The definition of cryptogenic stroke or stroke of undetermined origin is affected by the current knowledge of the cause and pathogenesis of stroke and by the availability, comprehensiveness, quality, and timeliness of the ancillary investigations undertaken to discover the cause of the stroke.¹ In The Lancet Neurology, Linxin Li and colleagues² report findings from a population-based study of the burden, outcome, risk factors, and long-term prognosis of cryptogenic stroke in patients with a first transient ischaemic attack (TIA) or ischaemic stroke. They found that of 2555 first ischaemic events, 812 (32%) were cryptogenic. The study shows that the prognosis of cryptogenic stroke and the risk of recurrence are similar to those of large artery disease and small vessel disease. For example, death or dependency at 6 months was similar after cryptogenic stroke compared with large artery and small vessel subtypes combined (23% vs 27%; p=0.26), as was the 10-year risk of recurrence (32% vs 27%; p=0.91). Secondary stroke prevention must be similarly aggressive and appropriate in stroke with and without identified cause. The findings from this Article question the role of paroxysmal atrial fibrillation as the major cause of cryptogenic stroke, which contrasts with the present enthusiasm for the use of technology to detect paroxysmal atrial fibrillation³ and for the possibility to prevent recurrent cryptogenic stroke with anticoagulants.

The results of this study are especially important for health-care policy makers, because they show the burden of cryptogenic stroke, the rationale for a comprehensive investigation into the cause of every ischaemic stroke, and the need to provide stroke centres with access to the necessary ancillary diagnostic procedures. The diagnostic work up used in this study is unfortunately still not routinely used for every patient with ischaemic stroke, neither in the UK nor in mainland Europe. In developing countries, such diagnostic instruments are a distant mirage.

This study has some limitations that hamper the translation of its results into routine practice: both TIAs and strokes were included, and the diagnosis of TIA can be erroneous even when done by a specialist; the causative investigation was incomplete, especially in phase 1; the search for paroxysmal atrial fibrillation was not pursued intensively; the investigation of the cause of stroke in recurrent strokes was incomplete; and the newest devices for prolonged heart rhythm monitoring were not used. All these limitations might have resulted in misclassification of some strokes as cryptogenic and decrease the probability of detecting atrial fibrillation and of classifying a stroke as cardioembolic during follow-up.
Other aspects in the investigation of cryptogenic stroke are difficult to enforce in population-based studies. Examples include emergent echocardiography so as not to miss intracardiac thrombus; early imaging of the neck vessels, including cervical MRI with fat suppression, to detect arterial dissection; and transoesophageal echocardiogram to exclude patent foramen ovale in all age groups and to rule out prominent or complicated atheroma in elderly patients. Patients with evidence of right-to-left shunt but no patent foramen ovale should be assessed for pulmonary fistulae. In middle aged and elderly patients with no cause for their stroke, searching for an occult neoplasm should be considered. In a systematic review and meta-analysis, a four-phase sequential search for paroxysmal atrial fibrillation—using (1) electrocardiogram (ECG); (2) serial ECG, in-hospital continuous monitoring, and Holter; (3) ambulatory Holter; and (4) mobile cardiac telemetry and external and implantable loop recorders—increased the percentage of detected atrial fibrillation from 8% after an admission ECG only to an overall detection yield of 24%.

Nevertheless, the messages from the present Article for the practising neurologist are clear: (1) do not be surprised to find no cause in a third of ischaemic strokes; (2) do not label a patient as having a cryptogenic stroke before completion of a comprehensive investigation of possible causes; (3) educate the patient on risk-factor control and prescribe an antihypertensive, a statin, and an antiplatelet drug to prevent recurrence; and (4) do not expect that detection of paroxysmal atrial fibrillation and anticoagulation will solve the mystery of cryptogenic stroke and eliminate stroke recurrence in these patients.

The aim of future research on this topic should be to decrease the proportion of strokes classified as cryptogenic and to prevent vascular recurrences in patients with these strokes. Technological priorities in research include user-friendly devices to detect atrial fibrillation, cardiac MRI to depict structural and functional abnormalities associated with increased stroke risk, and high-resolution MRI of intracranial vessels to visualise strategic or unstable atheroma. Multicentre collaborative studies will be necessary to identify biomarkers of new genetic, inflammatory, infectious, and oncological disorders associated with stroke (eg, NCT01934725). Results of ongoing trials with novel oral anticoagulants in patients with embolic strokes of unknown origin will be available in a few years (NCT02313909, NCT02239120). Even if the results of these trials are negative, anticoagulation will still be indicated in all patients with cryptogenic stroke if de-novo atrial fibrillation is detected. Psychosocial outcomes and their determinants (eg, insecurity for having no cause for their stroke or fear of recurrence) also need to be investigated in these patients with stroke in whom no cause is discovered.