



National Prescribing Service Limited



**Case study 56 report:
Antithrombotic options in
stroke prevention**

May 2009

NPS is an independent, non-profit organisation for Quality Use of Medicines
funded by the Australian Government Department of Health and Ageing.

**ABN 61 082 034 393 | Level 7/418A Elizabeth Street Surry Hills 2010 | PO Box 1147 Strawberry Hills 2012
Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | web: www.nps.org.au**

Inside

Case study 56: Antithrombotic options in stroke prevention

Scenario and questions page 3

Summary of results page 5

Results in detail

Risk stratification in stroke prevention page 7

Advantages and disadvantages of antithrombotic agents page 8

Choice of antithrombotic therapy page 11

Using warfarin effectively and safely page 13

Commentaries

Dr John Worthington page 15

Dr Parker Magin page 18

References page 19

This case study was published with *NPS News 62*, February 2009 ' Using antithrombotics wisely in stroke prevention ', which discussed 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.

Case study 56

Antithrombotic options in stroke prevention

Scenario

Anne is a 75-year-old retired professional who has recently moved to the area. You are seeing her for the first time. Anne is very worried because she is currently experiencing some fatigue and palpitations.

Anne was diagnosed with paroxysmal atrial fibrillation (AF) 3 years ago. The investigations at that time included a trans-oesophageal echocardiogram, which showed normal left ventricular function, cardiac valves and left atrium. Since then her AF has been mostly asymptomatic with few episodes of prolonged rapid palpitations which were controlled by a beta blocker at the time.

She gave up smoking 5 years ago and does not drink alcohol. Currently, she is not taking any medication. She has no history of previous bleeding episodes. Anne’s father had a non-fatal stroke of presumed ischaemic origin. Her mother had undergone coronary artery bypass surgery.

Physical examination shows an irregularly irregular heart rhythm with a rate around 100 beats per minute. Blood pressure is 130/80 mmHg. An electrocardiogram shows AF. Otherwise, her cardiovascular and pulmonary examinations are unremarkable. Anne has brought her pathology results from 1 month earlier. These show normal full blood count, thyroid function tests, serum creatinine and liver function tests.

1.a) What is the stroke risk for Anne? (Tick one box only)

- Low
 Moderate
 High

b) What factor(s) led to you decision?

2. In Anne’s case, what are the potential advantages and disadvantages of the following?

	Advantages	Disadvantages
Aspirin	_____	_____
Clopidogrel	_____	_____
Dipyridamole	_____	_____
Warfarin	_____	_____

3. a) **Would you recommend antithrombotic therapy for Anne at this stage?**

Yes (go to 3b)

No (go to 3c)

b) **If yes, please specify:**

Medication

Starting dose and frequency

Time to next review

Why did you recommend this specific medication(s)?

c) **If you did recommend any antithrombotic treatment, why not?**

4. **Regardless of your answers in question 3, if Anne was started on warfarin:**

a) **Are there any existing factor(s) that may increase her risk of major bleeding? If yes, please specify**

b) **What information would you give her to achieve optimal anticoagulation?**

Summary of results

At the time of publication, 1176 responses had been received. This report summarises responses from 200 general practitioners (GPs).

Case synopsis

Anne, a 75-year-old who was diagnosed with atrial fibrillation (AF) 3 years ago, complains of fatigue and palpitations. Her current BP is 130/80 mmHg and an electrocardiogram shows AF. Past investigations showed normal cardiac structure and valves, and normal haematological investigations. There is a family history of non-fatal stroke in her father and cardiovascular disease in her mother. (See page 3 for more details.)

Risk stratification in stroke prevention

- 74.5% of respondents considered the stroke risk for Anne to be moderate; 23% to be high and 8.5% to be low.
- The main factors present in Anne which influenced participants' stroke risk stratification were:
 - age (75%)
 - ongoing atrial fibrillation (47.5%)
 - family history (22.5%)
 - absence of heart disease (14%)
 - past smoking history (11%).

Advantages and disadvantages of antithrombotic agents

- Main advantages of using aspirin include that it:
 - is inexpensive (48.5%)
 - reduces risk of thromboembolism 36.0%
 - is safer than warfarin (25.5%).
- Main disadvantages of using aspirin include that it:
 - is not as effective as warfarin (42.5%)
 - causes gastric bleeding/ulceration/gastrointestinal upset (25.5%)
 - increases risk of major bleeding (15.0%).
- Main advantages of using clopidogrel include that it:
 - reduces risk of thromboembolism (30.0%)
 - is similar in effectiveness to aspirin and dipyridamole (24.0%)
 - is well tolerated compared to aspirin (20.0%).
- Main disadvantages of using clopidogrel include:
 - risk of major bleeding (36.5%)
 - that it is not effective as warfarin (23.5%)
 - its authority required PBS listing (14.0%).
- Main advantages of using dipyridamole include that it:
 - is more effective when combined with aspirin for stroke risk reduction (37.0%)
 - reduces risk of thromboembolism (30.5%)
 - does not require monitoring (13.0%).
- Main disadvantages of using dipyridamole include that it is not well tolerated because of headache (66.5%) and other adverse effects, such as gastrointestinal upset, flushing and tachycardia (15.0%).

