

# WARFARIN vs. ASPIRIN

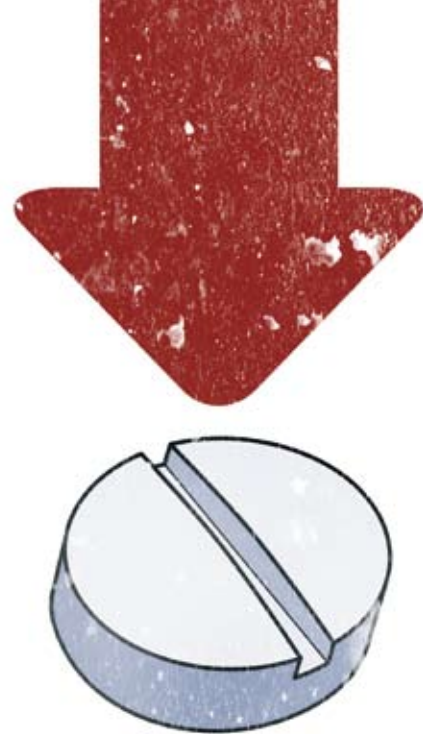
FOR THE PREVENTION OF ATRIAL FIBRILLATION RELATED STROKE

## Key Concepts

- In atrial fibrillation (AF) warfarin is more effective than aspirin for stroke prevention.
- Warfarin is preferred in people at high risk of stroke and aspirin for those at low risk. In people at intermediate risk the choice of treatment is determined by assessment of the benefits versus risks on an individual basis.
- The risk of bleeding with warfarin is increased in elderly people however with correct monitoring it appears to be as safe as aspirin.
- Clear communication and monitoring is required for the safe and effective use of warfarin in all people, particularly the elderly.

## Key Reviewer:

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Both warfarin and aspirin are indicated for the prevention of stroke in people with AF. Over 50% of strokes occur in people over the age of 75 years.<sup>1</sup> Stroke risk doubles approximately every ten years after age 55. The prevalence of AF increases at a similar rate with age. Elderly people therefore are at increased risk of AF and stroke and are likely to benefit from anticoagulation.

The decision whether to choose aspirin or warfarin for stroke prevention is often not clear cut. Although most people can take warfarin safely, it is under utilised in both primary care and hospital practice, particularly in elderly people.<sup>2, 3</sup>

### Warfarin is more effective for prevention of stroke than aspirin

There is evidence to show that treatment with warfarin can reduce stroke risk more effectively than aspirin in patients with AF. A recent meta-analysis showed that warfarin reduced AF related stroke by 64% compared to 22% for aspirin therapy.<sup>4</sup> If warfarin is contraindicated (see box over page), not indicated or is declined by the patient, aspirin should be prescribed, as it reduces the risk of stroke compared to placebo.

### Which therapy to choose depends on the risk of stroke

Current guidelines recommend the use of warfarin for those at high risk of stroke and aspirin for those at low risk (Table 1).<sup>2, 5</sup> For those at intermediate risk of stroke the benefits of warfarin may not always outweigh the risks. Individual patient preference and the availability of effective monitoring may be the most important deciding factors.<sup>6</sup>

**Table 1:** Choice of therapy guided by thromboembolic risk. Adapted from New Zealand guidelines for management of atrial fibrillation and flutter, 2005.<sup>2</sup>

Thromboembolic risk – 5 years	Therapy
High risk of stroke $\geq 15\%$	Warfarin usually advantageous
Intermediate risk of stroke 10–14%	Warfarin may be advantageous but patient preference may influence decision
Low risk of stroke $< 10\%$	Aspirin usually preferred

### Contraindications to warfarin use include:

- Haemorrhagic tendencies and blood dyscrasias
- Past history of intracranial haemorrhage
- Recent history of GI or GU bleeding (previous six months)
- Uncontrolled hypertension
- Severe liver disease
- Alcoholism
- Recurrent unexplained syncope
- Planned surgery
- Pregnancy

### Other aspects to consider when prescribing warfarin include:

- Comorbidities
- Concomitant use of medications
- Poor compliance with medication and monitoring (e.g. cognitive impairment, confusion, mental illness, inability to access services)
- Activities that increase the risk of trauma
- Increased risk of bleeding in elderly people
- Potential for falls
- Changes in diet, supplement use and general wellbeing (e.g. new illness)

