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Stroke is the second leading cause of death in Australia, and often results in significant long-term disability.¹ This *NPS News* outlines the appropriate use of antithrombotic (antiplatelet and anticoagulant) therapies in the long-term prevention of ischaemic stroke and provides tools for communicating risks and benefits to patients.

People at high risk benefit most from antithrombotic therapy

The risk of ischaemic stroke increases with age, but can vary widely depending on risk factors (see Table 1).^{2,3}

Table 1: Major risk factors for ischaemic stroke^{2,4,5}

Risk factor	Estimated rate of stroke
Valvular atrial fibrillation (mitral stenosis)	15% to 20% p.a.
Nonvalvular atrial fibrillation	2% to 18% p.a.
Transient ischaemic attack (TIA)	5% to 7% p.a.*
Previous stroke	4% to 5% p.a.
Hypertension	2% to 3% p.a.
Smoking, diabetes mellitus, or cardiovascular disease	1% to 2% p.a.

* May be between 10% and 18% in some patients e.g. those with ipsilateral high-grade ($\geq 70\%$) carotid stenosis.

The approach to antithrombotic therapy depends on the pathology of stroke. Use long-term antiplatelet therapy in all people with a previous stroke or transient ischaemic attack (TIA) due to arterial disease (atherothromboembolism).⁴ Anticoagulant therapy with warfarin should be considered to prevent a first, or recurrent, stroke in patients with atrial fibrillation (AF).⁴

The decision to use antiplatelet therapy for primary prevention of atherothromboembolic stroke depends on the balance of overall cardiovascular risk and the risk of major bleeding with treatment.^{3,5} Consider low-dose aspirin if the 5-year absolute risk of both coronary heart disease and stroke events is $> 15\%$.⁶ To estimate risk, use the New Zealand Guidelines Group Cardiovascular Risk Calculator (available at www.nps.org.au/cv_risk_calculator).^{3,6}

Communicating risk effectively

Patients differ in their perceptions of risk — common risks are often underestimated and rare risks overestimated.⁷ How risk is communicated to patients can influence their treatment decisions.^{7,8} Health practitioners can help improve a patient's understanding of the benefits and harms of antithrombotic therapy by:

- providing individualised information on stroke risk
- describing risk in absolute terms, using numbers and words
- presenting both positive and negative scenarios
- using visual aids that put risk into perspective.⁸

Patient decision aids (web, audiovisual or paper-based) — used with health practitioner counselling — improve knowledge and realistic expectations about the benefits and harms of treatment options.⁹ The New Zealand Guideline Group's Cardiovascular Risk Calculator is also useful for explaining the risk of vascular events.

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Antiplatelet therapy prevents stroke due to arterial disease

Using antiplatelet therapy for 3 years in 1000 people who have an ischaemic stroke or TIA can prevent 25 stroke recurrences; this outweighs the risk of major extracranial bleeding (1–2 additional bleeds per year).¹⁰

Low-dose aspirin or aspirin plus dipyridamole SR are effective options

Aspirin (100–300 mg daily) is given as soon as possible after the onset of ischaemic stroke and can be continued as long-term antiplatelet therapy.^{3,4} Aspirin plus dipyridamole sustained release (SR) is also an option for long-term therapy and if stroke re-occurs while taking aspirin.^{3,4}

In people with ischaemic stroke or TIA, aspirin plus dipyridamole reduces the relative risk of non-fatal stroke by 23% (95% confidence interval [CI], 11% to 33%) compared with aspirin alone.¹¹ However, this combination does not prevent more vascular deaths than aspirin and is often not tolerated because of headache.^{12,13}

Clopidogrel is also an acceptable choice

Clopidogrel has similar efficacy to aspirin plus dipyridamole in preventing recurrent stroke, and a comparable risk of bleeding.¹⁴ Clopidogrel may be used if aspirin plus dipyridamole is not tolerated, or there is co-existing coronary heart disease for which adding dipyridamole to aspirin has less evidence.^{4,12}

In the CAPRIE trial, the rate of serious vascular events was only slightly lower with clopidogrel than for aspirin (5.3% vs 5.8%), while the overall risk of bleeding was similar (9.3%).¹⁵

Low-dose aspirin is a more affordable option for people who do not meet the PBS authority restrictions for clopidogrel, which include:

- hypersensitivity to aspirin or NSAIDs (anaphylaxis, urticaria or asthma)
- unacceptable risk of gastrointestinal bleeding
- recurrent vascular episodes while taking aspirin.

