Oral anticoagulation

Oral anticoagulation is indicated for prevention and treatment of thromboembolism (deep venous thrombosis and pulmonary embolism) and for primary and secondary prevention of stroke in patients with atrial fibrillation; see also Stroke prevention p 80 and Atrial fibrillation p 82. For information on the use of oral anticoagulants for the prevention and treatment of thromboembolism, see *AMH*.

Optimal anticoagulation is associated with lowering the risk of stroke and minimising bleeding. Patient education, communication of results and dose decisions (both with the patient and between health care settings), and regular follow-up are important aspects of management.

Increasingly, non-vitamin K oral anticoagulants (NOACs, eg dabigatran, apixaban, rivaroxaban) are preferred to warfarin because of fewer food and drug interactions, lower risk of intracranial haemorrhage (ICH) and no requirement for routine laboratory monitoring. However, in trials when the INR was well controlled, dabigatran, apixaban or rivaroxaban were not superior to warfarin in reducing the risk of stroke or systemic embolism, and evidence for NOACs in some situations (eg patients with valvular heart disease, severe renal or hepatic impairment, antiphospholipid syndrome) is lacking.

Warfarin

Starting treatment

Local guidelines for starting warfarin may exist; for one example, see Table 19 – Warfarin: age-adjusted initiation protocol p 254.

The target INR range is 2–3 for all indications other than heart valves (for heart valves, seek specialist advice). The goal is to attain a stable therapeutic INR without over-anticoagulation.

warfarin

Usual maintenance dose is 1–10 mg daily, taken at the same time each day, adjusted according to INR.

Monitoring

Whilst the need for INR monitoring is often considered an impediment to using warfarin, it can be a useful tool to assess adherence and treatment efficacy.

Determine INR shortly before starting warfarin, and then daily until INR is stable in the target range; then monitor each week. In the long term, determine INR at regular intervals of no more than 4 weeks.

The full effect of a dose change is not seen for 2–3 days.

Determine INR more frequently if there are changes in the patient's condition, including intercurrent illness (eg heart failure, hepatic disease, GI disturbances, infections, thyroid disorders), changes in concurrent drug administration, a major change in the diet (eg green leafy vegetable consumption) or in the amount of alcohol consumed.

Table 5 – Warfarin dose changes to maintain INR 2–3

INR	Dose change based on weekly intake of warfarin
<1.5	increase by 15% per week
1.6–1.9	increase by 10% per week
2–2.9	unchanged
3–3.9	decrease by 10% per week
4–4.9	hold 1 dose, then restart at dose reduced by 10% per week

Managing out-of-range INRs

Dosing algorithms can be used to manage out-of-range INRs and increase the time in therapeutic range (TTR); for an example, see Table 5 – Warfarin dose changes to maintain INR 2–3 p 76.

For INR >5 follow the Australian consensus guidelines; see Useful resources p 79.

Adherence

Encourage patients to record their dose and INR results using a calendar, 'anticoagulant book', or the NPS MedicineWise Warfarin Dose Tracker (see Useful resources p 79).

Tracking INR results provides an indication of the TTR; generally, a TTR >70% indicates good INR control.

For patients with low TTR (eg <70%) despite good adherence, or due to unavoidable drug interactions, consider switching to a NOAC; see *AMH* for guidance on switching between anticoagulants.

Some patients have no clear benefit in switching to one of the NOACs, eg patients with a TTR >70% or with a history of non-adherence. In patients where adherence is a concern, arrange more frequent reviews and INR monitoring, in addition to further education and counselling.

Non-vitamin K oral anticoagulants (NOACs)

NOACs are also known as direct-acting oral anticoagulants (DOACs). See also the Oral anticoagulants table, as well as apixaban, dabigatran and rivaroxaban, in *AMH*.

Starting treatment

NOACs have a relatively short onset of action and can be started at a fixed dose based on indication.

Before starting treatment, use the Cockcroft-Gault equation to estimate CrCl; and also consider patient-specific factors that may affect the starting dose, eg low body weight (<60 kg), advanced age (>75 years), history of bleeding, concomitant medications.

Chronic kidney disease

Apixaban or rivaroxaban are preferred when CrCl 30–50 mL/ minute.

If anticoagulation is necessary in patients with CrCl 15–30 mL/ minute, consider apixaban, rivaroxaban or warfarin; seek specialist advice.

Monitoring

Although routine laboratory monitoring is not used with NOACs, clinical monitoring is essential: ask the patient to report signs of bleeding; assess renal and hepatic function at least annually (more frequently in some situations, eg chronic kidney disease (below), multiple comorbidities, acute illness).

Chronic kidney disease

In patients with CrCl <60 mL/ minute, the frequency of monitoring (in months) can be guided by the CrCl divided by 10, eg if CrCl is 30 mL/ minute, reassess renal function and the dose every 3 months.

