GUIDELINE

Maintenance of Warfarin Therapy at an Anticoagulation Clinic

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The objectives of an anticoagulation clinic are to:

- Optimise control of a patient's anticoagulation
- Educate patients, because warfarin has a narrow therapeutic range.

Patients should be referred to an anticoagulation clinic only after being adequately anticoagulated. The referring doctor should perform any adjustments to the initial dosage of warfarin. The general care of the patient remains the responsibility of the referring doctor. Any bleeding and thrombo-embolic events must be reported and managed by the referring doctor and/or referred to an appropriate specialist.

1. Contraindications to warfarin therapy

Ensure there are no contraindications to warfarin therapy. The absolute contraindications to warfarin are:

- The presence of severe bleeding
- Non-compliance, and
- The first trimester of pregnancy and from 34 - 36 weeks onwards.

Warfarin is associated with a dose-dependent (>5 mg[1]) teratogenic effect between 6 and 12 weeks'gestation.[2,3] In addition warfarin therapy is associated with an increased risk of miscarriage and prematurity, and of fetal bleeding (including intracranial haemorrhage resulting in brain damage) at any time during pregnancy but in particular at delivery.[4]

Warfarin is therefore generally avoided during pregnancy, and patients are given a low-molecular-weight heparin (LMWH) that does not cross the placenta.[5] A specialist with expertise in this field should monitor pregnant patients.

Warfarin[6] and heparins can safely be administered to nursing mothers.

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In the absence of controlled trials, it is difficult to make reliable recommendations about optimal anticoagulant therapy in pregnant patients with mechanical prosthetic valves. The use of closely monitored twice-daily LMWH therapy throughout pregnancy (anti-Xa level 1 - 1.2 U/l) is favoured.[7,8]

Some relative contraindications include:

- Uncontrolled hypertension (i.e. systolic blood pressure >180 mmHg, diastolic >100 mmHg)
- Severe liver disease, and
- Recent surgery involving the nervous system, spine or eye.

2. Target INR and duration of therapy

The goal of anticoagulant therapy with warfarin is to administer the lowest effective dose to maintain the target international normalised ratio (INR).

- The target INR is 2.5 (range 2.0 - 3.0) for most indications, including:
  - Deep-vein thrombosis treatment and prophylaxis
  - Pulmonary embolism
  - Cardiac conditions, including atrial fibrillation, left ventricular systolic dysfunction, the first 3 months following anterior myocardial infarction, mural thrombus.
- The target INR is 3.0 (range 2.5 - 3.5) for the following indications:
  - Most patients with mechanical prosthetic valves. However, a range of 2.0 - 3.0 is recommended for low-risk patients with bi-leaflet mechanical valves (such as the St Jude Medical device) in the aortic position.[9]
  - Patients with warfarin failure.

3. Monitoring the INR at initiation of therapy

At the initiation of therapy, the INR should be monitored initially after 2 - 3 days and then daily until a therapeutic range is achieved.

Frequent adjustments of dosage are not recommended because changes in warfarin dosage may take several days to affect the INR.

4. Monitoring the INR once stable

Once stable, the INR should be monitored every 1 - 4 weeks.[10]

- Patients on a chronic, stable dose of warfarin should be tested every 4 weeks.
- Patients with an unstable dose response will require more frequent monitoring (every 1 - 2 weeks).
- More frequent monitoring is indicated for patients with mechanical prosthetic valves in the first postoperative month. This is a period during which the patient is at high risk for thrombo-embolism, and the target INR should be maintained.[2,11]
- More frequent monitoring is indicated when medications are changed, when there is intercurrent illness, and in the pre- and postoperative periods.

5. Fluctuations of the INR

Fluctuations of the INR outside the desired target range should be investigated. The following causes should be considered:

- Patient compliance and patient error
- Change in warfarin dosage
- Intercurrent illness
- Dietary interactions
- Drug interactions
- Liver and renal dysfunction
- Patients >60 years, who may require a lower warfarin dose as the clearance of warfarin decreases with age.[10] In addition, elderly patients are more likely to have medical conditions or concurrent drug use that may influence the INR.[12] These patients should be carefully monitored.
- Laboratory error, viz.:
  - Correct citrate concentration (3.2%)
  - Adequate filling of tube
  - The first draw specimen should not be used for anticoagulation studies
  - The sample must be processed within 4 hours of collection.

