A GUIDE TO

deprescribing

ANTIPLATELET AGENTS

KEY POINTS

- **Aspirin treatment is effective in preventing recurrence of cardiovascular events in people with previous cardiovascular events. The ARR in for secondary prevention is 2-4% per year (NNT 25-50).**
- **For primary prevention, the ARR for aspirin is significantly lower. In people with one or two risk factors for cardiovascular disease, the ARR is of the order of 0.2-0.4% (NNT 250-500 per year). In healthier patients, the NNT for aspirin primary prevention approaches 2000 for one year.**
- **The risk of gastrointestinal and other extracranial bleeding increases with age and by other factors such as previous GI bleeding and ulceration, concurrent medications, smoking and alcohol use.**
- **The risk of major bleeding with dual antiplatelet agents is more than twice that of either agent alone.**
- **Recurrent minor bleeding can have a significant impact on quality of life.**

CONTEXT

This guide considers the use of antiplatelet agents in the prevention of primary and secondary cardiovascular 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.

EFFICACY

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 (4 vs 38 per 1000 patients benefit).

There are nine available trials examining the use of aspirin for primary prevention (BDT[1], PHS[2], TPT[3], HOT[4] PPP[5] WHS[6] POPADAD[7], JPAD[8], and AAA[9]). The key significant results are summarised below:

- PHS : 34% reduction in MI (ARR 0.185% pa, NNT=540)
- TPT : 20% reduction in MI (ARR 0.23% pa, NNT= 435)
- HOT ,: 15% reduction in any cardiovascular event (ARR 0.16% pa, NNT= 625); 36% reduction in MI (ARR 0.13% pa, NNT=769)
- PPP : 23% reduction in any cardiovascular event (ARR 1.9% over 4 years, NNT 53) and 44% reduction in cardiovascular mortality (ARR 0.6% over 4 years, NNT= 167)
- WHS : 17% reduction in stroke (ARR 0.255%, NNT=392)
- BDT ,POPADAD , AAA , JPAD : No significant findings

(NNT = Number needed to treat, ARR = Absolute Risk Reduction)

Trial results were mixed to some degree, but the preponderance of evidence suggested that aspirin decreases CVD risk, including MI and stroke by 6-30%.

A number of meta-analyses of these trials have been undertaken.[17, 10, 11] 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. In **Figure 1**, the NNT to prevent a vascular event increases from 20 in patients with stable angina to 1667 in healthy subjects.[12]

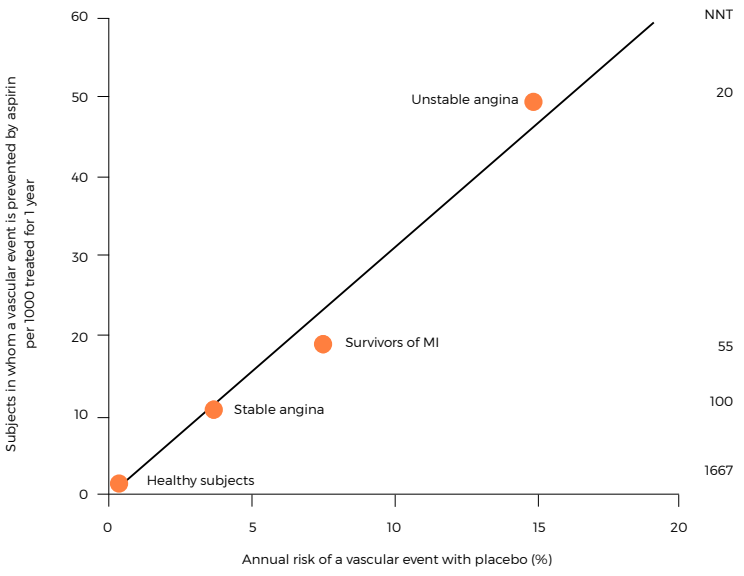

Figure 1: Absolute benefit of aspirin for patients with different cardiovascular risk[12]

DUAL ANTIPLATELET THERAPY

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.

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 NSTE-ACS should be patient centred, and consider patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy."[13]

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.[14,15,16,17]

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,[18] 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.[17] 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.

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.

