The rationale for the search of biomarkers of vulnerable plaques seems sound. Plaque rupture is a key step in the initiation of an acute coronary syndrome (ACS). The atherosclerotic plaque contains large numbers of inflammatory cells that may release hydrolytic enzymes and cytokines, thereby destabilizing the plaque and thus presenting symptoms. These concepts are described briefly below.

Biomarker of Plaque Rupture

A biomarker of plaque rupture would show an increasing concentration when a (coronary) atherosclerotic plaque ruptures. A biomarker of plaque rupture would be potentially useful for early diagnosis of acute myocardial infarction (AMI) because plaque rupture precedes myocardial necrosis. Another potential application would be for unstable angina in which plaque rupture, but not myocardial necrosis, occurs. The requirements that a biomarker of plaque rupture must meet to have clinical utility are considerable, however. The biomarker must be abundant in atherosclerotic plaques and be released immediately into the circulation in high concentration after rupture of the plaque. The biomarker concentration must remain increased for quite some time, because plaque rupture might occur up to several days before the patient gets ischemia and thus presents symptoms. Biomarker specificity is another demanding requirement. The biomarker should be not only highly specific for atherosclerotic plaques but also, ideally, specific for coronary plaques only. An important limitation on the use of a biomarker of plaque rupture for early diagnosis of AMI is that a large proportion of all infarctions are not caused by plaque rupture. Autopsy studies have shown that approximately 60% of fatal cases are associated with plaque rupture, and this proportion is probably even lower in real-life situations involving mainly non-fatal AMIs, especially if type 2 AMIs are included. Thus, even with a very good biomarker of plaque rupture, the sensitivity for AMI diagnosis would be limited. On the other hand, plaque rupture might occur without being followed by the formation of a flow-limiting thrombus and the development of AMI. Coronary plaque ruptures have been shown in 7%–27% of stable angina patients and in 3% of patients dying of noncardiac causes. In a study that evaluated 3 biomarkers suggested to indicate plaque rupture [myeloperoxidase (MPO), matrix metalloproteinase 9 (MMP-9), and pregnancy-associated plasma protein A (PAPP-A)] for the early diagnosis of AMI, the diagnostic information was almost nil. For all 3 biomarkers, the areas under the curve in ROC curve analyses were not significantly different from 0.50.

Biomarker of Plaque Instability or Vulnerability

A biomarker of plaque instability or vulnerability would show increased concentrations in patients who have atherosclerotic lesions in their coronary arteries that are more prone to rupture. Such individuals would thereby constitute a population of individuals at increased risk of cardiac events in the future. A biomarker of plaque instability is intended to be used not for diagnosis but for risk prediction. The concept also implies some sort of mechanistic link between the biomarker and plaque rupture. Otherwise, biomarkers such as cardiac troponin might be considered erroneously as biomarkers of plaque instability, given that troponin increases are associated with an increased risk of a new AMI (i.e., irreversible myocardial cell death). The chain of reasoning is as follows: The biomarker of plaque instability is found in atherosclerotic plaques and is more abundant in plaques with unstable characteristics than in plaques with stable characteristics; an increased concentration of the biomarker in the circulation signals that the patient has plaques with unstable characteristics that are more prone to rupture; and plaque rupture leads to unstable angina or AMI. The results for clinical evaluations of suggested biomarkers

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Nonstandard abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; MPO, myeloperoxidase; MMP-9, matrix metalloproteinase 9; PAPP-A, pregnancy-associated plasma protein A; PIGF, placental growth factor.
of plaque vulnerability are conflicting, however. Generally, these biomarkers seem to be more strongly associated with mortality than with the risk of AMI or major adverse cardiac events, which is illogical given that the biomarkers predict plaque rupture. Furthermore, their associations with prognosis seem to be positive more often when studies test these biomarkers by themselves than when studies evaluate several biomarkers simultaneously. In a study that evaluated multiple biomarkers as indicators of the risk of major cardiac events over a 42-day follow-up for patients admitted with ACS, neither placental growth factor (PIGF) nor lipoprotein-associated phospholipase A2 was found to be predictive as a single biomarker (7). In another study, MPO, MMP-9, and PIGF were not found to predict the occurrence of a composite of cardiac events within 4 months after an ACS episode, although PIGF taken alone predicted all-cause mortality (8). In a third study, the biomarkers MPO, MMP-9, and PAPP-A did not predict death or AMI within 1 year (9), and a fourth study found that none of the biomarkers (MPO, MMP-9, and PAPP-A) predicted the recurrence of a troponin T–positive coronary event or cardiac death within 45 months (10). Several possible explanations for these negative findings need to be considered, however: A given biomarker might not, in fact, be a biomarker of vulnerable atherosclerotic plaques (e.g., the excretion of PAPP-A from vulnerable plaques has been questioned) (11); inappropriate assays (or sample types) might have been used (e.g., the results for PAPP-A might be different depending on whether free or total PAPP-A was measured) (12); the biomarker might have been measured only at admission when serial measurements might have supplied more information (13); biomarker results in a stable-angina population might differ from those for a population with ACS (14); and the biomarker might have been evaluated as part of a single-biomarker strategy rather than as part of a stepwise multibiomarker strategy (7). Several other questions need clarification before a specific biomarker can be considered useful in a clinical routine. Has the short- and long-term biological variation of the biomarker been characterized? Does the biomarker increase immediately before a plaque rupture, and should we look for a change in concentration over time rather than for the absolute value? Are there differences in predictive value regarding different cardiac events (e.g., between AMI and cardiac death) and in short-term versus long-term follow-up?

The choice of gold standard represents a challenging problem when evaluating a suggested biomarker of plaque vulnerability. Ideally, the gold standard should include a vascular-imaging technique capable of reliably detecting plaque rupture in the coronary artery, such as intracoronary optical coherence tomography (1); however, such techniques are currently not feasible for large clinical studies of end points.

**Biomarker of Vulnerable Patients**

A biomarker of vulnerable patients would be a biomarker demonstrating increased concentrations in patients prone to a new cardiac event (i.e., new AMI). This definition encompasses a much broader concept that does not imply a direct association with the risk of plaque ruptures (e.g., the biomarker could be associated with the risk of flow-limiting thrombus formation once a plaque rupture has occurred). Hence, a biomarker of plaque instability is a biomarker of vulnerable patients, but the opposite is not necessarily the case. I suggest that most biomarkers that are claimed to be biomarkers of plaque instability or vulnerability indeed belong to this category, and virtually any biomarker that is predictive of new cardiac events could be labeled as a biomarker of vulnerable patients. Thus, the term “biomarker of vulnerable plaque” should be separated from the term “biomarker of vulnerable patient.”

The concept of a biomarker capable of predicting plaque rupture is appealing. A biomarker of vulnerable plaque would allow the possibility to better target preventive measures against plaque rupture and thereby decrease the occurrence of ACS; however, are there really biomarkers of vulnerable plaque? If the question is slightly rephrased to, “Are any useful, scientifically proven biomarkers of vulnerable plaque currently available?” the answer is, unfortunately, “No.” If the question is rephrased to, “Will there be a useful biomarker of vulnerable plaque available in the future?” the answer must be, “Let us hope so, but it is still a long way to get there.”

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