevations of homocysteine in the general population predispose to atherosclerosis in a manner akin to the classic risk factors (Hackam & Anand, 2003). Additionally, the adaptive and protective responses of arterial vasculature against oxidative stress are important in the prevention of atherosclerosis (Hoekstra et al, 2004).

4.1 CRP or hs-CRP

An evolving body of work suggests that even small increases in CRP within the normal range are predictive of future vascular events in apparently healthy, asymptomatic individuals (Ridker et al, 2002). Danesh et al reported a meta-analysis of 14 prospective long-term studies of CRP and the risk of nonfatal myocardial infarction or death from coronary heart disease (Danesh et al., 2000). The attention in this protein stems in part from a recent shift in thinking about the pathogenesis of CVD, an entity once primarily considered to be a bland lipid storage disease. Inflammation is now widely accepted as central to every aspect of the atherosclerotic process, from its initiation to its progression to plaque rupture, the latter being the essential event underlying the acute coronary syndromes (Hackam & Anand, 2003). Debate exists about the utility of CRP as a marker of cardiovascular risk, given its role as an acute-phase reactant and hence its elevation in the presence of any inflammatory focus or injury. This has been countered somewhat by the development in recent times of an ultrasensitive assay, which has been shown to have a degree of measurement stability similar to that of total cholesterol (Davison & Davis, 2003). In other words, the guidelines identify CRP (as measured by a high-sensitivity [hs] assay--hence the name hs-CRP) as the inflammatory marker of choice for cardiovascular risk stratification. Although a number of other inflammatory markers such as serum amyloid A, white blood cell count, and fibrinogen have been investigated, the "hs-CRP" level has the most stability, assay precision, accuracy, and availability (Shishehbor et al, 2003).

4.2 Homocysteine

Interest in homocysteine as a causal factor was spurred by the observation that more than 50% of children with the genetic disorder homocystinuria die of premature vascular disease and strategies that reduce homocysteine levels in these children have been shown to decrease vascular event rates (Humphrey et al, 2008). Mechanistic studies have demonstrated that homocysteine might induce vascular damage by promoting platelet activation, oxidative stress, endothelial dysfunction, hypercoagulability, vascular smooth muscle cell proliferation, and endoplasmic reticulum stress (De Bree et al., 2002; Mangoni & Jackson, 2002). In their meta-analysis, Humphrey et al evaluated homocysteine levels as a predictor of new CAD events in persons without known CAD. Their review showed an association between elevated homocysteine levels and CAD that was independent of Framingham risk factors. In the overall analysis, the risk of any CAD event increased approximately 20% for each increase of 5 $\mu\text{mol/L}$ of homocysteine. Consequently, elevated

homocysteine levels independently and moderately increased the risk of developing CAD either in a causal manner or as a risk marker by approximately 20% (Humphrey et al, 2008).

4.3 Oxidative stress and bilirubin

Imbalances in the redox status in which excess oxidation occurs or reducing power cannot be maintained (e.g. in inflammation, age, smoking, high lipid content and oxidation) creates a state in which molecular and tissue modifications progress rapidly, leading to development of lesions and full-blown atherogenesis. Oxidative stress does not replace the recognized role of lipids and cholesterol in atherosclerosis, but rather underline that role. Indeed, quantifying redox processes may well elucidate some molecular mechanisms by which lipids mediate atherogenesis (Gamkrelidze et al., 2008). Bilirubin has been considered an antioxidant, with capacity to remove reactive species of oxygen. Recent data advocates the idea that an increased bilirubin level promotes protection against atherosclerosis (Ghem et al., 2010).

The heme oxygenase responsible for the degradation of heme grouping of hemoglobin is a stress inducible enzyme with antioxidative properties. The products of its reaction (bilirubine, carbon monoxide and iron) develop a potential protective role against atherosclerosis (Hoekstra et al, 2004). Studies have suggested that different circulating forms of bilirubin have the capacity to remove a variety of reactive species of oxygen, and inhibit the oxidation of LDL particles and the chemotaxis of monocytes, all of which are crucial steps in atherogenesis (Ghem et al., 2010).

In a study we have done, we assessed the diagnostic performance and relationship of bilirubin with hs-CRP and t-Hcy for cardiovascular disease in men and women in an angiographically documented design. The study demonstrated that patients with angiographically confirmed coronary artery disease (CAD) had significantly higher serum hs-CRP and t-Hcy levels than non-stenotic patients (patients with normal angiogram) and the apparently healthy control group. Optimal cut-off levels and the associated diagnostic performances (sensitivity, specificity and diagnostic value) of serum bilirubin, hs-CRP, t-Hcy, based on ROC analysis, are given in Table 3. Optimal cut-off levels for bilirubin, hs-CRP and t-Hcy providing the maximum efficiency found in patients (n = 319) with CAD were 0.59 mg/dL, 1.09 mg/dL and 12.1 μ mol/L respectively.

