

The warfarin dilemma

Oral anticoagulation with warfarin in older people with atrial fibrillation

Atrial fibrillation and increasing age are both risk factors for stroke

Atrial fibrillation (AF) is associated with increased morbidity and mortality from stroke, thromboembolism and heart failure. AF increases the risk of ischaemic stroke approximately five-fold and the prevalence of AF increases with age. It is estimated that 5% of people aged over 65 years and 10% of people aged 80 years and older have AF.¹

Stroke risk doubles every ten years after age 55, with over 50% of strokes occurring in people aged over 75 years.² Approximately one-third of strokes in patients aged 80–89 years are related to AF.³ Evidence also shows that people with AF related strokes have a poorer prognosis when compared with people who have non-AF strokes, with larger neurological deficits, increased medical complications and higher inpatient mortality.⁴ In people with non-valvular AF, anticoagulation with warfarin is more effective at reducing stroke than the antiplatelet agent aspirin.⁵

Older people with AF are at the highest risk of stroke, so they stand to benefit the most from treatment. Providing bleeding risks can be managed, the most effective treatment, i.e. warfarin, should be offered. Evidence suggests however, that warfarin is under utilised in elderly people, both in primary care and hospital practice.⁶ The dilemma in older patients with AF is that the same factors indicating a need for anticoagulation with warfarin, e.g. hypertension, older age, previous stroke, are also the risk factors for intracranial haemorrhage.

Key Concepts

- Evidence suggests that warfarin is under utilised in older people
- The dilemma is that in older people with atrial fibrillation, the factors indicating a need for anticoagulation with warfarin are also the risk factors for intracranial haemorrhage
- Providing bleeding risks can be managed, warfarin is still the most effective treatment in this group of people and should be considered on an individual basis
- The decision whether to prescribe warfarin is based on an assessment of bleeding risk, stroke risk, co-morbidities, concurrent medicines and likely compliance with monitoring
- Increasing age alone is not a contraindication for warfarin use

Warfarin or aspirin?

Both warfarin and aspirin increase the risk of bleeding via different mechanisms. Warfarin requires careful monitoring and is susceptible to drug interactions which increases the hazards associated with its use compared with aspirin. However, bleeding rates in comparative clinical trials between aspirin and warfarin for AF are generally very similar, which may partly reflect close monitoring in the study situation. Until recently, clinical trials for stroke prevention in AF did not include, or were under-represented by, older people. Trials such as the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) and recent review articles indicate that warfarin has significant net beneficial effects compared with aspirin, in people with AF aged 75 years and older, who are at the highest risk of stroke.^{7,8} In the BAFTA trial, which included people with AF aged over 75 years, the risk of a primary endpoint (stroke, intracranial haemorrhage or arterial embolism) was significantly lower with warfarin (1.8%) compared with aspirin (3.8%), and there was no evidence that warfarin caused more bleeding complications than aspirin.⁷

The use of warfarin in older people

The decision to use warfarin in an older person requires consideration of the following:

- Risk factors for bleeding
- Tools to evaluate baseline stroke risk
- Individual assessment of the patient with regard to co-morbidities, medications and ability to comply with monitoring

Warfarin-related bleeding

The risk of bleeding while on warfarin is greatest in patients who have not previously received warfarin, and in the first 90 days of treatment.⁹ A lower starting dose is recommended in older people as they are more sensitive to the effects of warfarin. Lower maintenance doses are also often required, e.g. 2–4 mg.¹⁰ The potential for bleeding complications in older people is also increased by pathological changes that accompany ageing.

