Who needs antiplatelet therapy?

MICHAEL MOHER

TIM LANCASTER

SUMMARY

A series of overviews or meta-analyses of randomized clinical trials prepared by the Antiplatelet Trialists' Collaboration were published in the British Medical Journal *in January 1994. They demonstrated that prolonged courses of medium-dose aspirin were very effective at preventing both fatal and non-fatal myocardial infarction and stroke in patients at high risk of occlusive vascular disease. The aim of this review is to provide the general practitioner with a practical guide to the use of aspirin in patients at high and low risk of occlusive vascular disease and to discuss appropriate dosages and contraindications to treatment in the light of all the recent evidence.*

Keywords: antiplatelet therapy; occlusive vascular disease; randomized clinical trials.

Introduction

THE aim of this review is to provide a practical guide to the use of antiplatelet therapy in prevention of cardiovascular disease in general practice.

The effect of antiplatelet therapy on vascular events has been investigated in over 300 randomized trials, and data are available on a variety of outcomes, including non-fatal myocardial infarction, non-fatal stroke, vascular death and total mortality. A world-wide collaborative effort to obtain, check and synthesize data from these trials has been in progress for a number of years. The most recent summary of the evidence (up to March 1990) from this source[1-3] provides the main source of data for this review, supplemented by published evidence from randomized trials published since 1990. Detailed information on data collection and statistical methods (meta-analysis) used to combine trial results within the Antiplatelet Trialists' Collaboration are available elsewhere.[1-3] In brief, randomized trials, published or unpublished, were identified by computer-aided literature searches, manual searches of journals, reference lists of trials and review articles and by collaboration with the trial register of the International Committee on Thrombosis and Haemostasis. Where possible, individual patient data were obtained from the investigators, and the results synthesized to give a summary estimate of effectiveness from pooled data. All randomized trials included in the overview either compared prophylactic antiplatelet therapy with no antiplatelet therapy or compared two or more antiplatelet agents.

There is evidence that the way in which the effects of therapy are presented affects the extent to which clinicians consider the results clinically useful.[4] We have chosen to present both absolute and relative risk reductions, and have also calculated the number needed to treat (NNT) for each condition. The NNT[5] indicates how many individuals a clinician must treat within a given time to prevent one adverse event, and is probably the most readily understandable way of assessing the clinical implications of trial evidence. Unless otherwise stated, vascular events (combined stroke, myocardial infarction and vascular death) are the reported outcome measure.

Michael Moher, MRCGP, research fellow; and Tim Lancaster, MSc, MRCGP, deputy director, ICRF General Practice Research Group, University Department of Public Health and Primary Care, Oxford.
Submitted: 2 October 1995; accepted: 8 March 1996.

Patients with established coronary heart disease

Acute myocardial infarction

An estimated 300 000 people have an acute myocardial infarction (AMI) each year in the UK.[6] Mortality within the first month following an infarction is approximately 50%, about 80% of these deaths occurring in the first 2 h, often before hospitalization.[6] However, because of the high prevalence of the condition, there is still considerable potential to reduce mortality by early intervention.

The second international study of infarct survival[7] tested the effectiveness of treating 17 187 patients with suspected AMI with 160 mg aspirin daily for one month. Treatment was started within 24 h (median 5 h) of the onset of suspected AMI. The risk of vascular events was 10.6% in the treatment group and 14.4% in controls (absolute risk reduction 3.8%, relative risk reduction 29%, NNT for one month = 26). Follow-up of this study has confirmed that the benefits of aspirin on mortality rate continue for at least 4 years after initial treatment.[8] There is no direct evidence from this trial that very early administration (within the first few hours of infarction) is more effective than starting treatment at some point during the first 24 h. Nevertheless, it is a reasonable inference from the evidence that treatment should be started as early as possible (e.g. by the first medical contact) and continued after the acute episode for an indefinite period to reduce mortality.[9]

