Thrombolysis for acute ischaemic stroke in patients treated with dabigatran:

PRACTICAL GUIDANCE

Introduction

Oral anticoagulation reduces the risk of acute ischaemic stroke in patients with non-valvular atrial fibrillation (AF), but the risk is not entirely eliminated. Warfarin, for example, reduces the risk of ischaemic stroke by at least 65%,[1] but the residual risk is estimated at 1.4 to 1.9% per year.[2] Patients with AF taking oral anticoagulants might also experience an ischaemic stroke arising from other risk factors, especially atherosclerotic cerebrovascular disease.

Timely thrombolysis with recombinant tissue plasminogen activator (rt-PA) is an effective treatment for acute ischaemic stroke, increasing survival free of dependency.[3] If patients are fully anticoagulated, by any medication, then thrombolysis is contraindicated. However, thrombolysis may be considered in some circumstances if the level of anticoagulation is subtherapeutic.

Although there is growing evidence on the use of thrombolysis for acute ischaemic stroke in patients treated with warfarin[4] and discussion in clinical guidelines on the use of rt-PA in patients treated with warfarin,[5,6,7] there is limited experience with thrombolysis in patients who have taken novel oral anticoagulants (NOACs) including dabigatran, rivaroxaban or apixaban.

This document provides information for clinicians considering thrombolysis in patients with acute ischaemic stroke who have been treated with dabigatran, and was developed by an expert working group with support from an unrestricted educational grant by Boehringer Ingelheim. Please check for updates after January 2014.

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Dabigatran

The direct thrombin inhibitor dabigatran at a dose of 150 mg twice daily is superior to warfarin in preventing strokes in patients with AF and is associated with a similar rate of major haemorrhage.[8] A dose of 110 mg twice daily is non-inferior to warfarin in stroke prevention and has a significantly lower rate of any bleeding including major haemorrhage. The reduced dose of 110 mg twice daily is recommended in patients aged 75 and above, and may also be considered in patients with moderate renal impairment (as 80% of dabigatran excretion occurs through the kidneys) or a potentially higher risk of major bleeding.

In healthy volunteers, peak plasma concentrations of dabigatran are reached 0.5-2 hours after oral dosing.[9] The anticoagulant effect commences within minutes of administration. When at steady state, dabigatran has a half-life of 13 to 17 hours in patients with normal renal function. The time to peak plasma concentrations and the half-life may be extended in patients with renal impairment.

Dabigatran is approved in Australia for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) and at least one additional risk factor for stroke. Dabigatran is also indicated for the prevention of venous thromboembolic events in adults who have undergone elective total hip or knee replacement.

More than 25,000 Australian patients were treated with dabigatran under a patient familiarisation program managed by the medication's sponsor. The PBS listing of dabigatran in September 2013 for the prevention of stroke in patients with non-valvular AF is likely to markedly expand the number of people exposed to the medication.

Existing guidance

The approved Product Information for both dabigatran and rt-PA indicates that clinicians may "consider" concomitant treatment with dabigatran and thrombolysis for acute ischaemic stroke in some circumstances. The Product Information for Pradaxa (dabigatran) states:

> *The concomitant use of PRADAXA with fibrinolytic treatments has not been studied and may increase the risk of bleeding. The use of fibrinolytic agents for the treatment of acute ischemic stroke may be considered if the patient presents with a thrombin time (TT), or ecarin clotting time (ECT), or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range.*

The Product Information for Actilyse (rt-PA) states:

> *Patients receiving oral anticoagulant treatment: The use of ACTILYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity.*

Guidelines from the European Heart Rhythm Association discuss the treatment of patients presenting with an acute ischaemic stroke while taking dabigatran or other NOACs.[10] They urge caution unless anticoagulant activity can reliably be excluded:

> *"Until there are reliable and sensitive rapid (point-of-care) tests for the individual NOAC, we would discourage the use of thrombolytics in situations with uncertainty about the anticoagulation status. Therefore, we believe that only in exceptional single cases in which reliable coagulation assessment…is within the normal reference range, the use of fibrinolytic agents can be considered.*

Similarly, a recent review of acute ischaemic stroke in patients receiving anti-thrombotic treatment advised that, in a patient who took dabigatran at least 12 hours ago and laboratory markers of anticoagulation were normal or only slightly raised, treatment with thrombolysis could be considered if established exclusion criteria for thrombolysis were ruled out.[11] The severity of stroke symptoms, the vessel status and the perfusion deficit might be helpful in decision-making.

