EDITORIAL

C-reactive protein and efficacy of antiplatelet therapy in (intracranial) atherosclerosis

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High-sensitive C-reactive protein and dual antiplatelet in intracranial arterial stenosis
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C-reactive protein (CRP) and other inflammatory biomarkers can indicate both the severity and extent of atherosclerosis, reflecting the inflammatory nature of the disease process.[1] Atherogenesis begins with an inflammatory response to vascular injury with cells and mediators initiating the healing response and later inducing growth of atherosclerotic plaques. Inflammation then increases plaque instability, promoting rupture, fissuring, or erosion—the pathogenetic milieu of thrombosis in atherothrombotic ischemic strokes.

Few studies have examined the predictive role of inflammatory markers with regard to the efficacy of the most common cardiovascular drugs such as statins, antihypertensive drugs, and antiplatelet agents. Previous results from Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)[2] reported that, among patients with a high serum levels level of CRP, statin therapy resulted in a lower risk of cardiovascular events. In the Physicians Health Study,[3] baseline CRP levels influenced the magnitude of reduction in the risk of myocardial infarction with aspirin therapy.

In this issue of *Neurology*®, Li et al.[4] show the analysis of the relationship of high-sensitive CRP (hsCRP) to the efficacy of dual antiplatelet therapy in patients with and without intracranial arterial stenosis in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial. Among patients with minor stroke or high-risk TIA, they found a clear relationship between serum levels of hsCRP and the effectiveness of dual antiplatelet therapy for preventing recurrent stroke in patients with intracranial arterial stenosis even after correction for confounding factors. The authors observed that with dual antiplatelet therapy (clopidogrel plus aspirin) there was reduced stroke recurrence, but only in patients with low hsCRP serum levels. Moreover, patients with elevated hsCRP levels did not benefit from dual antiplatelet therapy, even after correction for use of antihypertensive agents and lipid-lowering agents, during the 90-day follow-up period. They found similar results for the outcome of composite vascular events. Patients without intracranial arterial stenosis did not demonstrate an interaction between hsCRP and antiplatelet therapy for either recurrent stroke or the combined vascular endpoint. Thus, the authors concluded that the protective role of dual antiplatelet therapy is strictly linked to atherosclerosis localization and ongoing inflammation.

Atherosclerosis of precerebral and intracerebral arteries characterized by chronic vessel inflammation is the main pathogenetic factor of atherosclerotic stroke. An acute cerebral atherothrombotic event reflects a dramatic change from a chronic indolent inflammatory process to a fulminate process with thrombosis on an active plaque. This transition begins with increased leukocytosis within the atheroma and recruitment of additional leukocytes, followed by degradation of the fibrous cap, and finally plaque rupture and exposure of subendothelial tissue factor to the hemostatic components of blood such as platelets.

Aspirin influences platelet function by acetylation of the platelet cyclooxygenase with irreversible inhibition of platelet-dependent thromboxane formation.[5] Clopidogrel, a thienopyridine and adenosine diphosphate receptor antagonist, inhibits platelet function through irreversible binding to the G-protein-coupled P2Y12 receptor.[6] Platelet activation caused by

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several factors, such as shear stress and inflammation, results in resistance against inhibition of platelet function by aspirin and other antiplatelet such as clopidogrel.

The results of this study provide food for thought that inflammatory marker levels, as a surrogate for ongoing inflammation, may influence cerebrovascular and vascular endpoints, but only in persons with intracranial arterial stenosis. The burden of intracerebral artery stenosis on the pathology of atherosclerotic ischemic stroke, although reported,[7,8] remains incompletely characterized. The study conducted by Li et al. can shift our attention to patients with intracranial atherosclerosis who demonstrate a clearer relationship between inflammatory burden and effectiveness of dual antiplatelet therapy than those with carotid atherosclerosis.[9]

This interesting relationship could reflect a particularly decisive role that local and systemic inflammation of plaques has in those with intracranial arterial stenosis, determining the complex local events that trigger the transition from chronic stability to the acute event. More advanced methods, such as MRI of plaque or FDG-PET used to evaluate inflammation status of carotid plaque,[10] may hold promise for assessing intracerebral atherosclerotic disease, but this needs formal investigation with characterization of inflammatory changes in intracranial arterial plaques. The difficulty of finding intracranial plaques to study has limited the investigation of intracerebral plaque composition, the frequency of intraplaque inflammatory cells, and the more general concept of plaque stability depending on the different inflammation grade. Nevertheless, important information emerges from this study regarding the role that the inflammatory background seems to play in the systemic platelet response and pathogenesis of local plaque microevents involved in the presence of activated platelets in acute ischemic stroke pathogenesis.

As indicated by the authors, this study has limitations. They used magnetic resonance angiography as a noninvasive, easily accessible technique rather than digital subtraction angiography, the gold standard of diagnosis of intracranial arterial stenosis. The venous blood samples were collected after administration of the first dosage of antiplatelet drug.

This article provides an important addition to the literature, offering clarification on several details on different therapeutic roles of cardiovascular drugs such as antiplatelets or statins in relation to atherosclerosis localization and inflammatory background. These results suggest new tools to characterize clinical and therapeutic phenotyping of patients at greater risk of stroke. Finally, this study addresses a key question: Does a relationship between inflammatory markers and antiplatelet drug effectiveness in persons with cerebrovascular atherosclerosis exist? This study offers an intriguing answer: yes, but only in intracranial vasculature.

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Disclosure

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