Past history of myocardial infarction

Patients who have previously suffered a myocardial infarction have a higher risk of recurrent fatal or non-fatal infarction than healthy individuals of the same age. For example, in the British regional heart study, patients with definite evidence of myocardial infarction were seven times more likely to suffer further infarctions in the 4.2-year follow-up period of the study than those with no such evidence.[10] Eleven randomized trials have tested the effectiveness of antiplatelet therapy in about 20 000 patients with a past history of myocardial infarction. The average duration of treatment was about 2 years and 13.5% of the intervention group suffered a vascular event, compared with 17.1% of controls[1] (absolute risk reduction 3.6%, relative risk reduction 25%, NNT for 2 years = 28). Although there is no direct evidence on how long treatment should be continued, it is probably reasonable to continue it indefinitely in such patients.

Unstable angina

Unstable angina is important clinically as it may herald the onset of AMI. Seven randomized trials comparing antiplatelet treatment with controls, involving about 4000 patients with unstable angina, have been reported.[1] Combining these trials showed a statistically significant reduction in vascular events (9.1% of the treatment group and 14.1% of controls, absolute risk reduction 5%, relative risk reduction 42%, NNT for 6 months = 20).[1]

Chronic stable angina

Individuals with chronic angina face an increased risk of vascular events and death (about 3–4% per year).[11,12] In five trials reviewed by the Antiplatelet Trialists' Collaboration, the numbers of patients studied were not large enough to show a statistically significant effect, although the data suggested benefits similar to those seen in unstable angina.[1]

Further weight has been added to this conclusion by the subsequent publication of results from the Swedish angina pectoris aspirin trial,[13] in which 2035 patients with chronic stable angina and without previous myocardial infarction were treated with either 75 mg of aspirin daily or placebo. All patients in the trial were treated with sotalol to control symptoms and the median duration of follow-up was 50 months. Vascular events occurred in 10.5% of the aspirin/sotalol group compared with 15.6% of the sotalol/placebo group (absolute risk reduction 5.1%, relative risk reduction 32%, NNT for 4 years = 20).

Following revascularization

Coronary artery and peripheral revascularization, by either bypass grafting or angioplasty, carry significant risks of reocclusion. In 20 trials involving over 5000 patients who underwent coronary artery bypass grafting, the rates of reocclusion after a mean of 7 months of therapy were 21.1% in the group receiving antiplatelet therapy and 30.3% in the controls (absolute risk reduction 9.2%, relative risk reduction 41%, NNT for 7 months = 11).[2] In three trials involving 833 patients who underwent percutaneous transluminal coronary angioplasty, reocclusion occurred in 4.1% of the group receiving antiplatelet therapy and in 8.0% of controls (absolute risk reduction 3.9%, relative risk reduction 50%, NNT for 6 months = 26).[2] Vascular events were also reduced by treatment in these studies.

In 14 trials comparing antiplatelet therapy with controls in about 3000 patients who had undergone peripheral vascular procedures or who had peripheral vascular disease (mean duration of treatment 19 months), reocclusion occurred in 15.7% of the group receiving antiplatelet therapy and in 24.9% of controls (absolute risk reduction 9.2%, relative risk reduction 43%, NNT for 19 months = 11).[2]

Atrial fibrillation

Non-rheumatic atrial fibrillation increases the risk of stroke approximately five-fold. It is a particularly important risk factor in the elderly, its prevalence rising sharply with age from 2% for patients in their 60s to over 10% in patients aged 80 years or over.[14] Randomized trials have shown that warfarin effectively removes the extra risk of stroke associated with non-rheumatic atrial fibrillation,[15] and should probably be the treatment of choice. Concern regarding the management of warfarin in general practice[16] has led to continuing interest in the role of aspirin in the treatment of non-rheumatic atrial fibrillation. Two primary prevention trials have tested whether use of aspirin as an antiplatelet agent can reduce the risk of stroke.[17,18] Meta-analysis of these trials suggests that aspirin reduces the relative risk of stroke by about 36% (compared with a 68% reduction with warfarin). In the single trial that has directly compared warfarin with aspirin, aspirin appeared to be as effective in patients at low to medium risk on the basis of age (under 75 years) and clinical variables.[19] Warfarin was more effective than aspirin in older patients (although they also faced a higher risk of bleeding on the dose of warfarin used in this study). Aspirin also appeared effective in the single trial in which it was tested for secondary prevention after stroke, although the reduction in stroke was not statistically significant, and was less than that seen with warfarin (relative risk reduction with aspirin 17%, absolute risk reduction 4%, NNT for one year = 25).[20]