The recommended dosage adjustments for patients with an INR target range of 2.0 - 3.0 are tabulated in Appendix 1. NB: These are general guidelines and management should be individualised according to the bleeding risk.

6. The INR record card

Patients should be monitored with an INR record card.

7. Duration of anticoagulant therapy

The duration of anticoagulant therapy should be individualised according to the patient's thrombotic risk.[13]

The indications for a patient's anticoagulant therapy should be reviewed 6-monthly by the referring doctor.

In general:

- Patients with venous thrombo-embolism (VTE) with a reversible risk factor should be treated for at least 3 months.[14] A d-dimer level should be checked before stopping warfarin therapy. Prolonged warfarin therapy may be indicated for patients with persistently raised d-dimers.[15,16]
- Patients with an idiopathic deep-vein thrombosis (DVT) and all patients with pulmonary emboli should be treated for at least 6 months.[17]
- Patients with recurrent DVTs or persistent risk factors may benefit from longer anticoagulation. However, anticoagulant treatment for >2 years has been shown to be associated with an increased risk of bleeding.[14,18]

8. Patient education (see Appendix 2)

- Warfarin tablets are taken once a day (usually in the evening), preferably at the same time. Some patients, however, may find it more convenient to take their dose in the morning. *INR tests* should be performed in the morning. This is merely for the convenience of adjusting the dose within 12 hours of the test.
- Importance of therapy and the duration of required anticoagulation (as indicated by the treating/referring doctor).
- Compliance.
- Bleeding and thrombotic complications; and when to come to hospital.
- The importance of INR monitoring.
- Consistent vitamin K content of the diet.
- Review of current medications.
- Drug and illness interactions.

9. Dental procedures

- In most cases, no change in the intensity of anticoagulation is needed. There are a number of documented cases of embolic events in patients whose warfarin therapy was discontinued for dental treatment.[2] The INR can be lowered to a target of 2.0.[19,20]
- Low risk of bleeding – continue warfarin.
- High risk of bleeding – refer to the referring doctor to consider discontinuation of warfarin. If necessary discuss with the cardiologist whether it is safe to discontinue.
- Cyclokapron tablets 1 g crushed and dissolved in half a glass of water used as a mouthwash 2 hours preoperatively then 3 times a day postoperatively, will assist in controlling local bleeding, without the need to interrupt warfarin.[21]

10. Surgical procedures

- Assess the patient's risk for venous thrombo-embolism in relation to the underlying condition for which warfarin therapy is required and the risk of bleeding associated with the surgical procedure.
- After warfarin therapy is stopped, it takes about 4 days for the INR to reach 1.5. Once the INR reaches 1.5, surgery can safely be performed.
- After warfarin therapy is restarted, it takes about 3 days for the INR to reach 2.0.[22]
- If warfarin is withheld for 4 days before surgery and treatment is restarted as soon as possible after surgery, patients can be expected to have a sub-therapeutic INR for approximately 4 days. The risk of thrombo-embolism associated with a few days of peri-operative sub-therapeutic anticoagulation is generally very low. However, the risk of bleeding associated with postoperative intravenous heparin therapy is often relatively high.

Low risk[9] – patients with conditions such as atrial fibrillation (without stroke) and venous thrombo-embolism for >3 months:

- If a patient's INR is between 2.0 and 3.0, 4 scheduled doses of warfarin should be withheld to allow the INR to fall to 1.5 or less before surgery. Warfarin should be withheld for a longer period if the INR is normally maintained above 3.0 or if it is necessary to achieve a lower level depending on the type of surgery.[23]
- The INR should be measured a day before surgery.
- Patients on warfarin for more than 3 months do not need pre-operative heparin, unless surgical prophylaxis is indicated. If surgical prophylaxis is required, start LMWH (e.g. enoxaparin 40 mg subcutaneously daily) or unfractionated heparin (5 000 U subcutaneously daily) until 12 - 24 hours before the procedure.
- Postoperative prophylaxis (e.g. enoxaparin 40 mg subcutaneously daily) is recommended until warfarin therapy is re-established and the INR is above 2.0. The original dose of warfarin can be started 8 - 12 hours postoperatively.

