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LDL-Cholesterol is not the only clinically relevant biomarker for Coronary Artery Disease or Acute Coronary Syndrome

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Introduction

Coronary artery disease is a progressive disorder and its risk is best determined using multiple biomarkers and risk factors. Many novel biomarkers have shown to improve cardiovascular disease risk beyond that of the traditional risk factors, including polygenic risk scores, small VLDL, ApoB, triglycerides, non-HDL-c, Lp(a), coronary calcium scores, CRP, BNP, troponins, and many other novel biomarkers that have been measured high throughput assays.

Coronary artery disease (CAD) is a multifactorial disorder that evolves over the life-course and involves the complex interplay of a host of risk factors from genetic susceptibility to diverse pathophysiological pathways that culminate in subclinical atherosclerosis, and eventually transition to clinical CAD events. It is intuitive, therefore, that a process with multiple determinants may offer a range of biomarkers for risk prediction and prognostication. The goal of physicians is to use clinical markers to identify patients at risk for CAD (including ACS) in order to help guide lifestyle changes and medical management. No single risk factor has shown to be effective by itself as a screening test for CAD risk; however, there are many well established clinically useful multi-marker CAD (and

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cardiovascular disease) risk models and many emerging biomarkers that may facilitate and guide risk stratification.

Multimarker Risk Assessment Tools are better than LDL alone

LDL-c alone is not an efficient screening test because the distributions of blood LDL-c among patients with and without CAD overlap, resulting in false positive and false negative detection rates. CAD and CVD risk can be more accurately and efficiently quantified by combining multiple risk factors and biomarkers into a robust global risk assessment calculator. Many risk calculators have been developed, and most incorporate some combination of the “traditional CAD risk factors” which include biomarkers (blood total cholesterol, LDL cholesterol, HDL cholesterol concentrations, and systolic blood pressure) and risk factors (age, gender, diabetes mellitus, and current smoking status). The current ACC/AHA 2013 guidelines recommend the pooled cohort 10-year ASCVD (atherosclerotic cardiovascular disease) risk calculator for its simplicity and strong performance.¹

There has been considerable attention to improve the performance of CAD risk calculators by incorporating other biomarkers. To be clinically useful, novel biomarkers must show improvement to the predictive capabilities of an established multimarker model. This is tested statistically by evaluating if the addition of a novel biomarker improves the model c-statistic and helps upgrade or downgrade (net reclassification) those at intermediate risk of CAD. In addition, the information given by the biomarker must affect clinical decision making. The current 2013 ACC/AHA guidelines recommend using the 10-year CVD risk equation to guide statin therapy; however, even after predicting risk, optimizing risk factors and lowering LDL cholesterol to current target levels, there is *residual* CV risk. A new set of biomarkers are being investigated to determine residual risk and guide management, viz., other atherogenic lipoproteins, markers of inflammation, genetic markers, and other novel biomarkers like troponin and natriuretic peptides.

Atherogenic Dyslipidemia

Atherogenic dyslipidemia (AD) is characterized by higher levels of small dense LDL and VLDL particles and is thought to be a major factor of residual CV risk. AD patients typically have high triglycerides and low HDL. Analysis of patients in the JUPITER trial already on statins showed that the smallest VLDL particles were associated with a 68% per SD increase in residual CV risk. ApoB, TG, and non-HDL-c were also associated with a 27%, 28% and 17% increase in residual risk.² There is a paucity of data on how to manage patient with elevated residual CV risk with AD, however experts recommend using fibrates for patients with elevated TG or non-HDL-c, or ezetimibe if LDL is not at goal.³

Lipoprotein(a), Lp(a), is a glycoprotein attached to LDL-like particles that has found to have an independent, causal association with CAD. Lp(a) concentration can be used to further risk stratify patients at intermediate CV risk. Statins have not been shown to be effective in reducing Lp(a); treatment with niacin or PCSK9 inhibitor can lower Lp(a), but niacin has not been shown to reduce CAD risk and it is undetermined whether reduction of Lp(a) contributes to risk reduction with PCSK9 inhibition.³

C-reactive protein

C-reactive protein (CRP) is an acute phase reactant that has been shown to have a robust association with CAD risk, although causality of the association has been debated. There still remains an open question regarding whether addition of CRP to contemporary risk prediction models offers incremental predictive utility. Given only modest improvement in the prediction of 10-year CV risk in most studies, the 2013 ACC/AHA guidelineless recommend considering its use in patients with intermediate CVD risk where a risk-based decision on statin use/management is unclear. However, recent results from the CANTOS trial will likely increase the use of CRP for risk prediction, with the demonstration that targeting and treating patients with elevated inflammatory markers may reduce residual CV risk. Results from the CANTOS trial showed that in patients with prior myocardial infarction (MI) and elevated CRP (≥ 2 mg/L), residual CV risk was decreased using canakinumab, an interleukin-1 β monoclonal antibody, to reduce inflammation. Treatment with 150mg of subcutaneous canakinumab monthly was accompanied by a reduction in hs-CRP along with reduction in non-fatal MI, stroke and CV death (hazard ratio 0.85, 95% CI 0.74-0.98) compared to placebo.⁴ These studies support the use of using CRP as a marker of secondary CV risk however, additional studies are warranted to evaluate the use of CRP and anti-inflammatory therapies in a primary prevention setting.