- Main advantages of using warfarin include that it offers best stroke protection for Anne (57.0%) and reduces risk of thromboembolism (35.0%).
- Main disadvantages of using warfarin include increased risk of major bleeding (89.5%) and regular INR (International Normalised Ratio) checking/monitoring (60.0%).

Choice of antithrombotic therapy

- 95.5% recommend antithrombotic therapy for Anne; of these, 71% recommend warfarin and 29% aspirin.
- Of those recommending warfarin, the main suggested starting dosage was 5 mg daily (81.7%), and time to next review varied from one day to two weeks.
- Of those recommending aspirin, the main suggested starting dosage was 100 mg daily (87.9%), and time to next review varied from one week to six months.
- The most common reasons for recommending warfarin were that it offered the greatest stroke risk reduction for Anne (61.0%) and that it was indicated for patients with moderate to high stroke risk (25.5%).
- The most common reasons for recommending aspirin were its reasonable efficacy in low-risk patients (34.5%) and its ease of use (22.4%).
- 4.5% did not recommend antithrombotic therapy for Anne as participants considered her to be at low risk for stroke.

Using warfarin effectively and safely

- 37% of respondents reported no existing factors that might increase Anne's risk of major bleeding whereas 63% reported one or more factors that could increase her risk of bleeding. Main factors that would increase her risk of bleeding included:
 - her age (46.5%)
 - any bleeding disorders (9.5%)
 - non-adherence (6.5%)
 - risk of falls (6.5%).
- Most common advice given to Anne to achieve optimal anticoagulation included:
 - regular monitoring of INR levels (75%)
 - regular and correct warfarin dose (49%)
 - possibility of interactions with other medicines or changing the doses (52%)
 - reducing food intake of food high in vitamin K (47.5%), such as green leafy vegetables.

Results in detail

Risk stratification in stroke prevention

Respondents were asked to comment on the level of stroke risk for Anne (see Table 1).

Table 1: Risk stratification	
Risk of stroke in Anne	% of respondents (n = 200)
Low	8.5
Moderate	74.5
High	17

Main factors leading to respondents' decision about Anne's stroke risk are summarised in Table 2.

Table 2: Factors to decide stroke risk	
Low stroke risk	% of respondents* (n = 17)
Age	52.9
Ongoing atrial fibrillation	35.3
No heart disease	35.3
No risk factor	23.5
Normal heart structure	17.6
Moderate stroke risk	% of respondents* (n = 149)
Age	83.2
Ongoing atrial fibrillation	39.6
Family history	15.4
No heart disease	14.1
CHADS2 [†] score	10.1
Past smoker	8.7
No risk factor	6.7
Normal heart structure	4.0
No anticoagulation	1.3
High stroke risk	% of respondents* (n = 34)
Ongoing atrial fibrillation	88.2
Family history	64.7
Age	50.0
Past smoker	26.5
No anticoagulation	11.8
CHADS2 [†] score	5.9

* Respondents may have more than one response

† CHADS2 score estimates the risk for stroke in patients with non-valvular atrial fibrillation

- The most commonly cited factor contributing to a determination of low and moderate stroke risk stratification was age (52.9% and 83.2%, respectively) whereas ongoing atrial fibrillation (88.2%) was the main factor used to determine stroke risk as high. Many respondents determined Anne's stroke risk as moderate and high based on her family history. CHADS2 score was also used to determine stroke risk as moderate and high.

Practice points



- The prevalence of atrial fibrillation (AF) steadily rises in patients older than 60 years and is highest in patients who are older than 80 years.¹
- The age-adjusted incidence of stroke is increased five-fold when atrial fibrillation is present.²
- Previous stroke or transient ischaemic attack (TIA), hypertension, advanced age and diabetes are independent risk factors consistently associated with stroke in AF patients.³ Female sex, coronary artery disease and thyrotoxicosis are less validated risk factors associated with stroke in AF patients.⁴
- The stroke risk stratification tool helps in selecting between aspirin and warfarin in patients with nonvalvular AF. The CHADS2 is a validated tool.^{4,5} One or two points are assigned on the presence of various risk factors (See Box 1 for details); the total score gives an indication of the degree of stroke risk.