Variable	Cut-off level	Sensitivity (%)	Specificity (%)	Diagnostic value (area under the curve)	+LR	-LR
Bilirubin	0.59 mg/dL	70.9	40.4	0.507	1.19	0.72
High-sensitivity C-reactive protein	1.09 mg/dL	50.0	80.7	0.648	2.59	0.62
Total homocysteine	12.1 μ mol/L	76.8	70.2	0.781	2.67	0.29

+LR = positive likelihood ratio

-LR = negative likelihood ratio

Table 3. Optimal cut-off levels and associated specificity, sensitivity and diagnostic value of concentrations of biomarkers for the diagnosis of angiographically documented coronary artery disease

These data strongly suggest that serum t-Hcy helps to identify individuals at risk of atherosclerosis (AUC value 0.781), especially among those with elevated hs-CRP and decreased bilirubin levels. t-Hcy showed the highest AUC value (0.781) compared to hs-CRP (0.648) and bilirubin (0.507). Area under the curve (AUC) values in receiving operating characteristics (ROC) curve (as a measure of discriminating efficacy) were used for comparison of the diagnostic values of different analyses (including only the CAD and non-CAD groups, using angiography as the gold standard). ROC curve-based sensitivities of bilirubin, hs-CRP and t-Hcy levels were 70.9%, 50.0%, 76.8% respectively. The specificities of bilirubin, hs-CRP and t-Hcy were 40.4%, 80.7% and 70.2% respectively (data of ROC curves are shown in Figures 1-3).

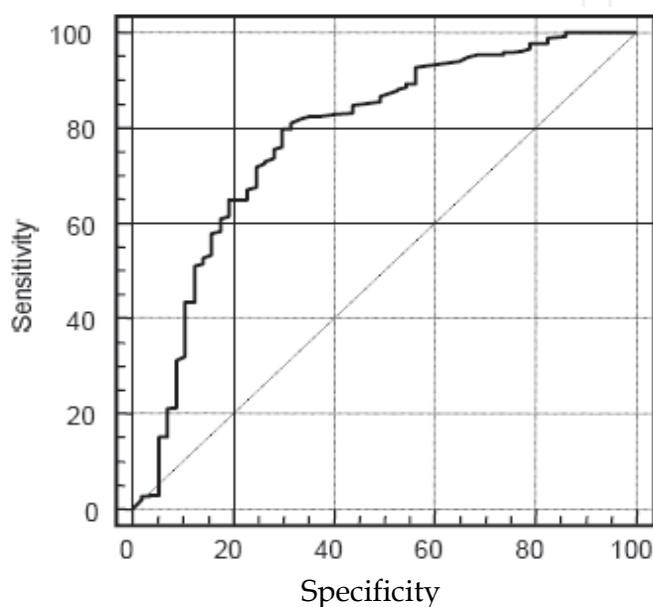


Fig. 1. ROC curve for total homocysteine.

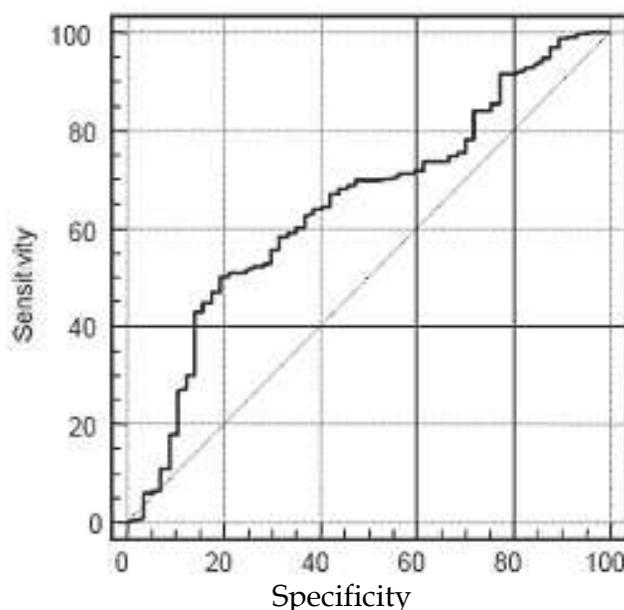


Fig. 2. ROC curve for hs-CRP.