Adherence

The anticoagulant effect of a NOAC declines 12–24 hours after the last dose; consequently, missed doses can result in inadequate anticoagulation, increasing the risk of thrombotic events.

Discuss the importance of adherence with the patient and make a plan for missed doses, eg take the missed dose as soon as the patient remembers but exclude the dose if there is:

- less than 6 hours before the next dose of apixaban or dabigatran
- less than 12 hours before the next dose of rivaroxaban.

Safety considerations

Contraindications to oral anticoagulation include severe active bleeding or disease states with an increased risk of severe bleeding (eg severe uncontrolled hypertension, severe hepatic disease, severe thrombocytopenia, alcoholism); see *AMH* for drug-specific contraindications.

Risk factors for major bleeding in patients on oral anticoagulants include:

- previous severe bleed
- advanced age
- polypharmacy (increased risk of drug interactions)
- recent drug changes
- occult GI lesions
- history of falls
- intercurrent illness
- previous stroke
- change in diet or poor nutrition (especially with warfarin).

Bleeding may be more of a concern in older people as they often have less physiologic reserve for responding to acute stress, such as GI haemorrhage.

Risk factors for anticoagulant-associated ICH are more prevalent in older people, eg fragile intracranial blood vessels, high BP, amyloid angiopathy, and factors predisposing to excessive anticoagulation such as confusion, dementia and alcoholic liver disease.

Bleeding rates in randomised controlled trials

In trials, NOACs and warfarin had similar rates of major bleeds when INR was well controlled.

Compared with warfarin, rates of ICH were significantly lower with all NOACs; rates of GI bleeds were increased with dabigatran and rivaroxaban, but decreased with apixaban.

Falls and intracranial haemorrhage

Risk of falls and subsequent bleeding events (eg ICH) is a common reason for not prescribing oral anticoagulants in the elderly. However, while there are no clear guidelines for using oral anticoagulants in patients who fall regularly, some evidence suggests that falls risk should not preclude their use. Base an assessment of anticoagulant use on risk of falls or stroke, while also considering comorbidities, life expectancy and patient preference.

Manage risk factors for ICH where possible, eg treat uncontrolled hypertension and implement fall prevention strategies (p 52).

Over-anticoagulation and major bleeding

Follow local protocols where they exist; management depends on the site and severity of bleeding, and coagulation status. Depending on the situation, supportive measures (eg blood products, hydration) and reversal agents may be required.

Reversal agents are available for warfarin (see vitamin K in *AMH*) and dabigatran (see idarucizumab in *AMH*) but not for apixaban or rivaroxaban.

Interactions

Drug interactions with oral anticoagulants may either increase the risk of bleeding or decrease efficacy; see drug interactions for warfarin, dabigatran, apixaban or rivaroxaban in *AMH*.

Complementary medicines are best avoided in people taking oral anticoagulants as there is often little or no information about safety of combinations.

Warfarin interacts with many drugs; monitor INR closely and watch for signs of bleeding when starting, stopping or changing dose of other drugs.

NOACs do not have as many reported interactions as warfarin, however, close clinical monitoring for signs of bleeding is still required when starting, stopping, or changing the dose of other drugs, especially because of the lack of regular laboratory monitoring.

Practice points

- encourage patients to report signs of bleeding, eg nose bleeds, unexplained bruising, red or dark brown urine, or red or black faeces
- encourage patients to avoid excessive or intermittent alcohol consumption (especially if taking warfarin)
- use paracetamol for pain relief; avoid NSAIDs as they increase the risk of bleeding
- in patients with impaired cognition, supervision is essential to ensure that instructions can be understood and implemented; consider stopping oral anticoagulation if adherence cannot be ensured, eg by a carer
- for information on stopping oral anticoagulants before surgery, see warfarin, dabigatran, apixaban or rivaroxaban in *AMH*

Warfarin

- avoid alternate-day dosing regimens where possible as they can be confusing
- encourage patients to eat a balanced and consistent diet when taking warfarin; major changes in eating habits, especially in dietary vitamin K intake, eg from green leafy vegetables, may cause changes in INR
- advise patients to take only one brand of warfarin (Coumadin® or Marevan®) as they are not interchangeable

Dabigatran

- dabigatran should not be repackaged in dose administration aids (such as tablet organisers or weekly medication packs) unless it can be done without removing it from its original packaging or it is stored in a refrigerator (for up to 28 days)
- capsules should not be opened, chewed or crushed as this increases bioavailability and risk of bleeding

Useful resources

NPS MedicineWise. Resources for consumers: *www.nps.org.au/consumers/warfarin*

NPS MedicineWise: *Warfarin Dose Tracker*

Guidelines for warfarin reversal: *www.mja.com.au/journal/2013/198/4/update-consensus-guidelines-warfarin-reversal*