Voice of Stroke — October 2026

Episode 9: Unmasking the aetiology of cryptogenic stroke: can imaging help?

Introduction: Welcome to Voice of Stroke – your rapid, reliable update on the science advancing stroke care – brought to you by the European Stroke Organisation.

In this episode of Voice of Stroke, we're turning to one of the oldest frustrations in stroke medicine: the stroke without a cause. Embolic stroke of undetermined source, or ESUS, accounts for a substantial proportion of ischaemic strokes, and the debate has always been whether the cause remains "undetermined" because it is genuinely unknown, or because we haven't yet looked in the right way. Today, we are looking at three papers exploring how different imaging approaches might help to resolve this mystery.

- First: can we image a thrombus directly, in a living patient, and find where a stroke actually came from?
- Second: can we use routine CT angiography to identify which non-stenotic carotid plaques are likely culprits rather than bystanders?
- And finally: can the clot retrieved during thrombectomy tell us which type of ESUS we're dealing with?

Let's get started.

Our first paper was published in Circulation in September.

Current stroke classification relies largely on inference. We find a potential stroke source, such as atrial fibrillation, and assume it's responsible for the stroke. This study asked whether we could do better by directly identifying the source of thrombosis.

The investigators used a novel radiotracer, fluorine-18 G-P-one, which binds to activated glycoprotein two-b-three-a receptors on platelets, allowing PET imaging to detect acute platelet-rich thrombi.

In a single-centre prospective study, 100 patients with acute ischaemic stroke underwent G-P-one PET combined with CT angiography within 21 days of symptom onset, alongside standard investigations. Most strokes were minor, with a median NIH stroke scale of 2. An expert stroke physician classified stroke cause using the Causative Classification System, blinded to the PET findings. Separately, the PET images were read by readers blinded to all clinical data.

The findings were striking.

Overall cardiac or vascular G-P-one uptake indicating thrombosis was detected in nearly two-thirds of participants. Carotid uptake was particularly common, with 60% showing uptake in an ipsilateral carotid artery supplying the territory of the stroke. Interestingly, most carotid plaques showing increased uptake caused less than 50% stenosis.

The cardiac findings were also intriguing. Relevant thrombosis was detected in only a minority of patients with atrial fibrillation or PFO. On the other hand, 11 patients had uptake involving the native aortic or mitral valves, suggesting that these may be under-recognised sources of embolism.

Perhaps most importantly, GP1 imaging changed the assigned stroke mechanism in over a quarter of patients. In particular, among those whose stroke cause was initially undetermined, 44% had a potential thrombus source identified and were reclassified as having either large-artery atherosclerosis or a cardioembolic mechanism.

Furthermore, GP1 uptake was also associated with a 10-fold increase in the risk of recurrent events.

Of course, this was a relatively small, single-centre study, and larger multicentre studies will be needed to establish the clinical utility of this technique. Nevertheless, the concept is compelling. Rather than inferring the source of embolism from associated risk factors, G-P-one PET may allow us to image active thrombosis directly, potentially moving towards a more mechanism-based classification of stroke.

Notably, one of the sources it uncovered, non-stenotic carotid plaque, is exactly where our next paper picks up.

Our second paper, assessing the potential causal link between non-stenotic carotid plaque and ESUS, was published in Neurology earlier this year.

Non-stenotic carotid plaques are plaques causing less than 50% luminal narrowing. Although they only cause mild stenosis, plaques with high risk features, such as a lipid-rich necrotic core, intraplaque haemorrhage,

ulceration, or intraluminal thrombus, have been associated with ipsilateral ESUS. However, definitions of “high risk” plaque varied between studies, making their findings difficult to compare and generalise.

To address this problem, a standardised multimodal imaging system, the Plaque Reporting and Data System, or Plaque-RADS was recently developed to harmonise plaque assessment and improve reproducibility. The original system requires access to ultrasound, CT and MRI, which may not always be feasible for every patient. A modified CT angiography based version was subsequently proposed, but had only been tested in a small cohort. In this study, the investigators applied this CTA based Plaque-RADS classification to a large ESUS cohort.

The scale grades plaques from 1 to 4. Grade 1 represents a normal vessel wall, and grade 2 is a plaque less than 3 millimetres thick; both are considered low risk. High risk plaques are grade 3, at least 3 millimetres thick or with surface ulceration, or grade 4, with intraplaque haemorrhage or intraluminal thrombus, regardless of thickness.

Among 512 patients with ESUS and unilateral anterior circulation stroke, the median age was 70 and just under half were women. Importantly, inter-rater agreement for Plaque-RADS was excellent, with a kappa of 0.83. This suggests that the CTA-based classification can be applied reliably and reproducibly.

Several other observations also supported the hypothesis that high-risk non-stenosing plaques may be causally associated with ESUS.

First, high-risk plaques were found in 21.3% of arteries on the side of the stroke, compared with 11.9% on the opposite side, corresponding to an adjusted odds ratio of 2.65.