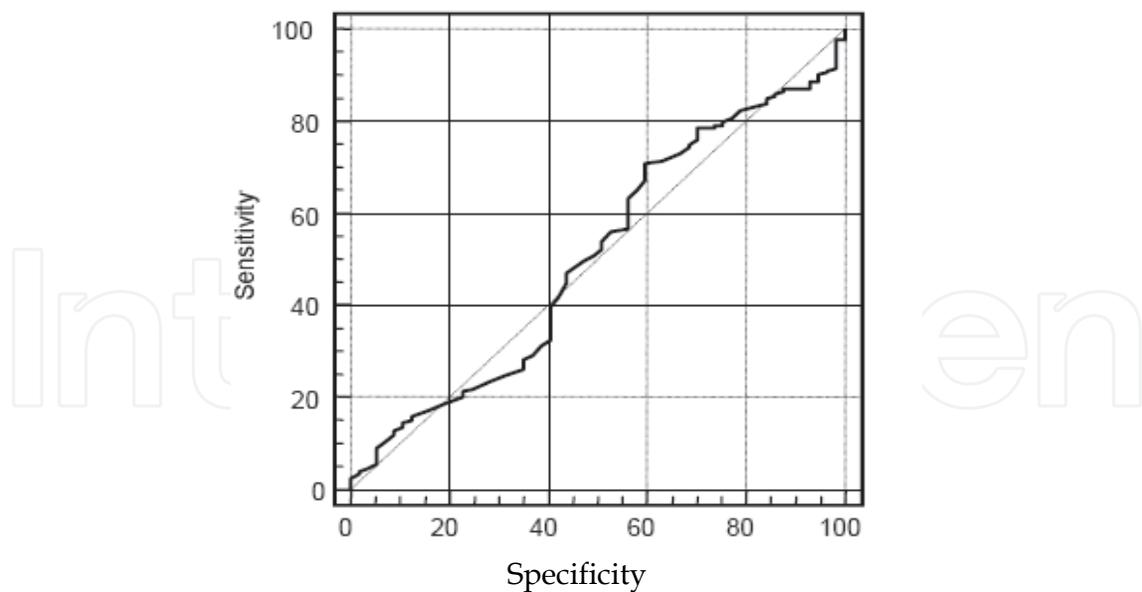


Fig. 3. ROC curve for bilirubin.

In agreement with previous reports, we found that the bilirubin levels in serum were significantly lower in the patients with CAD than in age- and sex-matched controls (Madhavan et al., 1997; Schwertner et al., 1994; Vitek et al., 2002). We found that a serum bilirubin concentration of 10.0 $\mu\text{mol/L}$ (0.58 mg/dL) discriminated between high and low cardiovascular risks.

Additionally, we found that the number of stenotic coronary arteries was significantly associated with elevated serum t-Hcy and hs-CRP concentrations. Several researchers have investigated the risk of myocardial infarction in individuals with the *UGT1A1*28* allele (Bosma et al., 2003; Schwertner, 2003). According to the “oxidative modification hypothesis”, which suggests atherogenesis is initiated by oxidation of low-density lipoprotein particles, it has been suggested that increased physiological concentrations of serum bilirubin may reduce atherogenic risk by reducing oxidation. An involvement of bilirubin in immune reactions and inflammatory processes has also been documented (Delores et al., 2000; Kronenberg et al., 2002; Lin et al., 2003).

Earlier studies have reported differences in the levels of t-Hcy, ranging between 13.9–20.1 $\mu\text{mol/L}$ in persons with CAD (Yu et al., 2000; Zylberstein et al., 2004). We found a mean t-Hcy level of 19.4 (SD 8.73) $\mu\text{mol/L}$ in the CAD group, 10.7 (SD 5.14) $\mu\text{mol/L}$ in the healthy group and 13.0 (SD 8.61) $\mu\text{mol/L}$ in the non-CAD group. Some differences between reported serum t-Hcy levels may be related to analytical methods and ethnic differences. A study in 19 centres in Europe reported high homocysteine levels and increased risk of CAD in smokers (Graham et al., 1997). We found that the t-Hcy levels tended to increase in the presence of more cardiovascular risk factors, i.e. male gender, older age, diabetes mellitus, hyperlipidaemia and certain chronic diseases. As expected, traditional coronary risk factors were more prevalent among those participants with elevated levels of t-Hcy and hs-CRP in our study, as in other studies (Abdemoutaleb et al., 2000; Sesso et al., 2003; Siri et al., 1998).

5. What is new about hyperhomocysteinemia?

Homocysteine is an accepted independent risk factor for several major pathologies including cardiovascular disease, birth defects, osteoporosis, Alzheimer’s disease, and renal

failure. Interestingly, many of the pathologies associated with homocysteine are also linked to oxidative stress (Suszynska et al., 2010). Evidence indicates that hyperhomocysteinemia, which occurs in 5–7% of the general population is a risk factor for CVD, but how? (Jakubowski, 2004). Hyperhomocysteinemia is accused of being responsible for elevating oxidative stress as a result of formation of Hcy- thiolactone or Hcy-thiyl radical, which may lead to impairment of cell signaling and cause pathology (Doshi et al., 2001; Lang et al., 2000). Many researchers, and especially Jakubowski, suggested that metabolic conversion of Hcy to Hcy-thiolactone followed by subsequent spontaneous protein N-homocysteinylation by Hcy-thiolactone might contribute to Hcy toxicity in humans. (Jakubowski, 2002). Hcy-thiolactone is a reactive intermediate that causes protein N-homocysteinylation through the formation of amide bonds with ϵ -amino groups of protein lysine residues; in the event, homocysteinylation may lose their biological activities (Jakubowski, 2003).

