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INVITED COMMENTARY

Commentary on: "Predicting Carotid Artery Disease and Plaque Instability from Cell-derived Microparticles"

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Better understanding of mechanisms behind carotid stenosis has challenged the traditional approach to carotid endarterectomy (CEA) as the gold standard for stroke prevention in symptomatic and asymptomatic carotid disease. For symptomatic patients, the high risk of new early embolic recurrence suggested not delaying surgical removal of the carotid embolic plaque for more than 2 weeks after the acute neurological event. For symptom-free patients management of the carotid stenosis by surgery has been even more debated because of the high likelihood of decreased stroke risks with systematic and intensive use of modern medical therapy including antiplatelets, statins, and antihypertensive drugs. However, in supporting this modern approach to carotid stenosis the sudden and often unpredictable nature of its acute manifestation (i.e. the embolization from a "high-risk" carotid plaque resulting in stroke) for both already or never symptomatic carotid patients remains a challenge. Emerging evidence has highlighted the role of inflammatory markers, such as vascular cell adhesion molecules (VCAMs), selectin, chemokines, and proteases (e.g. metalloproteinases), for their potential in triggering a previous quiescent atherosclerotic plaque. In this perspective, cell-derived membrane microparticles (MPs) are among the newest biomarkers suggested for their effect on triggering atherosclerotic plaque.[1–3] MPs, also known as "microvescicles" or "ectosomes",[2] are large (50–1000 nm diameter) extracellular vesicles surrounded by a phospholipid bilayer that are released into extracellular space or circulation by direct budding from the plasma membrane of multiple lines of activated cells including platelets, endothelial cells, and leukocytes. In this issue of the *European Journal of Vascular and Endovascular Surgery*, Wekesa et al.[4] performed a case–control pilot study analyzing levels of endothelial MPs and platelet MPs in addition to other atherosclerotic molecular biomarkers in plasma from 42 patients undergoing CEA for symptomatic ($n = 37$) and asymptomatic ($n = 4$) carotid stenosis patients (cases) and from 73-age and sex-matched patients without carotid disease used as controls. The excised carotid plaques from the cases group were also analyzed with immunohistochemistry and graded for stability according to the inflammatory cell infiltration in the plaque and cap and the evidence of plaque rupture and surface thrombus as defined by Redgrave.[5] Wekesa et al.[4] found significantly higher levels of subsets of platelet MP and annexin V^+ MPs in carotid stenosis patients than in controls ($p < .05$) while the other soluble vascular inflammatory biomarkers tested in the same study (soluble intercellular adhesion molecule [sICAM-I], soluble vascular cell adhesion molecule [sVCAM-I], and serum amyloid A [SAA]) did not significantly differ. Furthermore, annexin V^+ MP was independently associated with carotid stenosis in multivariable model analysis. In addition, endothelial MP subsets (but not any vascular, inflammatory, or proteolytic molecular tested biomarker) were found to be higher in unstable than in stable plaque patients and the association was confirmed in univariate and multivariable analyses.[4]

Although the message from Wekesa et al. may be relevant, suggesting higher sensitivity of MP than other molecular biomarkers for predicting both the plaque instability (endothelial MP) and the presence of advanced carotid disease (platelet MPs), the results of the study should be interpreted with caution.

As with most of the other literature studies testing biomarkers related to the concept of "unstable/vulnerable" plaque, the cross-sectional design in Wekesa study precluded evaluation of the true predictive utility of MPs as biomarkers of clinical events.[1]

Furthermore, because the "unstable" plaque is not an established medical diagnosis, the gold standard for reference was based on the immunohistochemistry pattern of carotid plaque stability; none of the plaques examined by Wekesa was documented to be responsible for cerebrovascular events.

Finally, biomarker research provides a powerful approach to understanding the spectrum of cerebrovascular disease and is expected to continue rapidly expand in the near future. However, the complexity of biomarker research and the need for specific laboratory tools and techniques do not allow an extensive application in current everyday practice, and the cost-effectiveness of this approach in identifying high-risk carotid plaque remains debatable.

During the past few years an increasing number of histopathology, but especially more advanced molecular

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imaging technology, in addition to biomarkers studies have been developed to help identify what may affect the "vulnerability" or "instability" of atherosclerotic plaque leading to rupture and symptoms. Despite the growing body of evidence supporting the current modern approach to carotid surgery for stroke prevention, the precise mechanisms that lead to embolization from a "high-risk" carotid plaque resulting in stroke remain not adequately understood. The research in this field is still inadequate and has failed to identify with certainty patients in whom disruption of a vulnerable plaque is likely to result in a clinical event. Regardless of the important contributions to knowledge of carotid diseases from biomarkers such as MPs, in the 21st century we do not know which of the patients with carotid plaque will suffer an event or when one will occur. The "unstable/vulnerable" plaque remains a probabilistic diagnosis and not a definite entity.[1] More and more sound research is needed to understand how to best manage surgery for symptomatic and asymptomatic carotid stenosis.

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