A GUIDE TO

deprescribing

phn TASMANIA
An Australian Government Initiative

primary health TASMANIA

CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

ANTIPLATELETS

KEY POINTS

Antiplatelet therapy is effective in reducing the incidence of recurrent vascular events in patients with a history of atherosclerotic disease (secondary prevention).

For primary prevention, the benefit on vascular events is low in magnitude and usually outweighed by the risk of bleeding. There is no benefit on fatal events.

Risk of antiplatelet associated bleeding varies greatly based on individual patient characteristics such as age, history of previous bleed, concomitant use of gastro-toxic drugs, comorbidities, and smoking.

Combination of antiplatelets with other antithrombotic agents is common in practice and is associated with higher bleeding rates. Deprescribing is often appropriate after a set period of time, which is often shorter in patients with a higher baseline bleed risk.

The decision to continue antiplatelet therapy should informed by individualised comparison of benefit on vascular events, and risk of major adverse events such as bleeding.

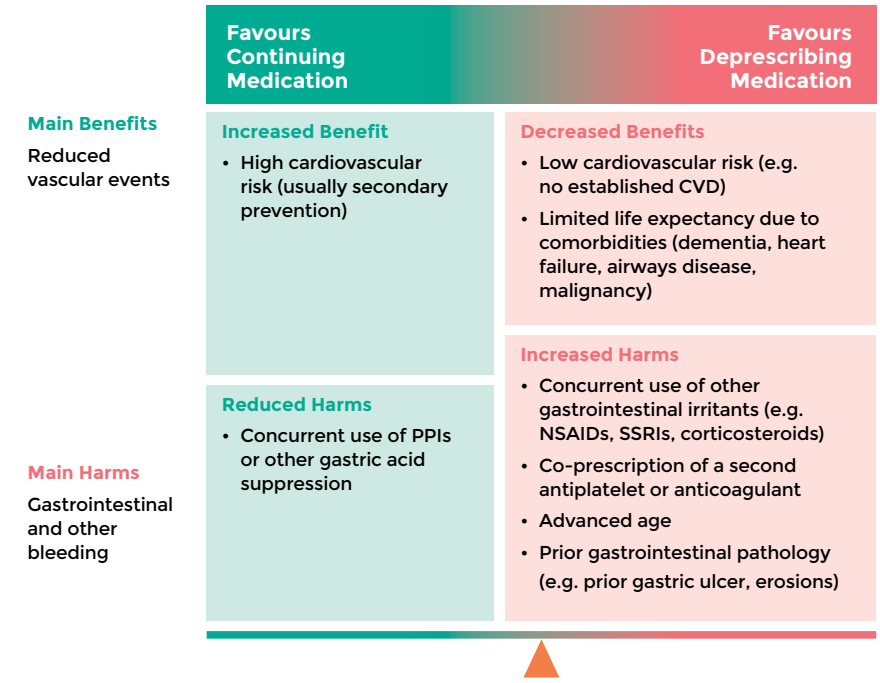
Recurrent minor bleeding or development of anaemia can have a significant impact on patients' quality of life and should trigger review of antiplatelet therapy, particularly in situations where comfort is the primary aim of treatment (e.g. palliative care).

deprescribing
FOR BETTER HEALTH OUTCOMES

CONTEXT

This guide considers the use of antiplatelet agents for prevention of vascular events.

BENEFIT VERSUS HARM



RECOMMENDED DEPRESCRIBING STRATEGY

- Patients with a high risk of gastrointestinal bleeding (e.g. older age, history of previous bleed, concomitant use of gastro-toxic drugs, significant comorbidity, and smoking) should have their use of antiplatelet therapy reviewed.
- Patients with a low absolute cardiovascular risk (primary prevention) should be considered for cessation of antiplatelet agents.
- Patients receiving dual antiplatelet therapy should generally have one of these ceased 12 months after the acute event, but for patients where bleeding risk is higher (e.g. > 75 years old with renal dysfunction), earlier cessation at 3-6 months may be appropriate.
- Patients requiring concurrent anticoagulant therapy should generally have antiplatelet therapy ceased 12 months after the most recent acute event. This can be shortened to 3-6 months when bleed risk is high (with the anticoagulant to continue as monotherapy).
- Patients with troublesome adverse effects associated with antiplatelet agents should be reassessed for the ongoing risk vs benefit of the antiplatelet agent.
- Patients approaching end of life where goals of care are focused on comfort should have antiplatelet agents reviewed.
- Antiplatelet can usually be stopped without the need for tapering.

