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Practical guide dabigatran
Guidance for use in particular situations
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Writing Committee

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Disclaimer

This practical guide has been developed in order to enhance the understanding on when and how to prescribe dabigatran. The guide is based - where possible - on available scientific literature, existing guidelines and/or the Summary of Product Characteristics of dabigatan. Some advice is, however, based on our clinical experience and extrapolation of existing knowledge about the concerned indications, the coagulation system and anticoagulant drugs. This guide should therefore not be considered as a formal recommendation but as an addition to the regular product information, providing pragmatic advice for the use of dabigatran in daily practice.
It is possible that the content of this document does not apply to individual cases or circumstances. The authors can not be held liable for the management resulting from this guidance.
Please note that the guidance provided in this document reflects our current state of knowledge about dabigatran but is likely to change in the future.

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Preamble

Dabigatran is a new, oral anticoagulant (NOAC) that has been approved by the European Medicines Agency (EMA) for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery since March 2008[4].

In August 2011, dabigatran was approved for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) with one or more of the following risk factors:

- Previous stroke, TIA, or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ NYHA Class 2
- Age ≥75 years
- Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension[4].

Dabigatran is the first available oral, direct thrombin inhibitor (DTI). It has a predictable pharmacokinetic and pharmacodynamic profile across a wide spectrum of patients (age, gender, weight and race).

After oral administration, dabigatran etexilate (the pro-drug) is rapidly converted to dabigatran, the active form in plasma The absolute bioavailability of dabigatran is approximately 6.5 % and is not affected by food.

Dabigatran is rapidly absorbed with C_{max} appearing within 0,5 to 2 hours.

Plasma protein binding is low (~35%).

Dabigatran is eliminated primarily in the unchanged form in the urine. Mean terminal half-life is 12-14 hours when renal function is normal[4].

Table 1: Pharmacokinetic and pharmacodynamic characteristics of dabigatran

	Dabigatran
Mode of action	Potent and reversible direct thrombin inhibitor
Oral bioavailability	6.5%
T_{max} (h)	0.5 – 2
$T_{1/2}$ (h)	12 – 14 (if normal renal function)
Plasma protein binding	Low (35%)
Hepatic metabolisation	Negligeable
Excretion	Unchanged via kidneys (>80%)

Guide to treatment with dabigatran

1. Dosing schemes in the different indications

Dabigatran is licensed for the indications mentioned in table 2. The dose regimens are presented as recommended in the summary of product characteristics (SmPC).

Table 2: Dabigatran dosing schemes in the different indications

Indication	Dose and regimen	Duration
VTE prevention after elective hip or knee replacement surgery	**Standard dose:** **220 mg once daily,** starting with a half dose (110 mg) 1 to 4h after the intervention Reduced dose for patients ▪ Aged ≥ 75 ▪ Moderate renal impairment (CrCL 30-50 ml/min) ▪ Treated with amiodarone, verapamil or quinidine 150 mg once daily starting with a half dose (75 mg) 1 to 4h after the intervention**	28-35 days after THR* 10 days after TKR*
Prevention of stroke and systemic embolism in patients with non-valvular AF	**Standard dose:** **150 mg twice daily** Reduced dose (110 mg twice daily) for patients ▪ Aged ≥ 80 ▪ Treated with verapamil This dose should also be considered for patients at increased bleeding risk.	Long term

* The registered duration of thromboprophylaxis with dabigatran for VTE prevention is 28-35 days after THR and 10 days after TKR. Individual patient management may differ from the registered durations.
** If moderate renal impairment + concomitant treatment with verapamil: consider a dose reduction to 75 mg once daily.

The recently updated ESC guidelines on the management of AF differ slightly from the SmPC of Pradaxa in terms of dosing recommendations in the stroke prevention indication[15].

In line with the guidelines, this Writing Committee recommends the use of the lower 110 mg BID dose for the following populations:

- Elderly patients (age ≥ 80)
- Concomitant use of interacting drugs (e.g. verapamil)
- High bleeding risk (HAS-BLED score ≥ 3)
- Moderate renal impairment (CrCl 30-49 ml/min).