Whereas epidemiological data indicate that elevation of plasma homocysteine is not associated with a significant change in plasma total cholesterol, some studies have reported a negative correlation with HDL concentrations (Ciaccio & Bellia, 2010; Domagała et al., 2006; Williams & Schalinske, 2010). Because low plasma HDL concentration sometimes is associated with increased risk of CVD, whereas other conditions with low plasma HDL concentration are associated with improved prognosis, it seems that it is not only the concentration per se but also the function of the HDL particles that is important for its antiatherogenic effects (Bełtowski, 2005; Mikael et al., 2006). HDL particles are susceptible to structural modifications mediated by various mechanisms, including oxidation, glycation, or enzymatic degradation, affecting their functional properties. Moreover, *in vitro* studies have shown that homocysteinylation of HDL may reduce the activity of the enzyme Paraoxonase (PON), which is associated with human HDL, thus rendering the HDL particle more susceptible to oxidative damage. Formation of inflammatory HDL has been suggested to correlate with decreases in the activities of various HDL associated enzymes, such as PON, a multifunctional enzyme with antioxidant capacity, and the ability to detoxify the homocysteine metabolite homocysteine thiolactone (Bełtowski, 2005; Liao et al., 2007).

Paraoxonase is thought to influence serum homocysteine concentrations, at least in part, due to its homocysteine thiolactonase activity and to play a role in atherosclerosis. (Yang et al., 2006). Hcy- thiolactonase activity is influenced by both PON1 and MTHFR genotypes and there is a direct relation between Hcy and Hcy- thiolactone levels. In relation to this matter, Jakubowski et al. hypothesized that high thiolactonase associated PON1 R and L alleles should confer significant cardiovascular protection in subjects with high Hcy levels (Jakubowski et al., 2001).

6. Conclusion

The availability of well-validated decision limits is vital to optimal integration of a new biomarker into clinical practice. Approaches to internal validation and data-mining methods lead to overfitting and overestimation of risk relationships and are generally not sufficient for selecting final clinical cutpoints. Such methods, when applied correctly, can be reasonable for suggesting cutpoints for external validation. Biomarkers that have monotonic linear relationships with risk are best handled as continuous variables when incorporated into comprehensive risk models. As consistently demonstrated in clinical practice and professional society guidelines, however, practitioners will almost always seek thresholds to provide structure for clinical decision-making, such as those existing for cholesterol.

Therefore, such cutpoints warrant development and validation. Although the approach is demanding, we recommend assessment of clinical decision limits by external validation in 2 or more data sets that are appropriate to each of the proposed clinical application(s), with attention paid to the possibility of differences in risk relationships in clinically relevant subpopulations (Morrow & Cook, 2011).

To conclude, there is little evidence of an association between the serum concentration of bilirubin and atherosclerosis. In contrast, the concentration of novel (t-Hcy and hs-CRP) and traditional risk markers may be stronger markers for atherosclerosis in CAD patients. Additional studies are still necessary to confirm and demonstrate the association of these findings with clinical outcomes.

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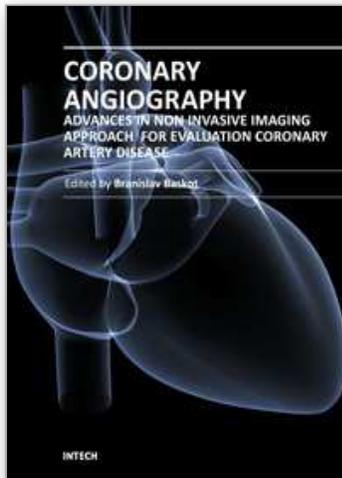
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In the intervening 10 years tremendous advances in the field of cardiac computed tomography have occurred. We now can legitimately claim that computed tomography angiography (CTA) of the coronary arteries is available. In the evaluation of patients with suspected coronary artery disease (CAD), many guidelines today consider CTA an alternative to stress testing. The use of CTA in primary prevention patients is more controversial in considering diagnostic test interpretation in populations with a low prevalence to disease. However the nuclear technique most frequently used by cardiologists is myocardial perfusion imaging (MPI). The combination of a nuclear camera with CTA allows for the attainment of coronary anatomic, cardiac function and MPI from one piece of equipment. PET/SPECT cameras can now assess perfusion, function, and metabolism. Assessing cardiac viability is now fairly routine with these enhancements to cardiac imaging. This issue is full of important information that every cardiologist needs to now.

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