The use of dabigatran in general practice:

a cautious approach is recommended

Dabigatran – practical considerations for General Practitioners

Dabigatran (Pradaxa) is now available in New Zealand, fully funded, without Special Authority, as an alternative oral anticoagulant to warfarin, to prevent stroke in people with non-valvular atrial fibrillation (AF). Dabigatran is also registered for short-term use for the prevention of venous thromboembolism (VTE) after major orthopaedic surgery. It is available in 75 mg, 110 mg and 150 mg capsules.

Dabigatran is the first new oral anticoagulant that has been made available for clinical use for more than fifty years. It was approved for use in AF in October 2010 in the United States and Canada, and in 2011 in Japan and some European countries. Although it has been used since 2008 for short term prophylaxis of VTE, clinical experience in the "real world" setting is still limited and data on longer term safety is lacking. Recommendations for its use in AF are based largely on the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (see Page 24 for further discussion on this trial).[1]

Warfarin has a history of many years of clinical use but has two major limitations – a narrow therapeutic range of safe anticoagulation and a highly variable dose response. Variation may also occur for individual patients over time due to interactions with certain dietary components and the use of other medicines. Laboratory monitoring with INR and dose adjustment is required to achieve individually

Key concepts

- Dabigatran etexilate (Pradaxa®) 75 mg, 110 mg and 150 mg capsules were listed on the Pharmaceutical Schedule on 1 July 2011, fully funded and without restriction.
- Dabigatran is licensed for use in New Zealand for stroke prevention in patients with non-valvular atrial fibrillation and for prevention of thromboembolism post major orthopaedic surgery
- If a patient taking warfarin has stable INR measurements and good venous access, then there is no clinical indication to switch to dabigatran.
- There is limited clinical experience with dabigatran in atrial fibrillation or with long-term use. Recommendations are based largely on a single, industry sponsored randomised controlled trial.
- Compliance with twice daily dosing is important as poor adherence may compromise the efficacy of dabigatran.
- Dabigatran is predominantly renally excreted, so patients must have creatinine clearance >30 mL/min. It should be used cautiously in patients with creatinine clearance between 30 – 50 mL/min. Older patients with normal serum creatinine may have low creatinine clearance.
- Potential adverse effects include bleeding, dyspepsia and gastrointestinal haemorrhage. The risk of myocardial infarction also appears to be increased.
- Potential interactions may occur with amiodarone, verapamil, aspirin, clopidogrel, NSAIDs, ketoconazole and St John's wort.
- No specific monitoring test is available for anticoagulant effect and routine monitoring is not required. Creatinine clearance (or eGFR) should, however, be reassessed during long term use.
- No reversal agent is available.
- Dabigatran capsules are not able to be re-packaged into blister packs.
- As with every medicine it is appropriate to discuss with the patient the potential benefits and risks of dabigatran use prior to commencing treatment.

tailored, adequate, safe anticoagulation. In contrast, dabigatran has a predictable effect on anticoagulation and therefore routine monitoring is unnecessary. For this reason, dabigatran is likely to be more convenient than warfarin, however, it requires twice daily dosing. Dabigatran appears to be at least as effective as warfarin for preventing stroke in patients with AF, and has similar rates of bleeding (see Page 24 for a discussion of the evidence).

What are the registered indications for dabigatran?

Dabigatran is indicated for people with non-valvular atrial fibrillation for:[2]

- Prevention of stroke
- Prevention of systemic embolism
- Reduction of vascular mortality

Treatment should be continued life-long unless the risk benefit ratio for the patient changes.

Dabigatran is also registered for short term use for the prevention of venous thromboembolism (VTE) after major orthopaedic surgery.[2] It therefore provides an oral alternative to low molecular weight heparin, e.g. enoxaparin.

What should dabigatran not be used for?

There has, as yet, been no research on the use of dabigatran in people with AF who have haemodynamically significant valvular heart disease or in people with artificial valves.[1, 3]

Dabigatran should not be used for patients who require long-term prophylaxis for deep venous thrombosis or pulmonary embolism. Trials are underway to determine the effectiveness of dabigatran for long-term prophylaxis. It is not known whether dabigatran is clinically effective for VTE prophylaxis for long haul flights.

There have also been no studies investigating the use of dabigatran in people aged under 18 years or in pregnant women.[2] Clinical data on the excretion of dabigatran into breast milk is not available.[2]

How does dabigatran work?

Dabigatran etexilate, a direct thrombin inhibitor, is a prodrug (a medicine administered in an inactive form) which is converted to the active medicine dabigatran after oral administration.[2] Conversion to the active form takes place rapidly in the plasma and liver and an effective anticoagulant effect can be attained within two to three hours of oral ingestion.[2, 4] It takes two to three days to reach steady state.[5]

The active form, dabigatran, is a potent, competitive and reversible (in vitro) direct inhibitor of the active site of thrombin (factor IIa).[2, 6] It has high affinity and specificity for thrombin. Warfarin, in contrast, produces its anticoagulant effect via activity on a number of different coagulation factors (see "How do warfarin and dabigatran affect coagulation?" – Page 14). The anticoagulant effect of dabigatran therefore, has been shown to be predictable and consistent with a wide therapeutic window which allows for a fixed dose regimen.[2, 4]

What are the recommended doses of dabigatran?

For the prevention of stroke in people with non-valvular atrial fibrillation the recommended dose of dabigatran is:[2]

- 150 mg, twice daily, for patients with a creatinine clearance >30 mL/min*
- 110 mg, twice daily, for patients aged ≥ 80 years (because of the likelihood of an age-related decline in renal function)

* See "Dabigatran dosing in renal impairment"

For VTE prophylaxis following major orthopaedic surgery the recommended dose of dabigatran is:[2]

- 220 mg (2 × 110 mg tablets), once daily, for patients with creatinine clearance > 50 mL/min
- 150 mg (2 × 75 mg tablets), once daily, for patients with creatinine clearance 30 – 50 mL/min

N.B. The length of the course varies with the type of surgery – knee replacement surgery ten days, hip replacement surgery 35 days.

