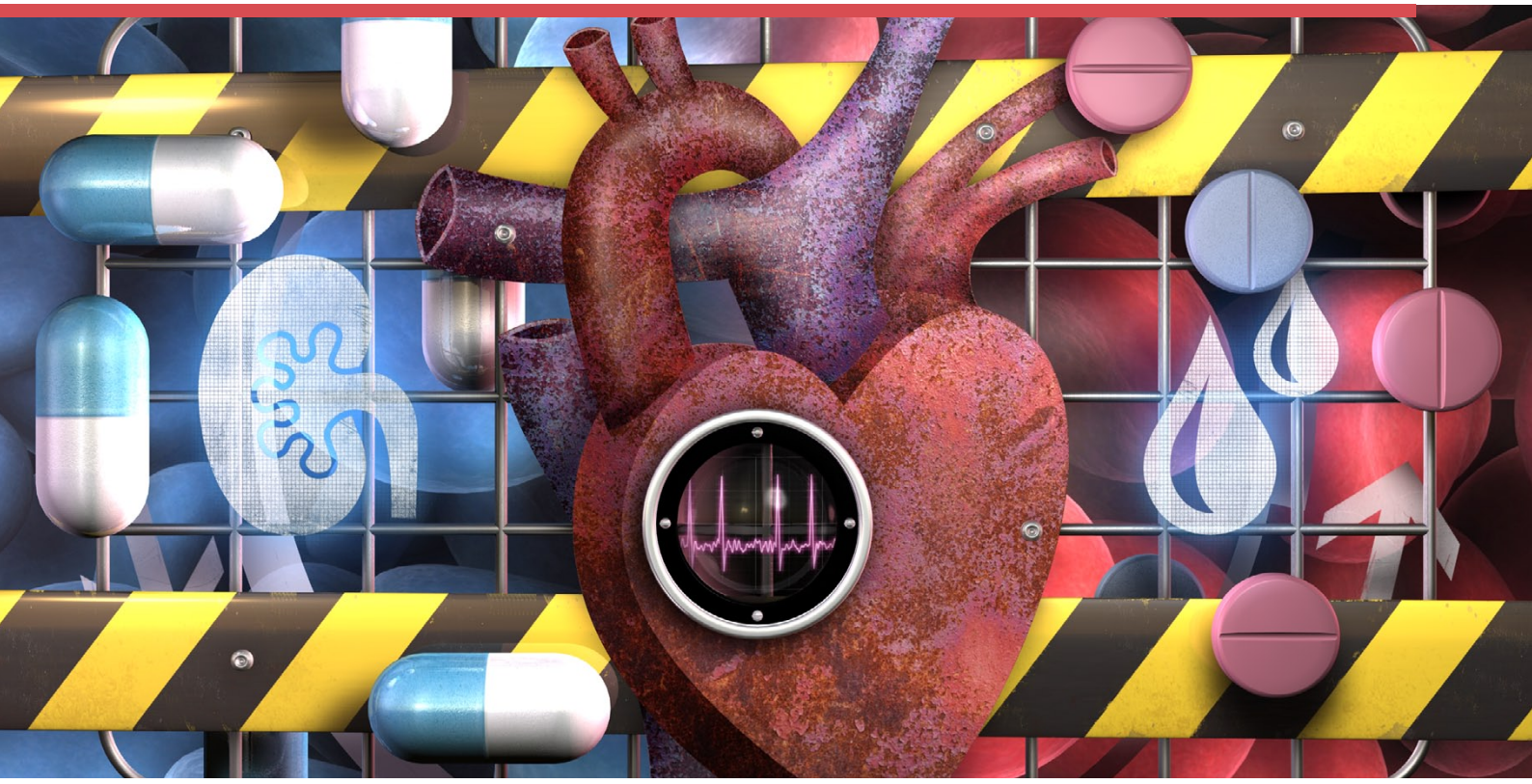

The safe and effective use of dabigatran and warfarin in primary care

Patients taking oral anticoagulants require appropriate management in order to receive the maximum benefit from treatment with the minimum risks. This includes deciding whether dabigatran or warfarin is most appropriate, managing risk factors for bleeding, ensuring treatment adherence and monitoring for adverse effects. Long-term treatment with dabigatran requires ongoing monitoring of renal function. Warfarin doses often need to be adjusted to optimise the time patients spend within the therapeutic range. As co-morbidities emerge over time a discussion about changing anticoagulants may be beneficial.

