

Risk of warfarin-associated intracerebral haemorrhage after ischaemic stroke is low and unchanged during the 2000s

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Context

Since its isolation during the early half of the 20th century from the mouldy hay responsible for 'sweet clover disease' in cattle, warfarin has become the most widely used oral anticoagulant.¹ Indications include atrial fibrillation (AF), mechanical prosthetic valves and venous thromboembolism treatment.² Warfarin reduces stroke risk in patients with AF by nearly two-thirds; AF accounts for 20% of ischaemic strokes, which tend to be more severe than those due to other aetiologies. In the late 1990s, reports began to emerge concluding that patients with AF were being undertreated with warfarin.³ This led to efforts to increase its use. Warfarin prescribing for patients with AF has been adopted as a quality metric.⁴ Despite proven effectiveness, the most feared complication of warfarin use is intracranial bleeding. The bleeding risk increases when international normalised ratio levels are supratherapeutic, and over a third of warfarin users are unable to maintain the therapeutic range. However, most intracranial haemorrhages develop within therapeutic levels. Other predictors of warfarin-associated bleeding include hypertension, old age, previous stroke, hepatic or renal dysfunction, predisposition to or previous haemorrhage and drug or alcohol abuse.⁵ Meta-analysis of novel oral anticoagulant trials in patients with AF has shown reductions in stroke, intracranial haemorrhage and mortality compared to warfarin.⁶

Methods

This observational study compared the warfarin-associated intracerebral haemorrhage rate in patients treated with warfarin after first-ever ischaemic stroke captured in the Swedish Stroke Register linked to the Cause of Death between 2001–2004 (period 1) and 2005–2008 (period 2).

Findings

Outcomes were analysed over a mean 2.6 years. The proportion of patients with atrial fibrillation (63.9% vs 72.1%; $p < 0.001$) and

hypertension (51.5% vs 59%; $p < 0.001$) increased between the study periods. The warfarin-associated intracerebral haemorrhage rate remained stable across the intervals (0.37% per year in period 1 vs 0.39% per year in period 2; adjusted HR, 1.04; 95% CI 0.73 to 1.48). The recurrent ischaemic stroke and death rates were similarly unchanged. Warfarin usage increased over time (24.6% in period 1 vs 29.9% in period 2; $p < 0.001$) and the utilisation of warfarin in combination with antiplatelet agents decreased (19.4% in period 1 vs 12% in period 2; $p < 0.001$).

Commentary

Although the number of first-ever ischaemic patients with stroke was similar between the two study periods, the proportions with AF, hypertension and warfarin treatment before admission significantly increased over time. This suggests increased utilisation of warfarin among patients with AF. Despite the fact that combining antiplatelet agents with warfarin increases bleeding risk and has never been shown to provide additional benefit over warfarin alone, this practice is commonly encountered. Notably, fewer patients in the present study were prescribed antiplatelet agents at discharge in period 2, possibly representing a shift away from this strategy.

Asberg and colleagues point out that their low warfarin-associated intracerebral haemorrhage after ischaemic stroke rate compares favourably with the warfarin arms of recent trials; however, prevalence of hypertension in their study is lower than in the meta-analysis (56% vs 79–94%) and could account for some of the difference.⁶ Only 18–55% of patients in the novel oral anticoagulant trials had previous stroke or transient ischaemic attack prior to enrolment, compared to 100% in the present study.

It is reassuring that, despite increased warfarin utilisation for AF, intracranial haemorrhage rates in patients with previous ischaemic stroke remain stable.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.



References

1. Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. *Br J Haematol* 2008;141:757–63.
2. Furie KL, Kasner SE, Adams RJ, *et al.* Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227–76.
3. Jencks SF, Cuerdon T, Burwen DR, *et al.* Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. *JAMA* 2000;284:1670–6.
4. Poisson SN, Josephson SA. Quality measures in stroke. *Neurohospitalist* 2011;1:71–7.
5. Pisters R, Lane DA, Nieuwlaat R, *et al.* A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation the Euro Heart Survey. *Chest* 2010;138:1093–100.
6. Ruff CT, Giugliano RP, Braunwald E, *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–62.