

ASPIRIN

KEY POINTS

- Aspirin treatment is effective in preventing recurrence of cardiovascular events in those patients with previous cardiovascular events. The absolute risk reduction for secondary prevention is 2-4% per year (NNT 25-50). This risk reduction may be lower in people whose event was greater than 5 years previously.
- For primary prevention, the absolute risk reduction for aspirin is significantly lower and is highly dependent on the underlying absolute risk. In patients with one or two risk factors for cardiovascular disease, the absolute risk reduction is of the order of 0.2-0.4% (NNT 250-500 per year). In healthier patients, the number needed to treat for aspirin primary prevention approaches 2000 for one year.
- Older patients have a significantly higher risk of major bleeding, with people over 85yo having up to a 7% annual bleeding risk.
- The risk of gastrointestinal and other extracranial bleeding is also increased by other patient factors (e.g. previous GI bleeding/ulceration history, severe renal dysfunction, concurrent medications, smoking and alcohol use).
- Recurrent minor bleeding can have a significant impact on patients' quality of life.

CONTEXT

This guide considers the use of aspirin for prevention of vascular events.

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients with a high risk of gastrointestinal bleeding (e.g. elderly, taking other GI bleed inducing agents such as NSAIDs, SSRIs and corticosteroids, alcohol users, smokers) should be considered for cessation of antiplatelet agents.
- Patients with a low cardiovascular risk should be considered for cessation of antiplatelet agents.
- Patients receiving dual antiplatelet agents should generally have one of these ceased within 12 months of the acute event. For patients where bleeding risk is higher, earlier cessation may be appropriate.
- Patients with troublesome adverse effects associated with antiplatelet agents should be reassessed for the ongoing risk vs benefit of the antiplatelet agent.
- Patients with a limited prognosis should be considered for cessation of antiplatelet agents.
- Antiplatelet agents can usually be stopped without the need for tapering.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits <ul style="list-style-type: none"> Reduced vascular events 	Increased Benefit <ul style="list-style-type: none"> High cardiovascular risk (usually secondary prevention) 	Decreased Benefits <ul style="list-style-type: none"> Low cardiovascular risk (no established CVD) Limited life expectancy due to comorbidities (dementia, heart failure, airways disease, malignancy)
Main Harms <ul style="list-style-type: none"> Gastrointestinal and other bleeding 	Reduced Harms <ul style="list-style-type: none"> Concurrent use of PPIs or other gastric acid suppression 	Increased Harms <ul style="list-style-type: none"> Concurrent use of other gastrointestinal irritants (e.g. NSAIDs, SSRIs, corticosteroids) Co-prescription of a second antiplatelet or anticoagulant Advanced age Prior gastrointestinal pathology (e.g. prior gastric ulcer, erosions)

EFFICACY

SECONDARY PREVENTION

Low-dose aspirin has been shown to be effective in preventing about one-fifth of atherothrombotic vascular complications (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in patients with previous myocardial infarction, stroke, or transient cerebral ischaemia.^{12,3,4}

This corresponds to an absolute reduction of about 10–20 per 1000 patients in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death.

In 1994, the Antiplatelet Trialists' Collaboration,⁵ concluded that owing to the higher baseline risk, the absolute benefit is greater in older than in younger patients. In patients below 65 years of age, 11% of patients taking aspirin had vascular events compared to the baseline risk of 14.3% for patients taking placebo (ARR 3.3%, **NNT= 30**). For patients over 65 years of age, the baseline event rate was 23.2% and this was compared to the aspirin event rate of 18.7% (ARR 4.5%, **NNT= 22**).

In 2002, the Antithrombotic Trialists' Collaboration analysed 16 trials of long-term aspirin use with doses ranging from 50–150 mg/day for secondary prevention of CVD events, including over 17,000 subjects and 3,306 serious vascular events.⁴ In these trials, aspirin use resulted in significant reductions in serious vascular events including stroke and coronary events in both men and women and low dose regimens (75–100 mg/day) were found to be as effective as higher doses.

Aspirin use as a secondary prevention measure for serious CVD events is well accepted and recommended by several major organizations.