KEY MESSAGES:

- Choose the most appropriate anticoagulant to maximise patient safety: dabigatran is often more convenient than warfarin, however, a number of patients are unable to take dabigatran, e.g. those with renal impairment or prosthetic heart valves
- Risk factors for bleeding should be identified and managed, where possible, before anticoagulation
- Before starting dabigatran, test the patient's renal function and repeat tests at least every 12 months thereafter. Some patients require more frequent monitoring depending on age and general health; those with declining renal function may be safer taking warfarin
- Warfarin is less likely to cause gastrointestinal adverse effects than dabigatran and it may be preferred by patients with a history of dyspepsia

Manage risk factors before anticoagulant treatment is initiated

Modifiable risk factors for bleeding should be managed before treatment with an anticoagulant is initiated, e.g. uncontrolled hypertension, alcohol use greater than eight standard drinks per week.[1] The HAS-BLED prediction tool* can be used to assess bleeding risk in patients with atrial fibrillation.[1]

Conduct a review to see if the patient is taking any medicines that might increase their risk of bleeding, e.g. over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs). This should also include checking for prescription medicines initiated in secondary care. For example antiplatelets (e.g. aspirin, clopidogrel or ticagrelor) may be prescribed following admission for an acute coronary syndrome or rivaroxaban may be initiated after surgery.

* See "An update on managing patients with atrial fibrillation" for further information on HASBLED: **www.bpac.org.nz/2017/af.aspx**

Testing before treatment is initiated

Before initiating anticoagulant treatment, investigations should be performed to assess for contraindications or risk factors for bleeding:[2]

- Full blood count – platelets to exclude thrombocytopaenia, haemoglobin to assess for anaemia
- Coagulation screen – APTT ratio to assess for bleeding or clotting disorders, INR for baseline
- Creatinine and electrolytes – to assess renal function
- Liver function tests

N.B. Many primary care clinicians may not currently request a coagulation screen before starting a patient on dabigatran or warfarin, but this is regarded as best practice.[2]

Chronic kidney disease (CKD) is associated with an increased risk of bleeding in patients taking anticoagulants,[1,3] particularly dabigatran. Renal testing is recommended at least annually for patients taking anticoagulants to detect CKD.[1] Declining renal function may necessitate a reduction in dose or even treatment withdrawal for patients taking dabigatran or increased INR monitoring and dose adjustments for those taking warfarin.[1]

Choosing between warfarin and dabigatran

The decision between initiating dabigatran or warfarin is influenced by indication and the patient's characteristics, e.g. dabigatran should not be used in patients with a prosthetic heart valve or with a creatinine clearance less than 30 mL/min.[4] Dabigatran is generally viewed as being more convenient than warfarin as monitoring of anticoagulation is not required, however, other factors should also be considered when discussing the advantages and disadvantages of dabigatran or warfarin with patients (Table 1).

Dabigatran: initiating and monitoring treatment

Dabigatran was the first direct oral anticoagulant (DOAC) subsidised on the New Zealand Pharmaceutical Schedule. Other DOACs available in New Zealand are rivaroxaban, which is subsidised with Special Authority approval for the short-term prevention of venous thromboembolism following major joint/orthopaedic surgery and apixaban, which is not subsidised.

Dabigatran etexilate is a prodrug which is converted to dabigatran after it is absorbed.[6] The active compound prevents platelet aggregation by binding directly to thrombin.[6,8] Anticoagulation with dabigatran occurs rapidly compared to warfarin.[8] Peak plasma concentrations are achieved within two hours of an oral dose, followed by a decrease in concentration over the next four to six hours.[8] With twice-daily dosing the elimination half-life of dabigatran is 12 – 17 hours.[8] Two to three days of treatment is required for patients to achieve steady-state levels of dabigatran.[8]

Table 1: The advantages and disadvantages of dabigatran compared to warfarin.[5–7]