People who also have an acute coronary syndrome (myocardial infarction or unstable angina) may receive clopidogrel on the PBS for use in combination with aspirin to prevent early and long-term atherothrombotic events.

Tiping the balance of benefit and harm with drug combinations

Avoid aspirin with clopidogrel in people with ischaemic stroke or TIA unless coronary heart disease is also present. The benefit of this combination only exceeds the risk of bleeding when used for acute coronary syndromes or where there are coronary stents.^{4,6}

Aspirin with clopidogrel is no more effective at reducing vascular risk than clopidogrel alone in people with ischaemic stroke or TIA, but causes more life-threatening bleeding.¹⁶ Aspirin with dipyridamole does not cause more bleeding than aspirin alone in these people.^{12,13}

Most people with AF should receive warfarin

The choice of antithrombotic therapy in AF is guided by an assessment and regular reassessment of the absolute risk of stroke and risk of major bleeding with warfarin (Figure 1).

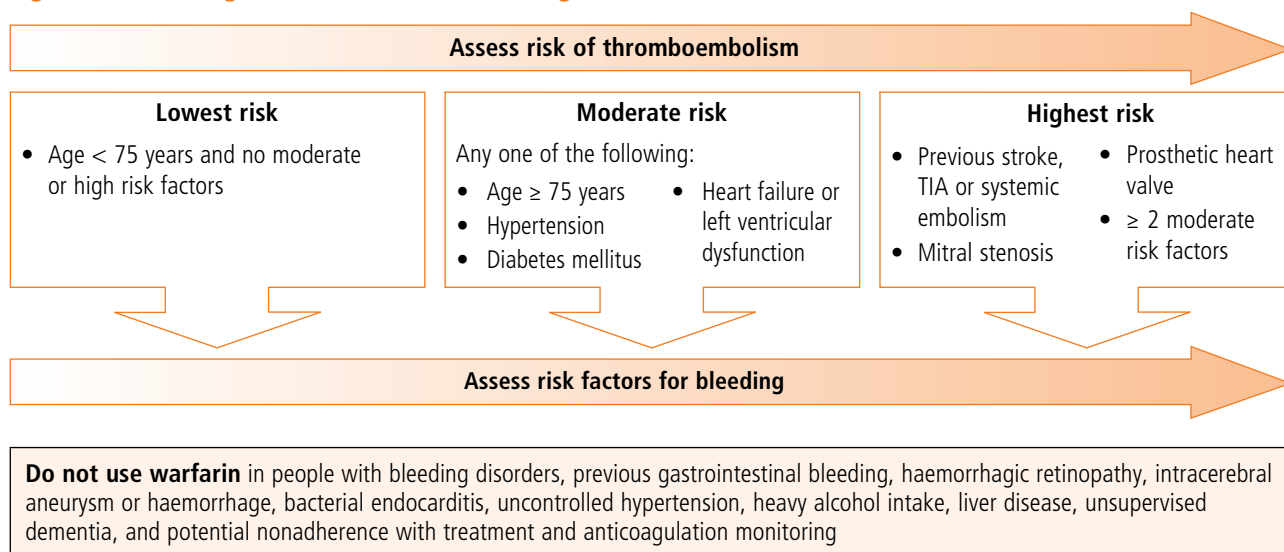
Consider long-term warfarin for every patient with AF at moderate to high risk of thromboembolism.^{3,4,6,17} Aspirin may be used for people at lower risk, or when warfarin is contraindicated.^{4,6,17}

Warfarin reduces the relative risk of stroke in non-valvular AF by 64% (95% CI, 49% to 74%) compared with placebo or no treatment.¹⁸ People with a previous

stroke or TIA gain the greatest absolute benefit from warfarin: 12 patients need to be treated for 1 year to prevent 1 stroke.¹⁸ In comparison, 37 people *without* a previous stroke or TIA need to be treated for 1 year to prevent 1 stroke.¹⁸

Aspirin is about half as effective as warfarin for stroke prevention in AF.¹⁸⁻²¹ However, the risk of major bleeding is doubled with warfarin compared with aspirin and can be even higher for some patients (see page 3).^{18,19} Clopidogrel with aspirin is not a safer or more effective alternative to warfarin in people with AF.^{22,23}