Most bleeding related to the use of warfarin occurs in the gastrointestinal tract, urinary tract, soft tissues and oropharynx with gastrointestinal haemorrhage being the most severe.¹⁰ Patients who have an extracranial haemorrhage while on warfarin are less likely to die from the initial event or in the first month after discharge and also less likely to have long term functional deficits, than those who have intracranial haemorrhage.¹¹

Although the absolute risk is relatively low at 0.2% per year, intracranial haemorrhage is the most serious complication of anticoagulation-related bleeding with a mortality rate reported of up to 50%.^{5,10,11} Intracranial haemorrhage includes bleeding that is intracerebral (approximately 70%), subdural or subarachnoid and is the cause of approximately 90% of the deaths from warfarin associated bleeding.¹¹ Patients who initially survive an intracranial haemorrhage are likely to be discharged with significant functional deficits or to die within the first 30 days after discharge.¹¹

There is good evidence that older age (>75 years), elevated INR level (>3.0), uncontrolled hypertension (e.g. systolic blood pressure > 160 mmHg) and a history of ischaemic stroke increase the likelihood of an intracranial haemorrhage. However, a previous stroke, hypertension and older age are also risk factors for ischaemic stroke.^{10,12,13} Risk factors for warfarin associated intracranial haemorrhage also overlap with risk factors for spontaneous intracranial haemorrhage (see sidebar over page). However, for older people on warfarin the beneficial reduction in the risk of stroke is greater than the small increase in the risk of serious haemorrhage.¹⁴

Many other risk factors for warfarin associated bleeding have been investigated, however, there is conflicting evidence and often a lack of consistency in the proposed risk factors. There is some evidence to support a higher risk of bleeding complications in people with the following risk factors:^{8,12,13}

- Concomitant use of aspirin, other antiplatelet medicines or NSAIDs
- Polypharmacy - seven or more medications
- Other co-morbidities e.g. diabetes, anaemia, alcohol or drug misuse, smoking, falls risk

- Patient factors e.g. Insufficient education on the use of warfarin, poor compliance, confusion

One of the most recent models that attempts to establish the risk of bleeding in older people on warfarin is the HAS-BLED Bleeding Risk Score (Table 1).¹⁵ This model would be ideal for use in general practice. It aims to provide a rapid, simple method to predict bleeding risk. A score of three or more indicates a patient who may be at high risk of bleeding complications and who therefore may benefit from more regular review of warfarin therapy.¹⁵

The clinical characteristics that may predict a high risk of bleeding are often thought of as contraindications to warfarin use in older people, however, the majority of these may be considered relative contraindications and will depend on individual patient characteristics and the clinical situation. In many cases the overall benefit of warfarin may still outweigh the potential risk of treatment. For patients in such clinical situations, for whom embolic risk is deemed to be high, consultation with a stroke specialist should be considered to discuss the possibility of treatment with warfarin or the use of other alternatives.

Table 1: HAS-BLED Bleeding Risk Score (adapted from Pisters et al, 2010¹⁵)

Letter	Clinical Characteristic	Points
H	Hypertension (systolic blood pressure > 160 mm Hg)	1
A	Abnormal renal and liver function	1 point each
S	Stroke (past history)	1
B	Bleeding (previous history of bleeding or predisposition to bleeding)	1
L	Labile INRs (unstable, high or insufficient time within therapeutic range)	1
E	Elderly (> 65 years)	1
D	Drugs or alcohol (including concomitant use of aspirin, other antiplatelet agents and NSAIDs)	1 point each
		Max 9 points

Spontaneous intracranial haemorrhage¹³

The rate of spontaneous intracranial haemorrhage in people aged over 70 years is approximately 0.15% per year. Risk factors for spontaneous intracranial haemorrhage include; uncontrolled hypertension, increasing age, an underlying pathological condition e.g. tumour, infection, vascular malformation, ethnicity (increased risk in people of Asian descent), and illicit drug use e.g. cocaine, amphetamine.