The advantages of dabigatran compared to warfarin	The disadvantages of dabigatran compared to warfarin
■ Anticoagulation is relatively rapid after initiation, i.e. hours compared to days with warfarin ■ There are fewer interactions with other medicines and foods compared to warfarin ■ Monitoring of anticoagulation is not required ■ Dabigatran 150 mg, twice daily, provides better protection against stroke and systemic embolism (1.1% per year) compared to warfarin (1.7% per year),* without a significant increase in the risk of major bleeding (other than gastrointestinal bleeding) ■ Dabigatran 110 mg, twice daily, is equally effective as warfarin at preventing stroke and systemic embolism with fewer major bleeds (2.7% per year) compared to warfarin (3.4% per year)	■ Renal function needs to be monitored and caution is required in patients with progressive kidney disease or at risk of acute kidney injury ■ Adherence to twice daily dosing is required for treatment to be effective for most indications ■ Dyspepsia is approximately twice as common, compared to patients taking warfarin ■ Dabigatran 150 mg, twice daily, is associated with an increased risk of major gastrointestinal bleeding (1.5% per year) compared to warfarin (1.0% per year). The risk in patients taking dabigatran 110 mg, twice daily, is not increased. ■ Dabigatran is associated with an increased risk of myocardial infarction (1.16%) compared to warfarin (0.72%);† the risk is greater in patients taking dabigatran 150 mg, twice daily.

* If patients are able to achieve good control of INR with warfarin, e.g. within the therapeutic range 70% of the time, dabigatran provides little or no additional protection against stroke or systemic embolism.

† This was a meta-analysis of 14 trials, therefore an event rate was not calculated

Indications and contraindications for dabigatran

Indications for dabigatran have widened and it is now indicated in New Zealand for the:[4, 9]

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors: previous stroke, transient ischaemic attack or systemic embolism, left ventricular ejection fraction < 40%, symptomatic heart failure, age ≥ 75 years, age ≥ 65 years with coronary artery disease, hypertension or diabetes. N.B. all of these risk factors, with the exception of left ventricular ejection fraction, are assessed as part of calculation of the CHA_2DS_2-VASc score* to determine whether anticoagulation is required in patients with atrial fibrillation.
- Prophylaxis of venous thromboembolism following major orthopaedic surgery
- Treatment of deep-vein thrombosis or pulmonary embolism following at least five days of parenteral anticoagulant treatment
- Prevention of recurrent deep-vein thrombosis or pulmonary embolism

Dabigatran is contraindicated in patients with active bleeding or at significant risk of major bleeding, a prosthetic heart valve or severe renal impairment, i.e. a creatinine clearance less than 30 mL/min.[4] Dabigatran is not recommended in patients with mitral stenosis, e.g. following rheumatic heart disease, as the safety and efficacy of treatment is unknown.[1]

* For further information on CHA_2DS_2-VASc, see: **www.bpac.org.nz/2017/af.aspx**

Assess renal function before starting dabigatran

Renal function should be assessed before prescribing dabigatran because the majority of the medicine (85%) is excreted unchanged by the kidneys and bleeding is more likely in patients with reduced renal function.[8] For example, in patients with moderately impaired renal function, i.e. creatinine clearance of 30 – 50 mL/min, the exposure to dabigatran is approximately 2.7 fold higher compared to patients with normal renal function.[4]

Use the Cockcroft-Gault equation for patients with reduced renal function

The Cockcroft-Gault equation is used to calculate creatinine clearance (in mL/min) and guide dabigatran dosing in preference to the estimated glomerular filtration rate (eGFR – mL/min/1.73m^2) supplied by the laboratory. This is because the Cockcroft-Gault equation was used in the original Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study and therefore dabigatran dosing has only been validated using these calculations.[4, 5] Significant variations can occur between estimates of renal function provided by Cockcroft-Gault and eGFR in people who are obese or very slim or in older people with reduced muscle mass. It is therefore good practice to confirm the correct dosing of dabigatran using the Cockcroft-Gault equation, particularly in patients with borderline eGFR values or in older patients.

A creatinine clearance calculator is available from the NZF: **http://nzf.org.nz/nzf/resource/Creatinine%20Clearance%20Calculator.htm**

Dabigatran dosing is determined by indication

The recommended dose of dabigatran differs depending on the indication, due to the different doses used in the original trials where safety and efficacy were established (Table 2). There are two standard doses for the prevention of stroke and systemic embolism: 150 mg, twice daily and 110 mg, twice daily, with the lower dose preferred for patients at increased risk of bleeding.