Dabigatran is predominately renally excreted

Renal excretion is the dominant elimination pathway for dabigatran. Up to 80% of circulating unchanged dabigatran and small amounts of dabigatran glucuronides are excreted via the kidneys.[2] Consequently, a reduction in renal function results in elevated plasma concentrations of dabigatran. Excretion via the kidneys also decreases with increasing age.[2, 4]

Creatinine clearance should be checked in all patients before treatment with dabigatran (see Page 15). Patients with severe renal impairment (creatinine clearance < 30 mL/min) should not be prescribed dabigatran.[2] Patients with this level of renal impairment were excluded from clinical trials and dabigatran datasheets list this as a contraindication.[2, 3, 4]

Any patient taking dabigatran, who has renal impairment or is at risk of developing renal impairment, should have their eGFR checked or creatinine clearance calculated every six to 12 months during long-term treatment.[6] In some patients, more frequent checks may be appropriate. If a patient develops acute renal failure while taking dabigatran it should be stopped.[2]

The remaining 20% of the medicine is eliminated via the liver.[4] Although hepatotoxicity has not been demonstrated with dabigatran, caution is advised when it is used in patients with severe liver disease. Patients with active liver disease or persistently raised liver enzymes (> two times upper limit of normal) were excluded from clinical trials.[2, 3] Earlier types of direct thrombin inhibitors failed to reach clinical use due to hepatotoxicity, e.g. ximelagatran.[8]

Twice daily dosing is required

Dabigatran has a short half life of approximately 12–14 hours in adults with normal renal function.[2] In people with impaired renal function, the half life is prolonged.[2] Regular twice daily dosing with an interval of approximately twelve hours is required. Efficacy is likely to be compromised with poor adherence.[6] Patients should be made aware that good compliance is important to sustain clinically effective anticoagulation.

Dabigatran dosing in renal impairment for patients with atrial fibrillation

Creatinine clearance < 30 mL/min – there is no clinical experience of the use of dabigatran in this group of patients. Dabigatran is currently contraindicated in the New Zealand medicine data sheet, for this group of patients.

Creatinine clearance 30 – 50 mL/min – use dabigatran with caution in this group of patients.

For patients with non-valvular AF, with creatinine clearance 30 – 50 mL/min, there are no specific recommendations to reduce the dose of dabigatran from 150 mg, twice daily. However, patients with renal function in this range may be at increased bleeding risk due to reduced dabigatran excretion, especially if other risk factors are present. Some practitioners recommend using a lower dose of 110 mg dabigatran, twice daily. However, it is not known if this dose is safer and evidence shows that it is likely to be less effective than the 150 mg dose.

The decision whether to prescribe dabigatran for patients in this group, and at what dose, should be individualised, with consideration given to factors such as the patient's overall bleeding risk and their specific creatinine clearance level. Discussion with a cardiologist may be helpful. Recommendations are likely to become clearer as more clinical experience becomes available with this medicine.

How do warfarin and dabigatran affect coagulation?

All anticoagulant agents work by inhibiting the activity of thrombin. Thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, therefore its inhibition prevents the development of thrombus.

The anticoagulatory effect of warfarin is due to inhibition of several components of the coagulation pathway including vitamin K-dependent factors II, VII, IX and X, and proteins C and S, therefore indirectly inhibiting thrombin. Dabigatran, in contrast, selectively and directly inhibits thrombin (Figure 1).[7]

By inhibiting thrombin, dabigatran prevents a number of processes in the coagulation pathway including:[6]

- The conversion of fibrinogen into fibrin
- Positive feedback amplification of coagulation activation
- Cross-linking of fibrin monomers
- Thrombin-induced platelet activation
- The inhibition of fibrinolysis