### CHADS<sub>2</sub>: alternative method of stroke risk assessment

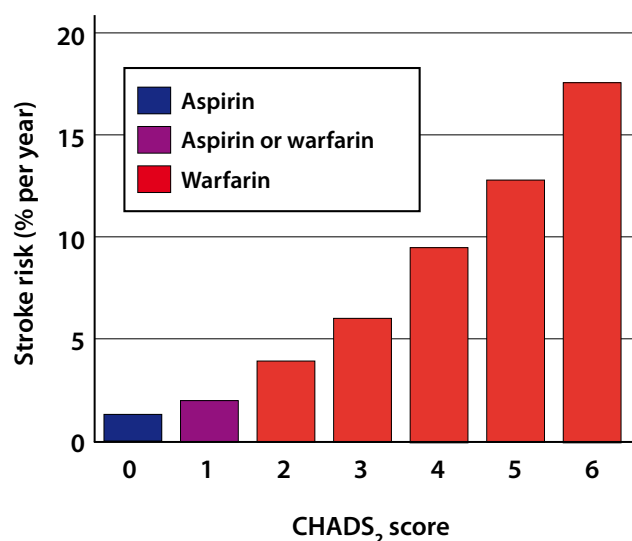
Another method to assess stroke risk that is widely used in research, but which may be applicable to daily clinical practice, is the CHADS<sub>2</sub> risk stratification scheme.<sup>7</sup>

CHADS<sub>2</sub> assigns a score to independent risk factors for stroke and guides drug selection. (Figure 1).<sup>1</sup> Scores are calculated as follows:

CHF	(1 point)
Hypertension	(1 point)
Age 75 years or older	(1 point)
Diabetes mellitus	(1 point)
previous Stroke or TIA	(2 points)

Coronary heart disease and female gender which are weaker risk factors for stroke are not included.

A calculated CHADS<sub>2</sub> score for example, in an 80 year old (+1) patient, with hypertension (+1), and a history of a previous stroke (+2) would be 4.



**Figure 1:** Stroke risk in patients with AF according to the CHADS<sub>2</sub> risk index. The colour coded bar graphs indicate the appropriate antithrombotic treatment strategy.<sup>1</sup>

## Bleeding risk of aspirin and warfarin

### Aspirin

The risk of major bleeding with aspirin therapy varies according to the dose taken. The rate of major bleeding with low dose aspirin is reported as approximately 1–2% per year.<sup>3, 8</sup> Mortality data is similar to that for warfarin. Other dose dependent adverse effects of aspirin use can include gastrointestinal irritation and bleeding and tinnitus.

### Warfarin

The risk of major bleeding with warfarin varies from 1% to 7.2% per year in clinical trial data. Of those that have a major haemorrhage on warfarin, up to 1% will die. Intracranial bleeding is associated with the highest risk to the patient, with up to 60% of major intracranial haemorrhages resulting in death.<sup>9</sup> The incidence of more minor bleeding is difficult to quantify.

### Risk of bleeding with warfarin is higher in elderly people

There is an increased risk of bleeding with warfarin use in elderly people. This is thought to be due to several factors. Elderly people are more likely to have co-morbid conditions and to be on multiple medications with increased interaction potential, therefore increasing the risk of bleeding. Age related changes in the pharmacodynamics and pharmacokinetics of warfarin may also contribute to the increased bleeding risk.

A recent study in patients over the age of 65 years found that those at the greatest risk of stroke were also the patients who experienced more problems with bleeding while on warfarin.<sup>10</sup> The risk of bleeding while taking warfarin was greatest in those aged 80 years or over (13.1 %) and the risk was higher in the first three months of treatment.<sup>10</sup>

## Warfarin can be used safely in elderly people with atrial fibrillation

The BAFTA study was a randomised controlled trial that looked at the use of warfarin versus aspirin for stroke prevention in primary care and was the first to include only people aged 75 years or older. The conclusions of the study were that:<sup>3</sup>

- Advanced age alone is not a contraindication to warfarin use
- Warfarin, in elderly patients with AF, is more effective for stroke prevention than aspirin
- Warfarin is as safe as aspirin (when monitored correctly)
- Warfarin use should be considered in all people with AF aged 75 years or older, unless there are contraindications to its use or the patient declines treatment
- Target INR should be 2–3

