

Guidance on the use of dabigatran for stroke prevention in AF

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Dabigatran is a novel oral anticoagulant recently licensed for use for stroke prevention in atrial fibrillation (SPAF). NICE has approved the use of dabigatran as an option for SPAF, for patients with additional risk factors.

In South London dabigatran should be considered, in line with its licensed indications, as an alternative to warfarin for SPAF in patients with CHADS₂ ≥ 1 who:

- have a warfarin allergy, warfarin specific-contraindication or are unable to tolerate warfarin therapy due to severe adverse effects¹
- are unable to comply with the specific monitoring requirements of warfarin²
- are unable to achieve a satisfactory INR after an adequate trial of warfarin (usually at least 3 months) despite compliance with drug therapy. Patients at particular risk are those that remain sub-therapeutic (INR persistently <2), those where the INR regularly fluctuates above 4 and those requiring dosages at the extreme ends of the dose range
- have had an ischaemic stroke whilst stable on warfarin therapy - this must be discussed and agreed with haematology prior to initiation

Patients currently stable on warfarin therapy should not usually be considered for a switch to dabigatran

Initiation of dabigatran should only be undertaken by clinicians with expertise in initiating anticoagulant therapy for SPAF. The initiating clinician is responsible for ensuring patient follow up and providing medicine supplies for the first 3 months of treatment. During this time efforts should be made to reinforce adherence and address adverse effects.

Transfer of prescribing responsibility to patient's own GP

Following the initial 3 month period, patients may be considered for transfer back to the patient's own GP, provided the patient meets the criteria for use of dabigatran (as above), the GP agrees to take over prescribing responsibility and SLCSN transfer of care guidance (in progress) is followed. If dabigatran is prescribed for patients / indications that do not meet the criteria above, prescribing responsibility will remain with the initiating clinician.

Contra-indications	Cautions
<ul style="list-style-type: none"> • Hypersensitivity to active substance or any excipients • Patients with severe renal impairment (CrCL < 30 ml/min / eGFR<30ml/min) • Active clinically significant bleeding • Organic lesion at risk of bleeding including current or recent gastrointestinal ulceration, malignant neoplasms, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, oesophageal varices, arteriovenous malformations, vascular aneurysms and major intraspinal or intracerebral vascular abnormalities • Spontaneous or pharmacological impairment of haemostasis • Hepatic impairment or liver disease expected to have any impact on survival • Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone 	<ul style="list-style-type: none"> • Use not recommended where liver enzymes are elevated > 2 x upper limit of normal (ULN) • People at increased risk of bleeding due to co-morbidities • Increased plasma dabigatran levels are expected with: <ul style="list-style-type: none"> - decreased renal function (eGFR 30-60ml/min) - age ≥ 75 years - low body weight < 50 kg - strong P-gp inhibitors (e.g. amiodarone, quinidine or verapamil) • Concomitant use of aspirin, clopidogrel, prasugrel, ticagrelor, NSAIDs will increase GI bleeding risk • Bleeding can occur at any site during therapy with dabigatran therefore any unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. • Presence of oesophagitis, gastritis or gastroesophageal reflux disease increases bleeding risk

Dose

- Dabigatran should be prescribed at a dose of 150mg twice daily; except for any patient ≥80 years old in whom a dose of 110mg twice daily is recommended. Dose reduction is therefore required when the patient reaches the age of 80 years old
- The lower dose (110mg twice daily) may also be appropriate in patients considered at high risk of bleeding, such as those with gastritis, oesophagitis, or gastroesophageal reflux disease. The co-prescription of a low-cost PPI may be considered to reduce the risk of gastrointestinal bleeding
- Once initiated, dabigatran therapy should be continued long term

Renal impairment

- Dabigatran is contraindicated in patients with CrCl<30ml/min (eGFR<30ml/min). Close clinical supervision is required in patients with stage 3 chronic kidney disease (eGFR 30-60ml/min) e.g. monitor renal function every 3 – 6 months or more frequently if clinically appropriate
- Renal function should be assessed at least annually in all patients

¹ Such as intolerable rash, significant alopecia, skin necrosis

² Inability to comply with warfarin monitoring may be due to lack of understanding of the monitoring process or inability to access any local monitoring service (this should be discussed with the patient's own GP, before a NOAC is initiated).