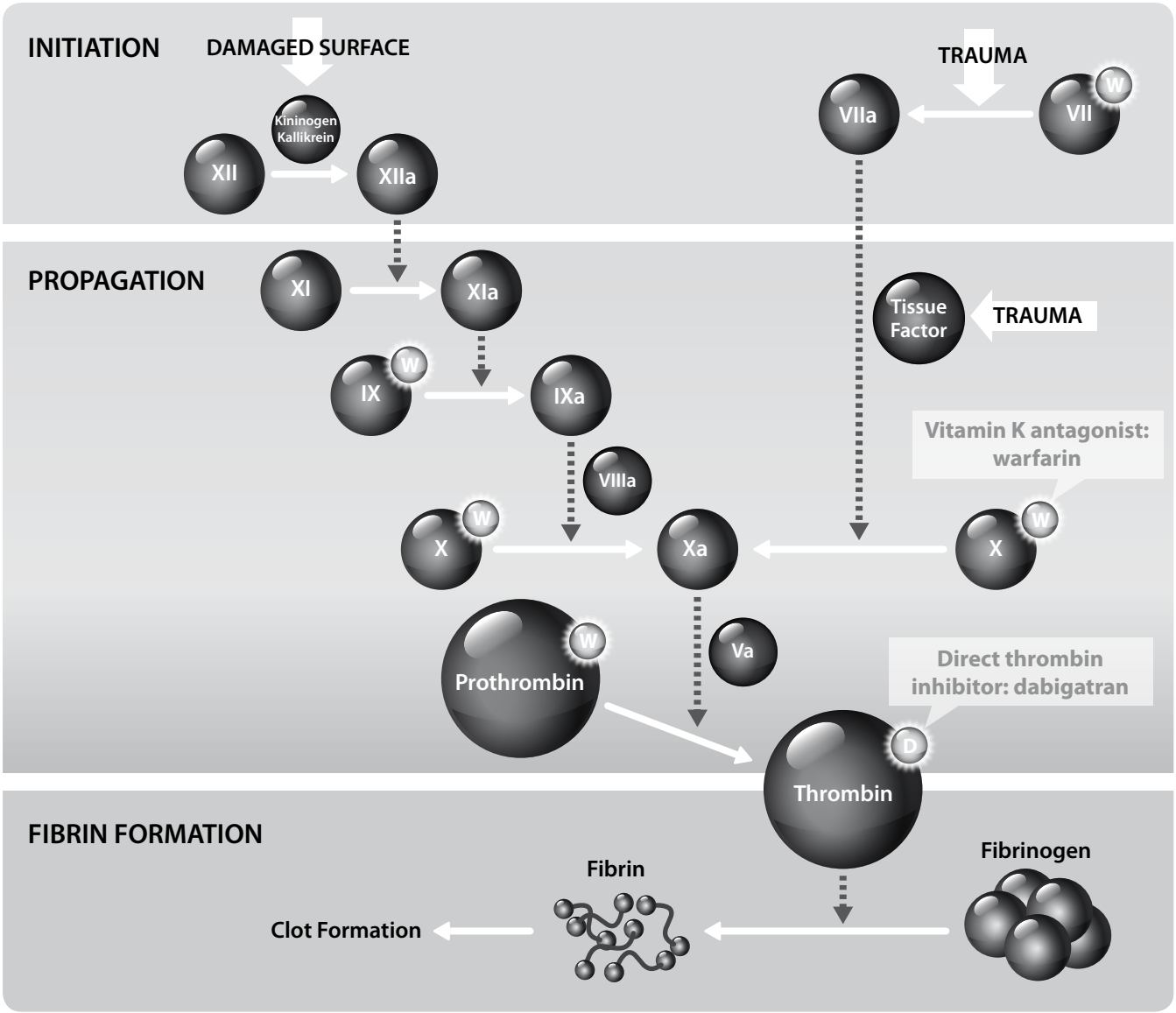


Figure 1. Coagulation cascade showing site of action of anticoagulants warfarin and dabigatran

There is limited evidence on the clinical effect of a missed dose. It is advised that:[2, 4]

- If a dose is missed, the dose can be taken when the patient remembers, provided it is more than six hours until the next scheduled dose
- If it is within six hours of the next scheduled dose, the patient should be advised not to take the missed dose
- A double dose should not be taken to make up for a missed dose

Dabigatran is not affected when taken with food

Although there is evidence that meals high in fat may delay the time taken to reach peak concentration in the plasma by approximately two hours, this does not appear to affect the bioavailability and clinical effectiveness of dabigatran.[2, 8] The capsules can therefore be taken with water, with or without food. Advising patients to take the capsules with breakfast and the evening meal may help with compliance.

The capsules should be swallowed whole and not chewed, or opened to sprinkle the contents on food or in fluids, as this significantly increases (75%) the oral bioavailability and may therefore increase the risk of bleeding.[2]

Dabigatran cannot be re-packaged into blister packs

Dabigatran capsules must be used within 30 days once the bottle is opened. If exposed to moisture the capsules have the potential to break down and there is a risk of loss of potency.[2, 10] It is recommended that the capsules are stored in their original bottle, with the lid tightly closed, to protect from moisture. The lid of the bottle contains a desiccant to help prevent moisture affecting the capsules. The manufacturer has recommended to pharmacies that dabigatran should not be re-packaged into weekly blister packs. New packaging to overcome this issue is likely to be supplied in the future.

What are the interactions with other medicines?

The knowledge on medicine and dietary interactions involving dabigatran is still in its infancy and few clinically significant interactions have been reported.[2, 11] Table 1 lists the major medicine interactions that are currently known. Unexpected or even potentially life-threatening medicine interactions may be identified with more widespread and prolonged use.[5] Vigilance is therefore required when initiating dabigatran or when any changes in the patient's medicine profile are made.

Metabolism of dabigatran etexilate to its active form does not use cytochrome P-450 pathways, which reduces the likelihood of drug-drug and drug-diet interactions.[2, 6] Dabigatran etexilate (the prodrug) is a substrate for the efflux transporter P-glycoprotein (P-gp) although the active medicine dabigatran is not.[2] Therefore there is the potential for interactions with medicines that are substrates, inhibitors or inducers of P-gp (Table 1, over page).[2, 8, 11]

Dabigatran is contraindicated in patients taking oral ketoconazole, a P-gp inhibitor.[2] Although no dose adjustment is recommended in the New Zealand datasheet, dabigatran should be used with caution in patients taking amiodarone or verapamil (also P-gp

Calculating creatinine clearance

Most laboratories report eGFR automatically with serum creatinine results, and eGFR can be used as an estimate of renal function. However, eGFR may not be a good estimate of renal function in people at extremes of body size (BMI < 18.5 or > 30 kg/m^2) or in older people. In this case, an estimate of creatinine clearance is preferable, determined using a hand held or electronic calculating tool or by using the Cockcroft-Gault equation:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times \text{constant}}{\text{serum creatinine (µmol/L)}}$$

The constant = 1.23 for men, 1.04 for women.

Table 1. Summary of known dabigatran interactions[2, 4, 9, 11]

Interaction	Medicine	Clinical considerations
Agents that increase gastric pH, decrease absorption: ⬇ dabigatran concentration	Antacids	No clinically significant reduction in plasma concentration has been shown with concomitant use of antacids. Two hour separation of dabigatran and antacids is advised by some, or use an alternative medicine.
	Proton-pump inhibitors*	Pantoprazole has been shown to reduce the plasma concentration of dabigatran by up to 30% and similar effects would be expected with other PPIs such as omeprazole. A subgroup analysis of the RE-LY trial indicated that the interaction is not clinically significant and that the combination of a PPI and dabigatran need not be avoided. Further studies are required.
P-gp inhibitors: ⬆ dabigatran concentration	Amiodarone Verapamil	Amiodarone and verapamil have been shown to increase the plasma concentration of dabigatran and although no dose adjustment is generally recommended, this combination of medicines should be used with caution. Two hour separation of dabigatran is advised by some but switching to an alternative medicine may be preferable, particularly for patients on verapamil
	Digoxin	Concomitant use of digoxin with dabigatran has been shown to result in a small, non-clinically significant, increase in plasma concentration. However, in practice this combination appears safe and well tolerated
CYP3A4 and P-gp inhibitors: ⬆ dabigatran concentration	Ketoconazole	Concurrent use of dabigatran with oral ketoconazole is **contraindicated** due to a marked increase in plasma concentration
	Clarithromycin	No dose adjustment is recommended for clarithromycin although it is known to cause a non-clinically significant increase in plasma concentration
CYP3A4 and P-gp inducers: ⬇ dabigatran concentration	Rifampicin	Avoid concurrent use of dabigatran with rifampicin if possible as this strong P-gp inducer significantly reduces the plasma concentration of dabigatran
	Carbamazepine	This P-gp inducer is expected to also reduce the plasma concentration of dabigatran and should be avoided or used with caution
Antiplatelet agents: ⬆ anticoagulant effect	Aspirin Clopidogrel	No dose adjustment is recommended, however, a cautious approach is necessary. Clopidogrel has been shown to increase plasma concentration and in the RE-LY trial the use of antiplatelet agents doubled the risk of major bleeding (although this also applied to warfarin). Current expert opinion is that these medicines should not be used with dabigatran, although in secondary care their use may be considered on a case by case basis.
NSAIDs: ⬆ bleeding risk ⬆ antiplatelet effect	All NSAIDs**	No dose adjustment is recommended Concurrent administration of NSAIDs may increase the risk or severity of a bleed. Monitor for any abnormal bleeding
St John's wort: ⬇ dabigatran concentration	St. John's wort preparations	This P-gp inducer is expected to reduce the plasma concentration of dabigatran. Avoid or use with caution.

