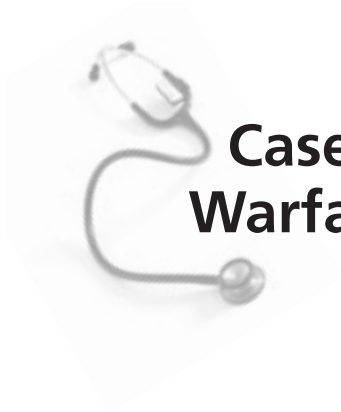




National Prescribing Service Limited



## **Case study 29: Warfarin therapy**

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

# Case study 29: Warfarin therapy

## Scenario

Bob, a 65-year-old man with atrial fibrillation, has been using warfarin for the past 12 months after he presented to the local emergency department with signs of a TIA. A head CT scan and trans-oesophageal echocardiogram done at the time were normal. He has been well since.

You have asked Bob to come in to see you as the INR taken this morning was 4.6. Up until now, his INR results (which have been measured every 2 weeks) have been stable and in the range of 2.0–3.0. He has not started any new prescribed medications recently.

Bob also has hypertension and osteoarthritis (for which he had a left total hip replacement 6 months ago). Current medications: atenolol 50 mg once daily, ramipril 10 mg once daily and warfarin 6 mg at night.

On examination: BP 140/80 mmHg; pulse rate 65, irregular. The remainder of the physical examination is normal with no evidence of bruising, epistaxis or gastrointestinal bleeding.

1. List potential drug interaction(s) with warfarin, which may **increase** the INR.

Foods/beverages

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Over-the-counter medications

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Complementary medicines

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2. Will you change tonight's therapy?

Yes, please specify:

decrease dose; specify new warfarin dose \_\_\_\_\_ mg

OR

omit dose

• number of days warfarin dose omitted \_\_\_\_\_ days

• new dose of warfarin (when restarted) \_\_\_\_\_ mg

No change (i.e. continue 6 mg nocte)

3. When would you next measure the INR?

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4. How often would you measure the INR during restabilisation?

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5. What other measures, if any, would you take to manage the raised INR?

Please specify (e.g. other treatment or investigations, communication with other health professionals, patient/carer instructions):

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6. List three factors, apart from drug interactions, associated with an increased risk of major bleeding whilst on warfarin.

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# Summary of results

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At the time of publication 835 responses had been received from doctors, and 200 of these have been compiled for feedback.

## Potential drug interactions with warfarin

- Foods/beverages:
  - 64% of respondents correctly indicated alcohol may increase INR.
  - 33% incorrectly indicated foods/beverages high in vitamin K (i.e. green leafy vegetables and green tea) may increase INR, as vitamin K decreases INR.
- Over-the-counter (OTC) medications:
  - 66% of respondents indicated nonsteroidal anti-inflammatory drugs (NSAIDs) may increase INR. Conventional NSAIDs can increase risk of bleeding without altering INR, due to antiplatelet effects and a tendency to cause gastrointestinal ulceration.
  - 8% incorrectly indicated vitamin K may increase INR.
- Complementary medicines:
  - All respondents correctly identified at least one potential drug interaction.
  - 33% incorrectly indicated St John's wort may increase INR, and 6.5% incorrectly indicated Coenzyme Q<sub>10</sub> may increase INR. Both of these decrease INR.
  - 23% indicated ginseng may increase INR. The finding of how ginseng affects INR is less conclusive, as one case report showed a decrease in INR and its exact mechanism of interaction is unknown.<sup>1</sup>

## Changes to warfarin dose

- 11% of respondents would decrease the dose of warfarin tonight. Of these:
  - 81% would reduce the dose of warfarin to 4–5 mg daily.
- 86% would omit warfarin. Of these:
  - 41% would omit the dose of warfarin tonight
  - 56% would omit warfarin for more than one day.
- Of those who would omit warfarin:
  - 59% would restart warfarin at 5 mg daily.

## Next INR measurement

- 16% of respondents would measure INR the next day
- 54% would measure INR in 2–3 days.

## Frequency of INR measurement during restabilisation

- 20% of respondents would measure INR daily or every second day
- 75% would measure INR once or twice weekly.

## Other management

- 7% of respondents would not employ any other measures to manage the raised INR
- > 40% would enquire about the use of complementary medicines or dietary changes
- 16% would check patient compliance with warfarin.

## Other factors associated with an increased risk of major bleeding

- 49% of respondents indicated liver disease as a risk factor for bleeding
- > 30% indicated uncontrolled hypertension, advanced age or social factors are associated with an increased risk of bleeding whilst using warfarin.