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 benefits and the extracranial bleeding risks are summarised in **Figure 3**. For patients at high cardiovascular risk (>10% per 5 years) the NNH was 1000 vs the NNT of 500. That is for every 100 high-risk patients treated for 5 years there is estimated to be two vascular events avoided and one major extracranial bleed.[12]

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.[21] Total bleeding occurred at mean rates of:

- 4.8% with aspirin (< or =325 mg/day) alone,
- 2.9% with clopidogrel alone,
- 3.6% with aspirin plus dipyridamole and
- 10.1% with aspirin plus clopidogrel.

Major bleeding occurred at mean rates of 1% with aspirin (< or =325 mg/day) alone, 0.85% with clopidogrel, 0.93% with aspirin plus dipyridamole and 1.7% with aspirin plus clopidogrel.[21]

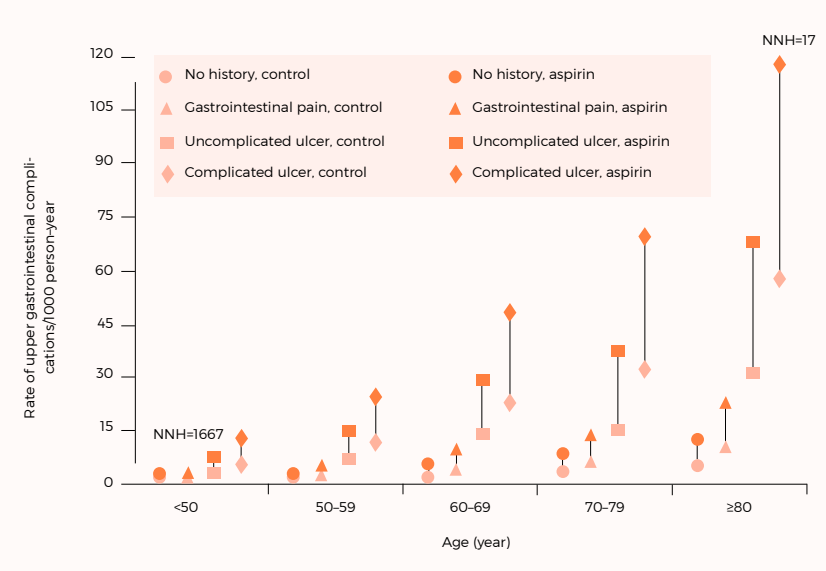

Figure 2: Estimated rates of gastrointestinal complications in men, according to age and presence or absence of GI complications.[12]

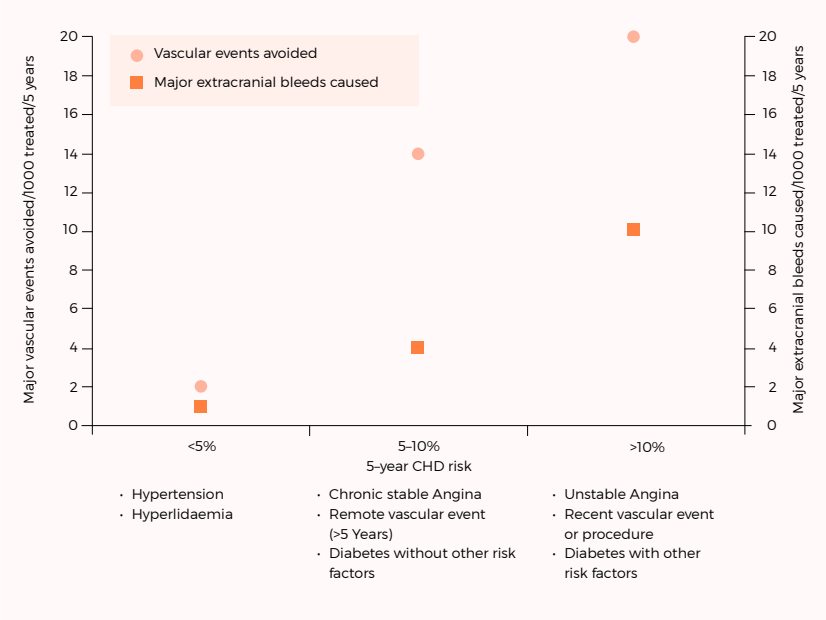

Figure 3: predicted 5-year effects of aspirin for patients with different levels of CHD risk.[12]

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 with 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,[22] and myocardial infarction[23] 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,[24] and is supported by some reports of ischaemic stroke, cardiovascular problems and lower limb ischaemia 7-10 days after cessation of aspirin.[25, 26, 27]

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.

RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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MAY 2016

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