Box 1. CHADS2 criteria⁵

CHADS2 criteria	Points
Congestive heart failure	1
Hypertension	1
Age \geq 75 years	1
Diabetes mellitus	1
prior Stroke/TIA	2

TIA: Transient ischaemic attack

- A CHADS2 score of 2–6 is considered high risk, 1 is considered moderate risk and CHADS2 score of zero is considered low risk of stroke. (See Box 2 for details). The score for Anne is 1 because her age is 75 years, and her stroke risk is moderate.

Box 2. CHADS2 score and annual risk of stroke⁵

Stroke risk score (total score)	Adjusted stroke rate
High (6)	18.2%
High (5)	12.5%
High (4)	8.5%
High (3)	5.9%
High (2)	4.0%
Moderate (1)	2.8%
Low (0)	1.9%

Advantages and disadvantages of antithrombotic agents

- Respondents were asked to list the advantages and disadvantages for aspirin, clopidogrel, dipyridamole and warfarin as antithrombotic agents (see Tables 3–6).
- 10% of respondents who reported International Normalised Ratio (INR) monitoring as a disadvantage for warfarin also reported lack of need for monitoring as an advantage for aspirin. 17% of respondents reported risk of bleeding as a disadvantage for both warfarin and aspirin.

Table 3: Benefits and harms in use of aspirin

Advantages	% of respondents* (n = 200)	Disadvantages	% of respondents* (n = 200)
Inexpensive	48.5	Not as effective as warfarin	43.5
Reduces risk of thromboembolism	36.0	Risk of gastric bleeding/ulceration	42.5
Safer than warfarin	25.5	Risk of major bleeding	25.5
Simple dosing schedule	22.0	Low stroke-prevention rate	15.0
Monitoring not required	22.0	Other adverse effects (e.g. allergy, asthma)	12.0
Effective treatment in low- and moderate-risk patients	4.0	Others [†]	2.0

* Respondents may have more than one response

† Includes the need to stop before surgery, and no disadvantages

- 11.5% of respondents who reported aspirin as inexpensive reported gastric complications as a disadvantage.

Table 4: Benefits and harms in use of clopidogrel

Advantages	% of respondents* (n = 200)	Disadvantages	% of respondents* (n = 200)
Reduces risk of thromboembolism	30.0	More expensive than aspirin	43.0
Similar in effectiveness to aspirin and dipyridamole	24.0	Risk of major bleeding	36.5
Useful for patients intolerant of aspirin	20.0	Not as effective as warfarin	23.5
Lower bleeding risk compared with aspirin/warfarin	18.0	Restricted PBS listing	14.0
More effective if ischaemic heart disease is present	15.5	Low stroke-prevention rate	5.5
Monitoring not required	14.0	Others [†]	3.5
Simple dosing schedule	9.5		
None / not indicated	7.5		

* Respondents may have more than one response

† Includes problems with half life, myelotoxicity, diarrhoea/abdominal pain and not indicated

- 13% of respondents who reported that clopidogrel reduces risk of thromboembolism also indicated it to be more expensive than aspirin.

Table 5: Benefits and harms in use of dipyridamole

Advantages	% of respondents* (n = 200)	Disadvantages	% of respondents* (n = 200)
Better in combination with aspirin	37.0	Headache	66.5
Reduces risk of thromboembolism	30.5	Other adverse effects	15.0
Monitoring not required	13.0	Not as effective as warfarin	13.0
Lower bleeding risk	9.0	Low stroke-prevention rate	12.0
Simple dosing schedule	8.0	Risk of major bleeding	7.0
Inexpensive	7.5	Need to use with aspirin	5.5
Not indicated	6.0	More expensive than aspirin	3.5
None	5.0	Not indicated	3.5
		Requires twice-daily dosing	2.0

* Respondents may have more than one response

- 28.5% respondents who reported that dipyridamole is better in combination with aspirin indicated headache as a major disadvantage.

Table 6: Benefits and harms in use of warfarin

Advantages	% of respondents* (n = 200)	Disadvantages	% of respondents* (n = 200)
Best risk prevention for Anne	57.0	Risk of major bleeding	89.5
Reduces risk of thromboembolism	35.0	Requires regular INR/monitoring	60.0
Inexpensive	9.3	Requires care with diet/medications/ alcohol	22.5
Twice as effective as aspirin	7.5	Low safety margin	5.5
Others [†]	1.5	Others [‡]	2.0

* Respondents may have more than one response

[†] Includes once daily dosing, no advantages over aspirin and not indicated

[‡] Includes warfarin intolerance, the need to stop before surgery, and delayed onset of action

- 46.5% of respondents who recognised that warfarin offers best protection for Anne also indicated risk of major bleeding as a major disadvantage.



