Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies


CRD summary
The authors concluded that the excess of microbleeds in warfarin users with intracerebral haemorrhage compared to other groups suggests that microbleeds increased the risk of warfarin-associated intracerebral haemorrhage. The reliability of the conclusion is uncertain given a number of weaknesses in the review (potential reviewer error and bias, unclear quality of included studies).

Authors' objectives
To compare the presence of cerebral microbleeds in: antithrombotic users versus non-antithrombotic users with intracerebral haemorrhage; antithrombotic users versus nonusers with ischaemic stroke/transient ischaemic attack; and intracerebral haemorrhage versus ischaemic events stratified by antithrombotic use.

Searching
MEDLINE was searched up to September 2009. Search terms were reported. Bibliographies of retrieved articles and reviews were handsearched. Unpublished data on stroke and transient ischaemic attack were sought from Oxford Regional Neurosciences Centres Cohort, Prognosis of Intracerebral Cerebral Hemorrhage study, Institute of Neurology Cohort, Edinburgh Stroke Study, Nishiogi-chuo Hospital Cohort and Suiseikai Kajikawa Hospital Cohort.

Study selection
Cohort studies of patients with stroke and transient ischaemic attack who had undergone gradient-recalled-echo magnetic resonance imaging (GRE MRI) to detect microbleeds were eligible for inclusion. Studies had to enrol at least 10 patients and present data on antithrombotic drug use for the presence or absence of microbleeds to be considered. Studies of patients with vascular dementia, chronic cerebrovascular disease andBinswanger disease were excluded.

Half of the published studies were conducted in Asian populations; others were in North American and European centres. Stroke types were varied (lacunar infarct, ischaemic stroke, intracerebral haemorrhage, ischaemic stroke/transient ischaemic attack). Mean age of patients (where reported) ranged from 60 to 71 years. The proportion with previous stroke ranged from 5% to 41%. The proportion of males ranged from 48% to 68%. The proportion of patients with microbleeds ranged from 18% to 77%. The proportion of antiplatelet users ranged from 1% to 100% and warfarin users ranged from zero to 100%. Included studies used GRE MRI to identify microbleeds; magnet strength, imaging sequences and slice thickness varied. Definitions of microbleed size were varied (≤10mm, ≤7mm, ≤5mm).

Unpublished cohorts with transient ischaemic attack and stroke included cohorts from UK, France and Japan. Mean age of patients ranged from 65 to 74 years. the proportion of patients with previous stroke ranged from 10% to 32%.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The authors did not state that they assessed the quality of included studies.

Data extraction
Data on number of patients with prespecified outcomes were extracted and used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for finding microbleeds in: antithrombotic users versus nonusers with intracerebral haemorrhage; antithrombotic users versus nonusers with ischaemic events; and intracerebral haemorrhage versus ischaemic stroke/transient ischaemic attack stratified by antithrombotic. Odds ratios and 95% CIs associated with a subsequent antithrombotic-associated intracerebral haemorrhage in patients with microbleeds versus patients without microbleeds were calculated.
Where data that were required to calculate odds ratios and 95% CIs were missing, a value of 0.05 was imputed in a 2x2 table.

The authors did not state how many reviewers were involved in data extraction.

**Methods of synthesis**

Pooled odds ratios and 95% CIs for prespecified outcomes were calculated using the Mantel-Haenszel method. Heterogeneity was assessed with $\chi^2$.

**Results of the review**

Twelve cohort studies were included (n=5,278 participants): six considered intracerebral haemorrhage (n=1,461) and eight considered ischaemic cerebrovascular events (n=3,817).

Frequency of microbleeds in warfarin users with intracerebral haemorrhage was significantly higher compared to non-antithrombotic users (OR 2.7, 95% CI 1.6 to 4.4). There was no significant difference in frequency of microbleeds in warfarin users with intracerebral haemorrhage and warfarin users with ischaemic stroke/transient ischaemic attack. The association between microbleed frequency and antiplatelet-associated intracerebral haemorrhage in comparisons that involved antiplatelet users was similar but weaker. Significant heterogeneity was detected.

In cohorts that included both intracerebral haemorrhage and ischaemic events, microbleeds were more frequent in intracerebral haemorrhage versus ischaemic stroke/transient ischaemic attack and the difference was greater among warfarin users (OR 8.0, 95% CI 3.5 to 17.8) and antiplatelet users (OR 5.7, 95% CI 3.4 to 9.7) compared with non-antithrombotic users (OR 2.8, 95% CI 2.3 to 3.5). Significant heterogeneity was detected.

For prospective data among all antithrombotic users, the odds of a subsequent intracerebral haemorrhage was significantly higher in patients with microbleeds compared to patients without microbleeds (OR 12.1, 95% CI 3.4 to 32.5). No significant differences were found among warfarin users.

**Authors' conclusions**

The excess of microbleeds in warfarin users with intracerebral haemorrhage compared to other groups suggested that microbleeds increased the risk of warfarin-associated intracerebral haemorrhage.

**CRD commentary**

The review question was clearly stated with regard to eligible patients and interventions. Eligible comparisons and outcomes were not clearly predefined. Only one major electronic database was searched, so some published articles may have been missed. It was unclear whether language restrictions were applied. Potential publication bias was minimised through searches of relevant sources of unpublished literature. It was unclear whether review processes were conducted in duplicate and so reviewer error and bias could not be excluded. Study quality was not assessed and so the quality of included studies was unclear. Statistical approaches used to combine data appeared appropriate. The authors acknowledged weaknesses in the review (heterogeneity in antiplatelet-associated intracerebral haemorrhage studies, inability to adjust for potential confounders in cross-sectional studies, small sample sizes in warfarin studies).

The reliability of the authors' conclusion is uncertain given weaknesses in the review (potential reviewer error and bias, unclear quality of included studies).

**Implications of the review for practice and research**

*Practice:* The authors did not state any implications for practice.

*Research:* The authors stated that further prospective studies of the safety of antithrombotic drugs in patients with microbleeds were needed. Further observational studies investigating the association between microbleeds and antiplatelet intracerebral haemorrhage were recommended.
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