2. Measuring the anticoagulant effect of dabigatran

2.1 General

Unlike vitamin K antagonists (VKA), dabigatran has a predictable pharmacodynamic profile, is not affected by food and has a low potential for clinically relevant drug– drug interactions[1,2,3]. Therefore, it **requires no routine coagulation monitoring**[1] and no dose adjustment to achieve the required therapeutic effect[3,4].
Determining the anticoagulant effect of dabigatran **is however possible** and may be relevant in certain clinical situations, such as potential overdose, bleeding or emergency surgery, where clinicians will need to make an assessment of the anticoagulant status of a patient receiving dabigatran before deciding on further management strategies[5].

2.2 Available tests and their interpretation:

As dabigatran acts on thrombin-mediated conversion of fibrinogen to fibrin, it has an effect on all the routine coagulation assays. The maximum effect of dabigatran on clotting tests occurs at the same time as maximal plasma concentrations (~ 2 hours post-dose)[5].

When interpreting a coagulation assay in a dabigatran treated patient, it is therefore essential to know when dabigatran was administered relative to the time of blood sampling. For example, coagulation assay results obtained in a blood sample taken 2h after dabigatran ingestion (peak level) will have different (higher) results than those obtained in a sample taken 12h after ingestion of the same dose (this in contrast to VKA)[5]. Time delay between dabigatran intake and blood sampling should therefore be carefully recorded when biological monitoring is performed.

Table 3 shows the mean dabigatran plasma concentration and the 25-75th percentiles, as measured at steady state in the registration trials for the indications of stroke prevention in AF and primary prevention of venous thrombo-embolism[4,5,6].

Table 3: Dabigatran plasma concentrations

	Mean (ng/mL)	25 -75th percentile (ng/mL)
Stroke prevention in AF (150 mg BID)		
Peak (2h after intake)	175	117 - 275
Trough (12h after intake)	91	61 - 143
Stroke prevention in AF (110 mg BID)		
Peak (2h after intake)	126	85 - 200
Trough (12h after intake)	65	43 - 102
VTE prevention (220 mg QD)		
Peak (2h after intake)	70,8	35,2 - 162
Trough (24h after intake)	22,0	13,0 - 35,7

In situations where an assessment of the anticoagulant activity of dabigatran is required

❖ The **activated partial thromboplastin time** (aPTT) test, which is widely available, provides an approximate indication of the anticoagulation intensity achieved with dabigatran.
❖ The **INR** is less affected by dabigatran and should therefore not be used.

❖ If required, a more sensitive quantitative test with a **calibrated diluted Thrombin Time** can be performed.
❖ The **ECT** can also provide a direct measure of the activity of direct thrombin inhibitors.

The aPTT, DTT and ECT can provide guidance for the assessment of bleeding risk: measurements exceeding the 90th percentile at trough are considered to be associated with an increased risk of bleeding[4].

A. Activated partial thromboplastin time (aPTT)

- The aPTT provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding or at risk of bleeding, the aPTT may be useful in determining an excess of anticoagulant activity. However, it has limited sensitivity and is not suitable for precise quantification of the anticoagulant effect, especially at high plasma concentrations of dabigatran[4,5].

- When dabigatran was used for the prevention of stroke in AF with a twice daily dosing regimen, an **aPTT ratio greater than 2 x the upper limit of normal (ULN)** (or an aPTT prolongation of about 80 seconds) at trough (10-16h after the previous dose) reflected the 90th percentile of observations and is considered to be associated with a higher risk of bleeding[4,6].

B. Thrombin Time (TT) and calibrated diluted thrombin time

- The actual TT test measure will depend on the coagulometer and the thrombin lot used for the measurement. It is therefore advisable to use a calibrated diluted thrombin time with dabigatran standards to calculate the dabigatran plasma concentration rather than to determine the TT[5]. There is a linear relationship between dabigatran concentration and the dTT, which is therefore suitable for the precise quantitative assessment of dabigatran concentrations[5].