Clinical situations that may be a contraindication to warfarin use include:^{16,17}

- Actual or potential haemorrhagic conditions e.g. peptic ulceration (or history of within the previous six months)
- Uncontrolled or severe hypertension (blood pressure consistently above 160/90 mmHg)
- Severe renal or liver disease
- Recurrent unexplained syncope or recurrent falls
- Planned surgery
- Unsupervised dementia

Tools to evaluate baseline stroke risk

The risk of stroke can be evaluated using a risk stratification tool such as CHADS₂ or the updated version, CHA₂DS₂-VAS, which now includes additional stroke risk factors (see sidebar next page).^{6,18} CHADS₂ is a simpler tool for use in general practice. These tools can be used to help decide whether to use warfarin in patients with non-valvular AF. However, they do not take into account bleeding risks, monitoring requirements and other factors that may make warfarin less suitable or potentially hazardous in a particular patient.

In general, warfarin is recommended in people at high risk of stroke (CHADS₂ score ≥ 2 or CHA₂DS₂-VAS score > 1). The updated tool attempts to simplify the decision of which agent to use for anticoagulation by also recommending warfarin for patients who have a CHA₂DS₂-VAS score = 1.¹⁸ Aspirin is still included as an option for those who score 1 but a clear preference is stated for anticoagulation with warfarin. Patients who score 0 are now considered truly low risk and although may still be prescribed aspirin, choosing not to use antithrombotic therapy may be preferred.⁸ Most older people will be in a higher risk group where warfarin is the most beneficial treatment.

If warfarin is contraindicated, not indicated or is declined by the patient, aspirin may be prescribed, as it reduces the risk of stroke compared to no treatment.

The importance of INR monitoring

Appropriately monitored and dose adjusted warfarin is effective and relatively safe in elderly patients. However, warfarin may be unsuitable or hazardous in some people if they are unable to manage the treatment and its monitoring.

Monitoring of INR is important in the context of both safety and effectiveness. Interactions, diet changes and unintentional overdosing can all increase INR and bleeding risk. The ability of the patient to commit to ongoing monitoring for the duration of warfarin therapy needs to be assessed. Older people may be at higher risk of bleeding for many reasons including poor monitoring of INR.

For warfarin to be effective in preventing stroke it has been estimated that the INR should be in the target range of 2.0 to 3.0 $\geq 65\%$ of the time.⁸ There is no lower threshold of INR that does not accentuate the risk of intracranial haemorrhage therefore targeting a lower INR range, e.g. 1.5 to 2.0, does not reduce the risk of bleeding and is less likely to prevent stroke.^{13,19}

A target INR of 2.5 within a therapeutic range of 2.0–3.0 is widely recommended for older patients. The rate of intracranial haemorrhage increases markedly in older people if the INR is > 3.5 and to a lesser extent if the INR is above 3.0.^{8,12} The difficulty is that although an INR above 3.0 increases the risk of intracranial haemorrhage, the majority of people on warfarin who have warfarin associated intracranial haemorrhage have been found to have an INR within the therapeutic range e.g. 2.0–3.0.¹³ Minimising the risk of intracranial haemorrhage therefore requires not only good control of anticoagulation but also effective management of other modifiable risk factors, particularly hypertension.¹³

Individual patient assessment is essential

An individual assessment of the patient with regard to co-morbidities, medications and the ability to comply with monitoring is essential for the safe use of warfarin.

Stroke assessment tools for patients with AF^{6,18}

The updated stroke assessment tool CHA₂DS₂-VAS puts greater emphasis on increasing age (≥ 75 years) and also incorporates additional risk factors for stroke – female gender, age group 65 – 75 years and a history of vascular disease e.g. myocardial infarction, peripheral arterial disease. Scores for each tool are calculated as follows:

CHADS ₂	Score
Congestive heart failure	1
Hypertension	1
Age 75 years or older	1
Diabetes mellitus	1
Previous Stroke or TIA	2
Maximum score	6

CHA ₂ DS ₂ -VAS	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (prior MI, peripheral vascular disease)	1
Age 65–75 years	1
Sex category (i.e. female gender)	1
Maximum score	9

N.B. The maximum score for CHA₂DS₂-VAS is 9 as only one age score is used in the calculation.

Co-morbidities may be risk factors for bleeding and they may also increase the potential for falls.