Regular monitoring of renal function is required

Patients taking dabigatran should have their renal function assessed every six to 12 months.[1, 10] More frequent monitoring is recommended in patients with reduced renal function, i.e. a creatinine clearance less than 50 mL/min, or in situations where renal function may decline rapidly e.g. dehydrating illness, initiation of a diuretic or hypovolaemia.[10] Decreasing renal function or increasing age may require a dose reduction or a switch to warfarin (see below).[10]

Managing dyspepsia associated with dabigatran use

Dyspepsia is reported by 3% to 12% of patients taking dabigatran, depending on the dose and the length of treatment.[6] Gastrointestinal symptoms are often transient and patients can be encouraged to persist with treatment.[11] Taking dabigatran with food and a glass of water can prevent the onset of dyspepsia, which in turn reduces the risk of rare complications such as contact ulceration of the oesophagus.[11, 12] A trial of treatment with a proton pump inhibitor (PPI) or an H2-receptor antagonist should be considered in patients with persistent dyspepsia.[11] Gastrointestinal bleeding is increased in patients taking dabigatran, in a dose-dependent manner.[13] The use of PPIs reduces this risk and prophylactic treatment with a PPI may be appropriate in patients taking dabigatran who have a history of peptic ulcers or gastrointestinal bleeds.[13] A switch to warfarin may be appropriate if the patient finds the adverse effects of dabigatran to be intolerable (see below).

Dabigatran is currently listed on Medsafe's M^2 Medicines Monitoring programme and prescribers are encouraged to report any adverse reactions to the Centre for Adverse Reactions Monitoring (CARM): **https://nzphvc.otago.ac.nz/report**

Table 2: Recommended dosing regimens for dabigatran by indication.* [9]

Indication	Dose	Duration
Prevention of stroke and systemic embolism in non-valvular atrial fibrillation	Dabigatran, 150 mg, twice daily OR Dabigatran 110 mg, twice daily, for patients: ■ aged ≥ 80 years; or ■ with a creatinine clearance of 30 – 50 mL/min; or ■ aged 75 – 80 years with a high risk of bleeding and a low risk of thromboembolism	Ongoing
Treatment of deep-vein thrombosis and pulmonary embolism	Dabigatran 150 mg, twice daily, after at least five days of parenteral anticoagulant treatment	Up to six months
Prevention of recurrent deep-vein thrombosis or pulmonary embolism	Dabigatran, 150 mg, twice daily	Ongoing
Prevention of venous thromboembolism following major joint surgery	Dabigatran 110 mg, one – four hours after surgery, then 220 mg, once daily OR 150 mg, once daily, if creatinine clearance 30 – 50 mL/min	For ten days following knee surgery and 28 – 35 days following hip surgery

* In practice lower doses may be prescribed according to clinical experience and patient factors such as age, renal function and frailty

Managing bleeding in patients taking dabigatran

The risk of bleeding in patients taking dabigatran is reduced by appropriate dosing and monitoring.

Patients with minor cuts and abrasions can be treated in primary care with mechanical compression. Oral tranexamic acid 15 mg/kg, four times daily, may be appropriate in some cases to increase clotting and prevent excessive blood loss.[14] Adequate fluid intake should be encouraged to ensure continued excretion of dabigatran in the urine.[14] Treatment of spontaneous bleeding in a patient taking dabigatran generally requires consultation with a haematology service.

A reversal agent for dabigatran, idarucizumab, has been subsidised for use in hospitals since September, 2016, although it may not be stocked in all hospitals. Idarucizumab is able to rapidly inhibit dabigatran in patients who have uncontrolled bleeding or who need to undergo urgent surgery.[15]

Medicine interactions with dabigatran

There are a number of medicines that have clinically significant interactions with dabigatran. For example, the combination of amiodarone or verapamil with dabigatran increases the amount of dabigatran absorbed, therefore increasing the risk of bleeding. This combination should be avoided or the dose of dabigatran reduced and the patient monitored for signs of bleeding.[16] The risk of bleeding is also increased in patients who are concurrently taking dabigatran and selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors or NSAIDs.[16]

The NZF interactions checker provides details on medicines that interact with dabigatran and their clinical significance. The interactions between dabigatran and amiodarone, verapamil, SSRIs, SNRIs and NSAIDs are all "orange category", which means that dose adjustment or close monitoring is required. Available from: **www.nzf.org.nz**

Changing from dabigatran to warfarin

Declining renal function or adverse effects, e.g. persistent dyspepsia, may require a change from dabigatran to warfarin. The patient's renal function determines when warfarin should be started:[4]

- Creatinine clearance ≥ 50 mL/min – start warfarin three days before stopping dabigatran
- Creatinine clearance 30 – 49 mL/min – start warfarin two days before stopping dabigatran

Warfarin is commenced as per the usual protocol, with the dose depending on risk of thrombosis (see below).