Side effects (for full details see the BNF or SPC)

- Bleeding occurs commonly during treatment with dabigatran. In the [RE-LY study](#), with higher dose dabigatran (150mg twice daily), bleeding rates were reported as 3.3% major bleeds, 1.6% gastrointestinal bleeds and 15% minor bleeds, such as epistaxis. Patients should be advised to seek medical advice if they experience persistent or frequent episodes of bleeding. Patients experiencing severe bleeding should seek urgent medical advice.
- Dyspepsia was also commonly reported in the RE-LY study occurring in approximately 11% of patients. If significant dyspepsia occurs affecting the patients' quality of life, consider an alternative anticoagulant agent.
- Dabigatran may be associated with a small increased risk of myocardial infarction during therapy
- If unable to tolerate dabigatran, patients should be instructed to immediately seek medical advice in order to be switched to a suitable alternate treatment for SPAF

Drug interactions (for full details on drug interactions – see BNF or SPC)

Drug / Drug class	Recommendation
Concomitant administration of P-gp inducers - such as rifampicin, St. John`s wort (<i>Hypericum perforatum</i>), carbamazepine or phenytoin	Will result in decreased dabigatran plasma concentrations, and therefore should be avoided
Use of fibrinolytic agents for the treatment of acute ischaemic stroke	May be considered by hyper-acute stroke units if the patient presents with a dTT, ECT or aPTT (measurements of clotting function) not exceeding the ULN according to the local reference range
Unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, sulfapyrazone, rivaroxaban and vitamin K antagonists	May increase the risk of bleeding when used concomitantly. Concomitant use with other oral anticoagulants is contraindicated, except the use of UFH to maintain venous or arterial catheter patency. Use in combination with antiplatelet agents increases bleeding risk twofold, therefore risks and benefits should be considered carefully before initiation.
Aspirin	Increased risk of bleeding, close monitoring required
NSAIDS	Increased risk of bleeding if used long-term. Avoid where possible, but if used, close monitoring required
Systemic ketoconazole, ciclosporin, itraconazole, tacrolimus and dronedarone	Concomitant use is contra-indicated due to increased plasma dabigatran levels
Amiodarone and quinidine	Use with caution as will increase plasma dabigatran levels. Consider using lower dose of dabigatran to minimise bleeding risk
Clarithromycin	May increase plasma dabigatran levels especially where there is moderate to severe renal impairment – use with caution
Protease inhibitors including ritonavir and its combinations with other protease inhibitors	Not recommended for concomitant treatment with dabigatran
SSRIs and SNRIs	Increased bleeding risk with dabigatran, close monitoring required
Verapamil	Increases plasma dabigatran level. Maximum dabigatran dose of 110mg twice daily when prescribed concurrently

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
<ul style="list-style-type: none"> To initiate dabigatran, in line with SLCSN position statement To supply dabigatran for the first 3 months of treatment To provide counselling to improve adherence and deal with any early adverse effects To seek agreement from the patient's own GP at 3 months to take over prescribing of dabigatran To transfer care to the GP in line with SLCSN transfer of care guidance (in progress) 	<ul style="list-style-type: none"> To ensure use of dabigatran is line with the SLCSN position statement To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation) To emphasise the importance of adherence to dabigatran therapy and address any patient concerns To ensure renal monitoring is undertaken at least annually throughout therapy and review treatment in line with contra-indications and cautions should renal function decline (see overleaf). If appropriate, seek specialist advice To ensure the dabigatran dose is adjusted as patients age (reduced dose required when age ≥80 years old)

Additional information

- Patients taking dabigatran should be encouraged to carry an anticoagulation card (available from initiating clinician / anticoagulation clinics) at all times
- There is no specific reversal agent should a patient experience a serious bleed on dabigatran. In the event of a serious bleed, the patient should be referred to A&E
- Other healthcare professionals should be made aware that dabigatran is prescribed for any patients undergoing invasive treatments, including elective surgery and dental treatment
- Dabigatran is moisture-sensitive and we do not recommend in medication compliance aids. Dabigatran capsules must remain in the original foil packaging until taken

References

- NICE TA249: dabigatran etexilate for the prevention of stroke and systemic embolism. March 2012
- SPC Pradaxa. Boehringer Ingelheim. April 2012. Accessed 22nd May 2012 at <http://www.medicines.org.uk/emc/medicine/20760/SPC/>
- Connolly SJ et al 2009. Dabigatran versus Warfarin in Patients with Atrial Fibrillation NEJM 2009; 361:1139-1151