



National Prescribing Service Limited

2 March 2009



000001* 000
Dr Sam Sample
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SAMPLETOWN ABC 9999



Prescribing Practice Review

No. 44 Antiplatelets and anticoagulants in stroke

Dear Dr Sample,

Please find enclosed practical information and confidential data on your prescribing of antiplatelet and anticoagulant therapy.

Around 40 000 to 48 000 strokes occur each year in Australia, with 70% of these being first-time events.¹ Antiplatelet therapy should be used long term after an ischaemic stroke or transient ischaemic attack, and warfarin is indicated for most people with atrial fibrillation. The choice of therapy depends on both the risk of stroke and risk of adverse effects.

The accompanying issue of *Prescribing Practice Review* outlines some key issues in primary and secondary stroke prevention, such as the role of different antiplatelet therapies, how to assess the balance of benefits and harms with warfarin, and tools for discussing risk with patients and supporting adherence.

The clinical audit *Antiplatelet and anticoagulant therapy in stroke prevention* is now available to assist with reviewing your practice and provide an update on clinical guidelines. See the enclosed enrolment form for more information, or enrol online at www.nps.org.au/clinical_audits.

Yours sincerely

Dr Janette Randall
Chair, National Prescribing Service Limited

Reference

1. Australian Institute of Health and Welfare (AIHW). Australia's health 2008. No. 11 Cat. No. AUS 99. AIHW: Canberra, 2008. <http://www.aihw.gov.au/publications/aus/ah08/ah08.pdf> (accessed 5 February 2009).

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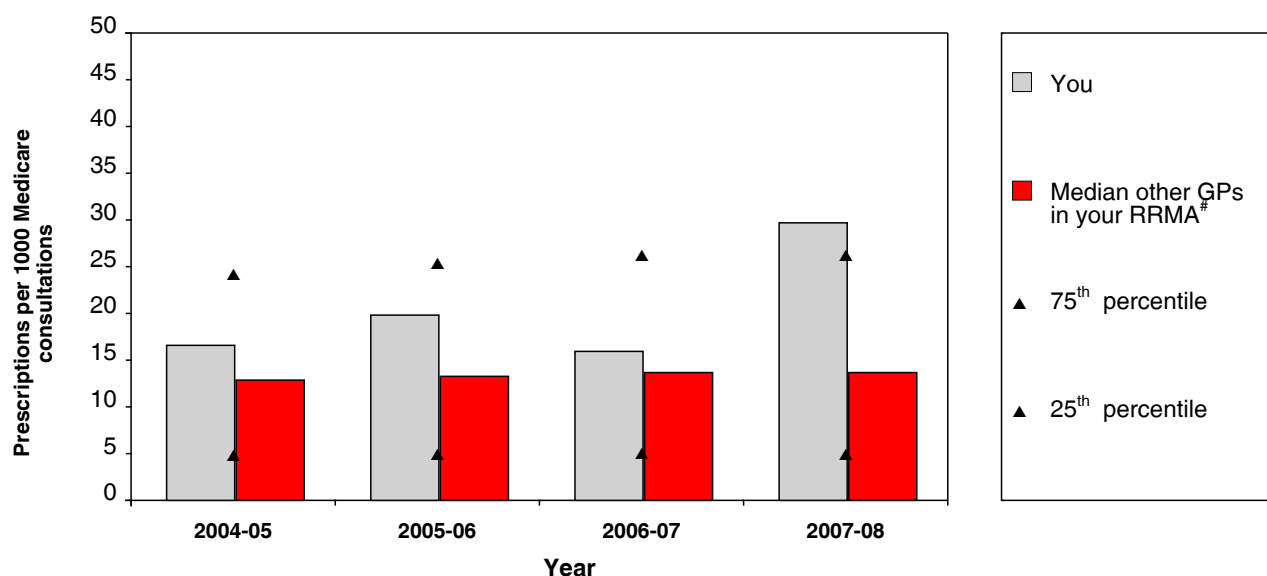
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Your confidential prescribing data

The data presented from Medicare Australia include PBS dispensed prescriptions for oral antiplatelet and anticoagulant agents for concession card holders and items above the general patient co-payment. Warfarin and aspirin are below general patient co-payment and many people will buy their aspirin over the counter. We cannot distinguish the indication for which the drugs are used and thus data will include the use of these drugs for the prevention or recurrence of all thrombotic events.