## Key points

- The primary threat to patients with atrial fibrillation (AF) comes from thromboembolism.<sup>2,3</sup> Consider warfarin in all patients with AF at moderate to high risk of stroke.<sup>4</sup>
- Consider the individual's ability and willingness to cope with the monitoring requirements and risks of warfarin therapy. Assess contra-indications and bleeding risks, and reassess regularly.<sup>5</sup>
- Patient participation and education are critical in both choosing to start and using warfarin.<sup>6</sup>
- For most conditions, including AF, a target INR range of 2.0–3.0 is recommended; specialists may recommend higher ranges in specific circumstances (e.g. for prosthetic heart valves).<sup>7</sup>
- Determine INR more frequently if there are changes in the patient's condition, including intercurrent illness, concurrent drug administration, a change in the amount of alcohol consumed, or a change of diet.<sup>8</sup>

# Results in detail

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## Question 1. List potential drug interaction(s) with warfarin, which may increase the INR

Table 1: Foods/beverages, OTC and complementary medicines that may increase INR

Medication	Percentage of respondents <sup>a</sup> (n=200)
Alcohol	64.0
Cranberry juice	2.5
Grapefruit juice <sup>b</sup>	2.0
NSAIDs	65.5
Vitamins:	
• Type not specified	9.5
• vitamin C (> 5 g per day)	12.0
• vitamin E <sup>c</sup>	3.5
Paracetamol	12.5
H <sub>2</sub> antagonists (i.e. cimetidine and ranitidine)	6.0
Antacids	3.0
Miconazole oral gel	2.5
Garlic/ginkgo	> 70.0
Celery/dong quai/danshen/ginger	> 40.0
Alfalfa/payaya	> 30.0
Other <sup>c</sup>	19.0

a. Respondents may have more than one response.

b. There is conflicting evidence reporting if grapefruit juice affects INR.<sup>9,10</sup>

c. Vitamin E has been reported to increase INR, but there is conflicting evidence in the literature.<sup>11</sup>

d. Includes devil's claw, red clover, liquorice, aniseed, arnica, chamomile, feverfew, fenugreek, horse chesnut and asafoetida.



### Practice points

- Maintain a consistent diet to stabilise intake of vitamin K, and avoid excessive alcohol consumption (1–2 standard drinks per day is generally safe).<sup>8</sup>
- Due to antiplatelet effects and a tendency to cause gastrointestinal ulceration, conventional NSAIDs can increase the bleeding risk of warfarin without altering INR. Patients should avoid concurrent use of these drugs.<sup>8</sup>
- Patients on a stable warfarin regimen who begin taking more than 3.5–7.0 g paracetamol per week should have an INR measurement 1–2 weeks after starting paracetamol.<sup>8</sup>
- Reported interactions of herbal medicines and warfarin are based on documented cases and plausible interactions. Herbal products may also increase the risk of bleeding without altering INR. The mechanism of these interactions is not always known.<sup>6</sup>
- Reports of confirmed or potential drug interactions of herbal products (e.g. garlic, papaya, ginger, celery, alfalfa) include only concentrated preparations that are dietary supplements.<sup>6</sup> There is a lack of evidence to suggest normal dietary intake of these foods will alter INR or increase bleeding risk.
- In case of a suspected drug interaction, contact the Therapeutic Advice and Information Service (TAIS) on 1300 138 677 for more information on drug interactions.

## Question 2. Will you change Bob's warfarin therapy tonight?

- 11% of respondents would decrease the dose of warfarin tonight. Of these:
  - 33% would reduce warfarin to 5 mg daily
  - 48% would reduce warfarin to 4 mg daily.
- 86% would omit warfarin. Of these:
  - 41% would omit the dose of warfarin tonight
  - 56% would omit warfarin for two days
  - 8% would omit warfarin for three days
  - 3% would omit warfarin for more than three days.
- Of those who would omit warfarin:
  - 59% would restart warfarin at 5 mg daily
  - 19% would restart warfarin at 4 mg daily.
- 2% would not change Bob's warfarin therapy tonight.

