

The minimum effective dose of aspirin for cardioprophylaxis

Key points

- Aspirin is an effective antithrombotic agent at doses of 50 - 100 mg/day
- High doses (approximately 1,200 mg/day) are not more effective than lower doses but are associated with a greater risk of adverse gastrointestinal effects
- On the basis of clinical trials, the minimum effective dose of aspirin lies within the range 50 - 160 mg/day and varies for different indications

Dose-response relationship

A 2001 review of the dose-response relationship of aspirin as an antithrombotic agent addresses most of the issues relevant to determining the minimum effective dose (1). The relevant section states:

Well-designed randomised trials have shown that aspirin is an effective antithrombotic agent when used in doses ranging between 50 and 100 mg/day, and there is a suggestion that it is effective in doses as low as 30 mg/day. Aspirin in a dose of 75 mg/day was shown to be effective in reducing the risk of acute myocardial infarction or death in patients with unstable angina and chronic stable angina, as well as in reducing stroke or death in patients with transient cerebral ischemia and the number of postoperative strokes after carotid endarterectomy. In the European Stroke Prevention Study (ESPS)-2, aspirin 25 mg twice daily was effective in reducing the risks of stroke or death in patients with prior stroke or transient ischemic attack. Finally, aspirin 30 mg/day was compared with a dose of 283 mg/day in 3,131 patients following a transient ischaemic attack or minor ischemic stroke; no statistically significant difference was found in the incidence of the combined outcome of vascular death, stroke, or myocardial infarction between the two aspirin regimens. The lowest effective dose of aspirin for these various indications is shown in Table 1.

Table 1. Vascular disorders for which aspirin has been shown to be effective and minimum effective dose

Disorder (mg/day)	Minimum Effective Dose
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina*	75
Acute myocardial infarction	160
Transient ischaemic attack and ischemic stroke*	50
Severe carotid artery stenosis*	75
Acute ischaemic stroke*	160

*Higher doses have been tested in other trials and not found to confer greater risk reduction

The efficacy of different doses of aspirin has been directly compared in a small number of randomized trials. In the United Kingdom-Transient Ischaemic Attack study, no difference in efficacy was found between regimens of 300 mg/day and 1,200 mg/day. The Dutch transient ischaemic attack study found no difference between regimens of 30 mg/day and 283 mg/day. The ACE trial (Acetylsalicylic acid and Carotid Endarterectomy) recently reported that the risk of stroke, myocardial infarction or death within 3 months of carotid endarterectomy is significantly lower for patients taking 81 or 325 mg/day than for those taking 650 or 1,300 mg/day (6.2% vs. 8.4%; p=0.03). These randomised studies therefore provide no convincing evidence of a dose-response relationship for the antithrombotic effect of aspirin.

The antithrombotic effects of aspirin 50 - 1,500 mg/day have also been compared with untreated controls in a number of thrombotic disorders. Aspirin has been shown to be effective in patients with the following conditions:

- **unstable angina** - the incidence of acute myocardial infarction or death was significantly reduced to a similar degree in four separate studies using daily doses of 75 mg, 325 mg, 650 mg, and 1,300 mg
- **stable angina** - a dose of 75 mg/day reduced the incidence of acute MI or sudden death
- **aortocoronary bypass surgery** - the incidence of early occlusion was similarly reduced with daily doses of 100 mg, 325 mg, 975 mg, and 1,200 mg
- **thromboprophylaxis** in patients with prosthetic heart valves who also received warfarin - the incidence of systemic embolism was reduced with daily doses of 100 mg, 500 mg, and 1,500 mg
- **thromboprophylaxis** in patients with arterial venous shunts who were undergoing long-term haemodialysis - a dose of 160 mg/day was effective

- **acute myocardial infarction** - a dose of 162.5 mg/day reduced early (35 days) mortality as well as non-fatal reinfarction and stroke
- **transient cerebral ischemia** - doses between 50 and 1,200 mg/day were effective
- **acute ischemic stroke** - doses of 160 - 300 mg/day reduced early mortality and stroke recurrence, although the proportional effects of aspirin on vascular events in these patients were small compared with the effects in other high-risk settings.

Aspirin is therefore an effective antithrombotic agent over the dose range 50 - 1,500 mg/day, and it may be effective at doses as low as 30 mg/day. There is no evidence that low doses (50 - 100 mg/day) are less effective than high doses (650 - 1,500 mg/day) - in fact, the opposite may be true. This conclusion is supported by data from the Antiplatelet Trialists' Collaboration (Table 2).

Table 2. Indirect comparison of aspirin doses: reduction of vascular events in high-risk patients*

Aspirin dose (%) (mg/day)	No. trials	No. patients	Odds Reduction
500 - 1500	30	18,471	21 ± 4
160 - 325	12	23,670	28 ± 3
75	4	5,012	29 ± 7

*Data from Antiplatelet Trialists' Collaboration.

There is evidence, however, that doses of approximately 300 mg/day are associated with fewer adverse gastrointestinal effects than doses of approximately 1,200 mg/day, and that a dose of 30 mg/day causes fewer adverse effects than 300 mg/day.

In summary, the results of biochemical studies on its mechanism of action, the lack of dose-response relationship in clinical studies evaluating its antithrombotic effects, and the dose-dependence of its adverse effects all support the use of the minimum effective dose identified in the treatment of various thromboembolic disorders.

Reference

1. Patrono C, Collier B, Dalen JE, FitzGerald GA, Fuster V, Gent M et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. Chest 2001;119:39S-63S. (www.chestjournal.org/cgi/reprint/119/1_suppl/39S.pdf)

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