- A normal TT measurement indicates no clinically relevant anticoagulant effect of dabigatran[6].

- When dabigatran is used for the prevention of stroke in AF with a twice daily dosing regimen, a TT measure **>200 ng/mL dabigatran plasma concentration** (i.e. the 90th percentile - TT of approximately > 65 seconds) measured at trough, is associated with an increased risk of bleeding[6].

C. Ecarin Clotting Time (ECT)

- The ECT assay provides a direct measure of the activity of direct thrombin inhibitors[5].

- When dabigatran was used for the prevention of stroke in AF with twice daily dosing, an ECT of **greater than 3 x ULN** (or an ECT prolongation of > 103 seconds) at trough reflected the 90th percentile of observations and is considered to be associated with a higher risk of bleeding[4,6].

D. Prothrombin time (PT) and INR

- The INR test is unreliable in patients on dabigatran and false positive INR elevations have been reported. Therefore, INR tests should not be performed[4].

3. Drug-drug interactions

Dabigatran etexilate and dabigatran are not metabolised by the **cytochrome P450** system and have no in vitro effects on human cytochrome P450 enzymes.
Therefore, related medicinal product interactions are not expected with dabigatran[4].

Dabigatran etexilate is a substrate of the efflux transporter **P-glycoprotein** (P-gp). Concomitant administration of P-gp inhibitors or P-gp inducers can increase or decrease dabigatran plasma concentrations respectively[4].

In patients concomitantly taking dabigatran and **other drugs which may impair haemostasis** (such as NSAIDs, antiplatelets, selective serotonin and serotonin-norepinephrin reuptake inhibitors [SSRIs and SNRIs]), bleeding risk may be increased; close clinical surveillance is recommended in these cases[4].

Apart from this, dabigatran has a low propensity for drug-drug interactions with frequently used medications.
Table 4 summarizes the interactions that have been noted along with the measures to take, as recommended in the summary of product characteristics (SmPC).

Medication	Recommendation	
Anticoagulants, antiplatelets and other drugs which may impair haemostasis		
Anticoagulant agents e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc.), oral anticoagulants (warfarin, rivaroxaban, apixaban etc.)	Contra-indicated except ▪ if switching therapy to or from dabigatran or ▪ when UFH is given at doses necessary to maintain an open central venous or arterial catheter	
ASA, clopidogrel, NSAID, SSRI, SNRI	Careful benefit-risk assessment and close clinical surveillance	
P-gp inhibitors		
Very strong		
▪ Systemic ketoconazole and itraconazole, cyclosporine, tacrolimus and dronedarone	Contra-indicated	
Strong	Stroke prevention indication	VTE indication
▪ Verapamil	Dose reduction to 110 mg BID	Reduce the dose to 150 mg 1x/d
▪ Amiodarone ▪ Quinidine	No mandatory dose reduction but use with caution. No clinical experience when a loading dose of amiodarone is used (total daily dose of 800-1600mg).	If moderate renal impairment + verapamil: consider a dose reduction to 75 mg 1x/d
Others		
▪ Clarithromycin	Close monitoring	
▪ Posaconazole and protease inhibitors such as ritonavir	Not recommended due to lack of data	
P-gp inducers		
Rifampicin, St John's Wort, carbamazepine and phenytoin	Avoid	

4. Measures to take in case of an overdose without bleeding, or a clotting test indicating risk of bleeding

Doses of dabigatran etexilate beyond those recommended, expose the patient to an increased risk of bleeding[4]. In terms of management, it is important to distinguish between an overdose with and without bleeding complications. In case of bleeding complications, see also question 5.

4.1 Lab testing

In case of an overdose suspicion, coagulation tests can help to determine bleeding risk (see question 2 for the interpretation of coagulation tests with dabigatran).
A calibrated quantitative dTT test or repetitive dTT measurements allow prediction of the time by when certain dabigatran plasma levels will be reached, also in case additional measures e.g. dialysis have been initiated[4].