Limitations of the study arise from possible selection bias as patients were excluded if there were clear clinical indications to use, or not to use, warfarin. Those who were included therefore were patients in whom there was clinical uncertainty. Although these are the very patients that we need guidance for, those in the study group were also shown to have a lower level of stroke risk than participants in other studies.<sup>11</sup> Critics suggest that this may give a false sense of safety with warfarin use.<sup>12</sup> The authors response to this, however is that they are likely then to have “underestimated the benefits of warfarin treatment over aspirin”.<sup>13</sup>





## Effective communication and monitoring is required for safe use of warfarin in all people, particularly elderly people

Safe use of warfarin depends on many factors but effective communication and monitoring are essential.

Useful strategies for safe warfarin use may include:

- Give clear verbal and written information.
- Ensure patients know which symptoms may signal abnormal bleeding
- Educate patients about the effects of diet, alcohol, acute illness and other medications (including herbal medicines and supplements) on INR control
- Encourage effective sharing of information between patient, whanau, carers, clinicians and pharmacists
- Use one brand only
- Use one tablet strength only during initiation (remind yourself what colour each strength of tablet is)

- Set up an alert on your practice software for patients on warfarin
- Consider ways to minimise the inconvenience of regular INR monitoring (e.g. most convenient place to have blood drawn, best way to convey results)

The results of the recent ACTIVE-W<sup>15</sup> trial (warfarin vs aspirin and clopidogrel) indicate that the benefits of warfarin also depend on individual factors and how well treatment is managed or monitored. Implications from the results of this trial include:

- Some patients may have an unstable INR which is difficult to manage
- Compliance or monitoring problems may compromise the benefits of warfarin
- The benefits of warfarin are mainly seen in patients who maintain a therapeutic INR most of the time

### Aspirin with warfarin in people with atrial fibrillation and vascular disease

Recent guidance has re-emphasised that for patients with AF and associated stable vascular disease, the risks from combined treatment with both warfarin and aspirin are greater than the benefits. Adding aspirin to warfarin increases the risk of bleeding and does not provide additional prevention from stroke.<sup>6, 14</sup>

However, this issue remains controversial amongst cardiologists, mainly because of the well proven benefit of antiplatelet agents in vascular disease versus more doubtful benefit of warfarin in this situation. So if a patient with severe vascular disease had AF as well, many cardiologists may still give combination therapy.



## References:

1. Blaauw Y, Crijns H. Treatment of atrial fibrillation. *Heart* 2008;94:1342-9.
2. New Zealand Guidelines Group (NZGG). Management of people with atrial fibrillation and flutter. May 2005. Available from [www.nzgg.org.nz](http://www.nzgg.org.nz) (Accessed January 2009).
3. 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.
4. 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.
5. National Institute for Clinical Excellence (NICE). The management of atrial fibrillation. Clinical guideline 2006. Available from [www.nice.org.uk](http://www.nice.org.uk). (accessed December 2008).
6. Aguilar MI, Hart RG, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischaemic attacks (Review). *The Cochrane Collaboration* 2008. Available from [www.thecochranelibrary.com](http://www.thecochranelibrary.com) (accessed December 2008).
7. Gage BF, Waterman AD, Shannon W et al. Validation of clinical classification schemes for predicting stroke. *JAMA* 2001;285(22):2864-70.
8. Wiedermann CJ, Stockner I. Warfarin-induced bleeding complications – clinical presentation and therapeutic options. *Thromb Res* 2008;122(suppl 2):S13-S18.
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. Borosak M, Choo S, Street A. Warfarin: balancing the benefits and harms. *Aust Prescr* 2004;27:88-92.
11. Garcia D, Hylek EM. Stroke prevention in elderly patients with atrial fibrillation. *Lancet* 2007;370:460-1.
12. Diug J, Lowthian J, Evans S. Warfarin versus aspirin for stroke prevention (BAFTA). *Lancet* 2007;370:1606.
13. Mant J, Hobbs R, Fletcher K et al. Warfarin versus aspirin for stroke prevention (BAFTA) – Authors' reply. *Lancet* 2007;370:1606-7.
14. Lip GYH. Don't add aspirin for associated stable vascular disease in a patient with atrial fibrillation receiving anticoagulation. *BMJ* 2008;336:614-5.
15. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367(9526):1903-12.