High-risk patients[23-25] with conditions such as mechanical valve replacements and venous thrombo-embolism for <3 months:

- Interruption of anticoagulant therapy should be avoided.[26]
- Elective surgery should be avoided in the first month after an acute episode of venous or arterial thrombo-embolism.
- Pre- and postoperative prophylaxis is indicated while the INR is below 2.0.
- If the patient is on anticoagulant therapy for a venous thrombo-embolism for more than 1 month but less than 3 months, pre-operative prophylaxis is not indicated unless additional risk factors for recurrent venous thrombo-embolism are present.
- For patients with a low risk of bleeding, warfarin therapy can be continued at a lower dose. This can be achieved by halving the warfarin dose 7 days pre-operatively.[27]
- The INR should be measured a day before surgery. Aim for a range of 1.5 - 2.0.[2] The desirable INR will depend on the type of surgery.
- If the INR is <1.5 prior to surgery, start unfractionated heparin (5 000 - 10 000 U as an intravenous infusion in 200 ml normal saline at 33 ml/h). LMWH (enoxaparin 1 mg/kg subcutaneously twice a day) can also be used.[8,28] LMWHs should be administered with caution in patients with renal failure, and anti-Xa monitoring is mandatory.
- Partial thromboplastin time (PTT) monitoring is indicated 12-hourly to monitor unfractionated heparin. Aim to achieve a PTT of 1.5 - 2 times the normal PTT.
- Continuous intravenous heparin therapy should be discontinued at least 6 hours before surgery. This should be individualised and determined by the risk of bleeding associated with the surgical procedure.
- Heparin therapy should not be restarted until 12 hours after major surgery and should be delayed even longer if there is any evidence of bleeding from the surgical site. Unfractionated heparin should be restarted without a bolus, at no more than the expected maintenance infusion rate.[29] The PTT should be checked 12 hours after restarting therapy to allow time for a stable anticoagulant response.

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Appendix 1: Dosage adjustments for patients on maintenance warfarin therapy[9] (target INR 2.0 - 3.0)

INR	Dosage adjustment
<1.5	Increase weekly dose by ~20%
1.5 - 1.9	Increase weekly dose by ~10%
2.0 - 3.0	No change
3.1 - 3.9	No change. Recheck weekly If persists decrease weekly dose by ~10 - 20%
4.0 - 5.0	Omit one dose Decrease weekly dose by ~10 - 20% and recheck in 5 - 7 days

5.0 - 9.0 without significant bleeding	Stop warfarin therapy Consider oral low-dose vitamin K 1 - 2.5 mg po (0.1 - 0.25 ml Konakion) and monitor daily[30,31] Vitamin K may need to be repeated Monitor INR every 2 - 3 days until in the therapeutic range Once INR in target range restart warfarin Decrease weekly dose by ~10 - 20% and recheck in 5 - 7 days
>9.0 without significant bleeding	Stop warfarin therapy Give oral vitamin K 5 mg po (0.5 ml Konakion)[31,32] Vitamin K may need to be repeated Monitor INR daily until therapeutic Once INR in target range restart warfarin Decrease weekly dose by ~20% and recheck in 3 - 5 days Monitor frequently until stable
Prolonged INR and significant bleeding	Stop warfarin therapy Call doctor Give prothrombin complex concentrates (50 U/kg) or fresh-frozen plasma (15 - 20 ml/kg) or Bioplasma FDP Give vitamin K 1 - 2 mg IVI slowly Monitor INR daily

Important considerations:

- All patients with an INR >10.0 and/or significant bleeding must be referred to the referring doctor.
- The target INR in patients with mechanical valve replacements is 2.5 - 3.5.
- Avoid the use of IV vitamin K in patients with mechanical valve replacements because of the risk of valve thrombosis.[2] Oral vitamin K 1 - 2 mg (0.1 - 0.2 ml Konakion) can be administered to such patients with an INR >10.0 or at high risk of bleeding.[33,34] Alternatively, these patients should be admitted to hospital for monitoring while the INR falls spontaneously.
- All patients with mechanical valve replacements and complications should be referred to the referring cardiologist.