4.2 Management

There is currently no specific antidote to dabigatran. Dabigatran however has a short half-life (12 to 14 hours in patients with a normal renal function)[4].

In case of an overdose, dabigatran treatment should first of all be **discontinued**[4].

If administered within 1–2 h of the overdose, classical **activated charcoal** therapy can successfully adsorb dabigatran[5]. In this case, we propose to use a suspension of 20g active charcoal / 240 ml H_2O, with a standard dosing scheme for adults of 30 to 50 g.

Since dabigatran is excreted predominantly by the renal route, **adequate diuresis** must be maintained[4].

The use of **hemodialysis** may be considered. It should however be noted that there is only limited clinical experience in using dialysis in this setting[4,5]. Moreover, the risks of bleeding at puncture sites for dialysis needs to be balanced versus the risk of waiting.
Due to dabigatran's relatively low (~35%) plasma protein binding, hemodialysis could be effective in accelerating plasma clearance of dabigatran in the event of uncontrolled bleeding, especially in patients with renal impairment[5]. In an open-label study in which a single 50 mg dose of dabigatran was administered to 6 patients with end-stage renal disease on maintenance hemodialysis, the mean fraction of drug removed by dialysis was 62% at 2 hours and 68% at 4 hours[7].
Whether enhanced removal of dabigatran from plasma is possible via hemoperfusion over a charcoal filter is under evaluation[5]. At this moment, it cannot be recommended in patients.

5. Management of bleeding complications

If uncertainty exists around the anticoagulation intensity achieved with dabigatran (e.g. possible overexposure; recent change in renal function; …), it can be evaluated as described under Question 2.
Determination of renal function should be performed in order to estimate dabigatran elimination time.

In the event of hemorrhagic complications on dabigatran, treatment should be **discontinued** and the source of bleeding investigated[4]. Dabigatran has a short half-life (12 to 14 hours in patients with a normal renal function)[4] hence in cases of less serious bleeding, interruption of treatment will be sufficient to reverse the anticoagulant effect[8]. Ask the patient about the dosing regimen and intake over the last days/hours, and inquire recent changes in co-morbidity that may have impacted plasma levels (mainly renal function).

Since dabigatran is excreted predominantly by the renal route, **adequate diuresis** must be maintained[4].

Appropriate standard treatment, like surgical hemostasis and blood volume replacement, should be undertaken at the physician's discretion[4,5].
Consideration should also be given to administration of platelet concentrates in cases in which thrombocytopenia (< 60 x 109/L) is present or long-acting antiplatelet drugs have been used[4,9].

If these measures fail to control bleeding, the use of **hemodialysis** may be considered. It should however be noted that there is only limited clinical experience in using dialysis in this setting[4,5]. Moreover, the risks of bleeding at puncture sites for dialysis needs to be balanced versus the risk of waiting.
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There is currently no specific **antidote** to dabigatran.The antidotes available for LMWH and VKA, protamine sulfate and vitamin K respectively, do not impact the anticoagulation activity of dabigatran. For non-specific pro-coagulants, the following data are available:

Prothrombin Complex Concentrate (PCC, 4 factor concentrate: II, VII, IX and X) : In a study in rabbits, PCC inhibited dabigatran-induced bleeding in a rapid, dose-dependent manner[10]. In another study, PCC did not reverse the prolonged aPTT, ECT or TT in healthy volunteers treated with dabigatran, but bleeding time was not assessed in this

trial[11]. In a mouse ICH (intracranial haemorrhage) model, PCC prevented excess intracerebral haematoma expansion associated with dabigatran and reversed the prolonged bleeding time in a dose-dependent manner[12].

Recombinant activated factor VII (rFVIIa) reversed the prolonged aPTT and the prolonged bleeding time in rats treated with a high dose of dabigatran[13].

