

EDITORIAL COMMENT

Prognostic Biomarkers in ST-Segment Elevation Myocardial Infarction

A Step Toward Personalized Medicine or a Tool in Search of an Application?*

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In recent years, much effort has been devoted to risk stratification of patients with acute coronary syndromes (ACS), mainly focusing on patients with non-ST-segment elevation (NSTE)-ACS. In this category of patients, biomarkers have been proven to be useful for: 1) the troublesome diagnosis; 2) therapeutic and strategic decision making (guiding the choice of more potent therapies, the indication and timing of invasive treatment, or both); 3) the long-term prognostication; and 4) a better understanding of the complex pathophysiological mechanisms (1–6). Scoring systems have been created that also include up to 3 biomarkers in addition to clinical variables (7). The studies published in these fields have made the history and the fortune of biomarkers in cardiology, leading, for example, to the extensive use of troponins and the recognition of inflammation as a fundamental player in plaque rupture.

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In ST-segment elevation myocardial infarction (STEMI), however, the main focus of interest has been the shortening of time from onset of symptoms to treatment, with relatively poor interest in prognostication, including biomarkers. In an era of high in-hospital mortality for STEMI, this position was reasonable on various grounds. First, the diagnosis and acute management of STEMI was considered to be simple compared with non-STEMI, with the main decision (whether to proceed to immediate revasculariza-

tion, either pharmacological or mechanical) based solely on ST-segment elevation and symptoms. Moreover, the prognosis of STEMI patients (excluding shock cases) who are revascularized promptly with primary percutaneous coronary intervention in a tertiary center is widely (but erroneously) perceived as being good, difficult to improve in the long term, and largely dependent on the efficacy of reperfusion (8). However, the striking reduction in acute mortality in STEMI, the still unacceptable rate of recurrent events after ACS, including STEMI, and the growing evidence that not all ST-segment elevation syndromes are ischemic myocardial infarctions are undoubtedly going to raise the interest for biomarkers in STEMI.

In this issue of the *Journal*, Damman et al. (9) address the role of biomarkers in STEMI. In their paper, many of these assumptions are tackled and somewhat disproved. First, 2-year mortality of this real-world, relatively low-risk population (shock patients and those undergoing rescue percutaneous coronary intervention were excluded; the mean symptoms-to-treatment time was relatively short, with most patients undergoing primary percutaneous coronary intervention within 2 to 5 h in a major tertiary center in the Netherlands) was almost 15%, comparing well with the results of other studies (10), but this result highlights the need for a cumulative effort to improve survival in STEMI, with appropriate treatment in the acute phase and beyond. The main result, however, concerns the additional prognostic value of a cohort of biomarkers (including C-reactive protein [CRP], N-terminal pro-brain natriuretic peptide, cardiac troponin T, glucose, and estimated glomerular filtration rate), which were shown (with the exclusion at multivariate analysis of cardiac troponin T and CRP) to predict mortality and, when added to other, more established, clinical variables, to improve their discriminatory power significantly.

These results, albeit novel and of potential clinical relevance, because only a few and small studies have addressed this topic, should be taken with caution and interpreted in their own context. At a careful reading, some methodological limitations emerge, such as the high number of patients excluded from the final analysis (acknowledged by the authors in a fairly large limitations paragraph), and the biased use of troponin and CRP. The non-high-sensitivity cardiac troponin T assay used in this study does not allow detection of troponin before 4 to 6 h from symptoms onset; therefore, this assay could not detect increased levels of troponin in a large part of the study population. Increase in CRP levels is detectable only 12 h after the onset of symptoms, whereas the cutoff value of 7 mg/l chosen by the authors is odd and different from what is recommended in the literature (11). More importantly, although the multivariate analysis confirms an independent prognostic value of the 3 biomarkers, the discriminative value analysis shows that the addition of all the investigated biomarkers en bloc resulted in an increment of discriminatory power compara-

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ble with that obtained after the addition of each of them. Thus, it seems that these biomarkers in fact may represent different ways of looking at the same picture, reflecting a more general metabolic derangement characteristic of higher-risk STEMI patients. Interestingly, a similar picture also is present in NSTEMI-ACS patients, underscoring the pathophysiological and clinical similarity of ACS as a continuum (12). The importance of unspecific markers of metabolic status (glucose), of left ventricular function and neuroendocrine activation (N-terminal pro-brain natriuretic peptide), and of renal function (estimated glomerular filtration rate) in determining the risk of death in ACS patients is in line with the unstable patient hypothesis and suggests that plaque rupture must be regarded as the consequence of the overall patient health also in STEMI patients. It is impossible to prove this hypothesis on the basis of this study, because an inherent limitation of such observational studies is the lack of exploration of plausible pathophysiological mechanisms and, more disturbing, because in this, as in almost all other prognostic studies, the design of the study and the database quality did not allow for separating mortality according to cause. That is, what is lacking, not only in the current study but also in general in the literature, is information on how many deaths are the result of recurrent infarction, how many are the result of sudden arrhythmic death, and how many are the result of heart failure. Only this kind of information may allow us to understand actual cause and effect and to design individual prevention and treatment regimens for individual conditions. At variance from NSTEMI-ACS, in which survival curves—at least for N-terminal pro-brain natriuretic peptide and renal function, as well as for troponin and CRP—continue to diverge over time, in the paper by Damman et al. (9), the curves generated using prediction of risk by biomarkers diverge very early and then run almost parallel (see Fig. 1 of their paper [9]), perhaps implying that these markers are informative in particular for the early risk. This can be explained by the prothrombotic and endothelium-damaging role of hyperglycemia and renal dysfunction in the acute phase (13,14), as well as by the more complex coronary anatomy observed in these conditions, and may recall and support the notion that prognosis after STEMI largely depends on efficacy of acute revascularization.

On this basis, the authors' hypothesis that use of a biomarker score may help to address the best therapies may seem consequential. However, this may represent a dangerous oversimplification: the step from higher nonspecific risk to more aggressive specific therapy is long and should not be considered until definitive data are provided. No new treatments directly addressed to any of these biomarkers are available yet. Specifically, renal function is a marker either of increased ischemic and hemorrhagic risk, and therefore, choice of antithrombotic and antiplatelets agents should be driven by the strength evidence or by specific tests, whereas the effect of an anti-injury treatment with delta protein

kinase C inhibitors on biomarkers of damage has not been proved (15).

In conclusion, Damman et al. (9) must be congratulated for having reopened the interest for biomarkers in STEMI and for having pursued the goal of a more personalized prognostication and therapy to improve outcome in this population. The study provides important pathophysiological information confirming the common roots of ACS, either ST-segment elevation or NSTEMI, and promising clinical improvements in STEMI treatment. Although their efforts fell short of the objectives, we hope that they will contribute to a more accurate and individualized prognostication and therapy, with consequent reduction in events and the flourishing of novel pathophysiological information.

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