Clinical experience

Seven case reports have been published describing patients with ischaemic stroke treated with thrombolysis while taking dabigatran.[12] Six patients experienced an improvement in their stroke symptoms. All had a normal or slightly elevated activated partial thromboplastin time (aPTT – see below for more information on coagulation tests). Four had taken dabigatran 7 to 18 hours previously, but the time of dosing was unknown in the other two cases. One of the seven patients, who had a mildly elevated aPTT and took dabigatran 6 hours previously, experienced a fatal intracerebral haemorrhage after thrombolysis.

Coagulation assays for dabigatran[9-11,13,14]

An advantage of NOACs is that, unlike warfarin, they do not require routine monitoring of coagulation. However, an assessment of exposure to the medications and their anticoagulant effect may be required in emergency situations including an apparent ischaemic stroke. In contrast to the international normalised ratio (INR) used to assess coagulation in patients treated with warfarin, the results of coagulation tests will depend on the timing of the last dose as there is a close correlation between the plasma dabigatran concentration and the degree of anticoagulant effect.[9] Anticoagulant activity may still be increasing if the dose was taken only 1-2 hours before the blood sample was taken. In addition, renal impairment is likely to prolong the elimination half-life of dabigatran.

The interpretation of coagulation tests is not influenced by whether the patient has been taking 110 mg or 150 mg of dabigatran.

The role of coagulation tests in quantitatively and qualitatively assessing current dabigatran activity are summarised below:

- **Prothrombin time (PT/INR)**
  Dabigatran causes only a small prolongation of PT and the dose-response curve is relatively flat. PT, expressed as INR, is too insensitive to reliably detect the anticoagulant activity of dabigatran and is not useful as a monitoring tool. If the PT/INR is prolonged the reason for this needs to be determined before thrombolysis is considered.

- **Thrombin clotting time (TT)**
  Dabigatran, a direct thrombin inhibitor, causes a substantial prolongation of TT. The dose response between dabigatran and TT is linear but the test is too sensitive to monitor the plasma concentration, as even a clinically insignificant concentration can prolong the TT two to three times. High concentrations of dabigatran may prolong TT to such an extent that it exceeds the maximum measurement time of coagulometers. A normal TT effectively excludes any dabigatran activity.

- **Diluted thrombin time (dTT)**
  A dTT calibrated for dabigatran can be measured by the Hemoclot® test. The dTT has a direct linear relationship with the dabigatran plasma concentration and is suitable for the quantitative assessment of dabigatran concentrations. When trough levels of dabigatran are reached at about 6 hours post the last dose, a dTT greater than 100 ng/mL or greater than 65 seconds suggests an excess risk of bleeding. A normal dTT result indicates there is no clinically-relevant dabigatran activity.

- **Ecarin clotting time (ECT)**
  Dabigatran causes a substantial prolongation of ECT, a specific assay for thrombin generation. When dabigatran is dosed twice daily, a prolongation of ECT to ≥3 times the upper limit of normal at trough is associated with excess bleeding risk. ECT is used largely as a research tool and has limited availability. A commercial kit which is standardised or validated for dabigatran is not yet available.

- **Activated partial thromboplastin time (aPTT)**
  The relationship between aPTT and dabigatran plasma concentrations is curvilinear, flattening at higher concentrations. It is, therefore, unable to provide a quantitative assessment of dabigatran concentrations. In practice, it is a useful qualitative tool. aPTT ≥2 times the upper limit of normal at trough (typically >65 seconds) suggests an increased bleeding risk. The sensitivity of aPTT reagents is variable, so the results must be interpreted according to the specific normal values of the laboratory. aPTT may be prolonged by factors other than anticoagulation, including diseases such as lupus that increase levels of acute phase proteins.

