

**Letter by Werring et al. Regarding Article, “Embolic Stroke, Atrial Fibrillation, and Microbleeds: Is There a Role for Anticoagulation?”**

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Keywords: Cerebral microbleeds, Ischemic stroke, Anticoagulation, Intracerebral hemorrhage

Letter to the editor regarding: Embolic Stroke, Atrial Fibrillation, and Microbleeds: Is There a Role for Anticoagulation? Diener HC, Selim MH, Molina CA, Greenberg SM. Stroke. 2016 Mar;47(3):904-7. doi: 10.1161/STROKEAHA.115.011150.

Total word count: 675

Dear Dr Fisher,

We read with interest the recent controversies in stroke article “Embolitic stroke, atrial fibrillation and microbleeds: is there a role for anticoagulation”<sup>1</sup>. We congratulate the authors for highlighting the increasingly common and difficult clinical dilemma of anticoagulation in patients with cardioembolic stroke who are found to have cerebral microbleeds (CMBs). They helpfully discuss some of the observational evidence, and articulate the persisting clinical uncertainty around this question. We agree with Dr Greenberg’s conclusion that holes in our knowledge need to be filled with hard data.

A systematic review and meta-analysis of published prospective studies of 3067 patients with ischemic stroke or TIA found that CMBs were associated with a significant increased odds ratio for the risk of any recurrent stroke (OR, 2.25; 95% confidence interval [95% CI], 1.70-2.98;  $P < 0.0001$ ). CMBs were associated with a higher odds ratio for the risk of intracerebral hemorrhage (OR, 8.52; 95%CI, 4.23-17.18;  $P = 0.007$ ) than ischemic stroke IS (OR, 1.55; 95% CI, 1.12-2.13;  $P < 0.0001$ ). However, the vast majority of these patients were treated with antiplatelet agents: only a minority (less than 200) received anticoagulants. Thus, there is an urgent need for more data on whether CMBs influence the risk of ICH and IS in patients on anticoagulants to inform the debate. Importantly, both absolute and relative risks of ischemic stroke and intracerebral hemorrhage are needed; furthermore, how the burden and location of CMBs affects the magnitude and balance of risks also remains unknown.

To address the many gaps in knowledge, observational studies are underway to specifically address the question of CMBs and stroke risk in individuals with cardioembolic (atrial fibrillation-associated) ischemic stroke treated by anticoagulation, including two large multicentre inception cohort studies: Clinical Relevance of Microbleeds in Stroke (CROMIS 2; see <https://www.ucl.ac.uk/cromis-2>, <https://clinicaltrials.gov/ct2/show/NCT02513316>)<sup>2</sup>

and Intracerebral Hemorrhage Due to Oral Anticoagulants: Prediction of the Risk by Magnetic Resonance (HERO; see <http://heropub.pic.es>, <https://clinicaltrials.gov/ct2/show/NCT02238470>). The teams leading these studies (which have recruited over 2500 patients) have begun a collective systematic international individual patient data meta-analysis including individuals with presumed cardioembolic ischemic stroke related to atrial fibrillation, started for the first time on oral anticoagulation. Since intracranial haemorrhage (including intracerebral haemorrhage) is, thankfully, a rare consequence of oral anticoagulation, only such large-scale international collaborative efforts will provide useful and precise estimates of the risks associated with antithrombotic drugs in patients with CMBs. We warmly encourage other investigators to join in this international collaborative effort. Until data from such international efforts are available, clinicians will need to make individualised decisions, and we – to once again quote C Miller Fisher - will continue to “wake up once a week or so in a cold sweat” each time we anticoagulate a patient, especially if they have CMBs.

**Disclosures: Dr Werring discloses speaker fees from Bayer.**

## **References**

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