Stoke prevention in atrial fibrillation: update with NOAC treatment and the impact of reversal

Dr. Allison Kirso(1)

1Rosswrite Medical Writing, Gorebridge, Midlothian, UK.

Received – 17 December 2018; Accepted – 18 December 2018

ABSTRACT

Results from RCTs and real-world analyses consistently demonstrate the safety and efficacy profiles of dabigatran in patients with atrial fibrillation. However, underdosing and under-prescribing of anticoagulants may leave patients at risk of stroke; both doses of dabigatran were fully tested and shown to be effective in stroke prevention. Although side effects of novel oral anticoagulants appear to be improved over vitamin K antagonists (VKA), there may be occasions where the therapeutic effect of the anticoagulant needs to be reversed, for instance, before an urgent surgical procedure. Idarucizumab has been established as an effective reversal agent for dabigatran-treated patients and can be administered promptly and safely in a mobile, pre-hospital setting.

Key words: anticoagulant; stroke; therapeutic reversal; dabigatran; idarucizumab; warfarin

Corresponding author: Allison Kirsop – allison@rosswrite.com

Acknowledgements: We thank the following faculty for their valuable contributions to the symposium:

R Bernstein, Northwestern Medicine Distinguished Physician in Vascular Neurology; Medical Director of Telehealth; Professor of Neurology, Feinberg School of Medicine of Northwestern University, Chicago, IL, USA.

T Steiner, Professor of Neurology and Neurointensive Care, and Director of Department of Neurology, Klinikum Frankfurt Hochst; Affiliated Professor, Heidelberg University Hospital, Germany; Honorary Professor, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

Acknowledgement of thanks is also extended to Oruen Ltd., for editorial assistance and to Dr Juliane Meyerhoff for support with medical writing in the preparation of this manuscript.

INTRODUCTION

Anticoagulation through novel oral anticoagulants (NOACs) or vitamin-K antagonists (VKAs) such as warfarin, has been demonstrated to greatly reduce the risk of ischaemic stroke in patients with atrial fibrillation (AF). NOACs have also been shown to significantly reduce the rate of haemorrhagic stroke compared with warfarin. Many advantages of NOACs (direct factor Xa (FXa) inhibitors rivaroxaban, apixaban and edoxaban, and the thrombin inhibitor dabigatran etexilate (dabigatran)) have been confirmed in clinical trials and in studies focussing on practice-based evidence, and these anticoagulants have essentially displaced VKAs for secondary stroke prevention in patients with AF due to convenience, efficacy, and an improved safety profile in many areas around the globe. However, both ischaemic and haemorrhagic stroke are challenging and urgent situations. Accordingly, the therapeutic effect of anticoagulation is a contraindication for intravenous thrombolysis in patients with ischaemic stroke(1,2) and it is only possible to reverse anticoagulation immediately in dabigatran-treated patients.

Latest insights on NOACs

A comparison of four NOACs in general use – dabigatran, apixaban, rivaroxaban, and edoxaban – highlights important differences for practitioners when making treatment decisions (Figure 1).
Stroke prevention in atrial fibrillation: update with NOAC treatment and the impact of reversal

Only dabigatran offers two fully tested dose options for patient treatment. In the pivotal RE-LY trial, the two doses were randomly assigned; ~6000 patients were administered 150 mg BID of dabigatran, and another 6000 received the 110 mg BID dose. There were no dose reductions for specific patient characteristics, such as renal function, age, or body weight. Both doses of dabigatran were randomised and compared with warfarin (target INR 2.0-3.0) as the primary comparison of the trial.

In the ARISTOTLE trial, apixaban was tested in ~7000 patients as compared with ~7000 patients receiving warfarin in a randomised, double blind study. If trial participants met two of three specific criteria related to creatinine clearance, low body weight, and age ≥80 years, the standard 5 mg dose of apixaban was lowered to 2.5 mg BID. However, this was a dose adjustment in one arm (and occurred in 428 patients) – and was not an independent arm of the study. This scenario was also used in the ROCKET AF study; a total of 14,264 patients were randomised to receive 20 mg rivaroxaban OD or dose-adjusted warfarin in this multi-centre, double-blind, double-dummy, event-driven trial. If trial participants had impaired creatinine clearance (30-49 mL per minute), the dose was lowered to 15 mg OD, and represented 20.7% of the total patients studied with rivaroxaban (N=1474).

Results: comparison with warfarin
All NOACs showed statistical non-inferiority for stroke/systemic embolism vs warfarin; dabigatran 150 mg and apixaban were even superior. Only dabigatran 150 mg BID showed a significant reduction in ischemic stroke compared with warfarin. All the trials conducted have differences that do not allow a direct comparison of NOACs with each other, and the results presented here describe the comparisons in each trial with the warfarin comparator.

