Multiple marker approach to risk stratification in patients with stable coronary artery disease: to have or have not

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This editorial refers to ‘Multiple marker approach to risk stratification in patients with stable coronary artery disease’,† by R.B. Schnabel et al., on page 3024

Individual biomarkers have expanding roles in risk assessment, diagnosis, and prognosis, and the list of up-and-coming markers is growing. Nonetheless, individual biomarkers have notable shortcomings, including day-to-day intra-individual variation and poor predictive values at the level of the individual patient, which limit their prognostic value. Combining multiple biomarkers from distinct pathophysiological pathways has the potential to overcome many of these pitfalls and to further improve risk stratification, and there has been a natural evolution towards studies evaluating such a multimarker approach. However, to date, a mixed picture has emerged on the clinical value of using multiple biomarkers for cardiovascular risk stratification.

A number of studies have evaluated combinations of biomarkers for predicting cardiovascular disease in the community. Several have found statistically significant yet clinically modest improvements in prediction with a multimarker panel compared with a model with traditional risk factors alone.1–3 A few, however, have found substantial improvements in risk prediction with a multimarker approach.4–6

Secondary prevention populations have been the focus of even fewer studies evaluating a multimarker risk stratification approach. Blankenberg et al.7 studied 11 biomarkers [including nine inflammatory markers plus N-terminal pro-B-type natriuretic peptide (Nt-proBNP), and microalbuminuria] in 3199 patients with a history of coronary heart disease, peripheral vascular disease, diabetes, or stroke. After a mean 4.5 year follow-up, only Nt-proBNP provided incremental prognostic information for prediction of cardiovascular events compared with a traditional risk factor model, based on an increase in the area under the receiver-operating characteristic curve, or c-statistic. Although several inflammatory markers were significantly related to future cardiovascular risk, they added little additional prognostic information to the traditional markers.

In this issue of the European Heart Journal, Schnabel et al.8 present findings of multimarker risk stratification from an additional secondary prevention population, based on 1781 consecutive patients with stable coronary artery disease from the AtheroGene cohort. For entrance into the study, patients had to be admitted with symptoms of possible coronary artery disease and have at least one major coronary artery with a stenosis of ≥30% at angiography; those with acute coronary syndrome were excluded. Patients were predominately male (78%) with a median age of 63 years. Twelve biomarkers of inflammation, lipid metabolism, renal function, vascular function, and haemodynamics/remodelling were evaluated individually for prediction of the combination of non-fatal myocardial infarction and cardiovascular death, an outcome that occurred in 137 subjects over a median follow-up of 3.6 years. The five markers that showed the strongest associations with cardiovascular events on Cox proportional hazards models, and that also had a significant integrated discrimination index (IDI), were Nt-proBNP, growth differentiation factor-15 (GDF-15), midregional pro-atrial natriuretic peptide (MR-proANP), cystatin C, and midregional pro-adrenomedullin (MR-proADM). Of the markers assessed, Nt-proBNP and GDF-15 were the strongest independent predictors of the combined outcome, and were the only two markers to show significant improvement in the net reclassification index (NRI). The authors found that the c-statistic increased with the addition of any of these five strongest markers to the established risk factors model, though the increases do not appear statistically significant, since the lower limit of the 95% confidence interval overlaps with the c-statistic of the baseline model in each case. The

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authors also found that combining all five markers failed to increase the c-statistic compared with simply adding the best markers (NT-proBNP or GDF-15) individually. On the other hand, the combination of the five biomarkers improved the NRI to 0.25 (P = 0.0001), which appears substantially higher that the NRI achieved with any of the best markers singly (NRI of 0.16 for GDF-15, and 0.15 for NT-proBNP). The combination also appears to have considerably improved the IDI.

Similar to prior studies using multimarker panels for risk stratification, most of the improvement in reclassification in the AtheroGene cohort was derived from correctly downgrading the risk level of individuals who did not go on to suffer an event. However, there was a minority of patients with events who did get correctly classified into a higher risk category.

This study has several strengths. The AtheroGene cohort is well characterized, with careful follow-up. The authors are also to be commended for including a strong and diverse panel of biomarkers, including both established and up-and-coming candidates and hailing from a variety of pathophysiological pathways. The inclusion of the emerging markers MR-proADM, GDF-15, and cystatin C along with the more established natriuretic peptides, puts this article on the cutting edge of prognostic models. Further, the authors reported several of the newer suggested statistical metrics for evaluating new markers. There are also several limitations. The 3.6 year follow-up is relatively modest, and may have limited the power of this study to demonstrate benefit from a multimarker approach. In addition, although this cohort is described as a stable coronary artery disease population, patients with only a single coronary stenosis of 30% were included if they had symptoms presumed to be cardiac in nature. The clinical significance of a single 30% stenosis is unclear, but these inclusion criteria have led to a relatively lower-risk population than would be presumed based on the ‘coronary artery disease’ moniker. Nonetheless, a significant portion (40%) did have a history of myocardial infarction, and clearly a number of the study participants were at significant future cardiac risk.