Practice points

- Undertake regular assessment of risk of stroke and major bleeding to guide antithrombotic therapy in patients with AF.
- Warfarin reduces the relative risk of stroke in patients with non-valvular AF by 64% (95% CI, 49% to 74%) compared with placebo or no treatment.⁶ Patients with a previous stroke or TIA gain the greatest absolute benefit from warfarin in prevention of one recurrence of stroke.⁶
- Aspirin reduces the relative risk of stroke in patients with non-valvular AF by 22% (95% CI, 2% to 39%) compared with placebo.⁶
- Warfarin reduces the relative risk of stroke by 38% (95% CI, 18% to 52%) compared with aspirin^{6,7} and increases the absolute bleeding risk by 0.2%.⁶ (See Box 3 for number needed to treat).
- There is currently no evidence for use of clopidogrel over aspirin or warfarin in non-valvular AF.⁸
- Dipyridamole sustained-release and aspirin are indicated in patients with previous ischaemic stroke or TIA due to arterial disease; there is currently no evidence for use of this combination in patients with AF.⁹

Box 3. Number needed to treat (NNT)* for stroke prevention in AF⁶

Comparison	Primary prevention	Secondary prevention
Warfarin vs control [†]	40	14
Antiplatelet [‡] vs control	111	34

*Calculated on the basis of relative risk reduction derived from meta-analysis of clinical trials applied to the following hypothetical rates to yield the NNT for 1 year to prevent 1 stroke: control patients, 4% per year and 13% per year; and patients who received antiplatelet therapy, 3% per year and 10% per year, for primary (no prior stroke or TIA) and secondary prevention, respectively

[†]Placebo or no treatment

[‡]Aspirin, clopidogrel

Choice of antithrombotic therapy

- 95.5% of respondents recommended antithrombotic treatment (with 71% of these recommending warfarin and 29% aspirin); 4.5% did not. Few respondents also prescribed clopidogrel, dipyridamole with aspirin, or enoxaparin with warfarin. Table 7 lists the main medications and common dosages recommended by the respondents.

Table 7: Main medications and their dosage and time to next review

Warfarin	% of respondents (n = 141)
Daily starting dose	
3 mg	3.5
4 mg	7.1
5 mg	81.7
Others*	7.7
Time to next review	
After 1 day	7.7
After 2–3 days	59.9
After 4–5 days	9.9
After 1 week	11.2
Daily until INR is 2–3	7.1
Others [†]	4.2
Aspirin	% of respondents (n = 58)
Daily starting dose	
100 mg	87.9
150 mg	8.6
300 mg	3.5
Time to next review	
After 1 week	5.2
After 2 weeks	29.3
After 4 weeks	25.9
After 12 weeks	20.7
Others [‡]	12.0
Not specified	6.9

* Includes warfarin 10 mg, 2 mg, 2.5 mg and 1 mg

[†] Includes week 2 and not specified

[‡] Includes day 1; week 3, 6, 24 and lifelong

- Of the respondents who considered Anne’s stroke risk as moderate, 29.8% recommended aspirin and 70.2% warfarin. Warfarin was recommended by 94.1% who determined high stroke risk whereas aspirin was recommended by 78.6% of those who reported low stroke risk.
- The respondents were asked to provide reasons for their antithrombotic therapy recommendation (see Table 8).

Table 8: Reasons for recommending antithrombotic treatment	
Reasons for recommending warfarin	% of respondents* (n = 141)
Offers greatest risk reduction for stroke	61.0
Indicated for patients with moderate to high risk of stroke	25.5
No known contraindications	20.6
Ongoing atrial fibrillation	13.5
Patient likely to be compliant	11.3
Family history	8.5
Age	7.8
Others†	2.1
Reasons for recommending aspirin	% of respondents* (n = 58)
Reasonable efficacy in low-risk patients	34.5
Less demanding/simple to use	22.4
No known contraindications	20.7
Reduces risk of stroke	18.9
Safe	18.9
Inexpensive	17.2
Indicated for patients with moderate to high risk	10.3
Ongoing atrial fibrillation	10.3
Family history and age	8.6
Patient likely to be compliant	6.9
Others‡	8.6

* Respondents may have more than one response

† Includes patient’s decision and inexpensive

‡ Includes patient’s decision, risk of fall, and that using warfarin is a big decision

- Reasons provided for not prescribing antithrombotic therapy include low stroke risk for Anne and the need for a cardiology review for treatment of atrial fibrillation.