Second, patients with high-risk plaques were less likely to have a competing potential stroke mechanism, including high-risk PFO or atrial fibrillation. However, the PFO finding needs some caution, as fewer of the older, plaque-positive patients underwent screening for it.

The recurrence data add a further layer. Over a median follow-up of 32 months, there were 44 recurrent strokes. Overall stroke recurrence was higher in patients with an ipsilateral high-risk plaque, although the association was no longer significant after adjustment for potential confounders. More interestingly, however, an ipsilateral high-risk plaque was associated with more than a threefold increase in recurrent stroke in the same vascular territory: 11% versus 3%, an association that remained significant after adjustment. This estimate should still be interpreted cautiously, as there were only 24 ipsilateral recurrent strokes in total. Nevertheless, that territorial specificity is what we might expect if these plaques are genuinely contributing to the mechanism of stroke.

The authors' message is therefore both practical and potentially important for future research. A standardised CTA-based plaque score appears to provide a reliable and reproducible way of identifying high-risk non-stenotic carotid plaques. It may help identify patients with ESUS whose stroke mechanism is related to carotid atherosclerosis, and could potentially be used to select patients for future ESUS trials.

One caveat worth pointing out is that whilst CT is more accessible than MRI, intraplaque haemorrhage, an important high risk feature strongly associated with recurrent stroke, is better characterised by MRI. Ongoing studies, including the IMPROVE trial, are also assessing whether incorporating intraplaque haemorrhage with other clinical predictors can better guide patient selection for revascularisation.

So this study gives us one way of identifying a potential culprit at its source - by looking at the carotid plaque. But what if we approach the same question from the other end, and examine the clot itself?

That brings us to our third and final paper, which moves from the vessel wall to the clot itself. It was published in Neurological Sciences. The question here was whether the histological make-up of thrombi retrieved during thrombectomy can reveal the hidden diversity of stroke mechanisms within ESUS.

This was a retrospective single-centre study of anterior-circulation strokes treated with thrombectomy. Of 344 treated patients, 159 had retrieved thrombus available and met the inclusion criteria: 91 cardioembolic, 18 large-artery atherosclerosis, and 50 ESUS. Investigators measured the proportion of red blood cells, fibrin, and white blood cells in each clot.

Thrombi from large artery and cardioembolic strokes showed distinct histological profiles, with thrombi from large artery atherosclerosis displaying lower fibrin and higher red blood cell content than those from cardioembolic strokes.

Taken as a single group, ESUS clots looked more cardioembolic but when the investigators split ESUS patients using the Plaque-RADS classification from our previous paper, two distinct patterns emerged. In patients without a high-risk ipsilateral plaque, the clots resembled cardioembolic thrombi. In contrast, patients with a high-risk ipsilateral plaque had clots that were red cell rich and fibrin poor, with no detectable difference from those associated with large-artery atherosclerosis.

It is worth noting, however, that the plaque-positive ESUS group contained just eight patients. Nevertheless, the study raises an interesting possibility: thrombus composition may provide complementary information about the underlying stroke mechanism when combined with clinical and imaging findings. And importantly, it provides another potential clue that ESUS patients with high-risk carotid plaques may represent a distinct

subgroup with an underlying atherosclerotic mechanism.

So to summarise,

- Fluorine-18 G-P-one PET is a promising new tool that frequently changed the assigned stroke mechanism, identifying a potential thrombus source in almost half of patients whose stroke cause was initially undetermined.
- Routine CTA, read with a standardised scale, Plaque-RADS, can reliably identify non-stenotic carotid plaques that behave like culprits: more often on the stroke side, and linked to recurrence in the same territory.
- And finally, thrombus composition might also be a useful tool as the clot itself carries a signature of its origin. ESUS with a high-risk plaque produces clots that look atherothrombotic rather than cardioembolic, although that conclusion currently rests on a very small subgroup.

Put together, these three studies also reinforce an increasingly important message: ESUS is probably not one disease, but a collection of different stroke mechanisms that our conventional diagnostic work-up has not been able to distinguish. This may also help explain why previous trials treating ESUS as a single entity failed to demonstrate benefit from a single therapeutic strategy. Perhaps the next generation of ESUS trials will need to start one step earlier by working out which disease each patient actually has, and then targeting treatment accordingly.

Full references and links to all the studies discussed are available in the episode notes.

Ending: That's all for this episode of Voice of Stroke, brought to you by the European Stroke Organisation. You can listen to Voice of Stroke on all your favourite podcast channels, including Spotify and Apple. Visit the European Stroke Organisation E-S-O-dash-stroke-dot-org for more information about our organisation, mission and our key activities. I'm Linxin Li. Thanks for listening.

Credit: This episode was written by Voice of Stroke Podcast editor Robert Hurford and editor-in-chief Linxin Li.

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Credit Notes

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