P-gp = P-glycoprotein, CYP3A4 = cytochrome P450 3A4, NSAIDs = non-steroidal anti-inflammatory drugs

* Patients taking PPIs may be at increased risk of gastrointestinal bleeding due to the indication for which the PPI was prescribed. Pantoprazole may reduce the bioavailability of dabigatran by up to 30%, however, this decrease does not appear to affect the anticoagulant efficacy of dabigatran.[8, 12]

** A study including dabigatran and diclofenac found no pharmacokinetic interaction appears to occur, although there have been limited studies on the use of NSAIDs and dabigatran. The concurrent use of NSAIDs may theoretically increase the risk of bleeding with dabigatran.[12] Evidence regarding interactions with Cox-2 inhibitors is lacking, however, it is expected that the risk of bleeding will be increased as with conventional NSAIDs.

inhibitors).[2, 9] Some experts advise that patients take dabigatran two hours before taking verapamil and antacids.[4, 9] However, this may be impractical and using an alternative medicine may be a safer course of action until there has been more clinical experience with dabigatran.

Key clinically relevant features from Table 1:

- Antiplatelet agents and NSAIDs (both conventional and Cox-2) should be used with caution in people taking dabigatran because the risk of bleeding may be increased.[2] Evidence shows that people taking dabigatran concomitantly with aspirin or clopidogrel have approximately double the risk of major bleeding, irrespective of the dose.[1, 2] (N.B. a similar risk applies to patients taking warfarin). Patients taking these medicines or NSAIDs should be monitored clinically for signs of bleeding, e.g. ask about bleeding noses, wounds that keep bleeding, gums that are bleeding more than usual. Some patients may require an intermittent check for anaemia.
- The use of dabigatran with oral ketoconazole is contraindicated because clinical trials have shown that ketoconazole increases the maximum plasma concentration by approximately 150%.[2]
- Amiodarone and verapamil are medicines that are used in a similar population of people to those that require anticoagulation. A cautious approach should be taken as there is evidence that if amiodarone and verapamil are taken within two hours of dabigatran, the plasma concentration of dabigatran increases.[2, 9] Clinical use over time may help determine whether this increase produces clinically significant adverse effects with combinations of these medicines.
- Proton pump inhibitors do not appear to affect the anticoagulant efficacy of dabigatran.[2, 12]

There are no known food interactions with dabigatran and there has been no direct interaction between alcohol and dabigatran in animal models.[4]

Is there any need for routine coagulation monitoring?

Routine coagulation monitoring is not required for patients taking dabigatran because of the rapid onset of action, a wide therapeutic window and predictable pharmacokinetics and pharmacodynamics.[13, 14] There is currently no test available to routinely guide dabigatran dosage. In particular, dabigatran has variable and unpredictable effects on INR, which is not useful for monitoring.[14]

If a patient taking dabigatran experiences bleeding symptoms, the following should be considered:

- Is the patient taking any other medicines that affect coagulation, e.g. aspirin?
- Is the patient taking any medicines known to interact with dabigatran?
- Does the patient have impaired renal function, or has renal function deteriorated?

Management of bleeding complications in patients taking dabigatran should be individualised according to the site and severity. Dabigatran should be stopped and the source of bleeding investigated. Unless the bleeding is mild and able to be managed within the community, patients with bleeding should be referred urgently to secondary care (see Figure 2, Page 20).

If bleeding is a problem for a patient on dabigatran, what laboratory tests can be used to assess coagulation?

The activated partial thromboplastin time (aPTT) and thrombin time (TT) can be used to guide management of patients with acute bleeding, but these tests are not suitable for fine tuning dabigatran dosage.[13, 14] These tests can indicate whether dabigatran is “on board”, i.e. whether there is anticoagulant activity, e.g. if compliance is an issue or to determine if the medicine has been excreted. The time of the last dose of dabigatran should be included on the blood request form as this is critical for interpreting results.

Activated Partial Thromboplastin Time (aPTT) – this test does not have a linear relationship with drug levels. The test is moderately sensitive to the effect of dabigatran but the response is blunted at higher doses.

Thrombin Time (TT) – at recommended doses, dabigatran increases TT. This test is very sensitive and although there is a linear dose-response relationship, the time is very prolonged at therapeutic doses and the effect is also method specific making results potentially difficult to interpret.

The Ecarin clotting time (ECT) – this test is sensitive and has a linear dose-response relationship but is not widely available in New Zealand.

The primary role of these tests is to give a general guide as to whether a patient taking dabigatran, who is bleeding, still has a significant anticoagulant effect from the medicine. If neither the aPTT nor TT is prolonged there is no significant residual anticoagulant activity.[14] If the TT only is prolonged, there is some residual anticoagulant effect, but at a low level only. If both tests are prolonged there is likely to be a significant effect from dabigatran present (or another haemostatic defect).[13, 14]

Other tests to monitor coagulation status in patients taking dabigatran are being developed, however, they are not widely available and require standardisation for use.

Dabigatran may also have an effect on a number of other coagulation tests and its use should be recorded on the request form if a patient taking dabigatran requires any coagulation test such as thrombophilia markers and lupus anticoagulant testing.

Adverse effects of dabigatran – bleeding is the most relevant

All anticoagulant medicines inherently increase the risk of bleeding and patients should be informed of the risks and advised to let their General Practitioner know if they have any concerns.

The most common adverse effect with dabigatran is bleeding and the risk of major bleeding is comparable to that of warfarin.[1] In the RE-LY trial, dabigatran (150 mg or 110 mg), caused fewer intracranial haemorrhages and life-threatening bleeds when compared to warfarin, however, rates of major gastrointestinal bleeding were higher for patients on dabigatran than those on warfarin.[1] Overall the bleeding risk for patients taking dabigatran is greater at the higher dose of 150 mg, twice daily, and decreases when lower doses are used.

Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes. Dabigatran should not be used in patients with clinically significant bleeding or who are at high risk for bleeding.

There is no antidote for bleeding from dabigatran, unlike vitamin K for warfarin. If haemorrhagic complications occur treatment should be stopped.

For advice about tools to estimate stroke and bleeding risk, see: "The warfarin dilemma", BPJ 31 (Oct, 2010).

Dyspepsia is a commonly reported adverse effect with dabigatran. In the RE-LY trial, 11.8% of people taking 110 mg, twice daily, and 11.3% of patients taking 150 mg, twice daily, experienced dyspepsia compared with 5.8% in patients taking warfarin.[1] Each capsule contains a tartaric acid core, because absorption of dabigatran elexilate requires an acid environment.[6, 11] It is thought that the acid core may contribute to the development of dyspepsia. Dabigatran, therefore, may not be well tolerated particularly in patients with a history of gastrointestinal problems.[5, 11]

Rates of myocardial infarction may be higher

The incidence of myocardial infarction (MI) in the RE-LY trial was significantly lower in patients in the warfarin group compared to the dabigatran group.[1] Some evidence suggests that dabigatran may not actually increase the risk of MI but rather that warfarin provides a protective

effect.[2, 15] Whether dabigatran poses a genuinely increased risk of MI is still unclear.[5]

What adjustments in dabigatran dose are required for operative procedures?

At present there is limited evidence and clinical experience with the use of dabigatran prior to surgery. It is anticipated that the risk of bleeding with dabigatran is likely to be similar to the risk for a patient taking warfarin. However, it should be considered that prolonged bleeding times with dabigatran cannot be reversed, unlike warfarin (with vitamin K able to be used).

Planning has always been required for patients taking warfarin and the situation will be no different for patients taking dabigatran. Good communication should be maintained between primary and secondary care so clear consistent instructions for patients can be given and followed. The bleeding risk, the type of surgery planned and the renal function of the patient should be considered.

For people with a standard risk of bleeding, dabigatran should be temporarily discontinued for 24 to 48 hours before elective surgical procedures.[2, 6] For people at increased risk (e.g. older people, concomitant use of antiplatelet medicines, cardiac, respiratory or liver disease) or those having procedures with a high bleeding risk (e.g. any major surgery, spinal anaesthesia), dabigatran should be discontinued two to four days prior to the surgery.[2] If the risk of bleeding is high, a normal aPTT result will indicate a lack of residual anticoagulant effect.[13, 14]

Warfarin does not need to be stopped for some procedures such as dental extractions and minor surgery if the patient's INR value is at the lower end of the therapeutic range and their individual risk of bleeding is low. There is limited information about

Reporting patient bleeds with dabigatran

The Haematological Society, in association with Medsafe, PHARMAC and the Centre for Adverse Reactions Monitoring (CARM) is collecting data about adverse bleeding events experienced by patients using dabigatran.

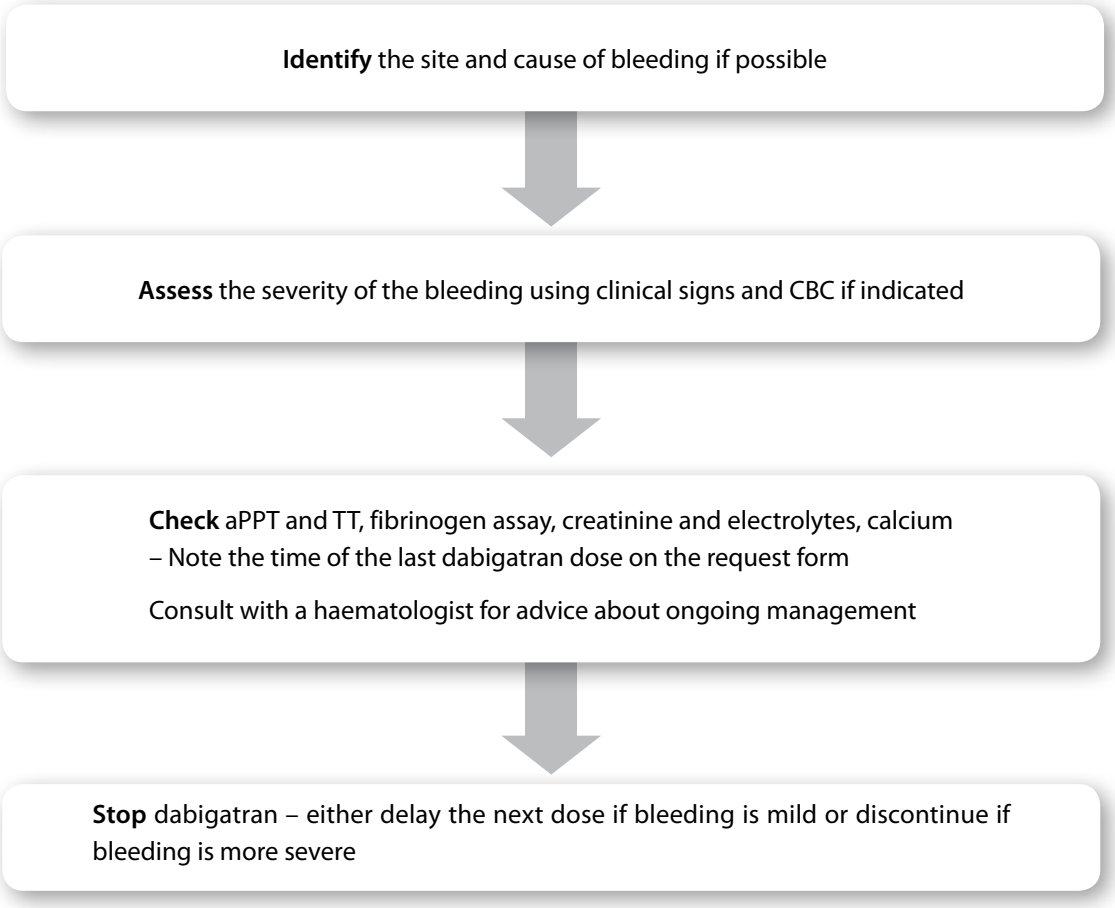
Dr Paul Harper, consultant haematologist at Palmerston North Hospital is co-ordinating this review. **He asks that all patient bleeds, adverse events or discontinuation of therapy with dabigatran (Pradaxa) be reported to CARM**. Events should be reported regardless of whether the patient required hospitalisation. If in doubt, report – it is not necessary to be certain that an adverse reaction is caused by a medicine in order to make reporting worthwhile.