Practical considerations

- In general, thrombolysis for acute ischaemic stroke is contraindicated in patients who are fully anticoagulated with dabigatran because the risk of bleeding complications, particularly intracerebral haemorrhage, is significantly increased.

- However, in patients who would otherwise be eligible for thrombolysis, uncertainty around dabigatran intake or time of dosage creates new clinical challenges. A history of treatment with dabigatran should not cause stroke patients to be inappropriately denied the opportunity of benefiting from thrombolytic therapy. For example, clinical judgment might support the use of thrombolysis if there is clear evidence that the patient has normal renal function, has not taken any dabigatran for at least the past 12 hours, and coagulation assays are consistent with an absence of dabigatran or a very low level of dabigatran activity. Other factors to consider in assessing the likely risks and benefits of thrombolysis include the severity of stroke symptoms and the extent of any perfusion deficit as assessed by imaging.

- If there is any uncertainty about the timing of the last dabigatran dose, coagulation assays must account for the possibility that the patient has taken the medication in the last few hours before obtaining the blood sample. Dabigatran concentrations, and anticoagulant activity, may continue to increase for 2-3 hours after dosing.

- Urgent coagulation assays should be requested if thrombolysis is being considered in patients known to have been prescribed dabigatran in the recent past. The availability of assays will vary between centres but aPTT is widely available, and whenever possible additional tests such as Hemoclot or TT should also be requested:

  - Clinically-significant anticoagulant activity of dabigatran is excluded by normal TT, ECT or Hemoclot. A normal aPTT supports the absence of dabigatran but does not completely exclude current dabigatran activity because the aPTT is dependent on factor VIII activity which can be elevated in response to an acute ischaemic event. For that reason we recommend that both a TT and an aPTT are requested where the ECT or Hemoclot test is not available.

  - A low level of dabigatran activity is suggested by TT less than twice the upper limit of normal, or a Hemoclot less than 40 ng/mL. There is insufficient data to provide clear guidance on ECT to establish acceptable limits above normal.

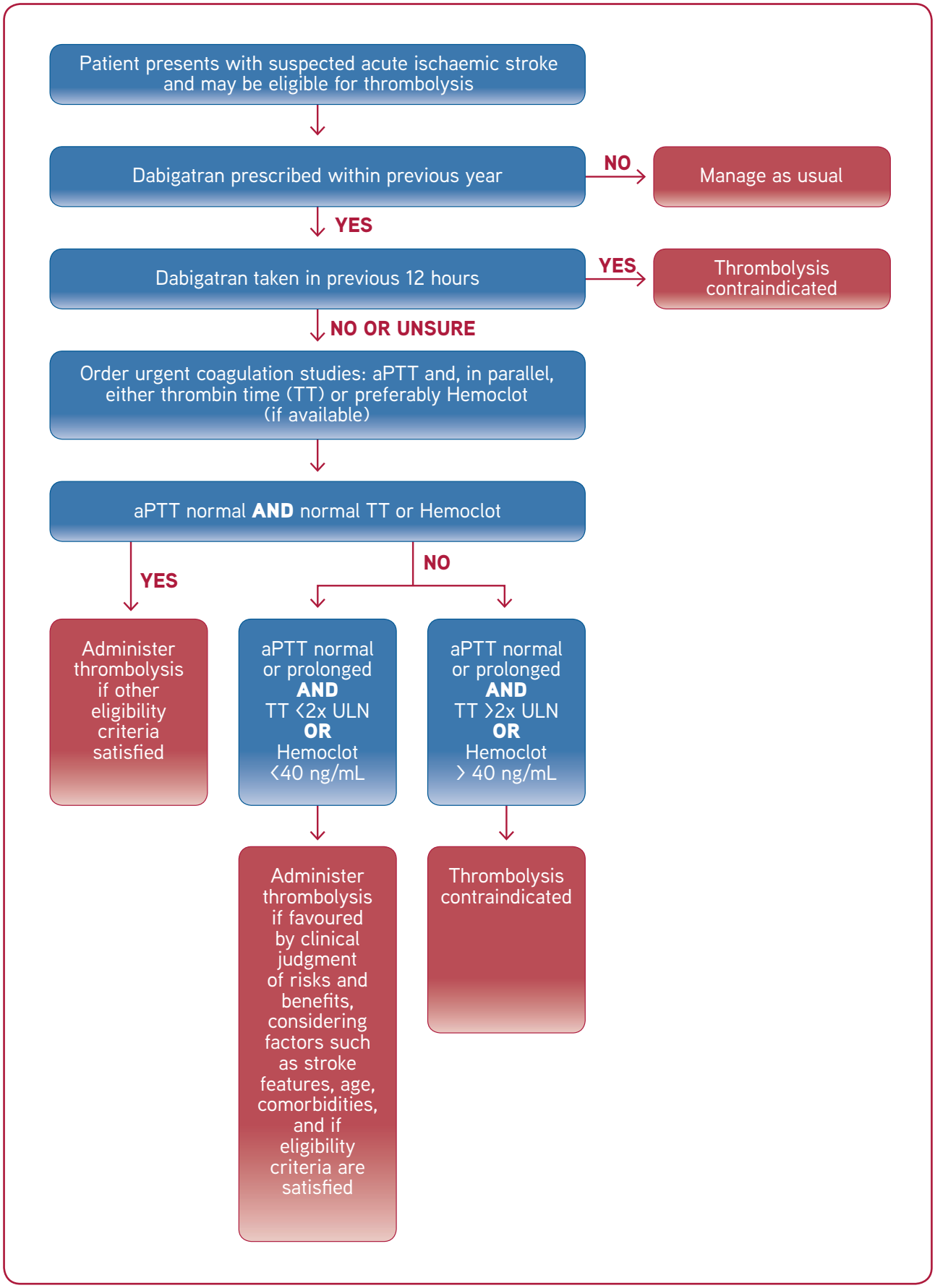
  Whether a low residual level of dabigatran activity excludes the patient from thrombolysis is a matter of clinical judgment, weighing up potential benefit, possible risk and likely natural history of stroke syndrome untreated.

