

## PRACTICE



## 10-MINUTE CONSULTATION

## High INR on warfarin

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This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.

A 72 year old woman, who had been diagnosed as having recurrent deep vein thrombosis six weeks earlier, attends the practice's phlebotomy clinic for an international normalised ratio (INR) check. Her INR is greater than 8.0 (target INR range: 2.0-3.0). During the consultation, you look through her previous INR readings and notice they have been supra-therapeutic over the past two weeks despite a reduction in the dose of warfarin.

## What you should cover

- Screen for "red flag" symptoms and signs of active, non-resolving bleeding:
  - Use a thorough systems review; in particular look for any evidence of gastrointestinal bleeding, such as vomiting blood and passing altered or fresh rectal blood. If ongoing gastrointestinal bleeding is suspected, inpatient warfarin reversal and an oesophagogastroduodenoscopy are indicated
  - Any evidence of intracranial bleeding? Ask about recent head trauma with an episode of amnesia, loss of consciousness, post-traumatic seizure, or more than one episode of vomiting. Examine for a reduced Glasgow coma score as well as focal neurological signs. All patients who sustain a head injury while taking warfarin require a computed tomography head scan within eight hours of the injury, even if these clinical features are absent, according to guidance from the National Institute for Health and Care Excellence (NICE).<sup>1</sup> However, those with a reduced Glasgow coma score, focal neurological signs, post-traumatic seizure, or more than one episode of vomiting require such a scan within one hour.<sup>1</sup>
  - Check pulse and sitting and standing blood pressure for evidence of haemodynamic compromise.
- Clarify the doses of warfarin the patient has been taking because some patients may overmedicate by mistake. If

this is the case, ask how often the patient takes warfarin and at what dose. Provide appropriate written information if necessary. A dosette box might help her comply with the prescribed dose.

- Is there an important medical problem, such as liver disease or cancer, that might result in impaired synthesis of clotting factors? Patients with underlying cancer are at a higher risk of haemorrhage with warfarin than with low molecular weight heparin. They are also more likely to experience polypharmacy, hepatic dysfunction, and poor nutrition, which can influence their INR control. In these patients, consider using low molecular weight heparin instead.<sup>2</sup>
- Take a thorough drug history. Ask about prescribed drugs, over the counter drugs, and herbal supplements. The cytochrome P450 enzyme metabolises warfarin, so P450 inhibitors can cause the INR to rise. Common inhibitors of warfarin metabolism include clarithromycin, erythromycin, and amiodarone—for a comprehensive list see: [www.medicinescomplete.com/mc/bnf/current/bnf\\_int222-warfarin.htm](http://www.medicinescomplete.com/mc/bnf/current/bnf_int222-warfarin.htm). Check the INR three to five days later after starting any drug that interacts with warfarin that will be taken for longer than seven days because the dose of warfarin may need adjusting.<sup>3</sup>
- Inquire about alcohol. Patients taking warfarin should be discouraged from binge drinking because large amounts of alcohol inhibit warfarin breakdown and affect liver function.
- Ask about changes to diet. Patients may become more sensitive to warfarin if cutting down on vitamin K rich foods, such as leafy green vegetables. Encourage the patient to consult a doctor before major diet changes. Consumption of fruit juices, particularly cranberry or grapefruit, which inhibit warfarin metabolism, can cause INR levels to increase. These juices should be avoided.

If any of the above "red flag" features are present and an active bleed is suspected, refer to secondary care. If bleeding is

**The bottom line**

- Clarify the warfarin dose that the patient is taking, and check for co-existing problems (such as liver disease or cancer), dietary changes, and intake of alcohol and other drugs that may increase risk of bleeding or affect international normalised ratio control
- Urgently refer all patients with suspected intracranial or gastrointestinal bleeding to secondary care

confirmed in hospital, urgent reversal of warfarin with a four factor prothrombin complex concentrate may be warranted.

**What you should do**

If this patient is not actively bleeding she can be managed in the community (table 1). The British Committee for Standards in Haematology and The Medicines and Healthcare products Regulatory Agency advise that patients with an INR >8.0 who are not bleeding have their warfarin omitted until the INR drops to <5.0.<sup>3,4</sup> They should also be given 1-5 mg oral vitamin K, which will take up to 24 hours to work.<sup>5</sup> Once the INR is <5.0, restart the patient on a reduced dose of warfarin.

**Advice and follow-up**

- Highlight the importance of presenting to a medical practitioner in the case of a head injury or if bleeding does not resolve with conservative measures.
- After administering vitamin K, ensure that daily INR checks are organised until the INR is stable within the target range.
- Patients on long term warfarin should be reviewed annually or more often if there is doubt about their safety on continued anticoagulation.
- If INR continues to be high despite efforts to identify a precipitating cause, refer to the local hospital anticoagulation clinic or consider switching to a new oral anticoagulant such as the factor Xa inhibitor rivaroxaban after appropriate counselling. The direct thrombin inhibitor dabigatran is another new oral anticoagulant approved by the National Institute for Health and Care Excellence (NICE) for non-valvular atrial fibrillation and recently also

for the treatment of venous thromboembolism. Compared with warfarin, both dabigatran and rivaroxaban seem to have fewer interactions with other drugs, so anticoagulant monitoring is not recommended by the manufacturers, although this advice remains controversial. Moreover, both drugs are contraindicated in patients with poor renal function and the pharmacological actions of these agents are irreversible in the event of bleeding.<sup>6</sup>

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- 1 National Institute for Health and Care Excellence. Head injury. (Clinical guideline CG176.) 2014. [www.nice.org.uk/guidance/cg176](http://www.nice.org.uk/guidance/cg176).
- 2 National Institute for Health and Care Excellence. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. (Clinical guideline CG144.) 2012. [www.nice.org.uk/guidance/cg144/chapter/1-guidance](http://www.nice.org.uk/guidance/cg144/chapter/1-guidance).
- 3 Keeling D, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin—fourth edition. *Br J Haematol* 2011;154:311-24.
- 4 Medicines and Healthcare Products Regulatory Agency. Warfarin: changes to product safety information. 2009:11. [www.mhra.gov.uk/safety-public-assessment-reports/CON079304](http://www.mhra.gov.uk/safety-public-assessment-reports/CON079304).
- 5 Watson HG, Baglin T. A comparison of the efficacy and rate of response to oral and intravenous vitamin K in reversal of over-anticoagulation with warfarin. *Br J Haematol* 2001;115:145-9.
- 6 Baglin T. Clinical use of new oral anticoagulant drugs: dabigatran and rivaroxaban. *Br J Haematol* 2013;163:160-7.

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## Table

Table 1 | Summary of the management of supra-therapeutic warfarin levels<sup>3,4</sup>

INR	Not bleeding	Bleeding*
3.0-5.0	Reduce warfarin dose; re-check INR in 48 hours†	Minor: stop warfarin and apply first aid measures; give 1-3 mg intravenous vitamin K if bleeding does not stop with such measures
5.0-8.0	Omit warfarin until INR <5.0, then start reduced dose; re-check INR in 48 hours†	
>8.0	Omit warfarin, give 1-5 mg oral vitamin K; re-check INR in 24 hours†	Limb or life threatening: refer to secondary care for warfarin reversal

\*The management of all types of bleeding applies to all INR categories.

†Advice on when to recheck INR values is based on the authors' experience and the half life of warfarin and vitamin K.

INR=international normalised ratio.