Adverse reaction reports should include as much information as possible, and can be made via:

- *bestpractice* Decision Support – click "Adverse drug reaction reporting" under the module list
- Or reporting cards – found inside the back cover of Prescriber Update and with the MIMS Catalogue
- Or directly with CARM, online at: https://nzphvc-01.otago.ac.nz/carm phone: 03 479-7247, fax: 03 479-7150 or email: carmnz@otago.ac.nz

The Safe and Quality Use of Medicines Group (SQM) has published an urgent alert following hospital admissions for the treatment of bleeding after dabigatran initiation. This report can be found on the SQM website at: www.safeuseofmedicines.co.nz

Dabigatran associated bleeding



Mild bleeding	For moderate, severe or life-threatening bleeding*
If applicable elevate affected body part and apply compression Consider use of oral tranexamic acid (15 mg/kg, four times per day) Ensure good fluid intake to maximise renal excretion	**Refer urgently to hospital** Measures as for mild bleeding Initiate standard resuscitation measures if required (e.g. establish IV access, give IV fluids, oxygen)

* **Moderate to severe bleedin**g – a reduction in Hb≥20g/L, symptomatic bleeding in an organ or critical area, e.g. intraocular, intracranial, intramuscular, retroperitoneal, intraarticular or pericardial bleeding.[2]

Life-threatening bleeding – a reduction in Hb≥50g/L, symptomatic intracranial bleed, hypotension requiring inotropic agents, e.g. dopamine, bleeding requiring surgery[2]

Figure 2: Treatment of dabigatran associated bleeding in primary care (adapted from van Ryn[14])

the use of dabigatran in this situation, but it can be assumed that a similar assessment of risk can take place, although bearing in mind that a bleeding event with dabigatran cannot be reversed.

Evidence shows that dabigatran can be used safely in patients undergoing cardioversion.[2, 16]

How can bleeding be managed for people taking dabigatran?

Unlike warfarin and heparin, no specific antidote is available to reverse the anticoagulant effects of dabigatran. Administration of vitamin K or an infusion of plasma will not reverse the anticoagulant effect.

Unless the bleeding is mild, it is anticipated that most patients will require referral to secondary care for urgent treatment, although this will depend on individual patients and the location and severity of the haemorrhage. Treatment in secondary care may involve the use of oral charcoal (if ingestion of dabigatran was less than two hours previous), transfusion of blood products or clotting factors, use of anti-fibrinolytic agents intravenously and consideration of haemodialysis, particularly if there is moderate to severe renal impairment (Figure 2).[14]

Severe or life-threatening bleeding may be immediately obvious due to the clinical state of the patient, e.g. tachycardia, pallor, hypotension, bleeding with injury. However, some patients, particularly younger patients, may have normal vital signs, even with a significant blood loss. In addition, there may be bleeding within a body cavity, e.g. stomach, bowel or chest, that is not clinically detectable until a large volume of blood has been lost. Although an urgent complete blood count to assess the haemoglobin level may be useful, in a general practice setting, unless the bleeding is mild, referral to secondary care is recommended for patients taking dabigatran who are bleeding. As a guide, the categories used in the RE-LY trial to define the severity of bleeding were; a decrease of 20g/L Hb signifying moderate to severe bleeding and a decrease of 50g/L Hb, life-threatening bleeding.[1]

Details of the management of moderate, severe or life-threatening bleeding is available from: www.pharmac.govt.nz/2011/06/13/Dabigatran%20bleeding%20management.pdf.

Which patients with non-valvular atrial fibrillation should use dabigatran?

Careful patient selection is important when considering dabigatran use[1, 2, 6, 17]

Patients with non-valvular atrial fibrillation **who may benefit** from dabigatran include those who:

- Require anticoagulation but are currently on no treatment, e.g. patients who have declined treatment with warfarin or aspirin or those taking medicines that are contraindicated with warfarin
- Are already on warfarin but where there are difficulties with monitoring, e.g. difficult venous access, problems with accessing lab facilities due to mobility issues, cost or lack of time, those who are non-compliant with monitoring
- Are already on warfarin but have INR values that are often sub-therapeutic or difficult to control
- Wish to change for convenience

Patients **who may not benefit** from dabigatran include those who:

- Are on warfarin with a stable (or easy to control) INR and who are comfortable with the need for INR monitoring. Patients on warfarin who have INR values that are consistently within the therapeutic range are less likely to benefit from a switch to dabigatran.
- Are unlikely to be compliant with the twice daily dosing required for dabigatran
- Prefer to continue with warfarin (some patients may like the reassurance of periodic monitoring)
- Require blister packed medicines

Comparison of dabigatran and warfarin

When treating patients with atrial fibrillation it must first be decided whether anticoagulation is indicated. This can be determined using a risk assessment tool such as $CHADS_2$ or CHA_2DS_2VASc. The next step is to choose the most suitable anticoagulant for that individual patient.

See "The warfarin dilemma" BPJ 31 (Oct, 2010) for further discussion on risk assessment tools.

Summary of properties of dabigatran and warfarin[2, 4, 6, 13]

Property	Dabigatran	Warfarin
Indication for AF	Non-valvular atrial fibrillation	Valvular or non-valvular atrial fibrillation
Mechanism of action	Direct inhibition of thrombin	Reduced synthesis of prothrombin and other clotting factors
Administration	Oral Twice daily (for AF)	Oral Once daily
Dosing	Fixed dose, dependent on creatinine clearance and age	Individualised to each patient and target INR
Onset of action	0.5–2 hours	36–72 hours
Elimination half-life	12–14 hours	20–60 hours
Duration of action	24 hours	48–96 hours
Stable, predictable pharmacokinetics	Yes	No
Interactions with diet and alcohol	No	Yes
Interactions with medicines	Interactions largely unknown, clinical experience over time likely to reveal more. Known interaction with p-glycoprotein inhibitors e.g. oral ketoconazole, verapamil, amiodarone	Multiple
Monitoring	No routine monitoring required. If tests are used, timing of blood sample is important for correct interpretation.	INR every one to eight weeks depending on clinical situation
Risk of major haemorrhage	Similar for both medicines Major GI bleeding rates may be higher than with warfarin, however, rates of intracranial haemorrhage and life-threatening bleeding may be lower with dabigatran.	Similar for both medicines.
Other adverse effects	Dyspepsia Possibly increased risk of MI	Multiple reported, however, in clinical practice these are relatively rare
Antidote	None available but can be removed by dialysis	Vitamin K Fresh-frozen plasma
Cost	Fully funded	Fully funded