Figure 1: Assessing risk of stroke and bleeding in AF^{3,6,17,24-26}



Warfarin or aspirin: tools for making choices

Stroke risk stratification tools can help with selecting warfarin or aspirin in non-valvular AF. The CHADS2 index (Figure 2) is the best validated tool.²⁷ Warfarin is indicated in people at high risk of stroke (CHADS2 score ≥ 2), while aspirin is sufficient for those at low risk.^{25,28} Warfarin or aspirin may be used for people classified as moderate risk.²⁵

Figure 2: Selecting antithrombotic therapy in non-valvular AF^{25,27,28}

CHADS2 criteria	Points	Stroke risk score*	Recommended therapy
Previous stroke or TIA	2	High 2–6	Warfarin (INR 2–3)
Age ≥ 75 years	1		
Hypertension	1	Moderate 1	Warfarin or aspirin
Diabetes mellitus	1		
Heart failure	1	Low 0	Aspirin 100–300 mg daily

* Sum points from CHADS2 criteria, e.g. patient aged ≥ 75 years (1 point) with previous stroke (2 points), score = 3 points.

There is less evidence for determining when the risk of bleeding with warfarin exceeds the benefit, particularly for people at moderate thromboembolic risk.^{25,28} Choice of therapy is therefore based on a subjective assessment of relative benefits and harms, patient preference, access to anticoagulation monitoring and other factors (e.g. drug interactions).^{17,25,28}

An audio booklet decision aid for patients with AF is available (www.canadianstrokenetwork.ca/eng/tools/index.php). It includes visual aids to show the benefits and harms of warfarin and aspirin, and outlines the need for regular blood testing.^{29,30}

When can bleeding risk outweigh benefit?

The absolute risk of major bleeding with warfarin is at least 0.5% to 1.0% per year and is greatest in the first few months of therapy.^{6,31} Some people, particularly the elderly, are at higher risk — around 13% of those aged 80 years or over may have a major bleed in their first year of treatment.³²

Not all people should be prescribed warfarin even when it is indicated (see Figure 1). People with AF at high risk of stroke tend also to be those at highest risk of bleeding: age ≥ 75 years, previous stroke and hypertension (systolic BP > 160 mmHg) are risk factors for both bleeding and stroke.^{17,28}

However, such people are still likely to benefit from warfarin despite their increased risk of bleeding. For example, if the annual risk of major bleeding is 5%, and that for stroke is 15%, treating 100 patients with warfarin for 1 year will cause 5 major bleeds, but prevent 9 strokes. If the risk of thromboembolism is low, aspirin is appropriate because warfarin is more likely to cause a major bleed than prevent a stroke.²⁴

Older age is not a contraindication

Warfarin is indicated in people ≥ 75 years of age with at least one other risk factor for stroke (see Figure 2).²⁸ Older age or propensity for falls do not preclude warfarin, unless these pose too high a risk of bleeding for the individual.²⁴ If possible, maintain INR at the lower end of the therapeutic range in older people.^{17,24}

In a trial of people with AF (age ≥ 75 years), the annual rate of stroke, intracranial haemorrhage and systemic embolism was significantly lower with warfarin (1.8%) compared with aspirin (3.8%), but similar for major extracranial bleeding (1.4% vs 1.6%).³³

Using antithrombotics safely

Antiplatelet drugs may need to be stopped before planned surgery and some dental procedures: this applies to aspirin (7 days before) and clopidogrel (5 days) but not dipyridamole.²⁶ The decision to stop warfarin before surgery (4–5 days) will depend on the patient's thromboembolic risk and the risk of bleeding associated with the procedure.³⁴

Targeting a lower INR range (e.g. 1.5–2.0) does not reduce the risk of bleeding with warfarin, and is less likely to prevent a stroke.^{35,36} To help minimise the risk of bleeding:

- do not use high loading doses: start warfarin at 5 mg daily (less for the elderly)
- target an INR that balances the therapeutic goal with bleeding risk
- avoid frequent or large dosage adjustments
- consider potential interactions with drugs and herbal medicines.^{31,34}

For guidance on managing elevated INR, refer to the Warfarin Reversal Consensus Group guidelines at www.asth.org.au/resources/publications.

Plan education on warfarin use for every patient — anticoagulant booklets are essential to inform patients about:

- their daily dose, date of blood test and INR result
- the importance of using the same brand of warfarin
- what to do when starting or stopping medicines (prescription, OTC or complementary)
- the effect of diet (vitamin-K rich foods) and alcohol intake
- signs and symptoms of bleeding and thrombotic events.⁶

Pharmacists have an important role in educating patients about warfarin: this can be organised as part of a Home Medicines Review, or be undertaken during hospital admission or in a community pharmacy.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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