Editorial

Combining biomarkers for the assessment of prognosis in acute coronary syndrome: More is not always better

Among patients with acute coronary syndrome (ACS) ischemic injury and myocardial necrosis incite an inflammatory reaction resulting in the release of various markers. These include markers of tissue necrosis (i.e troponin), response to inflammation (i.e C-reactive protein) and heart failure (i.e brain natriuretic peptide-BNP). The elevation of Biomarkers in ACS patients demonstrated significant value for the prediction of adverse cardiovascular outcomes. Various biomarkers have also been included in risk scores models for the assessment of mortality risk [1,2]. With every marker being tested against the others, very few studies attempted to evaluate the utility of biomarkers combination in order to achieve better prediction. As biomarkers vary in their pathophysiology, an integrated approach might be superior, but this was rarely assessed before.

NGAL, a 25-kDa protein covalently bound to gelatinase proteins in human neutrophils, was reported as an early marker of kidney tubular injury in various patient populations and hence was nicknamed "kidney troponin." [3]. Besides the well-described associations with inflammation and kidney function, NGAL is also produced by cardiomyocytes and increased gene expressions were observed in various pathological cardiac processes such as chronic heart failure,myocarditis, and chronic coronary artery disease [4–6], with even higher levels in acute myocardial infarction probably reflecting an ischemic inflammatory reaction [7]. Furthermore, by modulating the function of matrix metalloproteinases, NGAL has been proposed to affect plaque instability, potentially affecting ischemic event severity or the risk for future coronary events [8,9]. All these points that NGAL appears to be a promising biomarker in the context of ACS, offering insights into the presence of coronary artery disease, plaque instability, and the risk of adverse cardiovascular events. Combining NGAL with other biomarkers may enhance its predictive value, providing clinicians with valuable information for risk assessment and treatment decisions in ACS patients.

In this issue of the "International Journal of Cardiology - Heart and Vasculature", Tran et al. [10] evaluated the all-cause mortality prognosic value of serum NGAL, combination with N-terminal pro B-type natriuretic peptide (NT-proBNP), high sensitive Troponin (hsTnT), and GRACE score in patients with ACS. Study population included 58 ACS patients. Association of serum NGAL, NT-proBNP, hs-TnT concentration, C-reactive protein and GRACE score with mortality over 3 month were assessed by receiver operating characteristic (ROC) curve. ROC analysis demonstrated good ability for mortality prediction for all markers, being highest for NGAL and lowest for GRACE score. In addition, odds ratio for mortatlity was highest for NGAL compared to other biomarkers. The combination of NGAL with other biomarkers (individual biomarker or all together) while being associated with mortality was not significantly different compared with using NGAL alone. The small sample size (58 patients) and the very low event rate (5 cases of mortality) may suggest that at least some of the results may be attributed to type I error.

A report by Ziv-Baran and colleagues investigated the prognostic utility of elevated NGAL levels on clinical outcomes among myocardial infarction patients [11]. Study population included 273 patients with ST segment myocardial infarction assessed for the combine outcome of newly diagnosed heart failure,left ventricular ejection fraction <45 % and 30-day mortality. High NGAL levels (within the 4th quartile) was independently associated with adverse outcomes. These results were even more prominent following propensity score matching. The discrimination ability of NGAL to identify adverse outcomes was significantly better compared with hsTnT, CRP, white blood cell count and nueutrophil/lymphocyte ratio.

A report by Højagergaard and colleagues included a cohort of >1600 patients with myocardial infarction [12]. They demonstrated that admission NGAL plasma concentrations > the median was independently associated with a higher risk of death from all causes within 30 days. Their data also indicated the predictive value of NGAL plasma concentration to be higher 6–24 h after index admission. A few other reports investigated the combination of biomarkers in myocardial infarction patients. Lindberg et al previously described the interaction between NGAL and CRP in ST elevation myocardial infarction patients. In that report, the combination of high CRP/high NGAL significantly conferred the highest mortality, whereas low CRP/low NGAL conferred the lowest mortality [13].

Although the evidence that a multi-marker approach can be valuable for comprehensive risk assessment is compelling, several limitations must be recognized. First, the relative risk relationships for the individual biomarkers and specific endpoints differ as the specific process contributing to biomarker elevation (inflammation, myocyte necrosis, vascular damage, and hemodynamic stress-Fig. 1) is not the same for each individualized patient. For example, while BNP, NT-proBNP and CRP are potent predictors of mortality risk, they exhibit a weak association with recurrent ischemic events. Thus, the optimal weighting of each marker for assessment of mortality risk will differ from that for evaluating the risk of recurrent myocardial infarction. Biomarkers level measured following coronary intervention might express also contamination with contrast fluid and direct tissue damage of the kidney (i.e., ischemia–reperfusion injury caused by the PCI). To evaluate the prognostic value of biomarkers independently of renal function baseline levels before admission are advised, to make a true assessment of inflammation. It is also possible that additional blood sampling as inflammation peaked would have provided a more accurate correlation
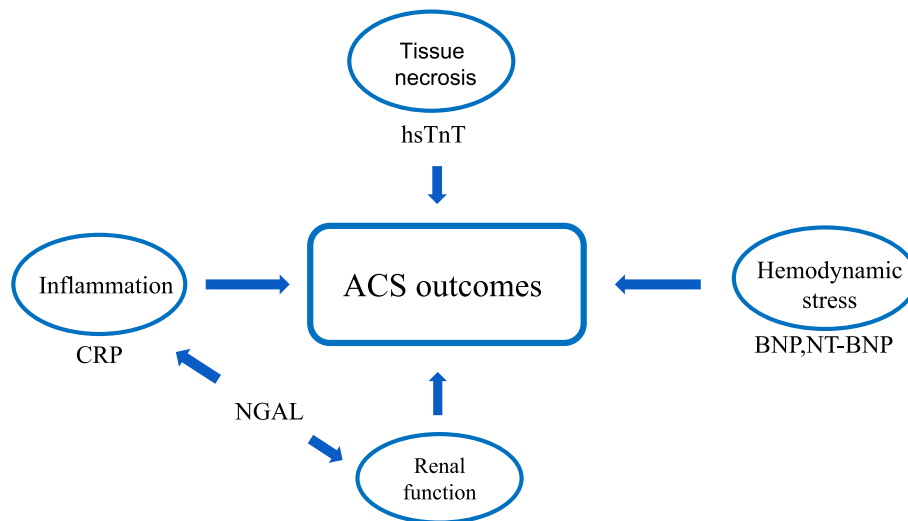
Fig. 1. Utilization of biomarkers in acute coronary syndromes (ACS); hsTnT-high sensitive troponin, CRP-C reactive protein, BNP-brain natriuretic peptide, NT-BNP-N terminal BNP,NGAL-neutrophil gelatinase associated lipocalin.

with the inflammatory state.

In conclusion, various biomarkers may shed new information on the possible outcomes of ACS patients. Biomarkers combination may not result, however, in higher predictive value, compared with each alone suggesting that sometimes more is not always better.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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