Warfarin use in 2004-05 to 2007-08



Practice points

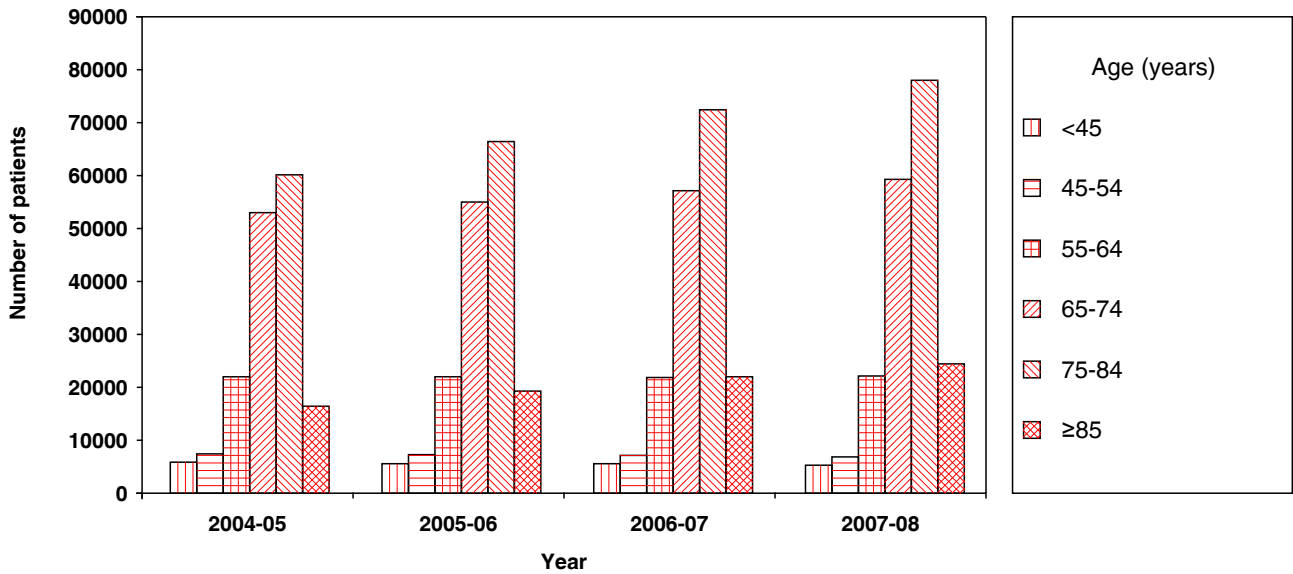
- Consider all patients with atrial fibrillation (AF) for long-term anticoagulant therapy to prevent a first or recurrent stroke.¹ Only about 50% of such patients who are candidates for anticoagulation are actually receiving anticoagulant therapy.^{2,3}
- Warfarin reduces the risk of stroke in patients with AF by about 60%. Choose an antithrombotic by balancing the risk of bleeding (e.g. higher in patients with renal or hepatic impairment or a history of gastrointestinal bleeding) against the risk of embolism (e.g. increased in heart failure, diabetes, valvular heart disease).⁴
- Aim for a target INR of 2-3 in patients with AF. Give patients an 'anticoagulant book' to keep a record of their warfarin dose and INR.
- The frequency of monitoring INR should be determined by the clinical situation. Initially, patients will require a few tests each week, but this can be gradually decreased to once every four weeks if the INR is stable.
- Monitor INR more frequently when changing drug treatment or when there are changes in the patient's condition (e.g. intercurrent illness).⁵

@ Data shown are an aggregate for all your provider locations

The comparator group "other GPs" includes all prescribers who are currently located in a similar geographical region i.e. 1. capital cities, 2. other metropolitan centres, 3. large rural centres, 4. small rural centres, 5. other rural centres, 6. remote centres and 7. other remote centres

▲ 25% to 75% of all doctors in the comparator group fall in the range shown by the triangular symbols