Activated prothrombin complex concentrate reversed the prolonged bleeding time but not the prolonged aPTT in rats treated with a high dose of dabigatran[13].

At this time, there is insufficient (pre)clinical experience on the administration of hemostatic agents in patients bleeding on dabigatran; the guidance provided in table 5 is based on expert consensus and is not clinically validated.

Table 5: Recommended a-specific pro-hemostatic agents

Hemostatic agent	Recommendations
PCC: 4 factor concentrate ▪ PPSB S.D. ® (vial 20 ml – FIX ≥ 400IE) ▪ Confidex® (vial 20 ml – FIX 500IE) ▪ Octaplex® (vial 20 ml – FIX 400 to 620IE)	The administration of Prothrombin Complex Concentrate (PCC) is suggested in case of life-threatening bleeding. After an initial administration of 25U/kg of the available PCC we recommend to clinically re-evaluate the need for a repeat administration of PCCs.
Desmopressin Minirin® Amp (4μg/ml) for IV use	Desmopressin can be considered in case of associated coagulopathy or thrombopathy. A standard dose scheme for bleeding disorders is 0,03μg/kg with a maximum of 20μg
aPCC: activated prothrombin concentrate Feiba S-Tim4®	There is some experimental evidence to support the role of aPCC in reversing the anticoagulant effect of dabigatran, but data on its usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited[4]. In view of the limited availability in Belgium, this writing group does currently not recommend the use of Feiba S-Tim4® for life-threatening bleeding in patients treated with dabigatran.
Recombinant human FVIIa Novoseven®	There is some experimental evidence to support the role of rhFVIIa in reversing the anticoagulant effect of dabigatran, but data on its usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited[4]. This writing group does therefore not recommend the use of Novoseven® for life-threatening bleeding in patients treated with dabigatran.

6. Patient undergoing a surgical intervention

6.1 General

Surgical interventions may require the temporary discontinuation of dabigatran[4]. One could opt to continue dabigatran for interventions with a low bleeding risk or for which hemostasis is straightforward. These can be superficial interventions, some dental procedures (see below), or interventions for cataract or glaucoma[14].

If the decision is to discontinue treatment, dabigatran should be stopped at least 24h prior to elective surgery, depending on renal function and risk of bleeding (see table 6)[4,5,6]

Table 6: Discontinuation rules before elective invasive or surgical procedures[4,5,6]

Renal function (CrCL ml/min)	Estimated half-life (h)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50-< 80	~ 15	2-3 days before	1-2 days before
≥ 30-< 50	~ 18	4 days before	2-3 days before (> 48 hours)

Given the rapid onset and offset of action of dabigatran, no bridging therapy with LMWH is required for the majority of interventions[15].

If an emergency intervention is required, dabigatran should be temporarily discontinued. Surgery or intervention should be delayed, if possible, until at least 12 hours after the last dose. If surgery cannot be delayed, the risk of bleeding may be increased. This risk of bleeding should then be weighed against the urgency of intervention[4,6].

Antithrombotic therapy should be restarted after the invasive procedure or surgical intervention as soon as effective hemostasis is achieved and the risk for bleeding complications is considered to be low.
For most procedures, it is appropriate to initiate a prophylactic dose of LMWH or dabigatran 110mg or 75mg (in case of total knee or hip replacement surgery) in the hours following the intervention, whereas therapeutic anticoagulation is deferred until at least 48 hours. Nevertheless, some surgical/invasive interventions that carry a high delayed bleeding risk might require a longer interval before restarting anticoagulation therapy.