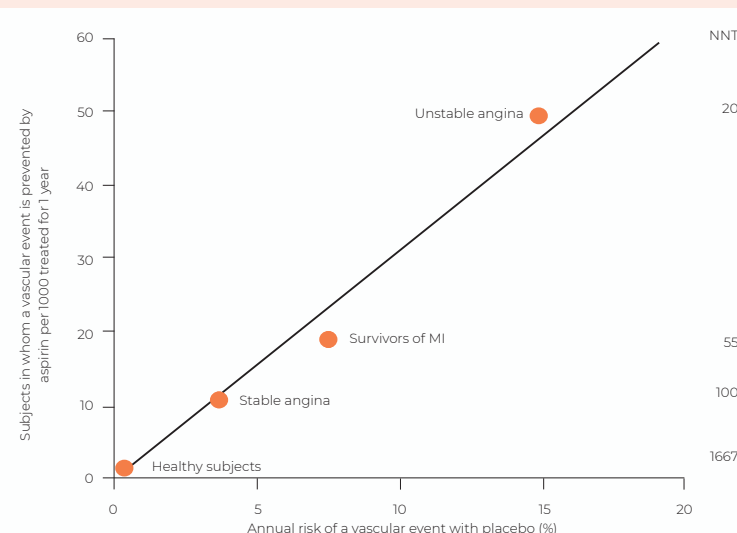


Figure 1: Absolute benefit of aspirin for patients with different cardiovascular risk²⁰

DUAL ANTIPLATELET THERAPY (ASPIRIN WITH CLOPIDOGREL, TICAGRELOR OR PRASUGREL)

Dual antiplatelet therapy is now recommended by the American Heart Association (AHA) guidelines for use after acute cardiac syndromes (unstable angina, myocardial infarction, coronary artery procedures) for 12 months, unless there are significant contraindications, in which case aspirin alone is recommended.²¹ In cerebrovascular disease, dual antiplatelet therapy may also be useful for up to 3 months after acute stroke or TIA.²² The reduction in cerebrovascular events occurred primarily in the first 30 days of dual antiplatelet treatment, while the bleeding complications occurred in the second and third months.

Patients age 75 and older have been underrepresented in clinical trials of acute coronary syndrome and specific guidance for duration of dual antiplatelet therapy is unclear. Indeed, the AHA guidelines state "Management decisions for older patients with NSTEMI-ACS should be patient centered, and consider patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy."²¹

PRIMARY PREVENTION

For primary prevention, the balance between vascular events avoided and major bleeds caused by aspirin is substantially uncertain because the risks without aspirin, and hence the absolute benefits of antiplatelet prophylaxis, are at approximately an order of magnitude lower than in secondary prevention (less than 4 vs 38 per 1000 patients benefit).

There are ten available trials examining the use of aspirin for primary prevention. The key significant results are summarised below:

- Physicians Health Study⁶: 34% reduction in MI (ARR 0.185% pa, **NNT=540**)
- Thrombosis Prevention Trial⁷: 20% reduction in MI (ARR 0.23% pa, **NNT= 435**)
- Hypertension Optimal Treatment⁸: 15% reduction in any cardiovascular event (ARR 0.16% pa, **NNT= 625**); 36% reduction in MI (ARR 0.13% pa, **NNT=769**)
- Primary Prevention Project⁹: 23% reduction in any cardiovascular event (Annualised ARR 0.475%, **NNT= 211**) and 44% reduction in cardiovascular mortality (Annualised ARR 0.15%, **NNT= 667**)
- Womens Health Study¹⁰: 17% reduction in stroke (ARR 0.255%, **NNT=392**)
- British Doctors Trial¹¹, Prevention Of Progression of Arterial Disease And Diabetes¹², Aspirin for Asymptomatic Atherosclerosis¹³, Japanese Primary prevention with Aspirin for Diabetes¹⁴, ASPirin for the Reduction of Events in the Elderly^{15,16,17} No significant benefit

Trial results were mixed to some degree, but the preponderance of evidence suggested that aspirin decreases relative CVD risk, including MI and stroke by 6-30% (absolute benefit varies from zero to 0.47% per year, **NNT=220** or more).

A number of meta-analyses of these trials have been undertaken.^{4,18,19} Overall, aspirin allocation yielded a 12% proportional reduction in major vascular events, due mainly to a reduction by about one-fifth in non-fatal myocardial infarction. This proportional benefit would translate into a number-needed-to-treat (NNT) of ~2000 low-risk individuals to prevent one non-fatal myocardial infarction.

Absolute benefit of aspirin therapy can therefore be related directly to absolute risk of a cardiovascular complication. The number needed to treat to prevent a vascular event increases from 20 in patients with stable angina to 1667 in healthy subjects (see **Figure 1**).²⁰

ADVERSE EFFECTS

The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic (see **Figure 2**) vs. haemorrhagic risk of the patient (**Figure 3**). In elderly patients with a history of a gastrointestinal ulcer, taking aspirin, the NNH is estimated as 17, while in younger patients with no prior GI history, the NNH is 1667. While patients at relatively low cardiovascular risk may not have a net clinical benefit, in patients at high risk of cardiovascular or cerebrovascular complications (e.g. patients with unstable angina or prior myocardial infarction), the absolute benefit of aspirin prophylaxis will likely outweigh the published rate of harm of a 1-2/1000 rate of GI bleeding per year.^{23,24}