More precise characterization of risk factors for stroke and for bleeding may permit a clearer understanding of how to treat individual patients with non-rheumatic atrial fibrillation. In practice, most patients encountered in general practice with this condition will be elderly and will have coexisting heart disease, placing them at higher risk of stroke. Serious consideration should be given to treating these patients with warfarin, but it is a sensible clinical strategy to prescribe aspirin to any in whom the decision not to anticoagulate is made.

Patients with a history of stroke or transient ischaemic attack (TIA)

Eighteen trials have tested the effectiveness of antiplatelet therapy in about 10 000 patients with a history of stroke or TIA.[1] The mean duration of these trials was 33 months; 18.4% of treated patients and 22.2% of controls suffered a vascular event (absolute risk reduction 3.8%, relative risk reduction 22%, NNT for 3 years = 26).

An important clinical issue for primary care is whether brain imaging is required in all such patients before starting aspirin therapy. Aspirin probably increases the risk of cerebral haemorrhage, and therefore, it may be important to distinguish whether stroke is the result of infarction or haemorrhage. Clinical findings are of limited value for making this distinction in completed stroke (although it is probably safe to assume that transient ischaemic attacks are non-haemorrhagic). Therefore, there is a reasonable argument for scanning at the time of stroke, before starting aspirin therapy. However, the ability of CT scanning to distinguish haemorrhage from infarction decays rapidly,[21] and it may be reasonable to treat all previous strokes, not known to be definitely haemorrhagic, with aspirin, as most (about 80%) will be ischaemic.[22]

Patients without evidence of occlusive vascular disease

Three trials, involving a total of 28 000 patients, have examined the effects of prophylactic antiplatelet therapy for 5 years in subjects with no definite history of vascular disease (i.e. primary prevention). These trials showed a small but significant reduction in non-fatal myocardial infarction (NNT = 200), but this was offset by a small increase in haemorrhagic stroke, with little resultant difference in overall vascular mortality.[1] This suggests that there is no clear evidence for the routine use of antiplatelet therapy in patients at low risk of occlusive vascular events.

It is not clear whether antithrombotic agents benefit patients with no history of vascular disease, but who are at relatively high risk because of other risk factors (family history, hypertension, diabetes, hypercholesterolaemia, smoking). A number of trials are under way to examine whether such individuals might benefit from treatment.

Which antiplatelet agent and what dosage?

In the trials identified above, there was no evidence that any antiplatelet agent, or combination of such drugs, was more effective than medium-dose aspirin (75–325 mg daily) used alone.[1] There was also no evidence that medium doses of aspirin (75–325 mg daily) were less effective than high doses (1 g daily), but lower doses were shown to be less toxic.[1]

The consensus view is that all patients with suspected or definite acute myocardial infarction or unstable angina require prompt suppression of platelet activity. In the absence of a clear contraindication, at least 300 mg aspirin should be given immediately and a daily dose of 150 mg of the drug continued indefi-

nitely. Furthermore, the trials also confirmed that, for those patients with a history of stable angina, TIA, recent revascularization, atrial fibrillation or peripheral vascular disease medium-dose aspirin (75–325 mg daily) was the most widely tested and effective antiplatelet regimen at preventing a further vascular event.[1] The consensus dosages and duration of treatment are detailed in Table 1.