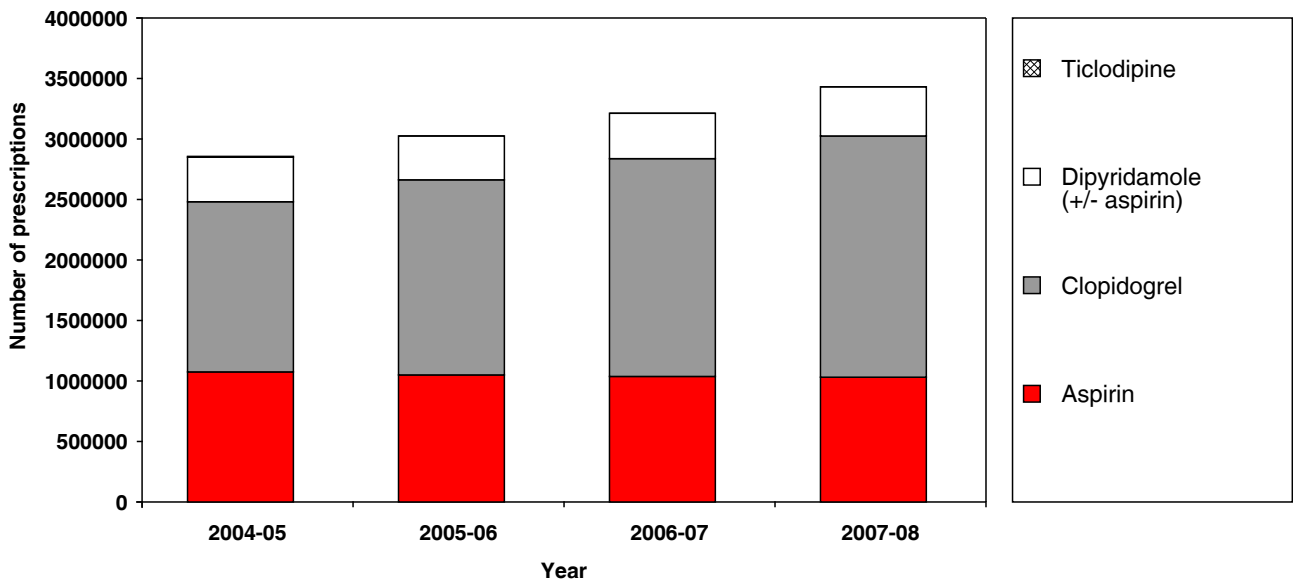
National warfarin use by patient age 2004-05 to 2007-08



Practice points

- Older age alone is not a contraindication to warfarin therapy in patients with AF. People aged 75 years and over are at increased risk of bleeding, but also benefit because of their high risk of stroke.
- Include all stroke risk factors in making an assessment.

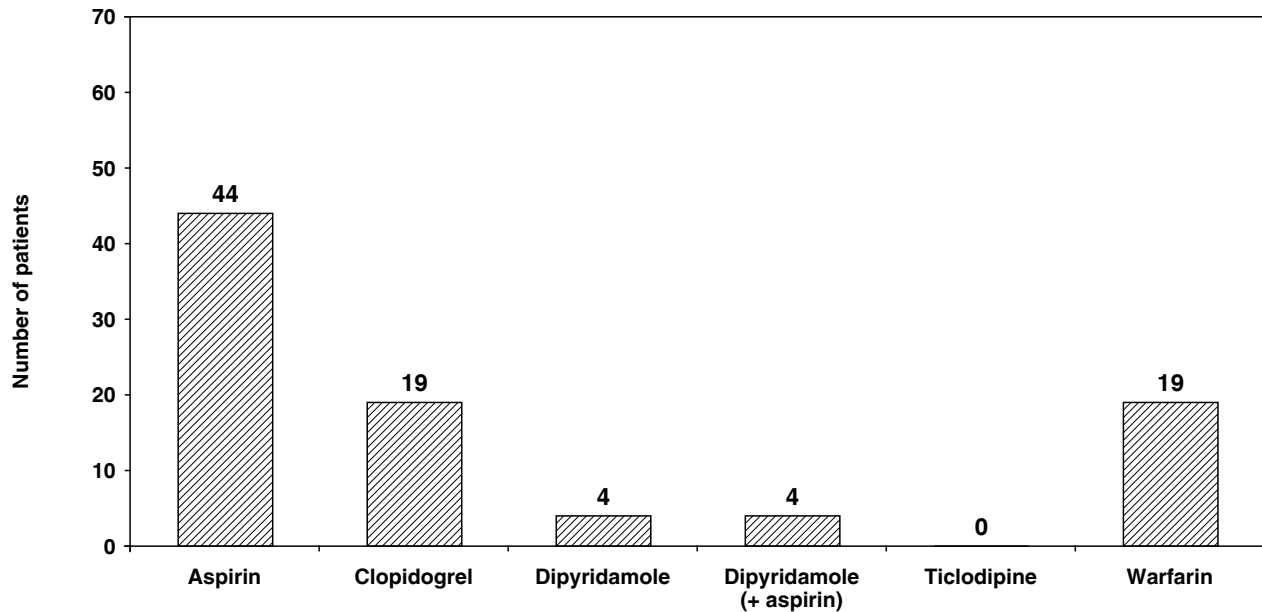
National antiplatelet use 2004-05 to 2007-08