### Practice points

- Management for over-anticoagulation<sup>8</sup>:



INR value	Management
< 5 (no significant bleeding)	Hold next dose; resume at lower dose when INR is therapeutic
5–9 (no significant bleeding)	Hold dose for 1–2 days or hold 1 dose and give 1–2.5 mg oral vitamin K; resume warfarin at lower dose when INR is therapeutic
> 9 (no significant bleeding)	Hold dose and give 3–5 mg oral vitamin K; resume warfarin at lower dose when INR is therapeutic
Serious bleeding	Hold dose and give 10 mg vitamin K by slow IV infusion; consider giving a concentrate of factors II, IX and X (with factor VII if available) or fresh frozen plasma

### Question 3. When would you next measure the INR?

- 16% of respondents would measure the INR the next day
- 26% would measure INR in 2 days
- 28% would measure INR in 3 days
- 15% would measure INR in 4–5 days
- 16% would measure INR after 5 days.

### Question 4. How often would you measure the INR during restabilisation?

- 20% of respondents would measure INR daily or every second day during restabilisation
- 35% would measure INR twice weekly
- 40% would measure INR once weekly
- 3% would measure INR less than once weekly.

### Practice points



- Determine INR more frequently if there are changes in the patient's condition, including intercurrent illness (e.g. congestive heart failure, hepatic disease, gastrointestinal disturbances, infections, thyroid disorders), concurrent drug administration, a change in the amount of alcohol consumed, or a change of diet.<sup>8</sup>
- Full effect of a dose change of warfarin on INR is not seen for 2–3 days. Determine INR daily or on alternate days until it is stable in the therapeutic range. Once stabilised, monitor INR at regular intervals of not more than 4 weeks.<sup>8</sup>

## Question 5. What other measures, if any, would you take to manage the raised INR?

Table 2: Other measures to manage raised INR

Measure	Percentage of respondents <sup>a</sup> (n=200)
Enquire about the use of OTC/complementary medicines	45.5
Enquire about dietary changes	41.0
Check patient compliance with warfarin	16.0
Provide education on potential drug interactions	13.0
Instruct to monitor signs/symptoms for bleeding	12.0
Enquire about new/changed medication	10.5
Perform other blood tests <sup>b</sup>	10.0
Involve partner/family in patient care	7.0
Liaise with pharmacist/nurse	6.0
Advise to avoid physical injuries	6.0
Consult a haematologist	5.0
Give oral/IV vitamin K	4.5
Provide written information	3.5
Check for other new illnesses	2.5
Check for warfarin brand substitution	2.0
Emphasise INR monitoring	2.0
Other <sup>c</sup>	6.0

a. Respondents may have more than one response.

b. Includes FBE, LFT and renal function tests.

c. Includes monitor blood pressure, contact laboratory, consult a cardiologist and use of a Dosette box.

### Practice points



- Patient information booklets, available from the warfarin manufacturer and through pharmacies and hospital clinics, should be provided to all people using warfarin.<sup>6</sup>
- Advise patient to immediately report any bruising or bleeding, pink, red or dark urine, or red or black faeces.<sup>8</sup>
- Always instruct patient to take the same brand of warfarin tablets<sup>8</sup>, as they are not bioequivalent.

**Question 6. List three factors, apart from drug interactions, associated with an increased risk of major bleeding whilst on warfarin**

**Table 3: Factors associated with an increased risk of bleeding**

Risk factor	Percentage of respondents <sup>a</sup> (n=200)
Liver disease	49.0
Uncontrolled hypertension	39.5
Social factors <sup>b</sup>	39.5
Advanced age	34.0
Bleeding lesions <sup>c</sup>	26.0
Bleeding tendency <sup>d</sup>	23.5
Physical injuries <sup>e</sup>	20.0
Cerebrovascular disease or peripheral vascular disease	12.0
Instability of INR control or high INR	8.0
Surgery	4.0
Inadequate INR monitoring	3.5
Congestive heart failure	3.0
Low body weight	3.0
Other <sup>f</sup>	6.0

a. Respondents may have more than three responses.

b. Includes poor drug compliance and forgetfulness.

c. Includes gastrointestinal ulceration and recent cerebral haemorrhage.

d. Includes coagulation disorders and thrombocytopenia.

e. Includes falls and cuts.

f. Includes renal dysfunction, infection, malignancy, fever and vitamin K deficiency.

**Practice points**



- For patients on warfarin, assess bleeding risk regularly and consider factors that might affect the decision to anticoagulate.<sup>6</sup>
- Apart from drug interactions, other factors, such as advanced age (> 75 years), social factors (e.g. forgetfulness and poor drug compliance), instability of INR control, INR > 3 and co-morbidity (e.g. bleeding lesions and tendency), also increase the risk of bleeding in people taking warfarin.<sup>5</sup>

# Commentary 1

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## Key points

- Regularly review benefits and risks of warfarin therapy.
- Look for causes of raised INR (e.g. changes in dose, diet, alcohol intake and medications including OTC products and complementary medicines).
- Patient education can improve compliance with warfarin use and monitoring.
- Measure INR every 1–3 days during restabilisation and up to 4 weekly intervals once stabilised.

