Reducing the risk of recurrent stroke in patients with AF

Previous stroke or transient ischaemic attack (TIA) is the most powerful independent predictor of stroke in patients with atrial fibrillation (AF), with an annual rate of subsequent stroke of between 6 and 10% per year in the absence of anticoagulation. The time interval from the most recent stroke or TIA is inversely related to stroke rate, but previous stroke or TIA occurring in the past 1–3 years still confers a high (>5% per year) risk of stroke. The rate seems to be lower for patients with AF and previous TIA versus those with AF and previous stroke, but it is still substantial, and the responses to anticoagulation are similar for patients with both types of brain ischaemia. The absolute reduction in stroke provided by anticoagulation for patients with AF and previous stroke is larger than that of any other medical intervention for stroke prevention.

Previous stroke or TIA is not a causal risk factor for stroke, but is a marker of underlying pathological factors that lead to thrombus formation in the left atrial appendage (not all strokes in patients with AF arise from this source, but most do). However, the rate of ischaemic stroke among patients with AF with previous stroke or TIA remains unaccountably high when adjusted for other known independent clinical predictors and markers of atrial stasis. This unaccountably high rate emphasises that important pieces of the pathological puzzle of stroke in AF are still missing.

On this background, in this issue of The Lancet Neurology, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) investigators report results from the subgroup of 3436 patients with previous stroke or TIA from a large randomised trial that compared apixaban with warfarin in patients with AF. In patients with previous stroke or TIA, the risk of stroke was 2.5 times higher than in those without. Although the relative risk reduction in stroke with apixaban versus warfarin was similar in patients with and without previous stroke or TIA, the absolute reduction in stroke or systemic embolism in the apixaban group compared with the warfarin group was more than three times greater in participants with previous stroke or TIA than in those without (0.77 [0.08 to 1.63] vs 0.22 [0.03 to 0.47] events per 100 patient-years of follow-up). Even so, the estimated number-needed-to-treat with apixaban versus warfarin to prevent one stroke in 1 year for those with previous stroke or TIA is 130 patients. Most of this benefit was due to a reduction in intracranial bleeding among those assigned apixaban, with similar rates of ischaemic or unknown strokes with the two anticoagulants. The numbers of major extracranial haemorrhages, obtained by subtracting the numbers of intracranial bleeds from those of major bleeds, were nearly equal with apixaban and warfarin in those with previous stroke or TIA.

The importance of reduced risk of intracranial haemorrhage with apixaban, also noted with other novel oral anticoagulants (eg, dabigatran and rivaroxaban) compared with warfarin, cannot be over-emphasised. These neurologically devastating events are the most critical complication of anticoagulation in elderly patients with AF. The substantial benefits and superior safety profiles of the selective oral anticoagulants compared with warfarin are largely driven by their reduction in intracranial haemorrhage and encourage their wider use to prevent disabling ischaemic stroke in patients with AF.

The rate of recurrent stroke within 2 weeks of an initial ischaemic stroke in patients with AF averages about 5%. The ARISTOTLE investigators randomly assigned 21 patients to apixaban between 7 and 14 days after stroke (probably minor strokes since 84% of all participants with stroke had minor strokes), but did not report the time interval between randomisation and initiation of apixaban. Although this number is small, that none of these patients experienced secondary haemorrhage is reassuring and supports the ARISTOTLE investigators’ recommendation to begin apixaban about 7 days after onset of minor stroke. We suggest waiting longer (14 days) before starting apixaban or other novel oral anticoagulants after large strokes, although this suggestion is based on our experience with heparin and warfarin, and the lower rates of intracranial bleeding with the novel oral anticoagulants might prove this recommendation to be too cautious. In our view, antiplatelet drugs should be discontinued at the time that novel oral anticoagulants are initiated for secondary stroke prevention unless there is a compelling indication for their continued use. For patients with AF and TIA, we suggest immediate initiation of apixaban.
or other novel anticoagulants if they are to be used long term in preference to warfarin.

Among patients with AF, those with previous stroke or TIA benefit most from anticoagulation with warfarin or the novel oral anticoagulants. Anticoagulation in patients with AF and previous stroke or TIA offers a golden opportunity for prevention of disabling ischaemic stroke. The most important advantage conferred by the novel selective oral anticoagulants versus warfarin for these patients is the reduction in anticoagulation-associated intracranial haemorrhage.

RGH and JWE served on the Steering Committee of the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) clinical trial that compared apixaban with aspirin in patients with atrial fibrillation, sponsored by Bristol-Myers Squibb (the sponsor of the ARISTOTLE trial), and received consulting fees from Bristol-Myers Squibb.

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