Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review


CRD summary
The authors concluded that antiplatelet therapy use at the time of pre-intracerebral haemorrhage compared to no antiplatelet therapy use was associated with increased mortality, but not with poor functional outcome. The authors' conclusions should be treated with caution due to uncertain quality of the included studies, some shortcomings in the review process and variability between studies.

Authors' objectives
To assess whether pre-intracerebral haemorrhage antiplatelet therapy use was associated with mortality and poor functional outcome following intracerebral haemorrhage.

Searching
MEDLINE and EMBASE were searched for English-language studies to February 2008; search terms were reported. Reference lists of relevant articles were handsearched to identify further studies. Authors of excluded articles, known cohort studies of intracerebral haemorrhage and experts in the area were contacted for unpublished studies.

Study selection
Cohort studies of consecutive adults with primary intracerebral haemorrhage by antiplatelet therapy use, verified by neuroimaging, that assessed mortality or functional outcome using widely accepted validated scales were eligible for inclusion. Studies had to report odds ratios (OR) or probabilities of outcomes according to antiplatelet therapy use. Studies were excluded if intracerebral haemorrhage was due to identified secondary causes (such as arteriovenous malformations or thrombolysis).

In the included studies intracerebral haemorrhage was either primary, supratentorial or identified by billing codes. Most studies defined poor outcome according to the modified Rankin Scale. Mean age was 68.9 years (range 61.3 to 74.9). The proportion of males was 54.3% (range 43.1% to 70.5%). Pre-intracerebral haemorrhage antiplatelet therapy was used for a weighted mean of 22.9% of patients (range 4.3% to 37.7%). The weighted mean proportion of antiplatelet therapy users who took non-aspirin antiplatelet therapy alone or in combination with aspirin was 15.9% (range zero to 46.7%). The weighted mean proportion who used more than one antiplatelet therapy was 8.3% (range zero to 33.3%). Time of assessment ranged from discharge to 90 days.

One reviewer selected studies for inclusion in the review. Uncertainties were reviewed by a second reviewer.

Assessment of study quality
Two reviewers independently assessed study quality using previously published criteria that included loss to follow-up and whether confounding was considered.

Data extraction
Odds ratios (univariate and multivariable adjusted) and 95% confidence intervals (CI) were extracted for the effect of antiplatelet therapy on intracerebral haemorrhage outcome. Study authors were contacted to provide data adjusted for age and pre-morbid disability (where this information was available).

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Odds ratios and 95% confidence intervals were pooled using a random-effects model. Heterogeneity was assessed using $I^2$ and $X^2$. Meta-regression was used to assess the relationship between the odds ratio for poor outcome following intracerebral haemorrhage and the percentage of pre-intracerebral haemorrhage antiplatelet therapy users who used non-aspirin antiplatelet therapy or multiple antiplatelet therapy. Where possible, results were reported that excluded patients who took oral anticoagulants (with or without antiplatelet therapy). Analyses were re-run, removing patients treated with warfarin. Pre-specified subgroup analyses were defined and included: time of assessment; definition of poor outcome; geographic location; study sample; published antiplatelet therapy relationship; intracerebral haemorrhage inclusion criteria; and whether controlled for pre-intracerebral haemorrhage disability.

Publication bias was estimated with funnel plots and Egger’s test.

**Results of the review**
Mortality data were reported from 25 cohorts (n=9,910 patients) of which 15 were unpublished. Functional outcome data were reported from 19 cohorts (n=7,458) of which 14 were unpublished.

Mortality was significantly increased for pre-intracerebral haemorrhage antiplatelet therapy users for both univariate (OR 1.41, 95% CI 1.21 to 1.64, $I^2=39.8\%$) and multivariable-adjusted (OR 1.27, 95% CI 1.10 to 1.47, $I^2=20.8\%$) pooled analyses. Heterogeneity was reported to be significant for the univariate analyses. The results were not altered by removal of the study that included patients treated with warfarin.

There was significantly increased poor functional outcome for univariate pooled analyses (OR 1.29, 95% CI 1.09 to 1.53, $I^2=44.7\%$), but not for multivariable-adjusted analyses. Heterogeneity was reported to be significant for the univariate analyses.

Mortality was comparable across all subgroups and for most subgroups for poor outcomes, with the exception that poor outcome in patients treated with antiplatelet therapy was higher in studies that measured disability at 30 days compared to hospital discharge.

There was no evidence of publication bias.

**Authors' conclusions**
In cohort studies, antiplatelet therapy use at the time of intracerebral haemorrhage compared to no antiplatelet therapy use was independently associated with increased mortality, but not with poor functional outcome.

**CRD commentary**
The review question and supporting inclusion criteria were stated clearly. Various search methods were used and attempts were made to identify unpublished articles. The literature search was limited to English-language articles, which may have introduced language bias. Study details were reported, but contained few details on antiplatelet therapy. Publication bias was assessed and found to be absent. Procedures to minimise bias and error were used during study quality assessment, but this did not appear to extend to study selection and data extraction. Study validity was reportedly assessed using previously published criteria, but the results were not reported and so the reliability of the included studies was uncertain. The authors investigated sources of heterogeneity. Given the levels of variability between studies, pooling may not have been appropriate.

The uncertain quality of the included studies, some shortcomings in the review process and variability between studies mean the authors' conclusions should be treated with caution.

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

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

**Research:** The authors stated that studies to assess the risk from combination antiplatelet therapy were required.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.