Although certain categories of patient without established vascular disease may benefit from antiplatelet therapy, there is currently no clear evidence for its routine use in patients who do not have established disease (primary prevention). This is important to emphasize, since aspirin is obtainable over the counter.

Side effects of aspirin treatment

Gastrointestinal toxicity

The long-term use of aspirin may cause gastrointestinal side-effects including dyspepsia, peptic ulcer and gastrointestinal haemorrhage. A recent overview of the randomized trials of aspirin against placebo in which information on gastrointestinal toxicity was available showed that the risks of gastrointestinal bleeding were increased by a factor of 1.5–2.0 by chronic aspirin use, but that fatal bleeding was very rare.[23] The risk of peptic ulcer was increased by 1.3 and of upper gastrointestinal symptoms by 1.7. The overview concludes that toxicity is strongly dose related, and is minimal within the dose range currently recommended for long-term administration (75–150 mg daily).[23] There is also some evidence that enteric-coated preparations may be less toxic to the upper gastrointestinal tract.

Intracranial haemorrhage

The long-term use of aspirin may be associated with a small risk of intracranial haemorrhage, but among patients at higher risk of a further vascular event, the net effect is to reduce the risk of all strokes.[1]

Table 1. Aspirin treatment guidelines: a practical guide.*

Acute myocardial infarction
Aspirin 300 mg (chewed) should be given immediately to all patients with suspected or definite myocardial infarction.

Past history of myocardial infarction
Aspirin 150 mg day^{-1} should be given to all patients and continued indefinitely.

Unstable angina
Aspirin 300 mg (chewed) should be given immediately to all patients with unstable angina.

Chronic stable angina
Aspirin 75–150 mg day^{-1} should be given to all patients and continued indefinitely.

Patients after revascularization
Post-coronary bypass grafts: Aspirin 150–300 mg day^{-1} should be given to all patients following surgery and continued indefinitely.
Coronary angioplasty: Aspirin 150–300 mg day^{-1} should be given to all patients following the procedure and continued indefinitely.

Peripheral vascular disease/surgery
Aspirin 150–300 mg day^{-1} should be given to all patients with peripheral vascular disease for an indefinite period of time,
Aspirin 75–150 mg day^{-1} should be given to all patients following carotid endartectomy and continued for an indefinite period.

Atrial fibrillation
Warfarin is primarily indicated in patients at higher risk of stroke: women, patients over 75 years, and those with left ventricular dysfunction, hypertension, valvular heart disease and previous thromboembolism.
Aspirin 75–150 mg day^{-1} should be used for an indefinite period of time in lower risk patients or high-risk patients for whom warfarin is contraindicated.

Past history of stroke or transient ischaemic attack
Aspirin 75–150 mg day^{-1} should be given to all patients with a diagnosis of non-haemorrhagic stroke or TIA and continued for an indefinite period.

*Contraindications to the use of aspirin are: a definite history of hypersensitivity (e.g. aspirin-induced asthma, angioedema or urticaria) — substitute with an alternative drug such as ticlopidine 250 mg twice daily; and a high risk of bleeding (e.g. active peptic ulceration, recent major injury or bleeding diathesis such as haemophilia).

Contraindications to aspirin treatment

The use of aspirin is contraindicated in two main groups of patients: firstly, in those with a definite history of hypersensitivity, such as aspirin-induced asthma, angioedema or urticaria; and secondly, in patients at high risk of bleeding (e.g. active peptic ulceration, recent major trauma or a history of bleeding diathesis such as haemophilia). If aspirin is contraindicated, then the antiplatelet agents ticlopidine (available on a named patient basis), dipyridamole or sulphinpyrazone may be used as alternatives.[1]

Cost-effectiveness of aspirin treatment

It has been estimated that treating 1000 high-risk vascular patients with aspirin (75–325 mg daily) for 2 years will avoid approximately 40 further vascular events.[1] This amounts to drug costs of less than £100 for each episode avoided, a considerable saving over hospitalization for myocardial infarction.[24]

Conclusions

Systematic review of available evidence has shown that antiplatelet agents are effective in reducing the risk of further vascular events and death in most patients with established vascular disease. Moreover, the benefits of antiplatelet agents have been demonstrated in patients with a range of clinical characteristics, including older as well as middle-aged patients, women and men, and individuals with and without diabetes or hypertension. Therefore, there are strong arguments for systematically identifying and treating most patients with established vascular disease with such agents.