Warfarin: initiating and monitoring treatment

Warfarin is a vitamin K antagonist that prevents the activation of coagulation factors by blocking vitamin K epoxide reductase.[17] Warfarin is rapidly absorbed and concentrations in the blood are maximal 1.5 hours after oral administration.[8, 18] However, it takes several days for the clinical benefits of warfarin to occur.[8, 18]

Indications and contraindications for warfarin

Warfarin is indicated for the:[9]

- Prevention and treatment of venous thrombosis and pulmonary embolism
- Prevention of stroke following myocardial infarction in patients with increased embolic risk
- Prevention of thromboembolism in patients with atrial fibrillation
- Prevention of thromboembolism in patients with prosthetic heart valves

Warfarin is contraindicated in patients with a history of haemorrhagic stroke, clinically significant bleeding (e.g. GI bleed) or risk of bleeding, or after recent child birth.[9]

Managing warfarin in primary care

The monitoring of warfarin treatment requires a systematic and practice-wide process to ensure consistent and optimal care. The target INR for patients treated with warfarin is 2.5, with a clinically acceptable range of 2.0 – 3.0, or 2.5 – 3.5 for patients with mechanical heart valves.[18] A "time in therapeutic range" of ≥ 70% is the goal of treatment,[1] however, this may be difficult to achieve for many patients. Variations in INR should be discussed with the patient to find out what has changed before adjusting the dose of warfarin.

Warfarin treatment may be monitored by a pharmacist as part of the Community Pharmacy-Based Anticoagulation Management Service (CPAMS), or using a home testing device.

Initiating warfarin

The regimen for initiating warfarin varies according to the indication and the patient's clinical characteristics. There are numerous protocols for warfarin initiation and monitoring; it is suggested that clinicians select one that they prefer and use it consistently. A protocol from Queensland Health for initiating patients with atrial fibrillation on warfarin is given as an example in Table 3. *Bestpractice* decision support has a warfarin initiation module and some DHBs have their own protocols.

In general:[18]

- For patients with a lower risk of thrombosis, e.g. with atrial fibrillation, begin treatment with warfarin 3 mg, daily, with baseline and then weekly INR testing for the first two weeks, with subsequent dose adjustments as appropriate
- For patients with a higher risk of thrombosis, e.g. prophylaxis or treatment of deep vein thrombosis, begin treatment with warfarin 5 mg, daily and concurrent subcutaneous LMWH (enoxaparin), with daily INR testing for the first five days (the higher frequency of INR testing is required due to the greater risk of bleeding and concurrent treatment with LMWH)
- Dose adjustments should be at least four days apart to allow for changes in steady state and older patients are more likely to have a slower response
- A system needs to be in place for the patient to record their current dose, any dose adjustment and their next required INR. Prescribing 1 mg tablets may make it easier for the patient to adjust the dose, e.g. from 3 mg to 2 mg.
- A small number of patients may be resistant or hypersensitive to warfarin due to genetic variations
- Once maintenance dosing begins, the frequency of INR testing and any dose adjustments are determined by the proximity of the patient's INR to target and the stability of results. Patients with stable results only require testing every four to six weeks, or possibly every eight weeks. Testing INR more frequently than every three days is unnecessary for dosing but may occasionally be done for safety reasons.

For a warfarin initiation protocol for high risk patients, e.g. for DVT prophylaxis or treatment, see: Guidelines for warfarin management in the community. Queensland Health. Available from: **https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines?a=165945**

Medicines that interact with warfarin

There are a large number of medicines that can interact with warfarin either by altering the INR, e.g. antibiotics, or by increasing the risk of bleeding, e.g. NSAIDs or SSRIs. Medicine interactions can be checked in the New Zealand Formulary.

Check the patient's INR two to three days after initiating a medicine that interacts with warfarin and continue to monitor the patient every two to three days while treatment continues or until their INR is stable.[18]

The NZF interactions checker provides details on medicines and compounds that interact with warfarin and their clinical significance, available from: **www.nzf.org.nz**

Table 3: Example of a protocol for initiating and monitoring warfarin treatment in patients at low risk of thrombosis, e.g. with atrial fibrillation, adapted from Queensland Health (2016).[18]