Of the novel agents have a dramatically lower risk of bleeding in the brain compared with warfarin, and this is emphasised as the principal reason to choose NOAC treatment over warfarin.

Cardiovascular mortality was reduced with 150 mg BID dabigatran and with edoxaban, whereas rates for 110 mg BID dabigatran and other novel agents were similar to warfarin. A reduction in major bleeding was reported with apixaban, 110 mg BID dabigatran, and edoxaban as compared with warfarin treatment; results for rivaroxaban were not significantly different.

Secondary stroke prevention
In addition to primary stroke prevention, the importance of secondary stroke prevention in patients with AF is emphasised in the 2016 guidelines for AF management of the European Society of Cardiology, which recommend the use of NOACs in preference to VKAs or aspirin in patients with AF. If a patient has a stroke while taking an anticoagulant, one potential reason may be that the patient is not adhering to the therapy as prescribed. Thus it is important for practitioners to assess patient adherence before assuming that a drug has failed.

Cerebrovascular events
In the RE-LY trial, around 20% of participants had a history of a prior cerebrovascular event, and for these patients, there is around a 2-fold higher risk of a recurrent event, compared with the risk of first stroke. Both 150 mg and 110 mg BID dabigatran had a consistent effect on preventing stroke in this population as in those without a prior stroke or TIA, i.e. the 150 mg dose was superior to warfarin and the 110 mg dose as effective as warfarin in preventing a further stroke. (Figure 2).
In atrial fibrillation, stroke prevention is a critical consideration. New oral anticoagulants (NOACs) have been introduced as alternatives to traditional agents like warfarin. The efficacy of NOACs, particularly dabigatran, in preventing stroke has been evaluated in several clinical trials.

**Intracerebral haemorrhage (ICH) and NOAC safety profile**

Reduced intracranial bleeding is the principal reason to encourage the use of NOACs, as a patient who may be well-controlled on warfarin is still at risk of increased intracerebral haemorrhage—a risk that can be dramatically lowered with one of the novel agents. This observation remains consistent in the subpopulation of patients in the clinical trials who had a prior stroke, according to a recent meta-analysis. In addition, a small study (~300 patients) in non-AF patients who presented with an acute minor stroke or transient ischaemic attack (TIA) were randomised to either aspirin, which would be the usual choice, or to 150/110 mg BID of dabigatran. There were no major bleeds in either group, haemorrhagic transformation, or frank intraparenchymal haemorrhage. Although the study was small, it is reassuring that no major safety problems arose on starting the medication early after a TIA or small, non-disabling stroke.

**Numerous real-world analyses demonstrate consistent dabigatran safety profile (major bleeding) vs rivaroxaban**

The randomised-controlled trial (RCT) is the gold standard of evidence-based medicine; carefully designed experiments which introduce a treatment or exposure to study the effect on real patients. Practice-based knowledge—an important component of evidence-based practice—arises from professional experience and is gained over time. Several retrospective studies have used health insurance databases and other means to monitor prescribing practice in clinical settings, and numerous real-world analyses consistently demonstrate a similar or improved safety profile (major bleeding) for dabigatran vs warfarin. This conclusion does not come from randomised trial data, but good clinical judgement, and highlights how practitioners have learned how to use this medication safely. The safety outcome is repeated in several other practice-based studies which demonstrate, in general, the advantage of dabigatran vs rivaroxaban (Figure 3).

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**Figure 2. Efficacy of 150 mg and 110 mg BID dabigatran compared with warfarin in patients with history of a prior cardiovascular event.**

**Figure 3. Comparison of safety profiles between dabigatran and rivaroxaban.**
Anticoagulation is the most effective preventive therapy for patients with AF at risk of stroke, yet despite this some patients fail treatment. In these circumstances, it is important to remember other potential causes of stroke; small vessel disease, aortic arch atheroma, and carotid disease. It may also be that a patient is non-compliant, with a low INR, or in the case of novel agents they may be taking too low a dose, or taking it incorrectly. However, increasing information demonstrates that patients are also inappropriately prescribed lower doses of NOACs to reduce the risk of bleeding, but which may put patients at a higher risk of ischaemic stroke. In the phase 3 trials, only a limited number of selected patients (i.e. elderly, impaired renal function, low body weight) on rivaroxaban and apixaban were given the lower dose regimen. However, in practice, many patients that do not meet these criteria, and should receive the higher dose as tested in the clinical trials, are being prescribed the lower dose. This may be one cause of medication failure. The only independently proven low dose NOAC which is effective compared with warfarin in preventing stroke is the 110 mg BID dose of dabigatran.