Practice points

- Use a stroke risk stratification tool to choose between warfarin and aspirin in non-valvular AF. Consider warfarin in patients with non-valvular AF at moderate or high risk of stroke.¹⁰
- Consider aspirin in patients with non-valvular AF at low risk of stroke.¹⁰ Aspirin is also an alternative in patients who have a higher risk of stroke where warfarin is contraindicated.¹⁰
- Assess the risk–benefit profile for the individual patient to guide the choice of therapy.⁴
- Avoid warfarin in patients with:
 - bleeding disorders
 - uncontrolled hypertension
 - non-compliance with INR monitoring
 - previous gastrointestinal/genitourinary bleeding
 - intracerebral haemorrhage
 - heavy alcohol intake

- dementia
- conventional non-steroidal anti-inflammatory drug (NSAID) use.¹¹
- Warfarin is not contraindicated in:
 - older patients (age \geq 75 years)
 - those with propensity for falls
 - previous ischaemic stroke
 - recent and resolved peptic ulcer disease
 - NSAID use with a proton pump inhibitor.¹¹
- Normally warfarin should be started at 5 mg daily for two days, and the subsequent dose adjusted depending on the INR level (targeted to between 2 and 3).¹⁰ Elderly patients may require lower starting doses.¹⁰
- Use aspirin at a dosage of 75–325 mg/day.⁸ The risk reductions for stroke are not significantly different between the doses in this range.¹² Aspirin is available as 100 mg and 300 mg tablets. Using 150 mg of soluble aspirin (half a standard 300 mg tablet) would be the least expensive option.¹²
- Anne has a CHADS2 score of 1 and therefore is at moderate risk of stroke. Either warfarin or aspirin could be an option because she has low risk of bleeding due to warfarin use and her stroke risk is at the lower end of moderate risk, as there are no other risk factors on history.

Using warfarin effectively and safely

- Respondents were asked to list existing factors that might increase Anne’s risk of major bleeding if she was started on warfarin; 37% did not identify any existing risk factors whereas 63% listed one or more risk factors. Table 9 summarises the factors that may cause major bleeding in Anne.

Table 9: Risk factors that may increase risk of major bleeding	
Factors that may cause bleeding in Anne	% of respondents* (n = 200)
Age	46.5
Bleeding disorders	9.5
Non-adherence	6.5
Risk of fall	6.5
Past smoker	5.0
Family history of vascular disease	4.5
Drug/food interactions	3.5
Other†	5.0

* Respondents may have more than one response

† Includes HT, atrial fibrillation and liver disease



Practice points

- Bleeding is the most common complication of warfarin therapy.¹⁰ Patient factors that can result in bleeding complications include:
 - age > 65 years
 - uncontrolled hypertension
 - bleeding disorders
 - history of stroke
 - renal insufficiency
 - gastrointestinal haemorrhage
 - recent trauma
 - history of falls

- excessive alcohol intake
- medications, especially NSAID's.¹³

- Respondents were also asked to comment on the nature of information that Anne should be provided to achieve optimal anticoagulation if started on warfarin. Table 10 summarises this advice.

Table 10: Advice given to achieve optimal anticoagulation	
Advice for Anne	% of respondents* (n = 200)
Education about warfarin	
Need for regular and correct dose	49.0
Importance of using the same brand of warfarin	26.5
Information on warning signs of bleeding	17.0
Inform other health professionals about warfarin use	8.0
Stop treatment before surgery	2.5
Possible adverse effects	1.0
Monitoring	
Importance of regular INR testing and clinical review	75.0
Maintain anticoagulant booklet	15.0
Importance of maintaining INR levels in range 2–3	13.5
Potential drug/food interactions	
Care with other medicines/changing doses	52.0
Care with herbal medicines/ over-the-counter products	6.0
Discuss with health professional when starting new medicines	4.5
Diet	
Reduce food high in vitamin K/ green leafy vegetables	47.5
Effect of alcohol	17.0
Maintain stable diet for stable INR levels	12.5

* Respondents may have more than one response



Practice points

- Provide verbal counselling and an anticoagulant booklet to each patient using warfarin. (See Box 4)

Box 4 Patient education components¹³

Explain the:

- Reason for treatment
- Mechanism of action of warfarin
- Time of day to take warfarin (same time of day)
- The INR, target range and need for regular testing
- Signs and symptoms of bleeding
- Effect of illness, injury or any changes in physical status
- Potential effect of invasive procedure, surgery or dental work
- The effects of common over-the-counter (OTC) medication interactions
- The need for consistent intake of vitamin-K-rich foods
- Effects of alcohol intake
- Appropriate action if diarrhoea or vomiting occurs

Commentary 1

Key points

- Primary prevention with either aspirin or warfarin is crucial to reduce the high ischaemic stroke risk in people aged over 65 years with paroxysmal and chronic non-valvular atrial fibrillation (NVAF). Rhythm-control medications are ineffective in stroke prevention.
- A brief history and physical examination combined with use of a recognised risk score such as CHADS2 can effectively guide antithrombotic choice in NVAF
- Based on evidence the vast majority of patients with NVAF require warfarin, but at present anticoagulation is under-prescribed
- Perceptions of anticoagulant risk are excessive and a major barrier to the evidence-based use of warfarin.