Practice points

- Aspirin is a highly cost effective agent for primary and secondary prevention of cardiovascular and cerebrovascular thrombotic events.⁶
- In those with a history of aspirin-induced ulcer bleeding, clopidogrel causes more recurrent bleeding than aspirin plus a proton pump inhibitor.⁴

Your antithrombotic prescribing in 2007-08

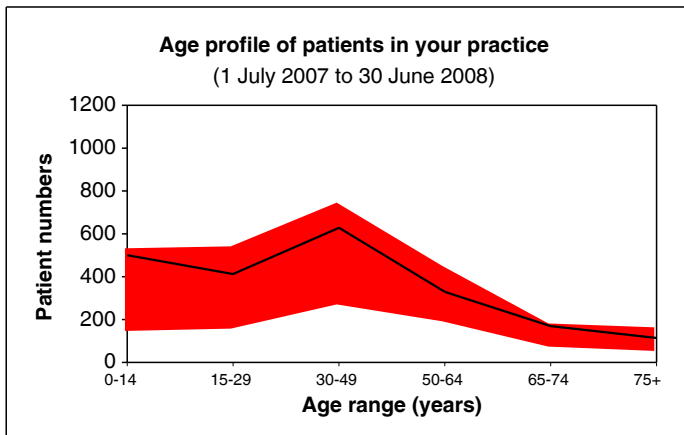


Practice points

- Modified-release dipyridamole plus low-dose aspirin adds a small additional benefit compared to aspirin alone in the secondary prevention of ischaemic stroke or transient ischaemic attack (TIA) of presumed arterial origin.⁵
- Aspirin alone or clopidogrel alone may be used for people who do not tolerate aspirin plus dipyridamole therapy. Clopidogrel alone should be used for those who are intolerant of aspirin or in whom aspirin is contraindicated.¹
- Avoid the combination of aspirin plus clopidogrel for secondary prevention of stroke (in patients without acute coronary syndrome). This combination is no more effective than clopidogrel alone in preventing serious vascular events, but causes more life-threatening bleeding.⁷
- There is no evidence that using enteric-coated or buffered formulations of aspirin reduce the risk of gastrointestinal bleeding.⁴

Practice profile

Some data shown earlier are presented as prescribing rates (per 1000 Medicare consultations) to adjust for volume of service. Age profile and concession card holding status of patients in your practice are provided to assist you in interpreting your prescribing data.



The black line represents the age profile of patients in your practice. 25% to 75% of other GPs in your RRMA[#] fall within the shaded area.

Medicare patients and concession card holders in your practice
(1 April 2008 to 30 June 2008)

Patients	You	Median other GPs in your RRMA [#]
Total Medicare	972	687
Concession card holders^{##}	276	177

Data from a three month period (1 April 2008 to 30 June 2008) that best represent your patient mix have been provided.