Appendix 2: Information for patients on warfarin therapy

What is warfarin?

Warfarin is an oral anticoagulant, which prolongs the time taken for blood to clot. This reduces the possibility of clot formation.

It is prescribed for conditions such as an irregular heart rhythm, artificial heart valves, clotting in veins, or stroke.

Too much warfarin may lead to serious bleeding, and too little will not prevent clotting. Warfarin must be taken exactly as prescribed and must be monitored with regular lab tests.

Before you start warfarin treatment:

- Tell your health care professional about all other illnesses you have and all the medicines, including over-the-counter drugs and special diets you are on.
- Many medications such as aspirin,[35,36] ibuprofen (e.g. Brufen and Myprodol) and herbal medicines, such as gingko, increase the effect of warfarin.
- Some sedatives decrease the effect of warfarin.
- For women: tell your health care professional if you are, or are planning to become pregnant. Warfarin can harm the developing fetus.
- If you are breastfeeding, you may safely take warfarin.

During your warfarin treatment:

- **Keepa written record of your target range, INR results and dosage.** This can help you and your health care professional manage your warfarin therapy.
- **Proper use.** Warfarin should be taken once a day, preferably at the same time at night. Store the medication in a cool dry place, away from the reach of children.
- **Regular blood tests are important.** A blood test called an 'INR' is required to determine how much warfarin you need. Because many factors can influence how your body responds to warfarin, you will need to have regular blood tests. Your health care professional will determine the range of INR that is right for you and decide how frequently it should be checked. Normally, the INR is checked at least once a month, but more frequent testing may be appropriate in some situations. Try to have your test performed in the morning so your dose can be adjusted if indicated.
- **Keep the vitamin K content of your diet consistent.** Changes in the amount of vitamin K in your diet can affect the warfarin level. Avoid changes to your normal eating patterns. Continue to eat a balanced diet containing a variety of foods. Limit yourself to a small portion of one of the following vitamin K-rich foods per day: cauliflower, cabbage, broccoli, spinach, Brussels sprouts, avocado pear, liver and marog. One orange or half a glass of orange juice or half a grapefruit may be taken per day.
- **Notifyyour health care professional of any new medications taken.**
- **Avoid heavy or binge alcohol consumption.** Moderate, consistent alcohol intake does not affect warfarin therapy.
- **Other precautions.** Avoid any activity or sport that may result in a serious fall or other injury. Use a soft toothbrush, and brush and floss gently to prevent bleeding from the gums.

- **Inform your health care professional if you:**
  - Develop side-effects (see below)
  - Miss a dose
  - Change your diet or medications
  - Become ill
  - Have a surgical or dental procedure planned
  - Plan to travel.
  - If you become pregnant, contact your health care professional immediately.
- **Side-effects.** Bleeding is the most serious potential side-effect of warfarin. If you experience any of the following symptoms, call your health care professional:
  - Red or dark brown urine
  - Red or black stool
  - Severe headache or dizzy spells
  - Unusual weakness
  - Excessive menstrual bleeding
  - Prolonged bleeding from gums or nose
  - Unusual pain, swelling or bruising
  - Dark, purplish or mottled fingers or toes
  - Vomiting or coughing up blood.
- **If you plan to travel:** Carry identification explaining the reason you are taking warfarin (including the target INR, and current dosage). Carry a copy of your warfarin record sheet. Make sure you have enough warfarin tablets. Carry your medications with you at all times. Try to maintain your usual diet.

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