Does aspirin therapy have an impact on the severity of a subsequent ischemic stroke?

Original article Ricci S *et al*. (2006) Previous use of aspirin and baseline stroke severity: an analysis of 17,850 patients in the International Stroke Trial. *Stroke* **37:** 1737–1740

SYNOPSIS

KEYWORDS anti-platelets, aspirin, ischemic stroke, functional outcome, severity

BACKGROUND

To date, studies investigating the association between aspirin use and the severity of a subsequent stroke have produced conflicting results.

OBJECTIVE

To assess in a large prospective data set whether aspirin therapy influences the severity of a subsequent stroke.

DESIGN AND INTERVENTION

This is an analysis of 17,850 patients with ischemic stroke who participated in the International Stroke Trial (IST). In that trial, stroke patients were randomly allocated within 48 h of symptom onset to receive aspirin, subcutaneous heparin, both or neither (control group: n = 4,466). In total, 3820 patients (21.4%; control group: n = 925, 20.7%) reported aspirin use in the 3 days before randomization. The investigators compared the relative frequencies of the following variables among those with and without previous aspirin use: male gender, presence of atrial fibrillation (AF), Oxfordshire Community Stroke Project (OCSP) stroke subtype, and presence of visible infarction on the baseline CT. Three methods were used to evaluate baseline stroke severity: the OCSP stroke classification system, the baseline-predicted probability of death within 14 days and of death or dependency at 6 months, and the observed outcome at 14 days and 6 months. Data at baseline and follow-up were available for 100% and 99% of patients, respectively.

OUTCOME MEASURES

Association between previous aspirin use and baseline stroke severity.

RESULTS

Previous aspirin users tended to be male (odds ratio [OR] 1.16, 95% CI 1.08–1.24), have AF (OR 1.11, 95% CI 1.01–1.22), be older (mean age 73 vs 71 years, $P < 0.0001$) and have been randomized with a slightly greater delay from symptom onset (21 vs 20 h, $P < 0.0001$). After logistic regression analysis, gender, age and time to randomization remained significantly different between the groups ($P < 0.0001$). There was no association between previous aspirin use and visible infarction on CT. Previous aspirin use did not predict the OCSP stroke subtype, even after adjustment for age, gender and AF ($P = 0.67$). Previous aspirin use also had no impact on the predicted probability of death within 14 days ($P = 0.057$) or on the probability of a poor outcome at 6 months ($P = 0.624$). When limiting the analysis to the control group, however, there was a significant association between previous aspirin use and the predicted probability of a poor outcome at 6 months ($P = 0.004$). The OR for a poor outcome at 6 months in control patients who reported previous use of aspirin was 1.31 (95% CI 1.13–1.53), but in a logistic regression analysis with outcome at 6 months as the dependent variable, adjusting for age, gender, AF and stroke type, the result was no longer statistically significant.

CONCLUSION

This study indicates that aspirin use has no effect on the baseline severity or the 6-month outcome of an ischemic stroke during aspirin therapy.

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COMMENTARY

Philip M Bath

Factors that modulate stroke severity and outcome are well described; for example, increased severity is associated with cortical (versus lacunar) stroke, and with cardioembolism or large-artery thrombosis (versus small-vessel disease). Similarly, a poor functional outcome is related to factors such as increasing age, more severe stroke, high blood pressure[1] and the presence of AF. These factors appear to be independent of each other when analyzed using statistical techniques that allow adjustment for potential confounding factors. Many patients presenting with acute stroke have existing vascular disease and are on prophylactic drugs that are given with the aim of preventing further events. Inevitably, the question then arises as to whether these interventions not only reduce the risk of events, but also decrease their severity and improve outcome.

From a theoretical perspective, aspirin might reduce the severity of ischemic stroke, perhaps by reducing thrombus size or propagation, or because it represents a marker of treatment compliance. Alternatively, it might be associated with worse severity due to confounding by indication, i.e. patients on aspirin are more likely to have co-morbid conditions that themselves contribute to severity and a poor outcome. Previous studies have given conflicting results, indicating that patients taking aspirin before their ischemic stroke have either milder or more-severe stroke than patients who are not on aspirin. Ricci and colleagues assessed this question using data from 17,850 patients with ischemic stroke who were randomized into the first IST.[2] The authors assessed whether aspirin was associated with differences in severity judged in three different ways: by baseline clinical syndrome, predicted outcome (based on baseline clinical variables) and observed outcome. In some univariate analyses, pre-stroke aspirin usage was associated with increased severity and a worse outcome. These associations became nonsignificant, however, when adjusted for baseline prognostic factors comprising age, sex and AF. These results differ from the earlier reports in that they are based on a prospective study with a far larger sample size. Furthermore, the results are likely to be representative of populations around the world, because the patients in IST came from multiple centers in 20 countries. As the authors acknowledge, however, pre-stroke aspirin use was self-reported, data on length of aspirin usage and its dose were not available (so no dose–response curve can be generated), and the comparison of aspirin and non-aspirin usage was not randomized. Further, while the authors adjusted analyses for some

important covariates, they left out other key prognostic factors such as diabetes and ischaemic heart disease.

As a result, these data do not indicate that aspirin modulates subsequent stroke severity or functional outcome, contrary to earlier findings in smaller studies. This finding does not suggest, however, that aspirin is ineffective in protecting against stroke recurrence and it must remain a key component of vascular prophylaxis.[3]

When considering other vascular prophylactic strategies, statins also do not appear to alter the severity of subsequent strokes.[4] In contrast, a recent report concludes that the combination of antiplatelets, angiotensin-converting enzyme inhibitors and statins might produce an additive reduction in stroke severity.[5] All these studies were small, however, and, ultimately, only randomised controlled trials will resolve this important question.

References

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Practice point

These data from the International Stroke Trial indicate that aspirin taken before a stroke does not alter subsequent stroke severity or functional outcome. However, aspirin remains an important therapy for preventing stroke and other vascular disease.

PM Bath is Stroke Association Professor of Stroke Medicine and Head of the Division of Stroke Medicine at the University of Nottingham, and a consultant in Stroke Medicine at Nottingham University Hospitals NHS Trust, UK.

Competing interests

The author was a local investigator in the International Stroke Trial.

Correspondence

Stroke Trials Unit
Division of Stroke Medicine
University of Nottingham
City Hospital campus
Nottingham NG5 1PB
UK
philip.bath@nottingham.ac.uk