AF = atrial fibrillation, INR = international normalised ratio, GI = gastrointestinal

Dabigatran is **contraindicated** in patients who:

- Have chronic kidney disease with a creatinine clearance less than 30 mL/min
- Have had a recent haemorrhagic stroke (within six months)
- Are taking oral ketoconazole
- Have any active bleeding or any impairment of haemostasis

Dabigatran **should not be used** (primarily due to lack of evidence) in patients who:

- Have haemodynamically significant valvular heart disease or mechanical heart valves (there is currently no evidence on the suitability of dabigatran in these conditions)
- Have severe liver disease

Dabigatran **should be used with caution** in patients who:

- Are aged ≥ 80 years (although this group may have an increased need for anticoagulation, they may also have impairment of renal function)
- Have moderate kidney disease, i.e. creatinine clearance of 30 – 50 mL/min
- Have existing or a history of gastrointestinal problems such as GI ulceration or poorly controlled gastro-oesophageal reflux
- Are taking amiodarone, verapamil, rifampacin, clarithromycin
- Are taking other medicines that affect haemostatis, e.g. aspirin, clopidogrel
- Have had recent trauma, major surgery or gastrointestinal bleeding

Initiating dabigatran or switching between oral anticoagulants

Initiation in patients not previously anticoagulated with warfarin

No loading dose is required when initiating dabigatran, the medicine is started and continued at the same dose.[2]

How do you change from warfarin to dabigatran?

Stop warfarin and start dabigatran when the INR is less than 2.0.[2]

How do you change a patient from dabigatran to warfarin?

Check the creatinine clearance. Warfarin should be started three days prior to stopping dabigatran if the creatinine clearance is > 50 mL/min. If the creatinine clearance is 30 – 50 mL/min, start warfarin two days before stopping dabigatran.[2]

Best Practice tip: If switching a patient from warfarin to dabigatran, notify the local laboratory by phone or email so that they can update their records and avoid unnecessary INR testing. Patients taking warfarin are often registered with a laboratory for regular, long-term repeat INR's.

The evidence for dabigatran – can we RE-LY on this?

The Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a "non-inferiority" trial.[1] In this type of trial, a new medicine is compared with a current standard treatment in an attempt to determine whether the new medicine is no worse than the usual medicine.[18] The new medicine does not have to be superior to the older medicine. In contrast, randomised trials usually assess if a new medicine is better than a current medicine or placebo and are called superiority trials.

The RE-LY trial therefore had to show that outcomes for the people who took dabigatran were at least as good as the outcomes for the people who took warfarin.

Summary of findings from the RE-LY trial

This large, randomised, non-inferiority clinical trial compared two doses of dabigatran (110 mg and 150 mg administered twice daily) to warfarin treatment (aiming for INR values of 2–3) in over 18,000 patients with atrial fibrillation.[1] The study was of hybrid design with medicine administration blinded for patients on dabigatran but not for warfarin.

Compared to warfarin, the 150 mg, twice daily dose of dabigatran significantly reduced the rate of stroke or systemic embolism.[1] The 150 mg dose was therefore found to be superior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference in the rate of stroke or systemic embolism with the 110 mg, twice daily dose of dabigatran when compared to warfarin. Twice daily dabigatran 110 mg was therefore found to be non-inferior to warfarin.[1]

Both doses of dabigatran were associated with fewer intracranial haemorrhages and other life-threatening bleeds

Comparison of adverse events in the RE-LY trial[1]

Event	% of incidents per year			Significance (P ≥ 0.05)
	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	
Stroke or systemic embolism	1.53	1.11	1.69	D150 **superior** to W D110 **not inferior** to W D150 **superior** to D110
Myocardial infarction	0.72	0.74	0.53	W **superior** to D150
Intracranial haemorrhage	0.23	0.30	0.74	D110 **superior** to W D150 **superior** to W
Life-threatening bleeding	1.22	1.45	1.80	D110 **superior** to W D150 **superior** to W
Gastrointestinal bleeding	1.12	1.51	1.02	W **superior** to D150 D110 **superior** to D150
Death from vascular causes	2.43	2.28	2.69	D150 **superior** to W
Death from any causes	3.75	3.64	4.13	No difference

when compared to warfarin, however, gastrointestinal bleeding events were significantly increased with the higher dose of dabigatran.[1] The rate of myocardial infarction was significantly higher (p = 0.048) in patients in the dabigatran group.[1]

There were no significant differences in the mortality rates from any cause between either of the dabigatran treatment groups and the warfarin group.[1]

What were the strengths of the RE-LY trial?

The trial was large, including over 18,000 patients from multiple countries. Follow up of participants was excellent with 99.9% of patients completing follow up assessments over a median time frame of two years.[1] Patients were allocated randomly into the three treatment groups (dabigatran 110 mg twice daily, dabigatran 150 mg twice daily or warfarin). Administration of dabigatran was blinded, however, warfarin was not because of the need for INR monitoring. The investigators were aware of this potential for bias and therefore implemented strategies to minimise bias such as arranging for assessment of the outcomes to be carried out by two independent parties who had no knowledge of the treatments received.

What were the limitations of the RE-LY trial?