Initiating warfarin for patients at low risk of thrombosis		
INR test	**INR level**	**Daily warfarin dose** (until next INR)
Day 0 (baseline)	≤ 1.4	3 mg
Day 7	< 1.4	Confirm adherence, check medicine interactions and then increase to 6 mg and check INR on day 11 or 12
	1.4 – 1.5	Increase to 5 mg
	1.6 – 1.8	Increase to 4 mg
	1.9 – 2.1	Maintain 3 mg
	2.2 – 2.5	Reduce to 2.5 mg
	2.6 – 2.7	Reduce to 2 mg
	2.8 – 3.0	Omit one to two daily doses and reduce to 1 mg
	> 3	Stop warfarin and repeat INR in three to five days and restart at 1mg
Day 14 +	Check INR and adjust dose if required (below) Monitor INR every two weeks until INR is in range for two to three consecutive tests, then monitor every four to six weeks or possibly every eight weeks in patients who are stable	
Maintenance dosing of warfarin		
	INR	**Dose adjustment**
	< 1.5	Increase weekly dose by 20% and re-check INR
	1.5 – 1.9	No adjustment – re-check INR in one week and if persistent increase weekly dose by 10%
	2 – 3	No adjustment
	3.1 – 3.9	No adjustment – re-check INR in one week and if persistent decrease weekly dose by 10 – 20%
	4 – 4.9	Omit one dose and decrease weekly dose by 10 – 20% and re-check INR in two to five days
Clinical scenario		**Recommended action**
No bleeding	INR 4.5 – 10	Stop warfarin and consider reasons for elevation. Vitamin K is not routinely required unless bleeding risk high* as restabilising INRs can be difficult. Check INR within 24 hours and resume warfarin once INR approaches therapeutic range.
	INR > 10	Stop warfarin and administer vitamin K either 3 – 5 mg orally† or 0.5 – 1 mg intravenously. Check INR in 12 to 24 hours and continue monitoring every one to two days for the following week. Resume warfarin at a lower dose once INR approaches therapeutic range.
Spontaneous bleeding or injury	Any INR with minor bleeding	Stop warfarin. Repeat INR the next day and adjust to warfarin dose to maintain INR in the therapeutic range. If bleeding risk is high or INR > 4.5 consider administering vitamin K.
	INR ≥ 2 with clinically significant bleeding	Send immediately to hospital and administer vitamin K if there will be a delay in transportation
	INR ≥ 1.5 with life-threatening bleeding	

* A major bleed in the last four weeks or major surgery in the last two weeks, liver disease, concurrent antiplatelet treatment, thrombocytopaenia with platelets < 50×10^9/L

† For oral administration use the injection preparation orally

Illness can affect INR

Encourage patients to report any changes in their health status as this can affect INR levels. For example, an adjustment in warfarin dosing may be required for patients who develop diarrhoea, fever, heart failure, hyper- or hypothyroidism or liver disease.[19]

A consistent diet and lifestyle promotes INR stability

Foods that contain high levels of vitamin K can affect INR, e.g. spinach, broccoli, Brussels sprouts, cabbage and lettuce.[18] Rather than avoiding these foods, a consistent and balanced diet is recommended for patients to maintain a stable INR. Drinking excessive alcohol or consuming large quantities of cranberry juice or cranberry-based products may cause an interaction with warfarin and increase the risk of bleeding.[9, 18] Moderate consumption, however, is unlikely to cause clinically significant interactions.[9]

Alternative medicines such as Rongoā rākau (native plant remedies) and supplements can contain substances that interact with warfarin, e.g. fish oil, gingko, garlic and ginger.[18] Patients taking warfarin do not necessarily need to avoid these remedies, but they should be encouraged to report any alternative medicine use, especially if they change their regimen, so warfarin can be adjusted as necessary.

Educate patients about the adverse effects of warfarin

Ensure that patients taking warfarin know to report symptoms of unexpected bleeding, e.g. bleeding gums, unusual bruising, blue or purple rashes, dark urine or red or black stool.

An information sheet for patients taking warfarin is available from the NZF: **www.mymedicines.nz/home/sheet/Warfarin?format=pdfA4&inline=true**

Changing from warfarin to dabigatran

If a patient's INR is not stable despite optimal management, a change from warfarin to dabigatran is appropriate if they do not have contraindications. For example, changing to dabigatran may be appropriate if a patient:[20]

- Has two INR values higher than five or one value higher than eight within the last six months
- Has two INR values less than 1.5 within the last six months
- Spends less than 65% of the time in the therapeutic range

The possibility of non-adherence should be carefully considered in patients with unstable INRs before changing treatment. Dabigatran is usually taken twice daily and a patient who is not adherent to once-daily warfarin is unlikely to be adherent to a twice-daily dosing regimen.

How to change from warfarin to dabigatran

Warfarin should be withdrawn and dabigatran initiated at the normal dose after waiting for the patient's INR to fall below 2.0.[4]

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