Upon the diagnosis of an embolic stroke, the absence of significant arterial pathology in the symptomatic vessels, major cardiac sources of emboli and "other specific causes of stroke" will allow the formal classification of an embolic stroke of undetermined source (ESUS). And what is there to do then?

Firstly, we should critically review the diagnostic work-up performed. Were all causes of embolic stroke really excluded? Regarding arterial pathology, occasionally the source of embolus is in less frequent locations that should be kept in mind. Complex atherosclerotic plaques in the aortic arch, distal extracranial or proximal intracranial vessels are locations often neglected. Moreover, attention should be paid to arterial pathology without hemodynamic impact, such as some cases of dissection or vasculitis, that may be overlooked, requiring specific exams. A routine ECG and 24-hour ECG monitoring excluding the presence of a potentially embolic arrhythmia may be enough for the formal classification of ESUS. However, they should not reassure the attending physician. Longer cardiac monitoring through implantable and non-implantable devices has been demonstrated to improved diagnostic labelling.

The remaining critical question is what thromboprophylaxis strategy to use. Considering the medical equipoise at this time point of knowledge, the logical answer, whenever possible, can be only one: randomize! In case no trial is available for a specific patient, the decision should, like always, be shared by physician and patient after careful consideration.

In sum, ESUS patients require a specific diagnostic and therapeutic approach that will surely be progressively reconsidered during the following years.