Confidentiality

NPS has a contract with Medicare Australia to provide your prescribing feedback data directly to you. NPS does not have access to these data. The data contained in this feedback are not used for any regulatory purposes.

Discrepancies may occur between the data provided and your own prescribing practice. This may be due to either inaccurate recording of your prescriber number in the pharmacy or your prescription pad having been used by another doctor.

If you consider your individual data to be incorrect, have other data queries or general feedback, please contact NPS on 02 8217 8700 or by email at info@nps.org.au

References

1. Clinical Guidelines for Stroke and TIA Management. A guide for general practice. Melbourne: National Stroke Foundation, 2008.
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@ Data shown are an aggregate for all your provider locations

The comparator group "other GPs" includes all prescribers who are currently located in a similar geographical region i.e. 1. capital cities, 2. other metropolitan centres, 3. large rural centres, 4. small rural centres, 5. other rural centres, 6. remote centres and 7. other remote centres

Your RRMA peer group is 1

Includes those reaching Safety Net

Antiplatelet and anticoagulant therapy in stroke prevention

Key Messages

- Systematically assess and re-assess the risk–benefit of warfarin and antiplatelet agents.
- Aspirin is the antithrombotic of choice in primary stroke prevention when cardiovascular risk is high, however in atrial fibrillation most patients require warfarin.
- Aspirin, aspirin plus dipyridamole, or clopidogrel are the main antiplatelet options in secondary stroke prevention.
- Use strategies to ensure concordance and maintain INR in therapeutic range.

Consider aspirin for primary prevention of cardiovascular events if risk is high

Select patients for aspirin by assessing their overall cardiovascular risk and risk of bleeding

Aspirin (100–300 mg daily) may be used to prevent a first coronary heart disease or stroke event due to arterial disease (atherothromboembolism) when the overall absolute risk is > 15% over 5 years.^{1,2}

Use an absolute risk assessment tool to identify patients at high cardiovascular risk.* To guide treatment decisions, assess risk factors for bleeding with aspirin including increasing age, any bleeding predisposition, history of peptic ulcer, uncontrolled hypertension, severe renal or hepatic impairment, and concurrent use of NSAIDs or anticoagulants.^{3,4}

* Use the National Vascular Disease Prevention Alliance (NVDPA) paper-based tool or online calculator, or until these are available, the New Zealand Guidelines Group Cardiovascular Risk Calculator (at nps.org.au/cv_risk_calculator).

Aspirin, aspirin plus dipyridamole, or clopidogrel are the main antiplatelet options for secondary prevention of stroke due to arterial disease

Use long-term antiplatelet therapy after an ischaemic stroke or transient ischaemic attack (TIA) due to arterial disease

Antiplatelet therapy reduces the relative risk of stroke, myocardial infarction or vascular death by 22% (95% confidence interval [CI] 14% to 30%) in people with an ischaemic stroke or TIA due to arterial disease, compared with no treatment.⁵

Aspirin should be given as soon as possible after the onset of ischaemic stroke and can be continued as long-term antiplatelet therapy.² Clopidogrel (Iscover, Plavix) or aspirin plus dipyridamole sustained release (Asasantin SR) are other options for initial long-term therapy, or if stroke re-occurs while taking aspirin.²

Reserve dipyridamole alone or ticlopidine for when neither aspirin nor clopidogrel is tolerated.² Severe adverse effects with ticlopidine limit its use: skin rash, diarrhoea and neutropenia are more common than with clopidogrel or aspirin.⁶

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Aspirin plus dipyridamole SR reduces stroke risk over aspirin alone, but is less well tolerated

In people with a previous stroke or TIA aspirin plus dipyridamole reduces the relative risk of non-fatal stroke by 23% (95% CI 11% to 33%) compared with aspirin alone, without causing excess bleeding.⁷⁻⁹ However, this combination is often not tolerated: in the ESPRIT trial, more patients stopped aspirin plus dipyridamole than they did aspirin (34% vs 13%), mainly because of headache.⁹

Headache may improve by substituting low-dose aspirin for the morning dose of aspirin plus dipyridamole SR for a short period (e.g. < 1 week).¹⁰ Avoid immediate-release dipyridamole; this has limited evidence of efficacy in stroke.⁷