The published rate is, however, based on clinical trial participants, and older patients and those with prior gastrointestinal issues are often excluded from such studies. Other important risk factors for extracranial (predominantly gastrointestinal) bleeds are diabetes, male gender, alcohol use, smoking, high blood pressure, concurrent medications (especially steroids, NSAIDs, SSRIs or anticoagulants). As an example, the risk of upper GI bleeding with aspirin was examined in a meta-analysis of both randomised controlled trials and observational studies.¹⁹ **The odds ratio for upper GI bleeding in randomised controlled trials was 1.5 (95% CI 1.2-1.8) whereas the ratio in observational studies was 3.1 (95% CI 2.5-3.7).**¹⁹ In addition, the rate of gastrointestinal mucosal injury in 281 of 3162 patients over 65 years of age who were low dose aspirin users was 36% compared to 27.5% in the non-users.²⁰

The suspicion that the bleeding risk of aspirin is higher in "real life" than that demonstrated in clinical trials has recently been strengthened by a followup study of over 75yos taking aspirin in the Oxford Vascular Study.²⁵ These authors undertook a 10 year prospective cohort study of 3166 patients taking antiplatelet therapy without concurrent proton pump inhibitor use. Bleeding requiring medical attention occurred more frequently in the over 85yo age group (6.6% of patients annually). Of these bleeds in the elderly, 35% were life-threatening (Absolute Risk 2.3%; NNH= 43) and 15% were fatal (Absolute risk 1%; NNH= 100). It is worth noting that this observational study, could not attribute the bleeding directly to the antiplatelet agent (not randomised controlled).

In the ASPREE study of healthy people over 75yo taking aspirin or placebo,¹⁵ only major haemorrhagic events were recorded (haemorrhagic stroke, intracranial bleeding, extracranial bleeding leading to transfusion, hospitalisation, surgery or death). The rate of bleeding in patients was 0.86% per year (compared to 0.62% for placebo), an excess bleeding rate of 0.24% per year (NNH= 416).

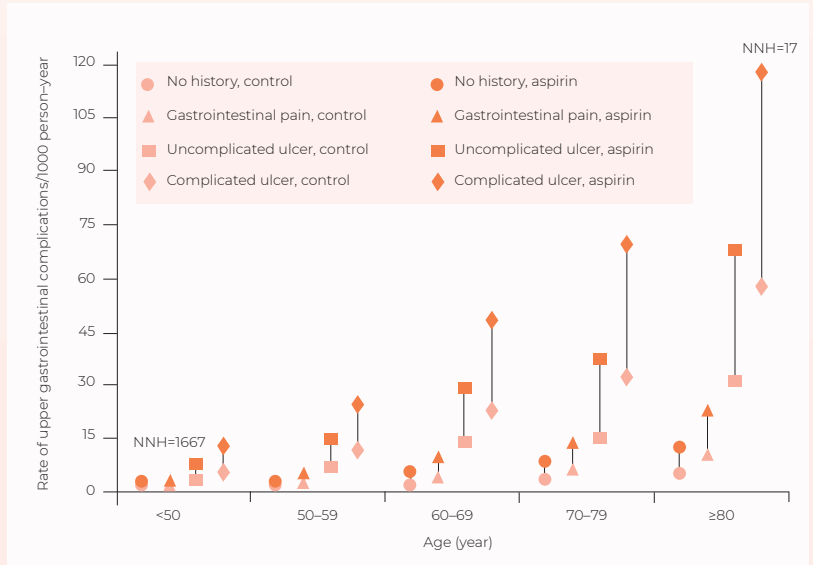


Figure 2: Estimated rates of gastrointestinal complications in men, according to age and presence or absence of GI complications.^{23,24}

