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Metabolic markers in predicting acute cardiovascular events

Alda Huqi, MD
Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy
E-mail: al.huqi@gmail.com

Cardiac biomarkers have a central role in the diagnosis of an acute coronary syndrome (ACS).[1] Recently, molecules such as heart-type fatty acid–binding protein (H-FABP), pro-substance P, and mast cell–derived tryptase, have been suggested to be superior to creatine kinase (CK)–MB or cardiac troponins in the early detection of ACS. However, their role has not been confirmed in clinical studies. On the other hand, the role of troponin testing has been repeatedly validated, with such awareness unintentionally leading to the overuse of the test. Measurements are often performed among those patients without symptoms suggestive of ACS, thus reducing the specificity of the test. Nonetheless, when troponin levels are interpreted with clinical findings and electrocardiogram results, the diagnosis of ACS is highly accurate.[2]

Corroboration or exclusion of a diagnosis of ACS remains a critical step in the management of patients presenting with chest pain. Treatment strategies of those patients diagnosed with ACS are dictated by multiple international guidelines and have been shown to significantly affect prognosis. However, given the burden of established cardiovascular (CV) disease, risk reduction strategies are assumed to confer a major benefit. In this regard, the Framingham risk score represents the most popular clinical tool for the estimation of CV risk. However, while there is an established power of the Framingham risk score in predicting obstructive coronary artery disease, the majority of acute CV events occur in individuals who are stratified as having low to intermediate risk.[3] In line with these considerations, stenosis severity is also a poor predictor of plaque rupture.[4] As such, there is an increasing need to develop specific markers that predict future ACS.

ACS is accompanied by an intense inflammatory response, and an interplay between the inflammatory and thrombotic systems has been proposed to be a key regulator of ischemic vascular events. Activated platelets bind to circulating leukocytes and recruit them to sites of vascular injury and thrombus. For this reason, circulating biomarkers of inflammation such as C-reactive protein (CRP), have represented the subject of many recent clinical studies. However, CRP measurements have been shown to confer only a modest predictive power for future cardiovascular events.[5]

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is an imaging modality that allows identification of small, metabolically active tissues such as tumors and inflamed lesions, by quantification of ^{18}F-FDG uptake.[6] In the cell, ^{18}F-FDG, an analogue of glucose, is phosphorylated to FDG-6-phosphate by hexokinase and adenosine triphosphate (ATP), a rate-limiting step in glycolysis. FDG-6-phosphate is not metabolized further in the glycolytic pathway, so it remains trapped inside the cell, in a process called “metabolic trapping.” Recently published studies have tested this technique in the CV research field. An increased ^{18}F-FDG uptake has been documented in activated proinflammatory macrophages, which play a major role in arterial plaque destabilization and consequent clinical manifestation of ACS.[7] The significance of such findings has been further evaluated in prognostic studies, with

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Abbreviations

ACS: acute coronary syndrome; **CK:** creatine kinase; **CRP:** C-reactive protein; **CT:** computerized tomography; **CV:** cardiovascular; **^{18}F-FDG:** ^{18}F-fluorodeoxyglucose; **PET:** positron emission tomography

increased arterial ^{18}F-FDG PET signals being inversely associated with the timing of acute CV disease manifestation.[8] In addition, assessment of the metabolic activity of the spleen, a much earlier marker of inflammation, independently predicted the risk for subsequent CV events.[9] Other studies have combined PET and computed tomography (CT) signals, and have shown that the link between the PET/CT signal and CV events is independent of the effects of coronary artery calcium score on both CV outcomes and arterial inflammation.[8] To further support these findings, there are studies that have demonstrated that arterial ^{18}F-FDG uptake is reduced by statins and by drugs that are thought to inhibit inflammatory pathways.[10]

In conclusion, the advent of specific biomarkers, such as cardiac troponins, has progressively increased our ability to diagnose an ACS. Following diagnosis, treatment strategies for patients with an ACS are also well standardized and proven to positively impact prognosis. However, the majority of acute CV events occur in patients deemed to have low to intermediate risk, thus suggesting that an intervention at this level (prediction/prevention of acute CV events) could have a potentially relevant impact.

As mentioned, platelet-leukocyte interactions offer an important mechanistic link between the inflammatory and thrombotic systems. The information provided by the ^{18}F-FDG PET signal appears to be distinct from that provided by circulating biomarkers of inflammation, which carry information from both vascular and nonvascular sources. Indeed, metabolic biomarkers appear to allow for the circumscription of a weak, systemic inflammatory disease that ultimately leads to acute CV events. Large clinical studies are needed to confirm such results. ■

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