BACKGROUND

Antiplatelet agents inhibit aggregation of platelets through a variety of mechanisms. They are useful in managing conditions where platelet aggregation leads to arterial thrombosis. While generally well tolerated and effective medications, utility is limited by the inherent risk of bleeding associated with platelet inhibition. Much guidance exists on when to initiate antiplatelet agents whereas relatively little exists for when to review or cease therapy. This guideline is intended to inform individualised discussion regarding the risk vs benefit of antiplatelet therapy, highlighting certain populations and clinical scenarios where minimising or stopping antiplatelets may be preferable. As older age is a major risk factor for both atherothrombotic events and haemorrhage, management of older people is of particular focus.

EFFICACY

SECONDARY PREVENTION

Low-dose aspirin (75 – 150 mg daily) has been shown to be effective in preventing about one-quarter to one-fifth of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in patients with a history of previous myocardial infarction (MI), cerebrovascular accident (CVA), or transient ischaemic attack (TIA).[1,2] This corresponds to an absolute risk reduction (ARR) of 1.5 - 2.5%, or 15 - 25 events per 1000 patient years.

In 1994, the Antiplatelet Trialists' Collaboration,[3] concluded that owing to the higher baseline risk, the absolute benefit is greater in older than in younger patients. In patients < 65 years of age, 11% who took aspirin had vascular events compared to 14.3% of those who took placebo (ARR 3.3%). For patients > 65 years of age, 18.7% who took aspirin had vascular events compared to 23.2% taking placebo (ARR 4.5%).

In 2002, the Antithrombotic Trialists' Collaboration analysed 195 trials of long-term aspirin use versus control for secondary prevention of CVD events, including 135,640 subjects and around 17,000 serious vascular events.[2] In these trials, aspirin use resulted in significant reductions in serious vascular events including stroke and coronary events, and low dose regimens (75 - 150 mg/day) were found to be as effective as higher doses (**Figure 1**).

Aspirin use as a secondary prevention intervention in patients with established CVD is well-accepted and recommended by various clinical guidelines in Australia and overseas.[4,5,6,7]

While the majority of data comes from studies using aspirin, several other antiplatelet agents are available, including the P2Y12 inhibitors (e.g. clopidogrel, ticagrelor). Compared with aspirin, event rates and mortality outcomes in the secondary prevention setting are similar.[8] However, data from one large study comparing clopidogrel with aspirin (325mg), found the P2Y12 inhibitor was associated with a slightly lower incidence of the composite outcome of MI, CVA, and vascular death (ARR 0.5% per year, NNT= 200 to prevent one extra event).[9]

PRIMARY PREVENTION

In the past, use of antiplatelet therapy for primary prevention of vascular events was widespread. However, contemporary studies have revealed that use in this setting provides only a small benefit on non-fatal vascular events, does not significantly benefit mortality, and significantly increases the risk of bleeding. As a result, routine use of aspirin for primary prevention is no longer recommended.

Nonetheless, some international guidelines still consider individuals with very high baseline cardiovascular risk, who also have a low risk of bleeding, to be reasonable candidates for antiplatelet therapy. A recent publication by the US Preventive Services Task Force recommended that aspirin for primary prevention could be considered in those aged 40-59 years with 10-year CV risk score >10%, but it should not be considered for people aged >60 years due to an unfavourable risk/benefit profile.[10]

Results of the key trials examining aspirin for primary prevention are summarised below in order of publication:

- British Doctors Trial[11]: **No significant benefit**
- Physicians Health Study[12]: 34% reduction in MI (ARR 0.185% per year, **NNT=540**)
- Hypertension Optimal Treatment[13]: 15% reduction in any CV event (ARR 0.16% per year, **NNT= 625**); 36% reduction in MI (ARR 0.13% per year, **NNT=769**)
- Thrombosis Prevention Trial[14]: 20% reduction in MI (ARR 0.23% per year, **NNT= 435**)
- Primary Prevention Project[15]: 23% reduction in any CV event (ARR 0.475% per year, **NNT 211**) and 44% reduction in CV mortality (ARR 0.15% per year, **NNT= 667**)
- Womens Health Study[16]: 17% reduction in stroke (ARR 0.255% per year, **NNT=392**)
- Japanese Primary prevention with Aspirin for Diabetes[17]: **No significant benefit**
- Prevention Of Progression of Arterial Disease And Diabetes[18]: **No significant benefit**
- Aspirin for Asymptomatic Atherosclerosis[19]: **No significant benefi**t
- Japanese Primary Prevention Project[20]: **No significant benefit**
- ASCEND[21]: 12% reduction in any cardiovascular event (ARR 0.15% per year, **NNT=667**)
- ARRIVE[22]: **No significant benefit**
- ASPREE[23,24,25]: **No significant benefit**

While many of the older trials showed significant benefit on atherothrombotic event and mortality rates, more contemporary trials have failed to show significant benefit on most outcomes. Population level improvements in cardiovascular disease management including reduction in smoking rates, and improved hypertension and cholesterol management have been proposed as a reason for this shift in evidence.[26]

A number of meta-analyses including the most recent trials have been undertaken. Overall, these demonstrate a lack of significant benefit on mortality outcomes. Over an average follow-up of 6.6 years, non-fatal MI is significantly reduced by around 18%, whereas fatal MI is unchanged. TIA incidence is also reduced by around 21%, but total stroke rate is not significantly different.[26,27,28] It is important to note that due to the low baseline cardiovascular risk of the studied populations, the absolute reduction in events is small; 0.25% and 0.27% for non-fatal MI and TIA respectively. This equates to numbers needed to treat (NNT) of 400 and 370, respectively.