The case scenario

Anne has a history of paroxysmal NVAF and at age 75 has a low-moderate stroke risk. Our discussion in this setting centres on the choice between aspirin and warfarin. However, most patients over 65 years with NVAF have a high stroke risk due to unfavorable characteristics such as hypertension, diabetes, cardiac failure, stroke and TIA⁵, and for these patients warfarin is the clear evidence-based choice for stroke prevention.⁶

People with NVAF have a high risk of stroke and make up 25% of stroke admissions.¹⁴ Eighty per cent of people with NVAF stroke will be left dead or disabled, and the NVAF stroke mortality rate of 20% is twice the average for non-NVAF stroke.¹⁵ With high risk and devastating outcomes, primary prevention for Anne is crucial.

Anne has symptoms of fatigue and palpitations. Patients with NVAF may complain of palpitations and have symptoms of compromise, such as fatigue and breathlessness, usually at faster heart rates. However, NVAF is often asymptomatic. Our patient may now be in

chronic NVAF, usually detected on history, examination or electrocardiograph. Paroxysmal NVAF can be more elusive and the clinician becomes aware of it when there has been a fortunate history of detection, as recorded 3 years earlier in this case. Anne has been at significant risk of stroke for at least 3 years

In all these discussions it is important to realise that a history of paroxysmal NVAF confers the same stroke risk as chronic NVAF over age 65. Anti-arrhythmic medications do not reduce stroke risk in either paroxysmal or chronic NVAF. Anne does not have an unfavorable history of hypertension, diabetes, cardiac failure, stroke or TIA, some of which are present in most elderly patients with NVAF, substantially increasing stroke risk. These risk-determining features and patient age form the basis of stroke risk stratification schemes such as CHADS2.⁵

Anne has a remarkably normal trans-oesophageal echocardiogram (TOE). The patient's structurally normal heart on TOE may be reassuring, but it was performed 3 years earlier. Left ventricular dysfunction on trans-thoracic echocardiography (TTE) is associated with a higher stroke risk, and this is recognised in some stratification schemes. TOE findings that probably influence stroke and other cardiovascular risk include left atrial spontaneous echo contrast (LASEC; an atrial flow abnormality) and significant aortic atheroma. The CHADS2 risk stratification score does not incorporate echo findings but these may usefully be considered in conjunction with the score.

Anne's CHADS2 score is 1, based on her age of 75 years. There are no other unfavourable factors on history. This score implies a 'moderate' stroke risk of 2.8% per year. Although this moderate risk usually attracts warfarin treatment, our patient is at the low end of moderate risk, and a CHADS2 score of 1 point can make aspirin a defensible choice. At this level of risk consensus guidelines do differ. The landmark Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study in general

practice can help us select an antithrombotic for Anne.¹⁶ Seventy per cent of the BAFTA sample had CHADS2 scores of 1–2, and this subgroup benefited significantly from treatment with warfarin compared with aspirin.

A family history of cardiovascular disease and smoking are significant concerns. They encourage scrupulous assessment and management of modifiable risk factors but do not alter antithrombotic choice.

Considering consensus guidelines and BAFTA results, I would choose warfarin for a patient with a CHADS2 score of 1. (While aspirin remains defensible we should note the BAFTA results have not yet been incorporated into guidelines.) I would use an INR range of 2–3 and a specific INR target of 2.5, starting warfarin at 5mg/day and performing an INR on day 2. There should be discussion of the potential impact of intercurrent illness, diet (including olive and canola oils), diet supplements (including common alternative therapies), over-the-counter medications and commonly prescribed medications on INR levels.

