Management of acute stroke in patients taking novel oral anticoagulants

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Each year, 1·0–2·0% of individuals with atrial fibrillation and 0·1–0·2% of those with venous thromboembolism who are receiving one of the novel oral anticoagulants (dabigatran, rivaroxaban, or apixaban) can be expected to experience an acute ischemic stroke. Additionally, 0·2–0·5% of individuals with atrial fibrillation who are receiving one of the novel oral anticoagulants can be expected to experience an intracranial hemorrhage. This opinion piece addresses the current literature and offers practical approaches to the management of patients receiving novel oral anticoagulants who present with an ischemic or hemorrhagic stroke. Specifically, we discuss the role of thrombolysis in anticoagulated patients with acute ischemic stroke and factors to consider concerning restarting anticoagulation after acute ischemic and hemorrhagic stroke.

Key words: acute stroke, anticoagulants, intracerebral hemorrhage, secondary prevention, thrombolytic therapy

Introduction

In recent years, the novel oral anticoagulant (NOAC) agents dabigatran (a direct thrombin inhibitor), rivaroxaban, and apixaban (direct Factor Xa inhibitors) have been approved for primary and secondary prevention of stroke in patients with atrial fibrillation (AF), and for the prevention of venous thromboembolism (VTE) in patients undergoing total hip or knee replacement (1–3). Compared with traditional agents such as the vitamin K antagonists (VKAs), the NOACs offer benefits in terms of efficacy, safety [reduced risk of intracranial hemorrhage (ICH)], and convenience (4,5). Hence, it is likely that the proportion of patients being prescribed and benefitting from these newer agents will increase in the coming years.

Clinical trials of the NOACs suggest that, each year, approximately 1·0–2·0% of individuals with AF and 0·1–0·2% of those with VTE who are receiving one of these agents can be expected to experience an acute ischemic stroke (AIS) (6–10). Furthermore, approximately 0·2–0·5% of individuals receiving a NOAC for the prevention of AF-related stroke can be expected to experience an ICH each year (6–8).

In this opinion piece, we discuss three controversies in the management of AIS and ICH in patients who are taking NOACs: the role of thrombolysis in anticoagulated patients with AIS, when to restart anticoagulation after AIS, and whether (and when) to reinstitute oral anticoagulation after a brain hemorrhage.

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Ischemic stroke

Thrombolysis in anticoagulated patients

Patients who experience AIS should be considered for urgent thrombolytic therapy to restore perfusion and function of the ischemic brain. However, effective anticoagulation present at the time of reperfusion is a contraindication for thrombolysis (11,12) because of the possibility of increased risk of symptomatic hemorrhage (13). Therefore, current guidelines recommend against using the intravenous recombinant tissue-type plasminogen activator alteplase in patients with AIS who have an international normalized ratio (INR) > 1·7 (14) or whose prothrombin time (PT) is >15 s (15).

However, INR or PT are not adequate to assess the coagulation status and risk of bleeding in patients who are on a NOAC. The challenge for clinicians evaluating and considering treatment options for patients with AIS who are taking NOACs is to determine reliably and rapidly the anticoagulant effect of these agents and to estimate the potential increased risk of symptomatic hemorrhage with reperfusion (to weigh against the potential benefits of early reperfusion). Given the potential impact of antiplatelet agents, especially acetylsalicylic acid (ASA) (16), their use in conjunction with anticoagulation should also be carefully considered.

Laboratory testing of the anticoagulant effects of the NOACs

Traditional tests of coagulation, such as the PT/INR and activated partial thromboplastin time (aPTT), are not reliable for measuring the anticoagulant effects of dabigatran, rivaroxaban, and apixaban. There are a number of reasons for this.

Plasma concentrations of dabigatran that cause a significant anticoagulant effect may not cause an alteration in the PT/INR, and, although the aPTT is altered by therapeutic plasma concentrations of dabigatran, the correlation between dabigatran plasma

concentrations and aPTT results is nonlinear. Therefore, the aPTT provides only a qualitative, and not a quantitative, indication of the presence of dabigatran (17). In contrast, thrombin time (TT) and the ecarin clotting time (ECT) are sensitive indicators of the presence of dabigatran activity. The TT and ECT both show a linear correlation with dabigatran; a normal TT and a normal ECT both exclude the possibility of a substantial effect of a direct thrombin inhibitor (18,19). Unlike TT, the ECT is not influenced by the use of other anticoagulants (20). However, the ECT is not as readily available as TT (18), and where thrombolytic therapy is necessary, it is not appropriate to delay thrombolysis for several hours to receive ECT results. The Hemoclot thrombin inhibitor assay (a diluted TT assay from Hyphen BioMed, Neuville-sur-Oise, France) is less sensitive than the TT and correlates linearly with plasma concentrations of dabigatran; however, it is not widely available yet.