Sub-group data analysis suggests these relative risk reductions are consistent across varying baseline cardiovascular risk groups and age groups.[29,30]

One tool which has been suggested to assist in selection of primary prevention patients for aspirin therapy is coronary artery calcium testing. In 2017 The Cardiac Society of Australia and New Zealand recommended aspirin for primary prevention in individuals with a coronary artery calcium score >100, due in large part to a study conducted in 2014 which estimated net benefit from aspirin in these patients.[31,32]

However, a more recent study published in 2020 suggested this should be limited to patients with a low baseline bleed risk, as harm outweighs benefit in those with a higher risk of bleeding.[33]

It has been suggested that aspirin may reduce the incidence of certain cancers and cancer associated deaths. This is not supported by the current evidence.[27] Indeed, one of the recent primary prevention studies raised a safety signal regarding cancer, with the data suggesting aspirin may negatively influence the progression of cancer in older adults.[34]

A summary of the results from meta-analyses of aspirin in primary and secondary prevention is shown in **Figure 1**. These numbers represent population averages and an individual's risk may be significantly higher or lower depending on their individual risk factors.

DUAL ANTIPLATELET THERAPY (ASPIRIN WITH CLOPIDOGREL OR TICAGRELOR)

Guidelines on the use of dual antiplatelet therapy (DAPT) and combination antithrombotics (see below) are available from several professional bodies and differ in their recommendations depending largely on the recency of publication. Those jointly developed in 2016 by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand are currently being updated[4], and a number of the more recent European Society of Cardiology (ESC) guidelines are therefore referred to for the purposes of this guide.

Following acute cardiac syndromes (unstable angina, myocardial infarction, percutaneous coronary intervention (PCI)) the ESC guidelines suggest DAPT for 12 months, but this may be shortened to 6 months in high bleed risk individuals, or 1 month in individuals with high bleed risk and medically managed events. In other cases, DAPT may be extended longer term for those not at high risk of bleeding who have particularly high risk of recurrent vascular events.[35]

Two decision making tools, the DAPT score and PRECISE-DAPT score, can be used to ascertain whether an individual who has undergone cardiac stenting will benefit from extended DAPT.[35] Factors that favour a change from DAPT to a single antiplatelet agent prior to 12 months include history of bleeding, older age, low Hb, and reduced renal function.

Based on PRECISE-DAPT, all patients with a cardiac stent over 75 with a creatinine clearance < 50 mL/min would be recommended to have a shortened duration of dual antiplatelet therapy. Similarly, anyone with prior bleeding should receive a shortened duration of therapy.

ESC guidelines on peripheral vascular disease (PVD) suggest DAPT for 1 month following peripheral or carotid PCI. This is based on results from two small RCTs and the optimal duration of therapy is unknown.[7]

In cerebrovascular disease, DAPT may be useful following minor stroke or high-risk TIA. A meta-analysis of the four major trials comparing dual antiplatelet therapy with aspirin demonstrated an approximately 25% reduction in the incidence of recurrent stroke and major vascular events without impact on mortality.[36] Risk of major bleeding was more than doubled in the DAPT group. The reduction in vascular events occurs primarily in the first 21 days of DAPT, while bleeding complications tended to occur in the second and third months.[37] As such, when indicated, DAPT with aspirin and clopidogrel is recommended to be used for only 21 days following an acute cerebral event.[6]

Patients aged 75 and older have been underrepresented in clinical trials of DAPT and specific guidance for duration of therapy in this population is unclear. Given that the risk of bleeding increases dramatically both with age and with DAPT compared to monotherapy (see later), caution should be exercised when considering use of these regimens in older people.