Compared with aspirin alone, adding dipyridamole to aspirin has not been found to:

- prevent more vascular deaths
- provide additional benefit in coronary heart disease.⁸

Clopidogrel may be a more suitable choice for some patients

Clopidogrel alone has similar efficacy to aspirin plus dipyridamole SR in preventing recurrent stroke, and a comparable risk of major bleeding.¹¹ Clopidogrel may be a useful alternative for patients who:

- do not tolerate aspirin plus dipyridamole SR, or
- have co-existing coronary heart disease.^{8,12}

Low-dose aspirin is also an effective option in these scenarios and is more affordable for people who do not meet the PBS authority restrictions for clopidogrel.* In the CAPRIE trial, the rate of serious vascular events in people with ischaemic stroke, myocardial infarction or peripheral arterial disease was slightly lower with clopidogrel than aspirin (5.3% vs 5.8%), but the overall risk of bleeding was similar (9.3% each).¹³

* Hypersensitivity to aspirin or NSAIDs (anaphylaxis, urticaria or asthma), unacceptable risk of gastrointestinal bleeding, recurrent vascular episodes while taking aspirin and use in combination with aspirin for acute coronary syndromes (myocardial infarction and unstable angina).

Avoid aspirin with clopidogrel, unless acute coronary heart disease is present

In the MATCH trial, aspirin with clopidogrel was no more effective than clopidogrel alone in preventing vascular events after ischaemic stroke or TIA (16% vs 17%), but caused more life-threatening bleeding (3% vs. 1%).¹⁴

The benefit of using aspirin with clopidogrel exceeds the risk of bleeding in patients with an acute coronary syndrome or coronary stent.^{1,12}

Warfarin is the antithrombotic drug of choice for most people with atrial fibrillation

Consider long-term warfarin for every patient with AF at moderate to high risk of thromboembolic stroke

People with atrial fibrillation (AF) should receive warfarin if they are at moderate or high risk of stroke (Box 1), provided the benefits exceed their bleeding risk.^{2,15-17} Valvular AF poses a particularly high risk of thromboembolism that needs anticoagulant therapy for stroke prevention.^{15,18}

Warfarin reduces the relative risk of stroke in people with non-valvular AF by 64% (95% CI 49% to 74%) compared with placebo or no treatment.¹⁹ Treating 12 patients for 1 year can prevent one recurrent stroke.¹⁹ Treating 37 patients for 1 year can prevent one stroke as a first event.¹⁹

Box 1: Risk of thromboembolic stroke in atrial fibrillation^{15,17}

Lowest risk	Moderate risk	Highest risk
<ul style="list-style-type: none"> • Age < 75 years and no moderate or high risk factors for stroke 	<p>Any one of the following:</p> <ul style="list-style-type: none"> • Age ≥ 75 years • Hypertension • Diabetes mellitus • Heart failure or left ventricular dysfunction 	<ul style="list-style-type: none"> • Previous stroke, TIA or systemic embolism • Valvular heart disease (mitral stenosis) • Prosthetic heart valve • ≥ 2 moderate risk factors

Aspirin is less effective than warfarin in AF, but is an alternative for some patients

In people with non-valvular AF, aspirin reduces the relative risk of stroke by 22% (95% CI 2% to 39%) compared with placebo.¹⁹ Warfarin is more effective but doubles the risk of major bleeding compared with aspirin: trials have found the absolute increase in risk to be small (0.2% per year), but this may be higher in practice for some patients.^{19,20}

Aspirin is recommended for people at low risk of thromboembolism, as warfarin is more likely to cause a major bleed than prevent a stroke in these patients.¹⁶ Aspirin is also an alternative for those at moderate risk of thromboembolic stroke or with contraindications to warfarin.^{1,12,15}

Using aspirin with clopidogrel is not safer or more effective than warfarin in AF

The annual rate of serious vascular events in a trial was higher for aspirin with clopidogrel (5.6%) than for warfarin (3.9%), while the rate of major bleeding was similar (2% per year).²¹

Some patients who take warfarin may be prescribed aspirin, with or without clopidogrel, to reduce their risk of recurrent coronary heart disease events.^{1,4,16}