6.2 Specific situations

A. Dental interventions

Dabigatran should not necessarily be discontinued for dental interventions like extraction of 1 to 3 teeth, paradontal surgery, incision of an abces or positioning of implants. The bleeding risk needs to be balanced against the thrombo-embolic risk. In such cases, the following precautions have to be taken:

- *The procedure should ideally be performed 12 hours after last dosing*
- *The procedure needs to be done with the least possible trauma*
- *After extraction, the wound should be sutured*
- *The patient can only leave the clinic when bleeding has completely stopped*
- *The patient should rinse his mouth gently with 10 ml of tranexamic acid 5%, 4 times a day for 5 days*
- *The patient should be instructed orally and in writing about the normal postprocedural course and the measures to be taken in case of bleeding*
- *The patient has to contact his dentist in case of bleeding that does not stop spontaneously*
- *The dentist (or his/her colleague) has to be accessible after hours[15].*

If the decision is to discontinue, dabigatran should be stopped 24h prior to tooth extraction or other dental procedure. It should be resumed as soon as haemostasis is achieved. For more extensive interventions, the patient should be referred to a maxillo-facial surgeon. Management of anticoagulation can then be guided by Table 6, above[4].

B. Neuraxial (spinal/epidural) anaesthesia

Procedures such as spinal anaesthesia, epidural anaesthesia and lumbar punction may require complete haemostatic function. Therefore, management of anticoagulation can be guided by Table 6, above, according the "high risk of bleeding" column[4].

The use of dabigatran in the presence of neuraxial anesthesia is not recommended by this working group. An ongoing treatment with high dose dabigatran (150 or 110 mg BID) particularly is an absolute contraindication to the use of neuraxial anesthesia and the presence of an indwelling neuraxial catheter. In a number of patients, and similar to VKAs, the interrupted treatment may have to be bridged temporarily with IV UFH or LMWH.

7. Patient presenting with an acute coronary syndrome (ACS)

7.1 Acute management

Patients who develop an ACS while on dabigatran should be treated according to usual clinical practice. Consideration should be given to temporarily suspend dabigatran treatment in the setting of ACS, should the treatment involve invasive procedures, such as percutaneous coronary intervention (PCI) or coronary artery bypass surgery, or if thrombolytic therapy is to be initiated.

It should be noted that dabigatran, relative to VKA, is a short acting agent. The timing of the last dose might therefore impact the level of anticoagulation prior to initiation of standard parenteral anticoagulation as used before and during (semi)urgent PCI. Recent intake of dabigatran might increase the risk of bleeding when initiating standard (full-dose) parenteral anticoagulant. The timing, choice and dose of standard anticoagulation thus needs to be balanced against the last intake of dabigatran (timing and dose) and the bleeding risk.

7.2 Long-term management

The addition of antiplatelet therapy to oral anticoagulants increases the risk of bleeding. Following an ACS and/or PCI in a patient with AF at risk of stroke, triple therapy (OAC, aspirin and clopidogrel) is recommended, provided it is kept short (e.g. 4 weeks) and the bleeding risk is low. Drug-eluting stents should hence be avoided and triple therapy used in the short term, followed by longer therapy with OAC plus a single antiplatelet drug (either clopidogrel or aspirin)[15,17].
The 2012 ESC guidelines state that, after one year, management can be with OAC alone in stable patients, where OAC can be adjusted-dose VKA therapy or probably one of the new oral anticoagulants[15].
Due to lack of data, this working group does however not recommend the use of dabigatran monotherapy at this stage.

8. Cardioversion in a dabigatran treated patient

Patients can stay on dabigatran while being cardioverted[4].
In patients with AF of > 48h duration (or AF of unknown duration) undergoing cardioversion, dabigatran should be given for at least 3 weeks prior to and continued for at least 4 weeks after cardioversion[15,17].

No prospective data are available concerning the safety of cardioversion under dabigatran treatment. Observational data from the RE-LY trial have shown a comparatively low stroke rate related to cardioversion in patients treated with dabigatran and VKA. However, more dabigatran patients underwent prior transesophageal echocardiography (TEE)[18]. Although there was no statistically higher

left atrial thrombus prevalence in dabigatran patients, it may be recommended to perform a TEE before planned cardioversion in patients taking dabigatran. Also, compliance of drug intake in the preceding 3 to 4 weeks should be inquired with the patient and the answer documented in the patient file.