COMBINATION WITH ANTICOAGULANT THERAPY

In situations where an acute atherosclerotic event occurs in an individual who also has an indication for anticoagulant therapy, one or more antiplatelet agents may be required in the short term. In this setting, the European Society of Cardiology (ESC) guidelines suggest there is no benefit from continuing the antiplatelet therapy longer than 12 months following an acute event, and in individuals with a high risk of bleeding, shortening duration of therapy to 6 months is suggested.[5]

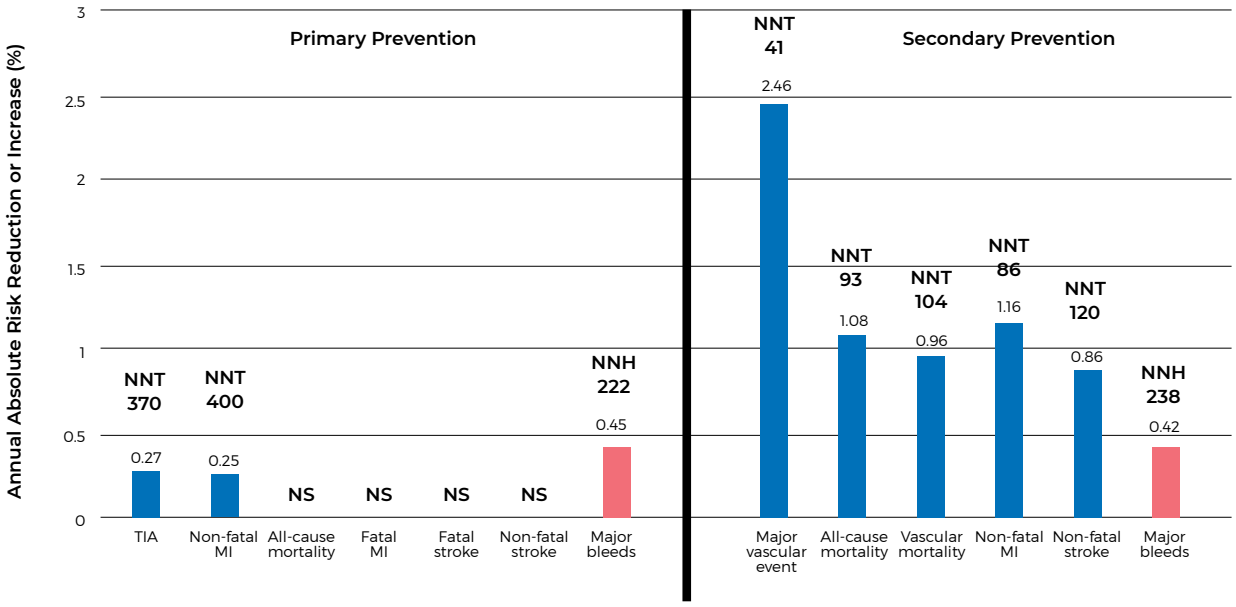


Figure 1: Results from meta-analysis of randomised trials investigating the benefit and harms of aspirin when used for primary prevention (27) and secondary prevention (2). NNT= number needed to treat, NNH= number needed to harm, NS= not significant.

Current Antithrombotic Strategy	Indication	Recommended duration before antiplatelet therapy is reduced (if dual) or ceased (if single)	
		General patient	High bleed risk patient
Dual antiplatelets + anticoagulant ○ ○ ●	**Coronary PCI + AF**	7 days (Up to 30 days if high ischaemic risk)	7 days
Single antiplatelet + anticoagulant ○ ●	**Ischaemic event + AF** (Or step down from triple therapy)	12 months	6 months
	PVD – Lower limb PCI + **AF**	1 - 12 months	Avoid antiplatelet use
Dual antiplatelets ○ ○	**ACS** – PCI or CABG – Medical management	12 months 12 months	6 months 1 month
	Stable IHD – PCI	6 months	3 months
	Minor CVA or **high-risk TIA**	21 days	21 days
	Carotid occlusion – PCI	1 month	1 month
	PVD – Lower limb PCI	1 month	1 month
Single antiplatelet ○	**No history - Primary prevention** (General patient)	Avoid antiplatelet use	Avoid antiplatelet use
	No history - Primary prevention (Selected high ischaemic, low bleed risk patient)	Do not use after age 75 (Do not initiate in patients >60 years old)	Avoid antiplatelet use
	Previous ischaemia - Secondary prevention	Continue long-term	Consider risk/benefit, GOC, and patient preferences.

○ = antiplatelet, ● = anticoagulant

Table 1: Recommended duration of antiplatelet therapy in various clinical situations. (Adapted from references 5, 6, 7, 10, and 35)

ADVERSE EFFECTS

The most important adverse effect of antiplatelet therapy is major bleeding due to the frequency and potentially serious nature of this adverse effect. An individual's risk of bleeding is highly variable depending on a number of factors including older age, history of previous bleed, concomitant use of gastro-toxic drugs (anticoagulants, other antiplatelets, NSAIDs, SSRIs, SNRIs, oral corticosteroids), significant comorbidity (renal disease, hepatic disease, malignancy), and smoking status.

Depending on the combination of risk factors present, the likelihood of an antiplatelet associated bleed can range from being relatively unlikely to being a significant factor in the decision to prescribe (or deprescribe). An example of this is shown in **Figure 2**. In older 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.