## Review benefits versus risks of warfarin

Bob has a definite indication for taking warfarin to reduce his risk of thromboembolic stroke. His risk factors, such as AF, history of transient ischaemic attack, hypertension and age 65 years, place him in the high-risk group, with 10–15% annual risk of stroke if untreated<sup>4</sup>, and the number-needed-to-treat for one year to prevent one stroke is 12.<sup>12</sup>

Bob does not have any contra-indications to anticoagulation. The annual risk of bleeding on warfarin is low at 0.5–1.5%.<sup>4</sup> He has maintained warfarin in the therapeutic range for 12 months (with fortnightly INR measurements) until the recent unexpectedly high reading of 4.6. The risk of bleeding steadily increases with INR levels greater than 3.0. At this medical consultation there were no signs of bleeding. It is important to look for causes of the raised INR, and to review medication and monitoring to reduce Bob's risk of bleeding.

## Investigate cause of raised INR

All respondents identified at least one potential drug interaction with warfarin, and two thirds correctly indicated an increased alcohol intake could increase INR. Bob's current prescribed medication is unchanged. The INR may have increased if Bob took OTC medications such as paracetamol (3.5–7.0 g/week) for pain

associated with his osteoarthritis. One third of respondents incorrectly indicated foods and beverages high in vitamin K may increase INR. In fact, vitamin K counteracts the effect of warfarin and is used to lower very high INR levels to reduce bleeding risk. Warfarin inhibits synthesis of activated vitamin K-dependent clotting factors (i.e. II, VII, IX and X) and antithrombotic factors protein C and protein S. INR is decreased by vitamin K intake from green leafy vegetables and green tea, as well as by St John's wort and Coenzyme Q<sub>10</sub>.

Increased INR also may be due to heart failure, or abnormal liver, thyroid or renal functions, so consider testing to exclude these if clinically indicated, or no other cause is apparent. It is important to determine whether Bob has had a change in the brand of warfarin (as they are not bioequivalent), or recent memory lapses or confusion in taking his medication.

Monitoring warfarin requires access to reliable INR testing facilities. Australian laboratories have adequate quality controls and produce accurate measures as long as they receive correctly collected blood sample volumes. In the UK and Europe, point-of-care INR testing is being increasingly introduced to avoid hospital attendance and enable self-dosage. However, point-of-care INR testing does not yet give dependable INR values, particularly at high levels.<sup>13</sup> Studies comparing point-of-care with laboratory INR levels are underway in Australia, as point-of-care testing would be of value particularly in remote locations and for Hospital in the Home.

## Patient education

Patient education on warfarin interactions and monitoring are essential for using warfarin safely and effectively. Patient adherence can be improved by a good doctor–patient relationship, prescribing a well-chosen drug treatment, and taking time to give the necessary information,

instructions and warnings.<sup>14</sup> Memory difficulties can be overcome by repeating instructions, providing written information to reinforce advice, involving the carer or family, and evaluating the patient's comprehension of drug instructions.<sup>15</sup> A warfarin information booklet is useful for Bob to keep track of his INR levels and warfarin doses over time.

Respondents identified many factors associated with increased risk of bleeding. Check whether Bob has an increased bleeding risk through increased doses of NSAIDs or aspirin for arthritis (can occur via antiplatelet effects or gastric ulceration), or physical activity that could lead to injury. Advise Bob to reduce physical activity while INR is raised, and to report any bruising, bleeding, dark red or brown urine, or red or black faeces.<sup>8</sup> GPs and patients are generally not familiar with many commonly used herbal products and their drug interactions. Bob's bleeding risk on warfarin may be increased by antiplatelet activity of ginkgo, garlic, ginger or liquorice at levels consumed in supplements or complementary medicines.

#### **Further management and follow-up**

Over 80% of respondents said they would withhold Bob's warfarin dose for one or two nights, but only 16% would check the level the next day. The recommendation for INR < 5 and no significant bleeding is to withhold the next dose and measure INR the next day.<sup>8</sup> This enables the GP to check for measurement error, rising INR level, or whether INR has fallen to within the therapeutic range.

It is recommended that warfarin be resumed at a lower dose once INR is within the therapeutic range. Of respondents who would omit warfarin, 78% would restart warfarin at a lower dose (5 or 4 mg), consistent with recommendations.