Assess the balance of benefits and harms of warfarin to guide choice of antithrombotic therapy in non-valvular AF

Stratify stroke risk in non-valvular AF using the CHADS₂ index

The CHADS₂ index is a validated stroke risk stratification tool that assists with selecting patients with non-valvular AF for warfarin or aspirin (Table 1).²¹

The sum of points from the CHADS₂ criteria gives a risk score. For example:

age ≥ 75 years + previous stroke = score of 3
(1 point) (2 points) (high stroke risk, warfarin is indicated)

Table 1: CHADS₂ stroke risk stratification in non-valvular atrial fibrillation^{17,20,21}

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

Assess bleeding risk subjectively and reassess regularly

There is limited evidence for informing decisions about warfarin or aspirin based on bleeding risk, particularly for people at moderate risk of thromboembolic stroke.^{18,23} Choice of therapy is thus guided by a subjective assessment of the benefit–harm profile for an individual.¹⁸

Avoid warfarin in people with: bleeding disorders; previous gastrointestinal, intracerebral or retinal haemorrhage; bacterial endocarditis; uncontrolled hypertension; heavy alcohol intake; significant liver disease; unsupervised dementia; or potential lack of adherence with monitoring.^{4,16}

Major risk factors for bleeding may not contraindicate warfarin

People at high risk of bleeding are often also at high risk of thromboembolic stroke, but warfarin may still be indicated in these people if they are likely to gain more benefit than harm from therapy.^{14,16,23} Older age (especially ≥ 75 years), propensity for falls and previous stroke are major risk factors for bleeding, but are not absolute contraindications to warfarin.¹⁶

Consider patient preference and other factors to guide choice of therapy

Explain to patients the relative benefits and harms of using warfarin or aspirin. Consider their preference, access to anticoagulation monitoring and other important factors (e.g. potential drug interactions) in treatment decisions.^{14,17,21}

Maintain INR in therapeutic range to reduce stroke and bleeding risk

Avoid high loading doses of warfarin and frequent or large dosage adjustments

Start warfarin at 5 mg daily for 2 days then adjust the dose to an INR of 2–3 (higher for patients with prosthetic heart valves).^{2,4,24} Elderly people may require lower doses.^{4,24} Do not target a lower INR range (e.g. 1.5–2.0): this does not reduce the risk of bleeding and is less effective at preventing stroke than adjusting the dose of warfarin to achieve an INR of 2–3.^{18,23,24}

Be aware of interactions with commonly used medicines and foods

The risk of bleeding with warfarin may be increased by amiodarone, antibiotics (particularly macrolides [e.g. erythromycin], metronidazole and quinolones [e.g. ciprofloxacin]), azole antifungals, paracetamol (> 3.5 g/week), selective serotonin re-uptake inhibitors (SSRIs) or large quantities of cranberry juice.⁴ Some drugs increase bleeding risk with warfarin without changing the INR (e.g. aspirin, NSAIDs).⁴ Refer to the *Australian Medicines Handbook* for information on interactions with warfarin.

Organise warfarin education for every patient

All patients starting warfarin should receive verbal counselling and an anticoagulant booklet. Pharmacists can undertake warfarin education during a Home Medicines Review, hospital admission or in a community pharmacy.

Use strategies that assist concordance with antithrombotic therapy

Discuss cardiovascular risk to help patients understand the need for antithrombotic therapy

Perceptions of risk differ between patients, and how risk is communicated can influence the decisions they make about treatments.^{27,28} Provide individualised information on absolute cardiovascular risk (using numbers and words) and present the positive and negative scenarios of therapeutic choices.²⁷

Use patient decision aids to guide treatment decisions

Using patient decision aids with health practitioner counselling improves levels of knowledge and realistic expectations about treatment options.²⁹ An audio booklet decision aid has been developed for patients with AF. It includes visual aids describing the benefits and harms of warfarin and aspirin (available at www.canadianstrokenetwork.ca/eng/tools/index.php).^{30,31}

Reviewer

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Clinical Professor, School of Medicine and Pharmacology,
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Citations available online at www.nps.org.au/healthpro

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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