



# Before Plaque Enhancement Can Predict Stroke Recurrence, Alternative Etiologies Must Be Off the Table

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I read with interest the article by Huang et al. [1] on a prospective study that estimated the risk of stroke recurrence in 25 patients with a history of unilateral ischemic stroke and carotid artery stenosis on the homolateral side by determining plaque enhancement on contrast-enhanced ultrasonography (CEUS) of the carotid arteries. Patients with plaque enhancement were found to have an increased risk of recurrent stroke with an adjusted hazard ratio of 38.3 (95% confidence interval [CI] 14.9–97.7,  $P < 0.001$ ) [1]. A net 32.0% of the recurrence group was appropriately reclassified upwards by the addition of plaque enhancement to the Essen Stroke Risk Score (ESRS) [1]. It was concluded that plaque enhancement was a significant and independent predictor of stroke recurrence in patients with prior ischemic stroke and that the addition of plaque enhancement improved the risk stratification ability of ESRS [1]. The study is excellent but has limitations that raise objections that should be discussed.

The main limitation of this study is that plaque-side stroke recurrence was attributed solely to the progression of

plaque morphology or the degree of internal carotid artery stenosis [1]. It was not considered that the stroke recurrence on the homolateral side of the first stroke could have several other reasons. Stroke recurrence can be due to stenosis or occlusion of the intracerebral artery, stenosis or occlusion of the distal internal carotid artery, or a plaque proximal to the internal carotid artery. Stroke recurrence can also be due to thrombus formation within the heart. Cardiac embolisms can be caused by atrial fibrillation, heart failure, left ventricular hypertrabeculation, or Takotsubo syndrome. Until these alternative mechanisms are reliably ruled out as causes of stroke recurrence, the data presented are unconvincing.

A second limitation of this study is that CEUS was not repeated after the second stroke. Knowing whether there was truly a progression in plaque morphology compared with the original study would support the notion that plaque dynamics are responsible for stroke recurrence.

Another limitation is that none of the magnetic resonance imaging (MRI) results were presented to show recurrence of the stroke. We should know how many of the 25 patients with recurrent stroke had available MRI showing recurrent stroke, how many had a lacunar stroke, how many had an embolic stroke, and how many had a territorial or hemispheric stroke. Knowing the location and size of the stroke territory is crucial for assessing the stroke etiology.

A fourth limitation of the study is that the number of included patients in the verum group ( $n = 25$ ) is very small. Therefore, it is not possible to draw generalized conclusions from this study. Larger cohorts should be examined using CEUS in a multicenter design. As noted by the authors [1], other limitations were that the follow-up time was short, only one plaque was assessed when there were multiple plaques, and the CEUS results were highly dependent on the image planes.

Overall, this study has limitations that call the results and their interpretations into question. Addressing these issues would have strengthened the conclusions and improved the status of the study. Before plaque enhancement is recommended as a predictor of stroke recurrence, alternative stroke etiologies must be adequately ruled out.

## Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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