The published average rate of antiplatelet associated GI bleeds is around 1.2/1000 patient years.[39] This is, however, based on clinical trial participants, and those at the highest risk of bleed are often excluded from such studies. Even in ASPREE, a placebo controlled primary prevention trial in older people (median age 74 years at randomisation),[21] the rate of major haemorrhagic events (haemorrhagic stroke, intracranial bleeding, extracranial bleeding leading to transfusion, hospitalisation, surgery or death) associated with aspirin was 2.4/1000 patient years (NNH= 417). Again, ASPREE excluded patients at high risk of bleeding.

Real world data provides a different perspective. An observational Danish public health registry study examining rates of antithrombotic-associated bleeding in people with a diagnosis of atrial fibrillation included data from 272,315 patients.[40] The average incidence of bleeding associated with aspirin monotherapy was 11/1000 patient years, much higher than the rate seen in highly selected study populations. Increasing age was clearly associated with a higher risk of major bleeding, the incidence in people >90 years old being 30/1000 patient years (See **Figure 3**).[40]

Older age also seems to be associated with poorer outcomes following aspirin associated bleeding. A population-based cohort study of patients in the Oxford Vascular Study found that the incidence of disability or fatality due to aspirin associated upper GI bleed was 10 times higher in people >75 years old than in those < 75 years old.[41] Far from this being an uncommon outcome in older patients, they found the majority of upper GI bleeds in >75 year-olds were disabling or fatal (62%).[41]

It is important to note that proton pump inhibitor (PPI) use can mitigate this risk. Using a statistical model, the authors estimated the NNT for PPI use to prevent one disabling or fatal upper GI bleed over 5 years as 338 for people <65 years but only 25 for people >85 years old.[41]

COMBINATION WITH OTHER ANTITHROMBOTIC AGENTS

Combining antiplatelet agents with other antiplatelets or anticoagulants is associated with higher risk of bleeding than use of a single antiplatelet alone. The Danish public health registry study of patients with atrial fibrillation examined rates of bleeding associated with prescription of several antithrombotic combinations. The number of excess bleeding events attributable to each agent/combination is shown in **Figure 4**.

In people with a high bleeding risk (older people, those with history of significant bleeding, and those with significant comorbidities) the decision to use combination antithrombotic therapy necessitates careful consideration of risk vs benefit. If they are used, addition of a low dose PPI in order to mitigate bleed risk may need to be considered.

OTHER RISK FACTORS FOR BLEEDING

The Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention has assembled a tool for assessment of bleed risk which combines a number of patient characteristics (**Table 2**). Bleeding risk is considered high if at least one major or two minor criteria are met. While primarily designed to assess bleeding risk prior to PCI, the 2020 ESC guidelines for management of non ST-elevation ACS suggest the pragmatic use of this tool across a broader clinical context.[5] Specifically, use of this tool when assessing appropriate duration of combination antithrombotic therapy is suggested.

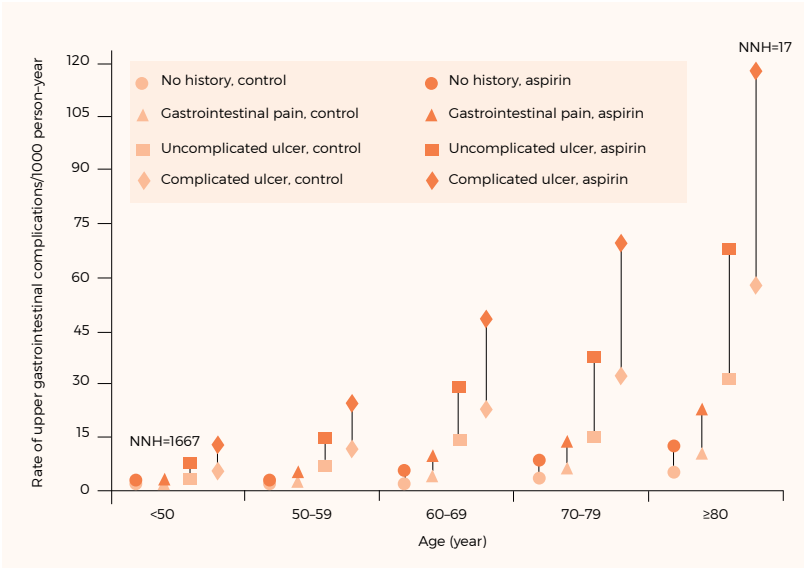


Figure 2: Estimated rates of gastrointestinal complications in men, according to age and presence or absence of GI complications.[38]