General consideration

When considering antithrombotics in patients with NVAf we weigh up risk–benefit using 20 years of high-level evidence, credible consensus guidelines and stroke risk scales. Aspirin is associated with an overall relative risk reduction in total stroke (ischaemic and haemorrhagic) of 19% and a relative risk reduction of 14% in all-cause mortality.⁶ Warfarin provides a much greater 64% relative risk reduction in stroke and a 26% relative risk reduction in all-cause mortality.⁶ Overall, warfarin compared with aspirin provides a 38% relative risk reduction for total stroke and reduces all-cause mortality by 9%.⁶ The analyses take into account haemorrhagic strokes and intracranial and subdural haemorrhages. Importantly aspirin becomes less effective with rising age and warfarin has even more to offer as age increases.¹⁷

The principle risk with antithrombotics is bleeding. In BAFTA — the key general practice study of warfarin vs aspirin in elderly patients (mean age 81.5 years) — there was no significant difference in intracranial bleeding (0.5 and 0.7%) or all-cause major bleeding (2.0 and 1.9%) between aspirin and warfarin.¹⁶

Warfarin and aspirin are the evidence-based choices in NVAf. Clopidogrel has not been shown to be more effective than aspirin or warfarin. Aspirin and clopidogrel in combination is substantially inferior to warfarin in NVAf and associated with high bleeding rates. The combination of aspirin with dipyridamole has shown some benefit over aspirin in one ‘on treatment’ analysis, which can exaggerate benefit, and this combination is not specifically recommended.⁶

Warfarin is effective even when the INR is only in the therapeutic 2–3 range 64% of the time.¹⁶ GPs achieve these effective levels of anticoagulation routinely, and a high level of safety is seen in usual practice despite the inconvenience of monitoring and dose adjustment.¹⁶

Barrier to anticoagulation

Australian general practitioners acknowledge the benefits of warfarin in NVAf, but warfarin is under-prescribed in this setting. This evidence–practice gap is an international phenomenon and the implications for patients are devastating.¹⁵ Evidence-based use of warfarin would reduce fatal and disabling stroke in Australia by up to 25%, depending on age. There are many perceived barriers to the prescription and maintenance of anticoagulants that are not evidence based.¹⁸ Anne’s case does not illustrate the greatest barriers to anticoagulant use. She has no history of falls, upper gastrointestinal tract (GIT) bleeding or minor bleeding. Such histories are common and they represent manageable or immaterial risks rather than contraindications to warfarin use. The under-prescribing of warfarin places the patient with NVAf at risk of worse outcomes.

In a national GP survey a history of treated upper GIT bleeding reduced intention to prescribe from 71% in patients with a CHADS2 score of 5 to just 17%. A modest falls risk (two falls in a year without injury on rough ground) reduced intention to prescribe to 46%.¹⁹ Usual treatment of upper GI bleeding by removing possible causes (eg: aspirin, clopidogrel or NSAIDs), starting a proton pump inhibitor and eradicating *Helicobacter pylori* greatly reduces risk of further bleeding. Even in patients with aspirin-induced ulcer the reported GI bleeding rate with aspirin is only 1 in 50.²⁰

The perception of falls as a barrier to anticoagulant use is not well founded. The quoted average for an elderly patient with a history of falls is 1.8 falls per year, and at that rate there is no negative impact on anticoagulant outcomes. For patients with a 'high falls risk' and a history of NVAF there is a substantially increased risk of intracranial haemorrhage, but this risk remains much less than their high ischaemic stroke rate of 13.5%.²¹ In such high-falls-risk patients, warfarin is actually protective for a composite endpoint of stroke, intracranial bleeding,

myocardial infarction and death. An elderly patient with NVAF must fall 295 times in one year to obviate the benefit of warfarin.²²

The single controversy for Anne is our choice of aspirin or warfarin. However, the welfare of most patients depends on overcoming the brand shock of 'Ratsak' and overcoming our perception that there is a high risk of adverse side effects and a high number of contraindications to warfarin use. If we overcome our 'omission bias' we can reduce all fatal and disabling stroke by 25%.

Commentary 2

Key points

- In this case study the diagnosis of NVAF is established, and the presentation is with fatigue and palpitations. These symptoms need to be addressed with regard to rhythm or rate control, but the opportunity should be taken to risk-stratify with regard to stroke risk and consider antithrombotic therapy.
- Use of the CHADS2 score helps to stratify risk of stroke.
- While stroke risk stratification is well established (including by use of the CHADS2 score), quantification of risk of adverse effects is less straightforward.
- Decisions on the use of antiplatelet agents or warfarin will require consideration of stratification of stroke risk, qualitative estimation of risk of adverse effects of therapy (taking into account the patient's past history and their current circumstances) and patient preference.

Stroke risk stratification

Most GP participants (74.5%) identified Anne as being at moderate risk of stroke. This is consistent with the CHADS2 risk stratification (score of 1: a point scored for age ≥ 75).

An assessment of risk as being 'moderate' in this situation takes into account⁴:

- an age of ≥ 75 is associated with a relative risk of stroke of 1.4 in a patient with unwarfarinised NVAF.
- the absolute risk of stroke in a patient with a CHADS2 score of 1 is 2.8% per year.