A review of medicines is recommended to avoid concomitant use of those that may increase the risk of bleeding e.g. aspirin, NSAIDs, Cox-2 inhibitors, dipyridamole. In addition bleeding risk should be reassessed when new medicines, including those used for short periods such as quinolone or macrolide antibiotics, are introduced.

Before initiating warfarin the possibility of non-adherence and monitoring should be considered. Factors to take into account may include any cognitive impairment, mental illness or an inability to access services.

Warfarin interacts with multiple other prescriptions medicines, as well as nutritional supplements, over-the-counter medicines and some foods e.g. foods that contain high levels of vitamin K such as broccoli, spinach and cabbage. Discuss the possibility of these interactions with patients and encourage them to consult about any major dietary changes they are planning to make. Also inform patients that their general wellbeing may also affect their warfarin therapy, e.g. a new illness such as fever or diarrhoea or a condition such as congestive heart failure. Poor quality patient education has been found to be a significant risk factor for both ineffective anticoagulation and warfarin associated bleeding in older patients.¹²

Bottom-line

Increasing age alone should not prevent the use of warfarin. The decision to use warfarin involves identification and assessment of those patients who are at high risk of ischaemic stroke without warfarin and weighing this against the risk of intracranial haemorrhage with warfarin treatment.¹¹ Further research that includes older participants and the ongoing development of risk assessment tools are first steps toward solving this problem.

Once the decision to use warfarin is made on an individual basis, prevention of bleeding complications relies on maintaining an INR between 2.0 and 3.0, appropriately monitoring and adjusting doses as required, providing quality patient education and effectively managing any modifiable risk factors.

ACKNOWLEDGMENT Thank you to **Dr Anna Ranta**, Lead Stroke Physician, Consultant Neurologist and Head of Department, Department of Neurology and Acute Stroke Services, Midcentral DHB, Palmerston North and Associate Dean of Undergraduate Studies, University of Otago, Wellington for expert guidance in developing this article.

References:

1. Miyasaka Y, Barnes ME, Gersh BJ et al. Circulation 2006;114:116-25.
2. Blaauw Y, Crijns H. Treatment of atrial fibrillation. Heart 2008;94:1342-9.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: the Framingham Study. Arch Intern Med 1987;147:1561-4.
4. Steger C, Pratter A, Martinek BM, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke Registry. Eur Heart J 2004;25:1734-40.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
6. Abcede HG, Ovbiagele B. Update on antithrombotic therapy for stroke prevention in atrial fibrillation. Curr Treat Options Cardiovasc Med 2010;12(3):250-60.
7. Mant J, Jobbs R, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493-503.
8. Marinigh R, Lip GYH, Fiotti N, et al. Age as a risk factor for stroke in atrial fibrillation. Implications for thromboprophylaxis. J Am Coll Cardiol 2010; 56(11):827-37.
9. Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689-96.
10. Pautas E, Gouin-Thibault I, Debray M, et al. Hemorrhagic complications of vitamin K antagonists in the elderly. Risk factors and management. Drugs Aging 2006;23(1):13-25.
11. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages Am J Med 2007;120:700-5.
12. Kagansky N, Knobler H, Rimon E, et al. Safety of anticoagulation therapy in well-informed older patients. Arch Intern Med 2004;164:2044-50.
13. Rordorf G, McDonald C. Spontaneous intracerebral hemorrhage. UpToDate 2010. Available from: www.uptodate.com (Accessed Sept, 2010).
14. van Walraven C, Hart R, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: The atrial fibrillation investigators. Stroke 2009;40:1410-6.
15. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. Chest 2010;[Epub ahead of print].
16. British National Formulary (BNF). London, BMJ Group, 2009.
17. GlaxoSmithKline NZ Limited. Marevan (warfarin) Medsafe Medicine Safety Data Sheet 2008. Available from: www.medsafe.govt.nz (Accessed Sept, 2010).
18. Lip YH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.
19. National Prescribing service Ltd (NPS). Using antithrombotics wisely in stroke prevention. NPS News 2009;62. NPS, NSW, Australia.