

## Carotid Intraplaque Hemorrhage: a Biomarker for Subsequent Ischemic Cerebrovascular Event?

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Stroke remains a major cause of death and disability with ~16.9 million new patients sustaining a clinical event worldwide<sup>1</sup>. 40% of ischaemic strokes are due to internal carotid artery thromboembolism with two-thirds of patients having  $\leq 50\%$  carotid luminal stenosis (North American Symptomatic Carotid Endarterectomy Trial (NASCET)<sup>2</sup> defined)<sup>3</sup>. However, the degree of stenosis remains the major determinant of patient risk assessment in current practice. This occurred as luminal stenosis can be easily quantified using ultrasound, which was the only validated imaging modality available during the design of landmark clinical trials in 1980s and 1990s.

Histopathological studies have improved our understanding of lesion instability, highlighting that luminal stenosis is not the only marker of future risk and that the presence of specific plaque features may be equally important<sup>4</sup>. In particular, carotid intra-plaque haemorrhage (IPH) has been showed to be a risk factor for ischaemic cerebrovascular events. Immature neovessels are thought to be the principal source of IPH, allowing plasma and red blood cells

to leak into the developing plaque. The red cells subsequently undergo apoptosis (Figure 1), which initiates complex cascade processes, including cellular degradation and cytophagy that act to promote lipid accumulation. IPH is therefore an important driving force for plaque progression<sup>5</sup>. In an 18-month follow-up study of asymptomatic patients with 50-70% luminal stenosis, percentage change in wall volume and lipid-rich necrotic core volume was significantly higher in the group of patients with IPH<sup>6</sup>.

High-resolution magnetic resonance imaging (hrMRI) can reliably identify IPH, which appears high intensity in T<sub>1</sub>-weighted images. MRI-identified IPH has been showed to be associated with patient clinical presentations and subsequent ischaemic cerebrovascular events in several small cohort studies. A meta-analysis demonstrated that the presence of IPH was associated with a ~6-fold higher risk for events (Hazard ratio = 5.69) in 8 studies with 689 patients and the annualized event rate in subjects with detectable IPH was 17.7% compared with 2.4% in patients without IPH<sup>7</sup>. However, the prevalence of IPH in differing patient cohort remains uncertain. Data on the prevalence of IPH in symptomatic patients (n = 1,000) is due to be released shortly from a recently completed multi-center clinical trial (CARE-II study)<sup>8</sup>. In the population-based Rotterdam study (n = 5,240; age >45 years; mean age = 70.3 years), the prevalence of IPH was high (34.5% of participants; n = 1,006) in plaques causing carotid wall thickness  $\geq 2.5$  mm<sup>9</sup>.

Kurosaki et al<sup>10</sup> reported that IPH appeared in 96 carotid atherosclerotic plaques in 96 subjects in 1,190 individuals (8.1%) who underwent annual medical check-up. During a mean follow-up period of 53 months, 16 (5 hemorrhagic and 11 ischemic events) patients experienced cerebrovascular events. Among these 16 patients, 4 of them with and 3 without IPH presenting in the carotid plaque. Among those ischemic events caused by a carotid lesion (n = 3), 2 events were associated with IPH. These observations indicated that in a general population, only 2.1% lesions with IPH would be responsible for ischemic events in ~4.5 years. Kurosaki et al<sup>10</sup> also noted that diabetic patients with IPH were at a higher risk of experiencing ischemic events. Among 8 diabetic patients with IPH presenting in the carotid plaque, 3 experienced ischemic events. This study again reinforces the association between IPH and cerebrovascular events. However, it highlights the challenge in identifying higher risk carotid lesions within the general population, as the annual event rate for hrMRI-defined IPH was extremely low at 0.47%. Thus, the probability of future cerebrovascular events

cannot be solely based on the presence of IPH and other biomarkers that improve risk stratification are urgently required.

Although wall thickness (alternatively, degree of luminal stenosis) also cannot serve as a robust biomarker for refined risk stratification, high-risk atherosclerotic plaque features are associated with maximum carotid wall thickness. IPH and lipid appeared in 5.6% of and 11.2% of plaques with thickness of 2.0-2.5 mm, and in 44.5% of and 37.4% of plaques with 3.7-9.9 mm thickness<sup>9</sup>. Both of these two higher risk features appeared simultaneously in 9.3% of plaques (17.7% of subjects)<sup>9</sup>. As the majority of ischemic events are induced by plaque rupture, high mechanical loading within the plaque structure due to blood pressure may be useful to assess the likelihood of rupture<sup>11</sup>, as fibrous cap integrity may be compromised if such loading exceeds its material strength. A pilot study in the coronary arteries demonstrated that mechanical analysis may improve risk prediction 2-3 fold for individual high-risk features<sup>12</sup>.

Integration of luminal stenosis, plaque composition and mechanical loading has potential to improve the prediction of future ischemic events. Rigorously designed large-scale studies are now warranted to provide evidence that these methods improves patient care.

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## **Reference**

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**Figure 1.** Red blood cells may leak from neovessels undergone apoptosis and contributed to the lipid accumulation and plaque progression (A: H&E stain showing the overall structure of a carotid plaque with severe luminal stenosis; B: local view of the area enclosed by the dash-box in A showing a neovessel; C: leaked red blood cells in the process of apoptosis; Red asterisks: neovessels; Green arrows: apoptotic red blood cells)

Figure 1