Age was correctly identified as a factor in assigning a stroke risk stratification of moderate by most of those who assigned this level of risk. Ongoing AF was cited as a factor in risk stratification by 35%, 40%, and 88%, respectively, for those who assessed risk as low, moderate or high. While a definition of 'ongoing' AF may be unclear, it is important to note that the risk of stroke in paroxysmal, persistent, and permanent AF is equivalent.¹¹

Family history and past smoking history were cited by a number of respondents as factors in risk stratification, but these are not among the significant prognostic factors for stroke in AF.⁴

Antithrombotic therapy

Ninety-six per cent of respondents reported that they would recommend antithrombotic treatment for Anne (71% of these GPs nominated warfarin, and 29% aspirin). Anne's CHADS2 score of 1 (moderate risk) and her lack of contraindications suggest that antithrombotic treatment is indicated and that either aspirin or warfarin is a reasonable choice.

Forty-six per cent of respondents nominated age as a factor that might cause Anne to be at increased risk of bleeding. This is certainly true, although it does not represent a contraindication to warfarin in itself, as it is also associated with higher risk of stroke. The other factors cited are either reasonable, but not apparent in the case vignette (e.g. bleeding disorders, non-adherence) or do not put Anne at increased risk (e.g. family history of vascular disease).

Eighty-two per cent of those who recommended warfarin started treatment with a dose of 5 mg (the recommended dose). Starting at lower doses may result in a longer time to titrate dosage and achieve therapeutic INR levels but is unlikely to be problematic in this situation where the use of warfarin is prophylactic in an elderly patient.¹⁰ A starting dose of 10 mg in this age group, by contrast, may predispose to overshooting the therapeutic INR of 2–3.

All the cited aspirin doses (100–300 mg) are reasonable choices.

For those starting warfarin, the patient's INR should be determined daily or every second day until it has stabilised within the therapeutic range. So the responses suggesting that time to next review of 4 or more days (over 21% of respondents) are not in keeping with current consensus guidelines.

References

1. Sturm JW, Davis SM, O'Sullivan JG, et al. The Avoid Stroke as Soon as Possible (ASAP) general practice stroke audit. *Med J Aust* 2002;176:312–6.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–8.
3. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke* 2008;39:1901–10.
4. Medi C, Hankey GJ, Freedman SB. Atrial fibrillation. *Med J Aust* 2007;186:197–202.
5. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70.
6. 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.
7. Aguilar Maria I, Hart R, Pearce Lesly A. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2007:
<http://www.mrw.interscience.wiley.com/cochrane/clsystrev/articles/CD006186/frame.html> (accessed 20 January, 2009)
8. Neurology Writing Group. Therapeutic Guidelines: Neurology, Version 3. Updated June 2008 [eTG complete CD-ROM]. Melbourne: Therapeutic Guidelines Limited, 2007.
9. Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke* 2008;39:1358–63.
10. Cardiovascular Writing Group. Therapeutic Guidelines: Cardiovascular, Version 5. Updated March 2009 [eTG complete CD-ROM]. Melbourne: Therapeutic Guidelines Ltd, 2008.
11. New Zealand Guidelines Group. The management of people with atrial fibrillation and flutter. NZGG, Wellington, May 2005.
12. Lloyd J, Bochner F. Aspirin: how low is low dose? *Australian Prescriber* 1996;19:79–81.
<http://www.australianprescriber.com/magazine/19/3/79/81/> (accessed 21 April 2009).
13. Baker RI, Coughlin PB, Gallus AS, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 2004;181:492–7.
14. Gattellari M, Worthington J, Jalaludin B, et al. Stroke unit care in a real-life setting: can results from randomized controlled trials be translated into every-day clinical practice? An observational study of hospital data in a large Australian population. *Stroke* 2009;40:10–7.
15. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009;40:235–40.
16. Mant J, Hobbs FD, 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.
17. van Walraven C, Hart RG, 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.
18. Peterson GM, Boom K, Jackson SL, Vial JH. Doctors' beliefs on the use of antithrombotic therapy in atrial fibrillation: identifying barriers to stroke prevention. *Intern Med J* 2002;32:15–23.

19. Gattellari M, Worthington J, Zwar N, et al. The management of non-valvular atrial fibrillation (NVAf) in Australian general practice: bridging the evidence-practice gap. A national, representative postal survey. *BMC Family Practice* 2008;9:62.
20. Chan FKL, Ching JYL, Hung LCT, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238–44.
21. Gage BF, Birman-Deych E, Kerzner R, et al. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. *Am J Med* 2005;118:612–7.
22. Man-Son-Hing M, Nichol G, Lau A, et al. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159:677–85.