



EDITORIAL COMMENT

Multimarker approach in risk stratification of patients with acute coronary syndromes: Towards the ideal stratification[☆]



Abordagem multimarcadores na estratificação de risco dos doentes com síndrome coronária aguda: rumo à estratificação ideal

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As with other cardiovascular diseases, advances in our understanding of the pathophysiology of acute coronary syndrome (ACS) have resulted in the use of new biomarkers (measurable plasma molecules) that reflect the different mechanisms that underlie the condition.

These biomarkers are valuable tools that are increasingly used not only for early diagnosis but for short- and long-term prognostic stratification.

A wide range of biomarkers are now available in ACS, including those that reflect vascular inflammation due to atherosclerotic disease (high-sensitivity C-reactive protein [CRP]), markers of protease activity associated with progression of atherosclerosis and plaque destabilization (cystatin C), and those indicating myocardial injury (troponin and ST2), renal damage (cystatin C, NGAL, glomerular filtration rate), or ventricular dysfunction (neurohormonal peptides

such as NT-proBNP, adrenomedullin and copeptin), as well as other parameters, such as red blood cell distribution width (RDW), that are markers of multiple mechanisms.

The complex pathophysiology of ACS means that combinations of biomarkers are more attractive targets for research than any one biomarker in isolation. This has led to the inclusion of groups of biomarkers in risk scores, some of which have been thoroughly validated and are in widespread use. Initially these scores only included markers of clinical risk, such as in the TIMI score, but other types – including the above-mentioned plasma biomarkers – are increasingly incorporated to improve their accuracy. The patient's risk can thus be stratified on an individual basis and action can be taken accordingly, with higher-risk individuals being treated more aggressively (such as early coronary revascularization for non-ST-elevation ACS).¹

There is, however, considerable debate concerning which biomarkers, in which combinations, should be selected.

The study by Vieira et al.² published in this issue of the *Journal* is centered on this question. Its main aim was to assess the value of a multimarker approach in the risk stratification of patients with ACS. The biomarkers selected were cystatin C, NT-proBNP, CRP and RDW, not only because individually they have demonstrated prognostic value in ACS,^{3–10}

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but, equally importantly, because they are easy to measure in clinical practice.

There are several interesting conclusions to be drawn from this study.

Firstly, the combination of these four markers was an independent predictor of all-cause 6-month mortality, even in a multivariate model that included the well-validated GRACE score. Patients with four biomarkers elevated on admission had almost 14 times greater risk of 6-month mortality than patients with none or one. Moreover, this multimarker approach provided additional prognostic information to the GRACE score, re-stratifying not only high-risk patients (those with ST- and non-ST-elevation ACS) but also patients with non-ST-elevation ACS at intermediate risk; of the latter, those with four elevated biomarkers had 6-month mortality of 40% (as opposed to 0% for those with one, two or three elevated biomarkers), placing them in the high-risk category. This forces us to reconsider the appropriateness of treatment regimes.

Secondly, as in other studies, cystatin C and NT-proBNP were the strongest individual predictors of mortality, with no statistically significant difference between their predictive power, followed by CRP (determined by conventional rather than high-sensitivity methods, which would have been preferable) and RDW.

Finally, but no less importantly, the study – as in other registries¹¹ – identified the treatment paradox by which patients at higher risk (as reflected by higher biomarker scores) are less often treated with an invasive treatment strategy, which goes against current guidelines.

Among the study's limitations (clearly stated by the authors) were that it was a non-randomized observational study conducted in a single center with a low event rate, and that the analysis was based on only one measurement of all biomarkers as opposed to sequential sampling, which would enable us to assess whether the prognostic information changes over time.

We are far from achieving the ideal risk stratification for ACS, but we are on the way. It is to be hoped that increasingly rigorous risk stratification will be reflected in more effective therapies in daily practice, in the ongoing quest for the ideal treatment of all patients.

Conflicts of interests

The author has no conflicts of interest to declare.

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