**Dabigatran reversal with idarucizumab in neurological emergencies**

**Thrombolysis in acute ischaemic stroke patients taking anticoagulation**

Guidelines recommend IV thrombolysis with rt-PA as the standard treatment for acute ischaemic stroke; thrombectomy should also be considered if available, although not all locations are amenable to the procedure. Patients are excluded from receiving this beneficial therapy if they are taking an anticoagulant and present in the clinic with evidence of systemic anticoagulation, as there is an increased risk of bleeding. Thrombolysis can be performed in patients taking VKAs if the INR is less than 1.7. However, guidelines for patients presenting with ischaemic stroke who are taking NOACs recommend thrombolysis only if the NOAC is no longer measurable in blood. Thus, the availability of a direct reversal agent for dabigatran allows the immediate reversal of its anticoagulant effect, thereby allowing thrombolytic treatment to be used.

A retrospective study (N=60) from 50 stroke centres in the German Neurology Network evaluated the outcomes of thrombolysis in dabigatran patients with acute stroke after idarucizumab administration. Around 80% of patients showed clinical improvement after administration of idarucizumab and alteplase, with a median NIHSS=6. There were no bleeding complications, and no thrombotic events related to idarucizumab. Only three of these 60 patients (5%) died during the investigation.

As an aid for practitioners in how NOACs should be used in the management of ischaemic stroke, the European Heart Rhythm Association (EHRA) has made some recommendations and produced a practical guide (Figure 5).
The speed and ability of idarucizumab to reverse dabigatran anticoagulation has a particular advantage in the mobile pre-hospital setting and allows patients to receive swift reperfusion therapy. The Melbourne mobile stroke unit is a specialised service where a multidisciplinary stroke team can deliver prehospital assessment, CT scans, and treatment. In a feasibility study, a total of 20 thrombolysis cases were identified through the mobile stroke unit treatment registry since its launch in November 2017. Three patients were treated with IV idarucizumab 5g as a dabigatran-reversal agent with a mean time of 10 minutes between anticoagulant reversal and thrombolysis. They were subsequently discharged for rehabilitation after neurological recovery was confirmed, and demonstrates how a mobile stroke unit can provide swift, instant treatment, and expedites hyperacute therapy. Therefore, a particular benefit of administering idarucizumab in a pre-hospital setting is the availability and prompt access to the drug.

**Treatment options for intracranial haemorrhage in patients taking anticoagulants**

A potentially devastating complication of oral anticoagulation in patients, albeit infrequent, is intracerebral haemorrhage (ICH); patients have considerably poor functional outcomes and high mortality rates. However, despite the introduction of NOACs which significantly reduced the rate of ICH as compared to VKAs, VKAs are still widely used in some countries for stroke prevention in patients with AF. Haematoma expansion can lead to severe disability or death, (also for patients who receive immediate treatment but with a very large ICH initially), and VKA reversal is usually augmented in routine clinical practice.

The randomised INCH safety and efficacy trial set out to investigate differences between fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) for normalising INR in patients with acute phase VKA-related ICH. Although a small study, the 4-factor PCC arm showed that there was a significant reduction in the INR to ~1.2, achieved within three hours after treatment with PCC. This faster normalisation over FFP also resulted in markedly reduced haematoma expansion. Current guidelines recommend PCC for routine management of factor Xa inhibitor-related haemorrhage, including ICH. A recent retrospective study presented findings of an analysis of PCC efficacy and performance in haematoma reduction, mortality, and functional outcomes in patients with NOAC-related ICH. It suggested that haemostatic management with PCC was not associated with a reduced risk for any of the outcomes investigated and that blood pressure management seemed to be more related to an improved outcome. Thus a recommendation was made for more clinical trials in patients with NOAC-related ICH, to determine how haemostatic treatments and blood pressure management influence haematoma expansion.

For dabigatran-related bleeding complications, idarucizumab is the only antidote and is highly effective as a reversal agent. Idarucizumab is a humanised monoclonal antibody fragment with a binding affinity for dabigatran of ~350x higher than dabigatran for thrombin. It is administered intravenously, and the agent has no known procoagulant or anticoagulant activity. Globally, idarucizumab is widely available and has been tested and approved for two indications; uncontrolled bleeding, and

