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EDITORIAL COMMENT

Novel Biomarkers in Acute Coronary Syndromes

New Molecules, New Concepts, But What About New Treatment Strategies?*

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The field of acute coronary syndromes (ACS) is rapidly changing. Besides new drugs, the evolution is mainly driven by the introduction of novel biomarkers in an effort to respond to the partly unmet need for better diagnosis, prognostication, and management of patients. Novel biomarkers may improve diagnostic accuracy, identify subgroups of patients who may benefit from a specific therapeutic modality in the acute phase, and reveal pathophysiological insights that need to be addressed by long-term medical treatment. In this context, the new-generation cardiac troponin (cTn) assays provide considerably more sensitive and timely diagnosis of ACS (1), whereas their combination with C-terminal provasopressin (copeptin) further enhances diagnostic accuracy (2).

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The introduction of new biomarkers has undoubtedly moved our approach several steps forward, but it also gave rise to novel issues that need to be addressed by future research. The highly sensitive new-generation cTn assays modify the classification of patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) by increasing the percentage of cases with NSTE myocardial infarction and limiting that of unstable angina (Fig. 1). As a result, this reclassification creates a need for novel prognostication models that would identify high-, moderate-, and low-risk patients and thus guide our treatment decisions. In particular, the long-term benefit of an invasive approach in the subgroup of patients who are reclassified from unstable angina to NSTE myocardial infarction has not yet been proven by large randomized trials. Whether this need is addressed by novel biomarkers remains to be seen (Fig. 1).

In this issue of the *Journal*, O'Malley et al. (3) report on the prognostic significance of copeptin, midregional proadrenomedullin (MR-proADM), and midregional proatrial natriuretic peptide (MR-proANP) in 4,432 patients with moderate-risk or high-risk NSTE-ACS. Confirming the results of previous smaller studies (4–6), all 3 novel biomarkers were independently associated with cardiovascular death or heart failure at 1 year. Furthermore, the addition of each of the 3 biomarkers to a predictive model consisting of clinical variables and a constellation of established or emerging biomarkers, including B-type natriuretic peptide (BNP), cTnI, pregnancy-associated plasma protein-A (PAPP-A), ST2, and myeloperoxidase (MPO), improved the statistical indicators of prognostic performance (integrated discrimination improvement and net reclassification improvement) for the same endpoint (3). In the same context, another novel biomarker that is currently undergoing rigorous research, growth differentiation factor 15, has been shown to increase the predictive value of the GRACE (Global Registry of Acute Coronary Events) score in patients with NSTE-ACS (7). Thus, those and other new biomarkers may help build novel prognostication models and treatment algorithms that would perform better in the currently evolving clinical setting. O'Malley et al. (3) used the previous-generation cTnI, and one question that may arise from this study is whether the results would have been the same if the new-generation cTn had been used.

The prognostic value of markers of myocardial stress in patients with ACS is not new knowledge. Natriuretic peptides have been known to be independently associated with prognosis in patients with ACS for nearly 2 decades (8). This association, which existed even without elevation of previous-generation cTn concentrations, was identified across the whole spectrum of ACS and concerned death and heart failure (9). Myocardial ischemia may cause release of natriuretic peptides as a protective mechanism against ischemia-induced hemodynamic changes, probably through increased regional ventricular wall stress (9). Ischemia may trigger expression of natriuretic peptides even independently of mechanical stress (10). Because ischemia usually precedes myocardial necrosis, concentrations of natriuretic peptides may increase even earlier than concentrations of troponins. However, evidence on the benefit of using natriuretic peptides in decision making for patients with NSTE-ACS has hitherto been inconclusive (9). What seems peculiar is that in the vast majority of studies on ACS, natriuretic peptides predicted endpoints such as mortality or heart failure, but not ischemic events, despite that ischemia seems to be implicated in their elevation in

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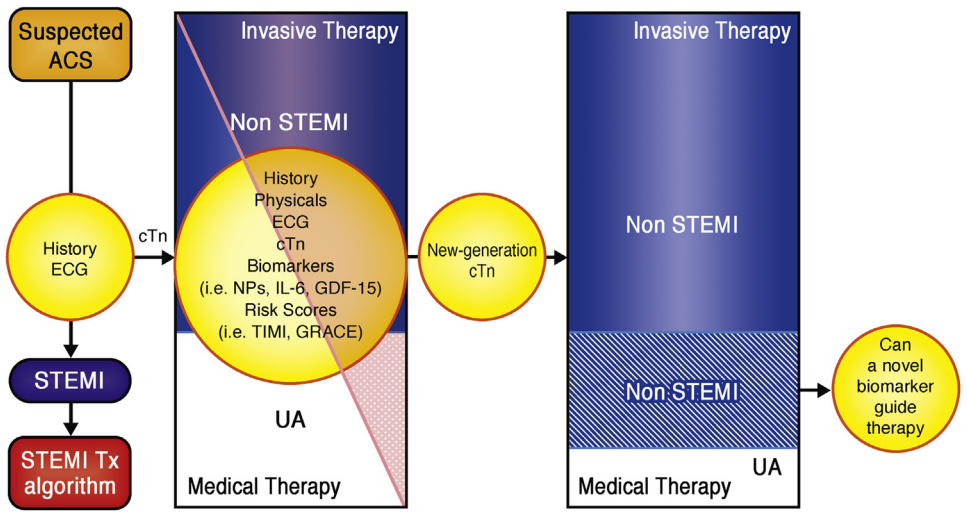

Figure 1 **The Role of Biomarkers in the Diagnosis and Risk Stratification of Patients With ACS**

Therapeutic guidance to invasive **(shaded red area)** or medical therapy for patients with non–ST-segment elevation ACS classified into non–ST-segment elevation myocardial infarction (non STEMI) and unstable angina (UA) by previous-generation cardiac troponins is offered by a number of variables. These include history, physical examination, electrocardiogram, biomarkers (i.e., troponin, natriuretic peptides [NPs], interleukin [IL]-6, and growth differentiation factor [GDF]-15, and risk scores (such as Thrombolysis In Myocardial Infarction [TIMI] and GRACE [Global Registry of Acute Coronary Events]). The new-generation cardiac troponins reclassify a number of patients from UA to NSTEMI **(shaded blue area)**. It is not yet known whether novel biomarkers may guide therapy in this particular subgroup of patients. ACS = acute coronary syndrome(s); cTn = cardiac troponin; ECG = electrocardiogram; NP = natriuretic peptides; STEMI = ST-segment elevation myocardial infarction; Tx = therapy.

ACS. This is also the case in the current study by O'Malley et al. (3). Those findings may imply that there is a role for natriuretic peptide–guided therapy with neurohormonal inhibitors in NSTE-ACS, although data concerning this approach remain conflicting (11,12).

Several additional issues have arisen regarding the emerging biomarkers. For example, the pathophysiology and clinical significance of minor elevations in cTn concentrations are not completely known, particularly given that cutoffs have been derived by healthy and relatively young populations, and factors such as aging or renal dysfunction may impair troponin release or clearance (13). Establishment of cutoffs will also be required for the emerging biomarkers on the basis of carefully selected study populations (9). Furthermore, the cost effectiveness of management strategies on the basis of the novel biomarkers should be evaluated (14).

The robust statistical results provided by O'Malley et al. (3) and several previous investigators do not translate into clinical benefit unless integrated into practical and cost-effective management strategies that improve established diagnostic and therapeutic approaches. This constitutes the most significant challenge that clinical research has to address in the field of biomarkers.

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Key Words: acute coronary syndrome(s) ■ biomarkers ■ copeptin ■ MR-proADM ■ troponin.