Although the PT and aPTT may be prolonged by the direct Factor Xa inhibitors rivaroxaban and apixaban, neither assay is reliable for quantifying the anticoagulant effects of these agents (18). Like the aPTT for dabigatran, the PT provides only a qualitative indication of the presence of rivaroxaban or apixaban (21,22), and is able to do so only when it is used with specific thromboplastin reagents that are known to be sensitive to the effects of rivaroxaban [such as Néoplastine® CI Plus (Diagnostica Stago, Asnières sur Seine, France) or RecombiPlasTin 2G (Instrumentation Laboratory, Bedford, MA, USA)] (21,22). Additionally, the PT for the patient must be known to be normal at baseline if a calibrated PT assay is used to estimate rivaroxaban concentration (23). Direct Factor Xa activity assays do correlate with plasma concentrations of rivaroxaban and apixaban, but these tests must be calibrated individually for each type of therapy being assessed (e.g. rivaroxaban or apixaban). Furthermore, they are not yet readily and rapidly available worldwide (24,25).

If the TT, ECT, Hemoclot, and anti-Factor Xa assay are available, a clinically relevant anticoagulant effect can be excluded in patients taking NOACs by detecting either a normal TT, ECT, or Hemoclot thrombin inhibitor assay ≥four-hours after the final dose has been administered to patients taking dabigatran, or a normal anti-Factor Xa assay ≥five-hours after the final dose has been administered to patients taking rivaroxaban or apixaban (15,24,26–29). The timing of these assessments reflects the peak levels of these agents, ensuring that the assays are performed at or after peak levels of the drugs have occurred (24).

Although the coagulation measurements discussed can facilitate the clinical decision concerning thrombolysis, more research is needed to better define 'cut-off' points for such assays that correlate accurately with risk of thrombosis and bleeding, to provide reliable and fast point-of-care tests, and to develop appropriate recommendations for their use.

Clinical assessment of the anticoagulant effects of the NOACs

Until a simple, fast, and reliable quantitative laboratory measure of the degree of anticoagulation in patients taking direct thrombin inhibitors or direct Factor Xa inhibitors is established, clinical assessment is also required to determine the anticoagulant effects of the NOACs, based on the time since the last dose was taken, the patient's renal function as measured by the creatinine clearance, and the concurrent intake of any medications that may interact with P–glycoprotein or cytochrome P450 3A4.

Recommendations

A patient taking one of the NOACs who experiences an AIS should not be considered a candidate for thrombolysis unless his/her clinical history and the results of laboratory tests reliably indicate the absence of an anticoagulant effect, or until at least two half-lives have elapsed since the most recent dose in patients with normal renal function (which is approximately 24 h for the NOACs) (16), and coagulation tests are normal (1–3,15,24,30). However, this is an arbitrary recommendation that has yet to be tested in clinical practice, and other authorities have recommended that 48 h (approximately four half-lives) should elapse prior to thrombolysis (31). For patients with renal impairment, this period should be extended even further and absence of anticoagulation confirmed by appropriate laboratory testing.

Laboratory assays should be used only to confirm the absence of a coagulation effect with the NOACs. There are no known assay values (i.e. analogous to the INR cutoff of 1·7 with warfarin) below which thrombolysis can be performed safely in a patient experiencing AIS while being treated with a NOAC.

Using these criteria, it is unlikely that patients taking a NOAC who experience an acute stroke would be suitable for thrombolysis, unless they have missed their daily (or twice-daily) dose(s) of the NOAC on the day of the stroke. Specific and accurate tests to evaluate the plasma concentrations and anticoagulant effects of the NOACs are in development. In Europe, approved commercial assays for the newer agents, such as BIOPHEN DiXal (Aniara, West Chester, OH, USA) (32,33) and TECHNOVIEW Rivaroxaban CAL Set (Stago BNL, Leiden, the Netherlands) (34–36), are now becoming available.