This was an industry funded trial, however, the coordination of the study, data management and analysis of the results were carried out on an independent basis at McMaster University in Canada.[1, 19]

The study participants represented a select group of people and the outcomes of treatment with dabigatran may be different in a "real world" setting.[20] Participants had AF and a minimum of one other risk factor for stroke, e.g. previous stroke, hypertension, coronary artery disease.[3] People excluded from the study included those with:[3]

- Haemodynamically significant valvular heart disease or a prosthetic valve
- Any stroke in the previous two weeks or a severe disabling stroke in the last six months
- An increased risk of bleeding, e.g. GI bleeding within the previous year, documented GI ulcer within the last month, major surgery within the last month, uncontrolled hypertension, a history of bleeding, any haemorrhagic disorder
- Severe renal impairment (creatinine clearance ≤ 30 mL/min)
- Active liver disease
- Anaemia or thrombocytopaenia

Although the administration of dabigatran was blinded, participants receiving warfarin could not be administered this medicine in a blinded manner due to the need for INR measurement and subsequent adjustment of doses. There have been comments in the literature stating that this may have altered the way patients in the warfarin arm of the trial were managed, i.e. performance bias.[21, 22]

The standard of anticoagulation in patients on warfarin, with INR values in the therapeutic range for 64% of the time, has been said to be poorer than that achieved in many centres, although the level is similar to that achieved in most randomised controlled trials.[22, 23] In addition, the INR values at which adverse events occurred were not reported. Some researchers believe that the benefits reported for dabigatran would be minimised if they were compared with patients taking warfarin who had INR values consistently within the therapeutic range.[22] To address some of the questions regarding INR control raised by the United States Food and Drug Administration and other researchers, a subsequent analysis of RE-LY data has reported that the primary outcomes remained consistent irrespective of the quality of INR control.[21, 24]

Other concerns that have been raised include the higher rates of withdrawal due to adverse effects in the dabigatran arms of the study and the concomitant use of antiplatelet agents in all three arms of the trial.[21]

At this stage the longer term effects (post two years) of dabigatran are not known although there is an ongoing multi-centre follow up study in place (RELY-ABLE).

There is still a lot to learn about dabigatran

Dabigatran may well provide a solution to some of the problems associated with the use of warfarin such as its unpredictable and significant inter-individual variability in response and narrow therapeutic window which necessitates frequent INR monitoring as well as numerous food and medicine interactions.[5] However, the importance of the frequent patient contact that accompanies INR monitoring should not be forgotten as this often goes beyond "a simple blood test".

The consequences of long-term use of dabigatran are unknown and this may be important in the setting of stroke prevention in patients with atrial fibrillation as these patients usually require life-long treatment.[5, 6] Thrombin plays an important role not only in coagulation but also in immune response, infection, angiogenesis, endothelial function, and tumour growth.[6]

The main clinical trial (RE-LY), which has prompted the review of recommendations in atrial fibrillation guidelines, included just over 18,000 people who took dabigatran for two years.[1] There is still a lot to learn about dabigatran – its effectiveness, adverse effects, longer term safety and interactions with other medicines. This information will only be gathered once it has been used extensively over the next few years.

Like all medicines the promise that dabigatran brings must be balanced against its potential risks and uncertainty, therefore a cautious approach to its use is recommended.

ACKNOWLEDGEMENT Thank you to **Professor Carl Burgess**, **Dr Gerry Devlin**, **Dr John Fink**, **Dr Sisira Jayathissa**, **Dr Nigel Lever**, **Associate Professor Stewart Mann**, **Dr Richard Medlicott**, **Dr Alan Panting**, **Dr Ralph Stewart, Dr Jim Vause** and **Dr Howard Wilson** for expert guidance in developing this article.

References:

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12):1139–51.
2. Boehringer Ingelheim (NZ) Ltd. Dabigatran etexilate (Pradaxa). Medicine data sheet. Available from: www.medsafe.govt.nz (Accessed Jul, 2011).
3. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805-10.
4. Boehringer Ingelheim Canada Ltd. Pradaxa. Product Monograph. Oct, 2010. Available from: www.boehringer-ingelheim.ca (Accessed Jul, 2011).
5. Ma TK, Yan BP, Lam YY. Dabigatran etexilate versus warfarin as the oral anticoagulant of choice? A review of clinical data. Pharmacol Ther. 2011 Feb; 129(2):185–94.
6. Hankey GJ, Eikelboom JW. Dabigatran etexilate: A new oral thrombin inhibitor. Circulation 2011;123:1436-50.
7. Ogawa S, Koretsune Y, Yasaka M, et al. Antithrombic therapy in atrial fibrillation – Evaluation and positioning of new oral anticoagulant agents. Circ J 2010;75:1539-47.
8. Douketis JD. Dabigatran as anticoagulant therapy for atrial fibrillation. Pol Arch Med Wewn. 2011;121(3):73-80.
9. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis (2011) 31:326–43.

10. U.S. Food and Drug Administration (FDA). Drug safety Communication: Special storage and handling requirements must be followed for Pradaxa (dabigatran etexilate mesylate) capsules. FDA. Mar 2011. Available from: www.fda.gov (Accessed Jul, 2011).

11. British National Formulary (BNF). BNF 60. London:BMJ Publishing Group and Royal Pharmaceutical Society of Great Britain, 2010.

12. Baxter K (Ed). Stockley's Interaction Alerts. [online] London: Pharmaceutical Press. Available from: www.medicinescomplete.com/mc/stockley/current/ (Accessed Jul, 2011).

13. Samama MM, Guinet C. Laboratory assessment of new anticoagulants. Clin Chem Lab Med 2011;49(5):761-72.

14. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116-27.

15. Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? Am J Med 2010;123:785-9.

16. Bendel SD, Bona R, Baker WL. Dabigatran: an oral direct thrombin inhibitor for use in atrial fibrillation. Adv Ther 2011; [Epub ahead of print].

17. Wann LS, Curtis AB, Ellenbogen KA, et al. ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:1144 –50.

18. Scott IA. Non-inferiority trials: determining whether alternative treatments are good enough. MJA 2009;190(6):326-30.

19. Kirley K, Rowland K. PURLs: Time to try this warfarin alternative? J Fam Pract. 2011 Apr;60(4):220-2.

20. Raju N, Hankey G. Dabigatran etexilate in people with atrial fibrillation. BMJ 2010;341:c3784.

21. University of British Columbia. Therapeutics Initiative. Dabigatran for atrial fibrillation. Why we can not rely on RE-LY. Therapeutics letter Jan-Mar 2011. Available from: www.ti.ubc.ca (Accessed Jul, 2011).

22. Unger EF. Application number 22-512. Summary Review. FDA – Center for drug evaluation and research. Dec 2010. Available from: www.fda.gov (Accessed Jul, 2011).

23. Edwards D. Dabigatran v warfarin. Compare with a higher standard. BMJ 2010;341:c5984.

24. Wallantin L, Yusuf, Ezekowitz M, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ration control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975-83.