**EHRA Practical Guide 2018 on management of acute ischemic stroke with NOAC use**

<table>
<thead>
<tr>
<th>Acute ischemic stroke with clinically relevant neurological deficit</th>
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<tbody>
<tr>
<td>NOAC plasma level below the lower limit of detection</td>
</tr>
<tr>
<td>Last NOAC intake &gt;45 hours, normal renal function</td>
</tr>
<tr>
<td>Direct antidote available*</td>
</tr>
<tr>
<td>Last NOAC intake within 24-48 hrs &amp; normal renal function OR NOAC plasma level &lt;30 ng/mL, for rivaroxaban, apixaban, or edoxaban (measured &gt;4 hrs after intake)*</td>
</tr>
<tr>
<td>Consider thrombolysis in selected patients* after reversal</td>
</tr>
<tr>
<td>Proceed with thrombolysis*</td>
</tr>
<tr>
<td>Proceed (simultaneously) with endovascular thrombectomy*</td>
</tr>
</tbody>
</table>

*Currently only available in the EU for dabigatran (idarucizumab). *Perform systemic thrombolysis only if there are no (other) contraindications for intravenous application of tPA. According to its label, *Perform endovascular thrombectomy only if there is a larger vessel occlusion and procedures is indicated and feasible according to present evidence. *According to expert consensus. EHRA, European Heart Rhythm Association. Stella et al. Eur Heart J 2015

Figure 5. EHRA practical guidance and recommendations for the management of NOACs in patients with acute ischaemic stroke.
where there is a need for anticoagulation reversal before an emergency procedure. It is easy to use, and because it binds so specifically to dabigatran, there are no known interactions with other molecules.

A German national data collection provided an insight into the clinical use of idarucizumab in patients under effective dabigatran anticoagulation therapy, and included a small cohort of patients with intracranial haemorrhage (N=12). Of this group, eight patients presented with ICH, three with subdural haemorrhage, and one with subarachnoid haemorrhage. Five patients were taking the higher dose of dabigatran (150 mg BID), and an important finding was that only two patients were documented with haematoma expansion; this supports the findings in the RE-LY trial where the incidence of ICH, but not mortality, was considerably lower in patients on dabigatran.51

**An example case study**

An 86-year-old woman on prescribed dabigatran for AF and a history of diabetes and hypertension, presented with intracranial haemorrhage. Her last dose of dabigatran was three hours before admission. In this patient, the practitioner’s goal is to prevent haematoma growth, normalise the level of anti-coagulant activity, control BP, and treat the patient quickly. Idarucizumab was administered immediately at which point coagulation test results normalised; thrombin time (TT) was reduced from >200 s to 18 s and activated partial thromboplastin time (aPTT) from 44 s to 34 s. Reversal of anticoagulation appeared to prevent further haematoma expansion, and the patient was discharged after three weeks to a rehabilitation clinic, with NIHSS=2.†

The RE-VERSE AD trial demonstrated that dabigatran was immediately reversed on administration of idarucizumab in patients with ICH, irrespective of whether patients had subarachnoid haemorrhage, subdural haematoma, or intraparenchymal haemorrhage. Complete reversal was measured by diluted thrombin time (dTT) and ecarin clotting time (ECT), and was achieved in 100% of patients; no patients required a second dose of idarucizumab. To highlight the clinical impact of these results, an indirect comparison of mortality rates can be made in dabigatran-treated patients with ICH from the RE-VERSE AD and RE-LY trials; mortality rates were 16% and 35-40%, respectively.52,53

The EHRA practical guide 2018 for the management of bleeding recommends that idarucizumab be used in patients who are taking dabigatran (Figure 6) and instructs on how to deal with life-threatening bleeding for dabigatran-treated patients.

**CONCLUSION**

RCTs and real-world analyses have consistently demonstrated the safety and efficacy profiles of dabigatran in patients with AF. These results are also reported in a two-year follow-up in clinical practice of patients in the GLORIA-AF study, with and without prior stroke or TIA. This further confirms the benefit of both doses of dabigatran that have been fully tested in AF patients for stroke prevention.

Fibrinolytic therapy is one available option for acute ischaemic stroke and better outcomes are associated with earlier treatment. Intravenous thrombolysis can be highly effective if administered rapidly after stroke onset, and the wide availability of idarucizumab – a fast-acting, specific, reversal agent for dabigatran – may have a significant impact on clinical practice in patients taking dabigatran. These initial data demonstrate that dabigatran is not a contraindication for thrombolysis if reversed prior to this procedure with idarucizumab.
In addition, by immediately inhibiting anticoagulation in patients with ICH, there appears to be a beneficial effect on reduced haematoma growth, and this may also improve outcomes in ICH patients. Administration of PCC has been demonstrated as advantageous over FPP to reverse the outcomes in ICH patients. Initial data show that rapid administration of idarucizumab in dabigatran-treated patients is successful both in the hospital and pre-hospital setting.

Details of any specific patient cases have been altered to protect patient confidentiality.

REFERENCES