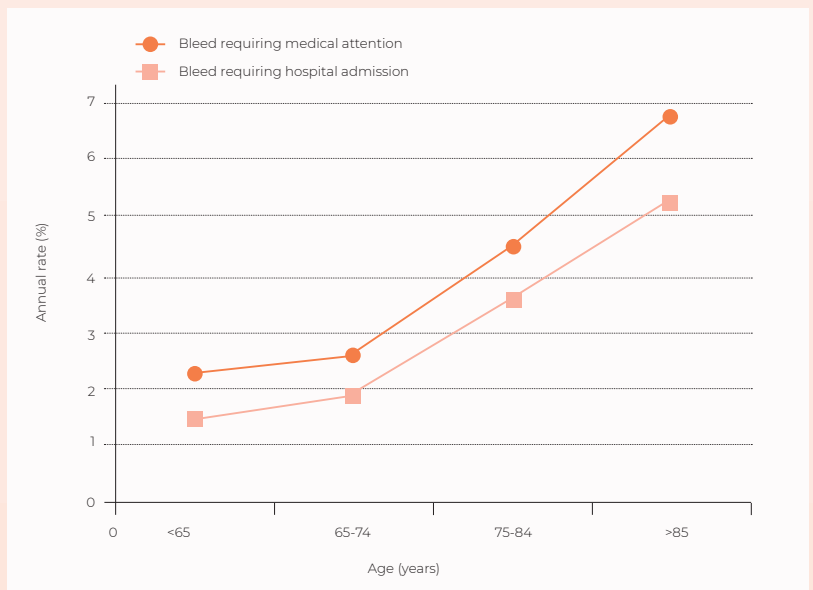


Figure 3: Annual rates of bleeding in people taking antiplatelet agents.²⁵

DUAL ANTIPLATELET THERAPY

It is clear that dual antiplatelet therapy (particularly clopidogrel plus aspirin) is associated with a higher risk of bleeding than a single antiplatelet agent. In 2009, authors studying stroke risk evaluated the bleeding risk of a range of antithrombotic agents and combinations (see **Figure 4**).²⁶

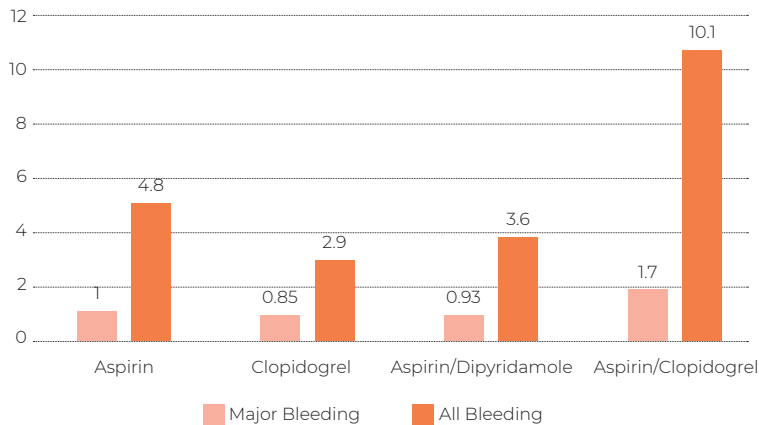


Figure 4: Risk of bleeding with dual antiplatelet therapy²⁵

In people with a high bleeding risk (the elderly, frail and those with significant gastrointestinal bleeding history) it would be prudent to minimise the use of combination antiplatelet therapy.

DISCONTINUATION SYNDROMES

Aspirin permanently disables platelet function for the duration of the life of that particular platelet. As such, the reduction of the antiplatelet effect is likely to be slow, as it will wear off as those platelets that are affected are replaced by ones that are not.

There are some reports, and some theoretical support for the contention, that ceasing antiplatelet agents is associated with a short-term increase in risk of thrombotic events.

In patients prescribed low-dose aspirin for the secondary prevention of cardiovascular or cerebrovascular events, discontinuation of antiplatelet therapy (for non-compliance, adverse effects, change of therapy or surgery) was associated with a 40% increase in the relative risk of ischaemic stroke,²⁷ and myocardial infarction²⁸ compared with continuation of therapy.

Aspirin suppresses thromboxane (TXA₂) thereby suppressing platelet aggregation, while simultaneously suppressing production of PGI₂, which may result in a prothrombotic effect. There is some support for the notion that cessation of aspirin allows an unopposed prothrombotic state to develop for a few days after cessation. This has been tested in an animal model,²⁹ and is supported by some reports of ischaemic stroke, cardiovascular problems and lower limb ischaemia 7-10 days after cessation of aspirin.^{30,31,32}

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

✓ **LOW CARDIOVASCULAR EVENT RISK**

The main factor to consider is the ongoing cardiovascular risk in the patient, as benefit seems to be related to cardiovascular risk. The difficulty is that no available cardiovascular risk calculators cater for patients older than 75 years. An individual assessment of coexisting risk factors, in association with the patient's prognosis and the potential impact of a cardiovascular event would assist in determining the benefits of continuing antiplatelet therapy.

✓ **PRESENCE OF SUSPECTED ADVERSE EFFECT**

Significant signs of excess effect of aspirin that impact on quality of life, for example recurrent minor bleeding interfering with daily activities.

- ✓ Covert gastrointestinal bleeding can contribute to the development of anaemia. The presence of anaemia in a patient taking aspirin should result in a review of the ongoing risk : benefit of antiplatelet therapy.

AGAINST DEPRESCRIBING

- ✗ Patients who are well and functionally independent and have a five or more year life expectancy may derive ongoing benefit from the use of antiplatelet agents as secondary prevention.

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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