As the full effect of warfarin on INR occurs over 2–3 days, INR should be monitored closely during restabilisation at intervals between 1–3 days depending on INR level and response. A high proportion (43%) of respondents said they would measure INR weekly or less often during restabilisation. This is not frequent enough for establishing INR within the therapeutic range in optimal time and may unnecessarily leave a high risk patient being exposed to thromboembolism or bleeding. INR measurements at intervals of not more than 4 weeks are recommended for monitoring stable therapeutic levels. Ask Bob to attend more frequently if there are changes in his diet, alcohol, medication, or medical condition.

Within the next few years, direct thrombin inhibitors may become an alternative to warfarin. The results of two large, randomised studies of ximelagatran compared to warfarin for prevention of thromboembolism in AF patients (SPORTIF-III and -V) are awaited.<sup>16</sup> If safety is established and these drugs become available, they will allow for fixed dosing without INR monitoring.

## Commentary 2

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### Key points

- Review patients regularly to ensure warfarin is still appropriate.
- It is important to ask about foods and use of OTC products but also consider clinical conditions that may alter warfarin clearance.
- Factors that increase risk of bleeding include many social factors, which may affect patient's ability to have INR measurement, subsequent dose alteration and ongoing compliance.

### Variability in INR values

GPs frequently encounter the scenario of an abnormally high INR among patients taking warfarin. It is important to remember that variability in INR values is an inherent part of warfarin therapy, and as such the INR will on occasion reach excessively high or low values. The important consideration is to determine whether this represents a normal variability in INR values, or whether there is an underlying process, which forces the INR value up or down. For instance, underlying processes, such as poor compliance, irregular alcohol intake, irregular use of OTC or complementary medicines, can lead to greater variability in INR values.

### Potential drug interactions

The response of the majority of GPs in identifying alcohol causing raised INR is certainly correct. With respect to complementary medicines, it is often difficult to remember which one can affect INR and in which direction! I think it is more important to be aware that complementary medicines and OTC products can affect INR and to regularly ask about the use of these medicines.

The interaction with NSAIDs requires further clarification. Although some NSAIDs may interact with warfarin, which increase INR (known as a pharmacokinetic interaction), and many practitioners still 'go on' about protein binding interactions, a more important issue is that many NSAIDs affect platelet function and

can also cause peptic ulcers resulting in bleeding lesions (known as pharmacodynamic interactions). Hence combination of an NSAID and warfarin can dramatically increase the bleeding risk, without affecting INR in any way. Therefore, combination of warfarin with a non-selective NSAID is absolutely contra-indicated. Whereas COX-2 selective NSAIDs, which are thought to have no impact on platelet function, have also been reported to cause raised INR or bleeding<sup>17</sup>, and hence great cautions still need to be taken if a COX-2 selective NSAID is used when an anti-inflammatory agent is definitely indicated.

The patient's health status is often a forgotten issue when an abnormally high INR is encountered. Conditions, such as worsening heart failure, exacerbation of asthma and chronic obstructive pulmonary disease and gastroenteritis, can all increase INR by interfering with warfarin metabolism or by reducing vitamin K absorption.

### Changes to warfarin dose

As far as changes to the dose of warfarin tonight, this should definitely be withheld then decreased, rather than simply decreased. The reason for this is that if there is an underlying reason for Bob's INR to be climbing, even by reducing the dose somewhat, Bob's INR may continue to climb further because of the long half-life of warfarin and duration of its effect. The best way of avoiding this is to withhold the dose for a short period of time.

There are few hard and fast rules about how long to withhold the medication for, what dose to reduce it to, and when to next review. Many of the respondents' answers are quite reasonable, and often it is a matter of having experience with a particular patient's warfarin dosing, and fitting in follow-up with the patient's schedule.

**Other factors associated with an increased risk of bleeding**

Finally, it is important to appreciate that a high INR is not the only risk factor for bleeding with warfarin. Although many respondents correctly identified poor compliance and advanced age as risk factors, it is important to appreciate that a history of falls or unstable gait, and declining cognitive function are probably more important risk factors than liver disease or uncontrolled hypertension.

In many cases, although the original prescription of warfarin may have been appropriate for the patient, due to altered circumstances such as history of falls, cognitive impairment, poor

compliance and inability to have INR measurements, warfarin therapy may no longer be appropriate. For this reason, it is important to regularly review patients to ensure that they have not developed a new contra-indication to warfarin therapy.

It is also important to inform the patient of not only the risks associated with warfarin, but also what to look out for (e.g. black bowel actions) if bleeding was to occur, and what actions to take at that time (e.g. present immediately to a hospital).

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