The identification of all eligible patients and formation of a patient register may be achieved from repeat prescriptions, hospital correspondence, opportunistic or systematic review of patient notes, and recall by partners, practice nurses, health visitors and reception staff. In addition, general practitioners need to ensure that all new diagnoses made by the primary health care team and the hospital are entered into this register. The notes of patients identified as being at risk should also have some indication or reminder (perhaps a red spot) to ensure that aspirin has been prescribed. This strategy would help reduce the overall morbidity, mortality and economic burden of patients with established vascular disease with a treatment that is cheap, easy to use and highly effective.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106.

2. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994; **308:** 159–168.
3. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; **308:** 235–246.
4. Fahey T, Newton J. Conveying the risks and benefits of treatment. *Br J Gen Pract* 1995; **45:** 339–341.
5. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; **318:** 1728–1733.
6. Langham S, Normand C, Piercy J, Rose G. Coronary Heart Disease: Epidemiologically based needs assessment. DHA project 1992: Research Programme. Report 10.
7. Second international study of infarct survival, collaborative group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **2:** 349–360.
8. Baigent C, Collins R. ISIS-2: 4-year mortality follow-up of 17,187 patients after fibrinolytic and antiplatelet therapy in suspected acute myocardial infarction. *Circulation* 1993; **88:** 1–291.
9. Deeks J, Watt I, Freemantle N. Aspirin and acute myocardial infarction: clarifying the message. *Br J Gen Pract* 1995; **45:** 395–396.
10. Shaper AG, Pocock SJ, Walker M, *et al.* Risk factors for ischaemic heart disease: The prospective phase of the British Regional Heart Study. *J Epidemiol Community Health* 1985; **39:** 197–209.
11. Kannel WB, Feinleib M. Natural history of angina in the Framingham study. Prognosis and survival. *Am J Cardiol* 1972; **29:** 154–162.
12. Fry J. The natural history of angina in a general practice. *J Roy Coll Gen Pract* 1976; **26:** 643–648.
13. Juul Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 1992; **340:** 1421–1425.
14. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987; **147:** 1561–1564.
15. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials: Atrial Fibrillation, Aspirin, Anticoagulation Study; Boston Area Anticoagulation Trial for Atrial Fibrillation Study; Canadian Atrial Fibrillation Anticoagulation Study; Stroke Prevention in Atrial Fibrillation Study; Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study. *Arch Intern Med* 1994; **154:** 1449–1457.
16. Sweeney KG, Gray DP, Steele R, Evans P. Use of warfarin in non-rheumatic atrial fibrillation: a commentary from general practice. *Br J Gen Pract* 1995; **45:** 153–158.
17. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989; **i:** 175–179.
18. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; **84:** 527–539.
19. Anon. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994; **343:** 687–691.
20. Anon. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993; **342:** 1255–1262.
21. Dennis MS, Bamford JM, Molyneux AJ, Warlow CP. Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain. *Br Med J Clin Res Ed* 1987; **295:** 379–381.
22. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. 1. The Oxfordshire Community Stroke Project – 1981–86. *J Neurol Neurosurg Psychiatry* 1990; **53:** 824–829.
23. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993; **35:** 219–226.
24. Anon. Aspirin to prevent heart attack or stroke. *Drug Ther Bull* 1994; **32:** 1–3.

Acknowledgements
We thank Colin Baigent and Jonathan Mant for their help in preparing this paper.

Address for correspondence
Dr Michael Moher, Southmead Surgery, Farnham Common, Bucks SL2 3ER.