I declare no competing interests.

1 Hoffmann TC, Del Mar C. Clinicians' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med* 2017; **177:** 407–19.
2 Al-Shahi Salman R, Minks DP, Mitra D, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *Lancet Neurol;* **18:** 643-52.
3 Thompson BB, Béjot Y, Caso V, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010; **75:** 1333–42.
4 RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet* 2019; published online May 22. http://dx.doi.org/10.1016/S0140-6736(19)30840-2.
5 Biffi A, Halpin A, Towfighi A, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology* 2010; **75:** 693–98.
6 Nandigam RN, Viswanathan A, Delgado P, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. *AJNR Am J Neuroradiol* 2009; **30:** 338–43.
7 Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis and recurrent intracerebral haemorrhage risk in cerebral amyloid angiopathy: large prospective cohort and preliminary meta-analysis. *Int J Stroke* 2019: published online Feb 20. DOI:10.1177/1747493019830065.
8 Charidimou A, Karayiannis C, Song TJ, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: meta-analysis in stroke patients with AF. *Neurology* 2017; **89:** 2317–26.

Can cerebral microbleeds predict stroke recurrence?

Published **Online** May 23, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30194-2

See **Articles** page 653

Should patients with a history of ischaemic stroke or transient ischaemic attack be treated with antithrombotic drugs? The answer to this question has been considered to be clear and straightforward for more than two decades.[1,2] However, the question regarding the balance of future intracranial bleeding risk compared with risk of recurrent ischaemic stroke in patients with high burden of cerebral microbleeds remains one of the most complicated problems of modern stroke medicine.[3]

In *The Lancet Neurology*, Duncan Wilson and colleagues[4] aim to elucidate the association between cerebral microbleed burden in baseline neuroimaging and the risk of recurrent stroke. The study was a pooled analysis of individual patient data from 20 322 patients (mean age 70 years [SD 13]) with history of ischaemic stroke or transient ischaemic attack from 38 cohort studies.[4] After a cumulative follow-up of 35 225 patient-years (median 1·34 years [IQR 0·19–2·44]) the investigators documented that cerebral microbleed presence in baseline neuroimaging was associated with increased risk for both ischaemic stroke and intracranial haemorrhage. Despite the fact that the adjusted hazard ratio (aHR) for intracranial haemorrhage was nearly five times higher than that for ischaemic stroke for patients with five or more or ten or more cerebral microbleeds and nearly eight times higher for patients with 20 or more cerebral microbleeds, the absolute rate of ischaemic stroke exceeded that of intracranial haemorrhage even in patients with high (≥20) cerebral microbleed burden.[4] Notably, all associations were independent from cerebral microbleed anatomical distribution (lobar *vs* mixed *vs* deep), antithrombotic treatment (antiplatelet or anticoagulant), ethnicity (white *vs* non-white), age (>80 years *vs* ≤80 years), and the presence of white-matter hyperintensities on baseline neuroimaging or the diagnosis of probable cerebral amyloid angiopathy.[4]

The main strengths of this study are the large sample size, including almost all available findings from published and unpublished cohort studies of adults with recent ischaemic stroke or transient ischaemic attack using appropriate MRI sequence sensitive to magnetic susceptibility, the prospective study design with strict inclusion and exclusion criteria, and the comprehensive, prespecified, and robust statistical analysis plan. This study offers novel and clinically relevant information that in patients with recent ischaemic stroke or transient ischaemic attack the absolute risk of ischaemic stroke is higher than that of intracranial haemorrhage, regardless of cerebral microbleed presence, burden, or pattern and independently of their secondary prevention treatment with antiplatelets or oral anticoagulants. Notably, the individual-patient-data meta-analysis credibly contradicts the findings of a previous meta-analysis that did not detect any association between cerebral microbleed presence or burden and recurrent ischaemic stroke in patients with ischaemic stroke treated with oral anticoagulants.[5]

However, the observational study design is prone to residual confounding, and selection and indication biases. Furthermore, the investigators were unable to adjust for other cofounders in their multivariable models,

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.

Georgios Tsivgoulis, Aristeidis H Katsanos
Second Department of Neurology, "Attikon" University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens 15344, Greece (GT, AHK); Department of Neurology, University of Tennessee Health Science Center, Memphis, Tennessee, USA (GT); Department of Neurology, St-Josef Hospital, Ruhr University of Bochum, Bochum, Germany (AHK)
tsivgoulisgiorg@yahoo.gr

We declare no competing interests.

1 Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; **3:** CD000029.
2 Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131:** 492–501.
3 Shoamanesh A, Charidimou A, Sharma M, Hart RG. Should patients with ischemic stroke or transient ischemic attack with atrial fibrillation and microbleeds be anticoagulated? *Stroke* 2017; **48:** 3408–12.
4 Wilson D, Ambler G, Lee K-J, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol* 2019; **18:** 653–65.
5 Charidimou A, Karayiannis C, Song TJ, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: meta-analysis in stroke patients with AF. *Neurology* 2017; **89:** 2317–26.
6 Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol* 2013; **70:** 1486–90.

Vertebral artery stenting: lifting the therapeutic fog

Nature's Images/SPL

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

Published Online
May 23, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30191-7

See Articles page 666

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