Considering all of the recent studies of multimarker approaches to risk stratification, a central question has emerged: if these different markers appear so individually promising, and seem to have significant in a single-marker study does not guarantee that the marker will be effective in a multimarker panel. Significant collinearity or overlap with other markers lessens a marker’s value within a multimarker panel. Rather, a selection of markers from independent pathophysiological pathways has the best chance of improving predictive information, as well as shedding light on potential novel targets for therapeutic interventions.

**Duration of follow-up**

When primary prevention or stable secondary prevention populations are targeted, an important goal of risk stratification is to identify increased lifetime risk of events. Since treatments aimed at lowering risk, including the institution of lifestyle changes and the initiation of medications to control blood pressure and cholesterol, are generally long-term (if not life-long), studies with long-term follow-up may be more clinically relevant than those with follow-up of only months to a few years. A shorter follow-up time could also reduce a study’s power to show a favourable effect with a multimarker panel, and may have been a factor in the present study.

**Clinical outcome**

Most studies of novel markers utilize combined outcomes, in part to increase the power of the study, and in part, perhaps, to encompass the broad range of risks reflected by the markers in question. Although combined outcomes can increase a study’s power by increasing the total number of accrued events, the outcome chosen can bias study results towards the null hypothesis if it does not reasonably reflect the pathophysiology of the biomarkers being evaluated.

**Statistical methods**

Biomarkers like blood pressure and cholesterol levels represent a continuum of risk, and a lot of information can be lost when biomarkers are modelled with cut-off points rather than as continuous.
variables. Classification and regression tree (CART) analyses, such as those used by Schnabel et al. to generate their multimarker model, are attractive because they produce a simple, bedside-friendly, clinical algorithm; conversely, logistic regression provides a more complex formula, but may be more accurate since it does not require binary cut-off points and since it often includes more variables. Thus, the statistical methods used in modelling various biomarkers can play a large role in study outcomes.

In addition, the statistical metrics used can paint divergent pictures of a biomarker’s value, and ideally a variety of statistical methods should be employed and scrutinized. Recent guidelines have focused on the shortcomings of relying on the c-statistic for selection of variables to be used in a predictive model. The c-statistic is a fairly insensitive marker of model fit, which can erroneously eliminate important clinical markers from inclusion in a multimarker score. The NRI and IDI are newer statistical analyses that assess model discrimination, or the difference between two models in the individual predicted probability that a case subject will be categorized as a case subject. A model with better predictive ability will more often correctly categorize case subjects as cases, and will less often categorize event-free subjects as cases. The NRI requires pre-specified risk categories, and evaluates changes in estimated probability that result in an individual changing from one category to another. The IDI, on the other hand, evaluates the change in the estimated prediction probabilities as a continuous variable. The combined use of likelihood-based measures such as the likelihood ratio statistic, plus metrics such as the NRI and IDI, in addition to the c-statistic, has now become the standard for analyses of new biomarkers.

However, statistical methods alone cannot measure the full clinical value of the information imparted by a new panel of risk markers. The goal of improving risk assessment is to improve how we respond to various risk categories, and so the data of most importance are ultimately how the multimarker panels affect clinical decisions and clinical outcomes.

**Conclusion**

As a first step, more accurate risk stratification is a worthy goal, but we must remember that our ultimate goal is improved prevention and treatment. Biomarker studies, especially those that evaluate multiple classes of markers together, can help us understand the interplay of the various pathophysiological pathways that underlie cardiovascular disease. They might also point to new avenues for potential therapeutic targets. As we await outcomes and cost-effectiveness studies to ultimately confirm the clinical utility of multimarker panels, investigations will continue to seek the best recipe of patient subgroups, biomarker combinations, and other testing modalities that can make assessing risk ever more accurate.

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1. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D’Agostino RB, Vasan RS. Multiple classification and regression tree (CART) analyses, such as those used by Schnabel et al. to generate their multimarker model, are attractive because they produce a simple, bedside-friendly, clinical algorithm; conversely, logistic regression provides a more complex formula, but may be more accurate since it does not require binary cut-off points and since it often includes more variables. Thus, the statistical methods used in modelling various biomarkers can play a large role in study outcomes.

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