- Prior dabigatran therapy is unlikely to influence the treatment of bleeding complications following rt-PA treatment. Protocols for managing haemorrhage in patients treated with anticoagulants are well-established, and generally limited to supportive therapy for an intracerebral haemorrhage, specific interventions for cerebellar and intraventricular haemorrhage, and standard measures such as compression, surgery and resuscitation for extra-cranial haemorrhage.

- The occurrence of stroke while on anticoagulant treatment strengthens, rather than reduces, the need for continuing anticoagulation. There are established guidelines for re-initiating anticoagulation: for example, the European Heart Rhythm Association recommends recommencing anticoagulation in patients with 1 day after a transient ischaemic attack, 3 days after a small non-disabling infarct, 6 days after a moderate stroke and 2 or 3 weeks after a large infarct.[10]

These practical considerations are summarised in the flow chart overleaf.

Flow chart


Patient presents with suspected acute ischaemic stroke and may be eligible for thrombolysis
Dabigatran prescribed within previous year
NO
Manage as usual
YES
Dabigatran taken in previous 12 hours
YES
Thrombolysis contraindicated
NO OR UNSURE
Order urgent coagulation studies: aPTT and, in parallel, either thrombin time (TT) or preferably Hemoclot (if available)
aPTT normal AND normal TT or Hemoclot
YES
NO
Administer thrombolysis if other eligibility criteria satisfied
aPTT normal or prolonged AND TT <2x ULN OR Hemoclot <40 ng/mL
aPTT normal or prolonged AND TT >2x ULN OR Hemoclot > 40 ng/mL
Administer thrombolysis if favoured by clinical judgment of risks and benefits, considering factors such as stroke features, age, comorbidities, and if eligibility criteria are satisfied
Thrombolysis contraindicated

Future developments

Resolving the clinical challenges of thrombolysis for acute ischaemic stroke in patients already receiving dabigatran and other anticoagulants will be facilitated by systematic accumulation of data. In the meantime, clinicians must continue to exercise their careful judgment about the risks and benefits of thrombolysis, accounting for the individual features of their patients.

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