Identification of potentially useful bloodborne markers in acute coronary syndromes (ACS) is steadily increasing. The clinical applications range from prediction and prognosis to definition and diagnosis. In the center of the markers stand the myocardial proteins and enzymes, because their presence in the circulation reflects myocardial damage and myocyte death (1). Their concentrations mirror the myocardial lesion size and, accordingly, provide information on the following prognosis. At the other end of the concentration scale are improved and sensitive methods that may provide new insight into the clinical relevance of even very low concentrations. For the individual patient, the concentrations therefore guide therapy directly (diagnosis) and indirectly (risk).

Most of the new markers are not included in the present recommendations for ACS. Several markers appear quite promising, and it may just be a matter of time before they are included in the biochemical evaluation of ACS. One such marker complex could be the cardiac-derived natriuretic peptides. Their release is a dynamic response, which even brings about the attractive concept that the peptides may be used to monitor reversible pathology rather than only the consequence of myocyte death. In this respect, measurement of cardiac-derived peptides in patients with ACS provides important prognostic information and may help the clinician in identifying patients at high risk of further morbidity and death (2). The underlying mechanism is not completely elucidated but appears to relate to changes in myocardial function or intermittent hypoxic conditions in the heart muscle—or both (3).

A thrombotic process precedes myocardial damage and altered heart function in patients with ACS. Obviously, the cause of disease is not in the heart muscle but in the coronary vasculature and is sometimes referred to as atherothrombosis. Atherothrombosis combines the low-grade but long-term lipid accumulation and vascular inflammation (years) with the subacute thrombotic build-up and symptom-causing occlusion (days). It therefore seems to be a logical site to search for new markers in ACS. In this issue of the Journal, Mega et al. (4) report on thrombus precursor protein (TpP) as a predictor in patients presenting with ACS. By TpP measurements in stored plasma from the OPUS–TIMI 16 (Oral Glycoprotein IIb/IIIa Inhibition With Orbofiban in Patients With Unstable Coronary Syndromes–Thrombolysis In Myocardial Infarction 16) trial, the authors report an approximately 2-fold TpP increase in ACS patients compared with healthy control subjects and that an increased concentration was prognostic for later death, myocardial infarction, or recurrent ischemia within the ACS patient group. The TpP concentrations only correlated weakly with other known markers in ACS, such as troponin I, high-sensitivity C-reactive protein, or B-type natriuretic peptide. In multivariable analysis, TpP measurement still remained prognostic, with hazard ratios of approximately 1.5 for later death or myocardial infarction.

The authors are to be congratulated for focusing on the thrombotic process in ACS. As such, the present study should stimulate further research into both TpP and other related markers of fibrin formation and thrombosis. Conceptually, the authors argue that a marker of activated thrombosis could contain useful information with regard to the ongoing thrombotic process in ACS. Several earlier studies corroborate that this may indeed be the case as, for instance, the concentrations of fibrinogen, soluble fibrin, and—at the other end of fibrin generation—the fibrinolytic pathway represented by the plasminogen activator inhibitor-1, are all associated with the risk of myocardial infarction (5–7). For these markers, however, it is not clear whether they reflect the low-grade but long-term inflammatory pathology in atherosclerosis or whether the concentrations also can be regarded as active features in the subacute thrombus formation in ACS. Notably, none of the former markers appear to possess enough clinical information to be included in an assessment of risk and prognosis in individual ACS patients. Other fibrin-related markers have also been tested. D-dimer measurement, for which most laboratories nowadays provide a routine analysis, seems to provide a similar performance to the present TpP marker (8). More coagulation markers have also been examined in ACS, and the findings have usually been suggestive of general associations but not suitable for individual patient assessment (9).

Several inherent troubles haunt the markers of coagulation in ACS. First, there is an obvious need for a better understanding of the causative mechanisms. Many of the markers are also associated with the inflammatory atherosclerotic process rather than just the subacute thrombus formation. This may also apply to TpP, and studies will be
needed to address whether the 2-fold increase in TpP is indeed specific to ACS or just a feature of general illness or inflammation. Acute disease causes a general prothrombotic state, which is reflected in several coagulation analyses, including “global” coagulation tests such as thromboelastography.

Second, the coronary thrombus in patients with ACS is physically quite small, and the potential markers of activated coagulation need to be very sensitive and possibly somewhat better than detecting the much larger venous thrombi. In the present report on TpP concentrations, this matter is left a bit unclear, as more severe ACS (ST-segment elevation myocardial infarction vs. unstable angina pectoris) was in fact associated with lower TpP concentrations. Such a marker profile may be tricky to make everyday decision limits for, because the relation to severity of disease is not straightforward. Essentially, the least and the most ill patient can have the same TpP concentration, and how is the clinician to extrapolate rational actions in this situation?

Third, patients with ACS are promptly treated with drugs that interfere with the coagulation process and also—to some extent—the coagulation analyses. Thus, the time of blood sampling for analysis becomes critically important. To that end, the use of catheter-guided therapy should also be considered here, because balloon inflation at the very site of occlusion is likely to affect the local biochemistry of the thrombus. Finally, the markers of coagulation can be a challenge from an analytical point of view. Measurement of fibrinogen and D-dimer is still not a straightforward matter, and different methods produce quite different results. For TpP, the assay issues are not yet well characterized, and more data on pre-analytical pitfalls and analytical details will be needed before the analysis can be introduced in routine laboratories. Moreover, although the theory may advocate for TpP measurement as a marker of activated coagulation, it still needs to be put to the test whether traditional markers of coagulation are actually reporting on the very same phenomenon. Head-to-head studies that use all putative markers in play should be performed. The increasing number of markers for prediction and prognosis in ACS could perhaps lead one to speculate that good clinical judgment may one day be replaced with risk charts based on various markers and perhaps even in a multimarker approach. After all, objective measurements “don’t lie” and can easily be validated and standardized. However, in reality, the identification of markers with only modest clinical performances underscores the need for robust clinicians who can safely guide the patients through the vast load of information (and disinformation) based on median values derived from large clinical studies from the past. Hard clinical data such as patient age, smoking habits, and comorbidities such as diabetes, obesity, and hypertension still beat most biochemistry.

Thus, the modern cardiologist should probably remain reluctant in the adoption of new markers for prediction and prognosis. Even if applying some of the markers, the clinician will have to serve as an academic translator of all of the information. All patients are different, and with hazard ratios of only 1.5, it is likely that some patients will be harmed by unreasonable clinical decisions if the same actions are to be introduced based on such assessments. To put it on the line, patients may even be “lost in translation” if introducing multiple markers in a complex syndrome like ACS. Markers of activated coagulation are not likely to make this any easier for patients and clinicians.

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