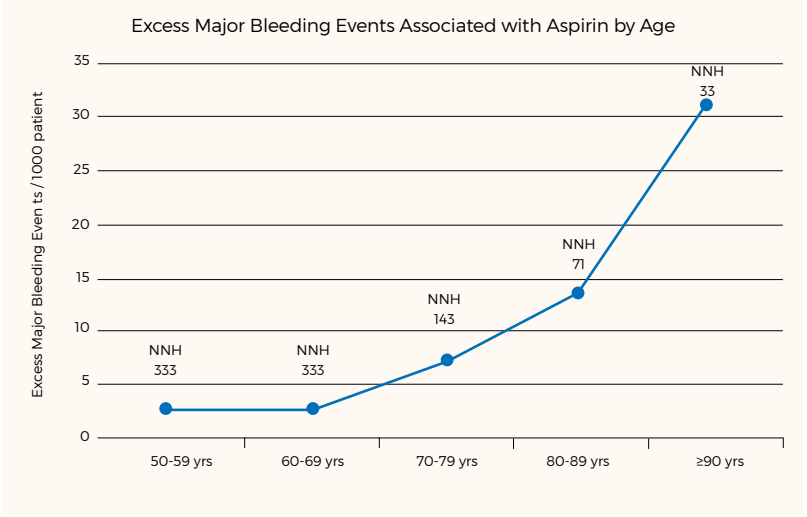


Figure 3: The Impact of Age on Aspirin Associated Major Bleeding. Adapted from reference 40.

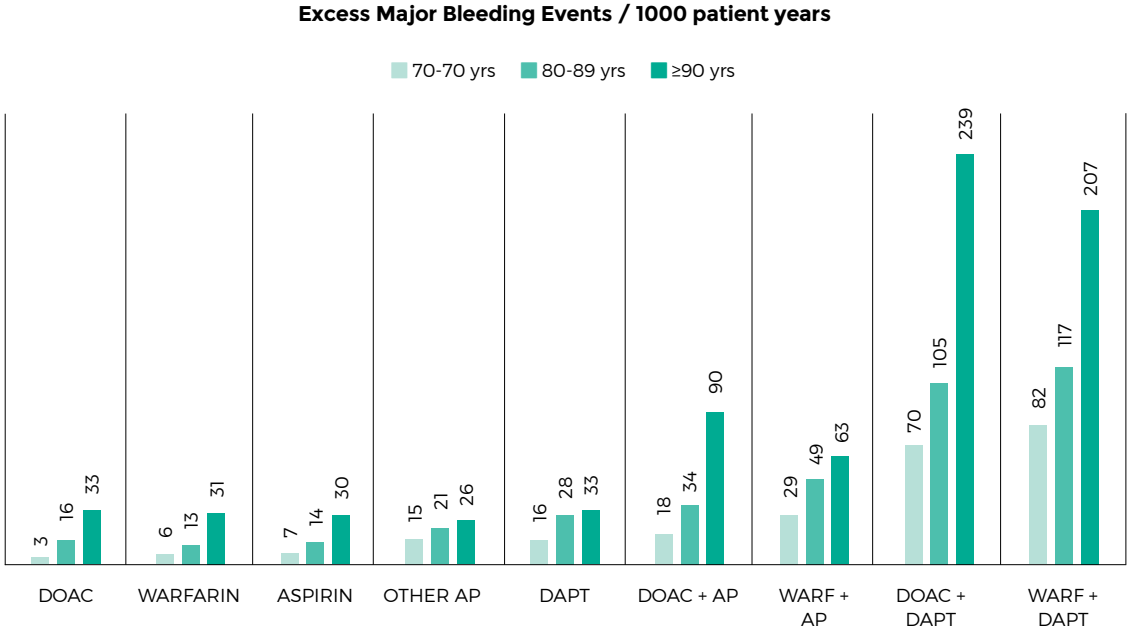


Figure 4: Incidence of major bleeding associated with different combinations of antithrombotic agents in excess of that observed with no antithrombotic use in a Danish public health registry study of 272,315 patients with atrial fibrillation (adapted from reference 40).

Major	Minor
Condition causing chronic bleeding	Age >75 years
eGFR <30 mL/min	eGFR 30-59 mL/min
Haemoglobin <110 g/L	Haemoglobin 110-129 g/L (men), 110-119 g/L (women)
Hospitalisation or transfusion for spontaneous bleeding in the last 6 months (or recurrent events)	Hospitalisation or transfusion for spontaneous bleeding in the last 12 months
Platelets <100 x 10^9/L	Long term oral NSAID or corticosteroid
Liver cirrhosis with portal hypertension	History of ischaemic stroke
Active malignancy	
History of spontaneous intracranial haemorrhage	
Traumatic intracranial haemorrhage in the last 12 months	
Brain arteriovenous malformation	
Moderate-severe ischaemic stroke in last 6 months	
Major surgery or major trauma in the last 30 days	

Table 2: Major and minor criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met).Adapted from reference 5

FACTORS TO CONSIDER

The balance between risk of bleeding, and the benefit on vascular events is core to the decision of whether to prescribe, and deprescribe, antiplatelet agents.