Coronary Calcium Score

Radiographic quantification of coronary artery calcification (CAC) via CT can detect subclinical atherosclerosis. CAC consistently adds independent prognostic information to traditional risk factors in numerous large studies. When CAC was added to the Framingham 10-year risk calculator for intermediate risk patients (10-20% Framingham 10-year CVD risk), it resulted in a net reclassification index of 21.7% ($p=0.0002$) and improved c-statistic from 0.681 to 0.749 ($p<0.003$).⁵ The added predictive value of CAC in intermediate CV risk patients can be useful if a decision about a risk-based treatment is uncertain, which is reflected in the current 2013 AHA/ACC guidelines.

Genetic Biomarkers

Several genetic biomarkers (variants in numerous loci) have also recently been found to be associated with CAD risk. Individual single nucleotide polymorphisms (SNPs) have been found to have relatively weak correlation with CAD, most with hazard ratios <1.2 ; however, the cumulative effect of many SNPs associated with CAD showed a more significant effect. For example, across more than 400,000 participants in the UK Biobank cohort, a genome wide polygenic risk score was created that included 6.6 million common SNPs. Increasing risk score was associated with increasing prevalence of CAD, and the participants with the top 2.5% for genetic CAD risk had an odds ratio of 3.96 (95% CI 3.62-4.31) for prevalent CAD, a risk ratio that approaches that of monogenic disorders.⁶

In randomized studies, patients with a high genetic risk have been reported to have increased risk reduction on statins compared to placebo. In the JUPITER and ASCOT cohorts, low, intermediate, and high GRS categories based on 27 SNPs were associated with 13%, 29% and 48% relative risk reduction with statin therapy, despite having similar LDL concentrations.⁷ The number needed to treat to prevent one coronary artery event for the

ASCOT and JUPITER groups was 20 and 25 in the high GRS and 57 and 66 for the low GRS. Genetic CAD risk will be increasingly utilized with the accessibility of genome-wide sequencing, and due to the potential for a greater benefit with statin therapy in patients with high GRS.

Natriuretic Peptides and Troponin

BNP and troponin, which have established roles in the diagnosis of acute heart failure and ACS, have recently been shown to predict CVD risk. In a meta-analysis of 40 prospective studies, BNP and NT-proBNP was found to have a risk ratio of 2.82 (2.40-3.33) for CVD comparing the top and bottom tertiles.⁸ Similarly, in a meta-analysis of 10 prospective studies, blood levels of troponin I were associated with CVD risk (HR 2.6, 95% CI 2.29–2.94, comparing the top and bottom quintile). When troponin I was added to traditional risk factors there was a net reclassification index of 0.017 (0.008-0.25).⁹ The study also found that patients with troponin I >6 ng/L had greater absolute risk reduction for cardiovascular events with statin therapy than patients with troponin <6 ng/L. Additional studies of large multi-ethnic samples are warranted to assess the predictive utility of blood BNP and troponin concentrations in the primary prevention setting.

High Throughput Biomarker Analysis

Traditionally, biomarkers were investigated after understanding their role in the atherosclerotic pathobiology. More recently, with advances in analytical techniques, studies evaluated large panels of biomarkers in a hypothesis-free, high throughput manner. 1130 proteins were measured in plasma samples using modified DNA aptamer technology in patients in the Heart and Soul Study Cohort. The 9 most significant markers (angiopoietin-2, matrix metalloproteinase-12 (MMP12), chemokine ligand 19 (CCL18), complement 7, α_1 -antichymotrypsin complex, angiopoietin-related protein 4, troponin I, growth differentiation factor, and α_2 -antiplasmin) were used to create a protein risk model to predict MI, stroke, heart failure, and all-cause death over 4 years. When the 9-protein model was added to the Framingham secondary event model, the c-statistic increased from 0.66 to 0.75.¹⁰ Initial results of high throughput methods to evaluate larger multimarker panels for predicting CVD risk suggest potential gains accruing from such a strategy in high risk patients. Additional studies are warranted to evaluate the performance of such a strategy in large multi-ethnic primary prevention samples and to compare their predictive utility relative to a polygenic risk score.

Conclusion

In conclusion, no single biomarker can sufficiently predict risk for CAD or CVD. Multimarker risk tools using the traditional CV risk factors have shown to be more effective for predicting CV risk. Many novel biomarkers have shown to improve CV risk beyond that of the traditional risk factors, including polygenic risk scores, small VLDL, ApoB, triglycerides, non-HDL-c, Lp(a), coronary calcium scores, CRP, BNP, troponins, and many other novel biomarkers that have been measured high throughput assays. LDL-c remains unique in that reduction of the biomarker is closely tied with reduction of CAD events; however, these biomarkers provide additional information in intermediate CV risk patients to help make a therapeutic decision and in high risk CV patients with residual CV risk. Besides

influencing lifestyle risk modification (which should be encouraged in all patients), novel biomarkers may be useful for tailoring statin therapy, further lipid management with other lipid lowering agents, and treatment with new anti-inflammatory medications like canakinumab. It is expected with further high throughput biomarker research and the increasing availability of genetic sequencing there will be a rapid expansion of CAD biomarkers that will be incorporated into improved multimarker risk models. Thus, in our opinion, it is inconceivable that the field of CAD risk prediction will be limited solely to the use of LDL concentrations. Undoubtedly, the evidentiary basis for suggesting the incremental predictive and clinical utility of several of these markers is currently lacking, but ongoing studies over the next decade will offer such data.

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