including MRI field strength, other secondary prevention therapies (eg, statins), and vascular risk factors such as diabetes mellitus and chronic kidney disease.

Additionally, no central adjudication of the outcome events and no formal assessment of recurrent stroke severity and residual disability were done. The authors report the absence of any interaction between oral anticoagulant type (vitamin K antagonists [*vs* non-vitamin K oral anticoagulants]) and cerebral microbleed presence for the outcomes of recurrent ischaemic stroke and intracranial haemorrhage, but this finding might be attributed to the modest number of outcome events and particularly intracranial haemorrhages (n=91) as well as to potential imbalances between vitamin K antagonists (n=5253) and non-vitamin K oral anticoagulants (n=2484) subgroups. The protective effect of non-vitamin K oral anticoagulants (compared with vitamin K antagonists) in the risk of incident intracranial bleeding in patients with atrial fibrillation receiving anticoagulation for secondary stroke prevention has been well established.[6]

In conclusion, the study by Wilson and colleagues[4] highlights that the absolute risk of recurrent ischaemic stroke consistently exceeds the absolute risk of intracranial haemorrhage in patients with a history of ischaemic stroke or transient ischaemic attack even in the presence of high cerebral microbleed load (≥20). These findings suggest that cerebral microbleed presence, burden, and pattern on neuroimaging should not influence the decision to select appropriate antithrombotic therapy for secondary stroke prevention. Additional research is required to establish whether cerebral microbleeds should be incorporated as a neuroimaging marker in clinical risk prediction scores of recurrent ischaemic stroke or intracranial haemorrhage in patients with recent cerebral ischaemia treated with oral anticoagulants or antiplatelet drugs.

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Vertebral artery stenting: lifting the therapeutic fog

Nature's Images/SPL

Clearing fog over Casa Grande, Chisos Mountains, Big Bend National Park, Texas

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In the four decades after the introduction of carotid endarterectomy, there were no hiqh-quality randomised clinical trials to help guide decision making. Therefore, the value of carotid surgery was intensely debated but remained unsettled. 17 years ago, the legendary neurologist Henry Barnett addressed the situation regarding interventional therapy for posterior circulation stenosis, including vertebral and basilar artery lesions, in a landmark article. He wrote that, unless high-quality randomised trials were performed, "these endovascular procedures will drift into the therapeutic fog that surrounded carotid endarterectomy before the major trials were conducted".[1]

In *The Lancet Neurology*, Hugh Markus and colleagues[2] try to lift part of the therapeutic fog surrounding the potential role of vertebral artery stenting.[2] They did a pooled analysis of individual patient data from three trials (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis [SAMMPRIS],[3] Vertebral Artery Stenting Trial [VAST],[4] and Vertebral Artery Ischaemia Stenting Trial [VIST][5]) that included comparisons of vertebral artery stenting versus medical treatment. The three trials collectively included 354 patients who had either intracranial or extracranial stenosis. The authors rightfully point out that the distinction between intracranial or extracranial

location of the stenosis is important because intracranial lesions are associated with a higher stroke risk than extracranial lesions.[6] Extracranial stenosis is also a relatively infrequent cause of stroke. In the New England Medical Center Posterior Circulation Registry, extracranial stenosis was identified as the cause of stroke or transient ischaemic attack in 9% of cases.[7]

Periprocedural outcomes with stenting were markedly different according to stenosis location. The frequency of 30-day any stroke or death events was 1% (one event in 121 patients) for extracranial stenosis and 16% (ten events in 64 patients) for intracranial stenosis. Over a median of 36·5 months' (IQR 24·2–49·4) follow-up, the frequency of fatal or non-fatal stroke events was 12% (23 of 186 patients) in the stenting group and 14% (24 of 168 patients) in the medical treatment group (hazard ratio 0·81, 95% CI 0·45–1·44). In the extracranial stenosis group (244 patients), the hazard ratio was 0·63 (95% CI 0·27–1·46) and in the intracranial stenosis group (110 patients) the HR was 1·06 (0·46–2·42). 161 (46%) of 354 patients had their last symptomatic event within 14 days of study enrolment.

Markus and colleagues have provided us with the best information available on the merits of vertebral artery stenting. However, we should recognise several limitations of this study. First, the three trials that contributed patient data were heterogeneous in several ways. SAMMPRIS included patients at a mean time of 10 days following the last stroke or transient ischaemic attack, whereas the other trials had a mean delay of about 36 days. Second, medical therapy followed a strict protocol in SAMMPRIS, with 90 days of dual antiplatelet therapy and high-potency statins mandated by the protocol. By contrast, VIST had an imbalance in dual antiplatelet therapy use at 1 month between the two treatment groups (33% in the medical treatment group and 57% in the stenting group). With the demonstrated benefit for dual antiplatelet therapy in patients with recent transient ischaemic attack or stroke, the imbalance in VIST might have led to overestimation of the observed stroke risk with medical therapy.[8] Finally, in VIST, a high proportion of patients enrolled on the basis of non-invasive radiological testing had less than 50% stenosis on angiography, which could artificially reduce the low complication rate for extracranial stenting reported by the authors.

We should also recognise that both medical therapy and stenting practice have evolved since these trials were initially performed. New therapies for reducing stroke risk (including pioglitazone and PCSK9 inhibitors) are now in the stroke prevention armamentarium. SAMMPRIS also demonstrated the benefits of increased physical activity for patients with severe intracranial stenosis.[9] This is a low-cost option that all patients should embrace as part of an integrated stroke prevention paradigm. Regarding stenting, delaying stenting for a couple of weeks to avoid so-called hot lesions and use of submaximal dilatation could lead to improved outcomes for intracranial lesions.[10]

Clinicians now face a common conundrum. Given the fact that intracranial stenosis has a worse natural history than extracranial stenosis, should we subject patients to a risky endovascular procedure as part of a high-risk, high-reward strategy? Or should we reserve vertebral artery stenting for extracranial lesions as part of a low-risk, low-reward treatment plan? Since both the extracranial and intracranial groups in this analysis did not have clear benefit with stenting, extracranial or intracranial stenting should certainly not be routine. In determining whether there are patients who would benefit from vertebral artery stenting, future investigators trying to clear the therapeutic fog still have plenty of work ahead.

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