In certain situations, such as primary prevention in older patients, this risk/benefit assessment is generally straight forward; benefit is limited to a small reduction in non-fatal events, and in most cases the risk of bleeding far outweighs the benefit.

When used for secondary prevention, however, the greater magnitude of benefit makes risk/benefit assessment more challenging. Rather than direct comparison between published population bleed rates and event rates, a more nuanced consideration including assessment of individualised risk factors, preferences, and goals of care is required.

Anecdotally individuals would generally prefer to avoid an atherosclerotic event at the expense of a bleed, but for those in whom a bleed may be fatal or is very likely (e.g. older age, history of bleeding, significant comorbidity), avoidance of bleeding may take precedence. Similarly, a history of relatively minor ischaemic disease (e.g. historical stable angina) and history of significant lifestyle change/long term preventative therapy with medication such as statins, the chance of deriving benefit may be lower and more likely to be outweighed by risk of bleeding.

Available cardiovascular risk calculators to inform decisions in primary prevention settings are not validated for patients older than 75 years and an individualised assessment based on clinical judgement is often the only option.

IN FAVOUR OF DEPRESCRIBING

Low Risk of Cardiovascular Event

Those without a history of symptomatic atherosclerotic disease (primary prevention) are unlikely to benefit from an antiplatelet agent.

Individuals with prognosis-limiting comorbidities (unrelated to atherosclerosis) may be less likely to obtain benefit from antiplatelet therapy.

In secondary prevention, a long-term history of lifestyle changes (e.g. smoking cessation) or preventative medication use (e.g. statins) may result in a lower absolute benefit being gained from antiplatelet therapy.

Risk of re-thrombosis decreases significantly in the months following an acute event/PCI. Combination antithrombotics often provide a net positive benefit initially but this changes over time and de-escalation of therapy should occur as appropriate.

History or high risk of an adverse effect (e.g. major bleeding)

Older age, history of previous bleed, unavoidable use of gastro-toxic drugs, significant comorbidity, and smoking all increase the risk of antiplatelet associated bleed. Individuals with multiple factors have the highest risk.

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 vs benefit of antiplatelet therapy.

Persistent minor bleeding can impact quality of life (e.g. recurrent nose bleeds, haemorrhoids). In individuals where goals of care are focused on comfort (e.g. palliative care) cessation of antiplatelet therapy may be justified.

Individual preference to avoid bleeding at the expense of increased vascular risk.

AGAINST DEPRESCRIBING

Secondary prevention patients who are well, functionally independent, and have a five year or more life expectancy may derive ongoing benefit from the use of antiplatelet therapy.

When benefit of therapy continuation clearly outweighs the risk of bleeding.

Informed support from the individual or decision makers to continue therapy.

DISCONTINUATION SYNDROMES

Aspirin suppresses thromboxane thereby inhibiting platelet aggregation, but also suppresses production of prostacyclin, which possesses antiplatelet effects. Following cessation of aspirin, it is possible that a prothrombotic state may develop for a few days due to a mismatch in the resumption of production of these agents. This has been tested in an animal model,[42] and is supported by some reports of ischaemic stroke, cardiovascular problems and lower limb ischaemia 7-10 days after cessation of aspirin.[43,44,45]

In secondary prevention patients prescribed low-dose aspirin, 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,[46] and myocardial infarction[47] compared with continuation of therapy.

REFERENCES

1. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860.
2. Antithrombotic Trialists' Collaboration. Collaborative metaanalysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
3. 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.
4. Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. Med J Aust. 2016;205(3):128-33.
5. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289-1367.
6. Stroke Foundation. Clinical Guidelines for Stroke Management. Available at https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management. Accessed [23, June 2022].
7. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763-816.
8. Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, Condorelli G, Ferrante G, Stefanini GG. Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. Lancet. 2020 May 9;395(10235):1487-1495.
9. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996 Nov 16;348(9038):1329-39.
10. Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR, et al. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. Jama. 2022;327(16):1577-84.
11. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988;296:313–316.
12. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;32:129-135.
13. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755–1762.
14. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and lowdose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998;351:233–241.
15. de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Lancet 2001;357:89–95.
16. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304.
17. Ogawa H, Makayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–2141.
18. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepher J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Ediburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.
19. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;303:841–848.
20. Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, Sugawara M, Ando K, Murata M, Yokoyama K, Ishizuka N. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA. 2014 Dec 17;312(23):2510-20.

21. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018 Oct 18;379(16):1529-1539.
22. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, Howard G, Pearson TA, Rothwell PM, Ruilope LM, Tendera M, Tognoni G; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018 Sep 22;392(10152):1036-1046.
23. ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379 (16) :1509-1518.
24. ASPREE Investigator Group. Effect of aspirin on disability free survival in the healthy elderly. N Engl J Med 2018;379 (16) :1499-1508.
25. ASPREE Investigator Group. Effect of aspirin on all cause mortality in the healthy elderly. N Engl J Med 2018;379 (16) :1519-1528.
26. Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. Eur Heart J. 2019 Feb 14;40(7):607-617.
27. Abdelaziz HK, Saad M, Pothineni NVK, Megaly M, Potluri R, Saleh M, Kon DLC, Roberts DH, Bhatt DL, Aronow HD, Abbott JD, Mehta JL. Aspirin for Primary Prevention of Cardiovascular Events. J Am Coll Cardiol. 2019 Jun 18;73(23):2915-2929.
28. Christiansen M, Grove EL, Hvas AM. Primary Prevention of Cardiovascular Events with Aspirin: Toward More Harm than Benefit-A Systematic Review and Meta-Analysis. Semin Thromb Hemost. 2019 Jul;45(5):478-489. doi: 10.1055/s-0039-1687905. Epub 2019 May 16.
29. Masson G, Lobo M, Masson W, Molinero G. Aspirin in primary prevention. Meta-analysis stratified by baseline cardiovascular risk. Arch Cardiol Mex. 2020;90(3):293-299. English.
30. Galli M, Andreotti F, D'Amario D, Vergallo R, Montone RA, Porto I, Crea F. Aspirin in primary prevention of cardiovascular disease in the elderly. Eur Heart J Cardiovasc Pharmacother. 2020 Sep 1;6(5):326-327.
31. Liew G, Chow C, van Pelt N, Younger J, Jelinek M, Chan J, et al. Cardiac Society of Australia and New Zealand Position Statement: Coronary Artery Calcium Scoring. Heart Lung Circ. 2017;26(12):1239-51.
32. Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silverman MG, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes. 2014;7(3):453-60.
33. Ajufo E, Ayers CR, Vigen R, Joshi PH, Rohatgi A, de Lemos JA, et al. Value of Coronary Artery Calcium Scanning in Association With the Net Benefit of Aspirin in Primary Prevention of Atherosclerotic Cardiovascular Disease. JAMA Cardiology. 2021;6(2):179-87.
34. McNeil JJ, Gibbs, *Peter, Orchard SG, Lockery JE, Bernstein WB, Cao Y, et al. Effect of Aspirin on Cancer Incidence and Mortality in Older Adults. JNCI: Journal of the National Cancer Institute. 2020;113(3):258-65.
35. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2018 Jan 1;53(1):34-78.
36. Bhatia K, Jain V, Aggarwal D, Vaduganathan M, Arora S, Hussain Z, Uberoi G, Tafur A, Zhang C, Ricciardi M, Qamar A. Dual Antiplatelet Therapy Versus Aspirin in Patients With Stroke or Transient Ischemic Attack: Meta-Analysis of Randomized Controlled Trials. Stroke. 2021 Jun;52(6):e217-e223.
37. Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RA, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. BMJ. 2018 Dec 18;363:k5108.
38. Patrono C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither? Eur Heart J. 2013 Nov;34(44):3403-11.
39. Vera E Valkhoff et al. Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: A meta-analysis of randomized clinical trials and observational studies. Can J Gastroenterol 2013;27(3):159-167.
40. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy. Circulation. 2019;139(6):775-86.
41. Li Linxin et al. Age-specific risks, severity, time course and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017; (17): 30770-30775
42. Christian Doutremepuich et al. Aspirin Discontinuation Syndromes: Clinical Implications of Basic Research Studies. Am J Cardiovasc Drugs (2013) 13:377–384.
43. Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a riskbfactor for ischemic stroke. Neurology. 2004;62(7):1187–9.
44. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol. 2005;62(8):1217–20.
45. Armstrong MJ, Schneck MJ, Biller J. Discontinuation of perioperative antiplatelet and anticoagulant therapy in stroke patients. Neurol Clin. 2006;24(4):607–30.
46. Garcıa Rodrıguez LA, Cea-Soriano L, Hill C, Johansson S. Increased risk of stroke after discontinuation of acetylsalicylic acid. A UK primary care study. Neurology 2011;76:740–746.
47. Garcıa Rodrıguez LA, Cea-Soriano L, Martı´n-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. Br Med J 2011;343:d4094

AUTHORSHIP

This guide was updated for Primary Health Tasmania by Stewart Mearns and reviewed by Dr David Dunbabin, Geriatrician, Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania, and the Deprescribing Project Advisory Group.

DEPRESCRIBING PROJECT ADVISORY GROUP

Nicole Bonner, Clinical Nurse, Masonic Care Tasmania

Dr Elizabeth Monks, Aged Care General Practitioner

Debbie Rigby, Consultant Pharmacist

Dr Andrew Stafford, Senior Lecturer, Curtin Medical School

Dr Joanne Stewart, General Practitioner

DECEMBER 2022