> **Cave:**
> The routinely performed INR test prior to cardioversion can not be used in case of dabigatran use.
> A dabigatran-specific coagulation assay will only show if the patient has taken dabigatran that particular morning but does not give information on treatment compliance over the preceding 3 week period.

9. Patient presenting with a stroke

If a stroke occurs in a patient taking dabigatran, the drug should be stopped and intracranial hemorrhage should be excluded (using a CT or MRI scan)[17].

-   If intracranial hemorrhage (ICH) is present, consultation with a neurosurgeon is recommended. Otherwise, ICH should be managed like any other serious or life-threatening bleeding on dabigatran (see question 5).

-   An ischemic stroke should be treated according to usual clinical practice[19,20]. In general, thrombolysis is not recommended, as there is no supporting evidence available from the RE-LY trial. However, the use of fibrinolytic agents may be considered if the patient presents with a thrombin time (TT), Ecarin clotting time (ECT) or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range[4].

10. Initiation of dabigatran following an ischaemic stroke or TIA

Initiation of dabigatran treatment following an ischaemic stroke or TIA should follow the same rules as for VKA[21]:

-   In case of a TIA, anticoagulation treatment with dabigatran should begin as soon as possible. Bridging with LMW heparin is generally not required as dabigatran has a quick onset of action.

-   Dabigatran has not been studied within the first two weeks after a stroke in the RE-LY trial. Although currently there is no published experience, it is felt that doctors should follow the same rules they currently apply to initiate VKA, with the difference that dabigatran has a quicker onset of action.

11. Ischaemic stroke on dabigatran: management post acute phase

- Check patient compliance

- Check for other possible causes for stroke (atherosclerotic)

- Based on the recommendations for the use of VKA, dabigatran treatment can be restored for secondary stroke prevention[21].

References

1. Stangier J et al. Br J Clin Pharmacol 2007; 64:292–303.
2. Stangier J et al. J Clin Pharmacol 2005; 45:555–563.
3. Stangier J. Clin Pharmacokinet 2008; 47:285–295.
4. Pradaxa® Summary of Product Characteristics.
5. Van Ryn J et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103(6):1116-27.
6. Educational material as part of the EMA Risk Minimisation Plan.
7. Stangier J et al. Clin Pharmacokinet 2010; 49:259–268.
8. Levi M et al. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost 2011 Sep;9(9):1705-12. doi: 10.1111/j.1538-7836.2011.04432.x.
9. Pradaxa® Summary of Product Characteristics Canada.
10. Van Ryn J et al. Beriplex P/N reverses bleeding in an acute renal injury model after dabigatran overdose in rabbits. Pathophysiol Haemost Thromb 37 (Suppl 1), A94 (2010).
11. Eerenberg et al. Reversal of rivaroxaban and dabigatran by Prothrombin Complex Concentrate. A randomized, placebo-controlled, crossover study in healthy subjects. Circulation September 6. Epub ahead of print.
12. Zhou W et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke. 2011 Dec;42(12):3594-9.
13. Van Ryn J et al. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. Haematologica 93 (Suppl 1), 148 (2008).
14. Cairns JA et al. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter. Canadian Journal of Cardiology 2011; 27: 74–90.
15. Camm AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation * Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012 Nov;33(21):2719-47.
16. ACTA-richtlijn: Beleid bij tandheelkundige ingrepen tijdens antitrombotische behandeling. 2010.
17. Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369-2429.
18. Nagarakanti R et al. Dabigatran Versus Warfarin in Patients With Atrial Fibrillation: An Analysis of Patients Undergoing Cardioversion. Circulation 2011: 123 , 131-136.
19. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. European Stroke Organisation (ESO) Executive Committee; ESO WritingCommittee. Cerebrovasc Dis. 2008;25(5):457-507.
20. http://www.eso-stroke.org/pdf/ESO%20Guidelines_update_Jan_2009.pdf
21. Antithrombotic and thrombolytic therapy, 8th edition: ACCP Guidelines. Chest June 2008: 133:6 Suppl.