Alternative strategies

Theoretically, reversing the effect of a NOAC before thrombolysis is appealing. However, this is not recommended, because reversing any anticoagulation therapy (e.g. with prothrombin complex concentrates) before initiating thrombolytic therapy is untested, and there are concerns that it might result in prothrombotic risks that are more substantial than the increased risk of hemorrhagic transformation of the brain infarct related to any residual anticoagulation (37). Furthermore, no specific reversal agents for the NOACs are currently available, although several are in development (24,38,39).

Currently, endovascular therapy encompasses a range of approaches, including endovascular pharmacological thrombolysis, mechanical and aspiration thrombectomy, the use of a guidewire or microcatheter to manipulate the clot, and stent retriever technology. Three recently published randomized trials have reported no benefit or harm associated with endovascular therapy compared with current best medical therapy with intravenous tissue plasminogen activator in a total of 1145 patients with AIS (40–42). Subgroup analyses have suggested that patients with severe ischemic stroke caused by major intracranial artery occlusion who are treated early (within six-hours of symptom onset) may benefit from thrombectomy (40). It must be noted

that in all three trials, first-generation recanalization devices were used. These are inferior in efficacy when compared with the newer endovascular devices (e.g. stent retrievers) (43,44). Trials to test the superiority of the new devices are under way. Theoretically, the presence of a NOAC should not interfere with the efficacy and safety of endovascular thrombectomy.

Restarting anticoagulation after AIS

Another challenge faced by clinicians is determining when to restart anticoagulation therapy after AIS. In a systematic review of 24 randomized controlled trials involving 23 748 patients with AIS, anticoagulant treatment within the first few days after the stroke reduced the incidence of recurrent ischemic stroke but increased the rate of symptomatic ICH, compared with no anticoagulant treatment. Hence, there was no net benefit in terms of a reduction of any type of recurrent stroke over the course of the subsequent few weeks, or in terms of mortality and disability at the end of the follow-up period (which lasted from 12 days to one-year) (45,46).

Similar results were suggested by a meta-analysis of seven trials of anticoagulation with unfractionated heparin, low molecular weight heparin, or heparinoids compared with other treatments (ASA or placebo), started within 48 h of cardioembolic ischemic stroke (47). Therefore, some guidelines recommend that after AIS in patients with nonvalvular AF, oral anticoagulation should be started (or restarted) one to two-weeks after stroke onset, by which time the risk of hemorrhagic transformation of the fresh brain infarct is likely to have subsided (31,48). Consequently, the pivotal trials of the NOACs (ROCKET AF, RE-LY, and ARISTOTLE) only permitted the inclusion and, therefore, the oral anticoagulation treatment of patients who had experienced an ischemic stroke if at least 7–14 days had elapsed between the stroke and the initiation of anticoagulant treatment (6–8).

When to reinstitute anticoagulation after an ischemic event is a frequent clinical challenge, for which, unfortunately, no prospective data are available, hence personal opinion generally shapes the decision. Some clinicians adopt a cautious approach and suggest waiting at least 2 weeks before anticoagulation is resumed. However, a recent practice guideline by the European Heart Rhythm Association (31) gives a more personalized recommendation, to quote:

> Continuation of NOACs after ischaemic stroke depends on the infarct size. If the infarct size is not expected to relevantly increase the risk of early secondary intracerebral bleeding, administration of NOACs should be continued by analogy to VKAs. Clinical study data regarding re-institution of anticoagulation are missing. Some advocate as a rule of thumb the 1–3–6–12 day rule, with re-institution of anticoagulation in patients with a transient ischaemic attack (TIA) after 1 day, with small, non-disabling infarct after 3 days, with a moderate stroke after 6 days, while large infarcts involving large parts of the arterial territory will be treated not before 2 (or even 3) weeks.
>
> (Heidbuchel *et al.*, Paragraph 14.2.2)

Although relevant clinical data are not available, in our opinion this is a reasonable recommendation. Additionally, exceptionally high thromboembolic risk (e.g. prosthetic valve) may also need to be considered.

The optimal time at which the risk of recurrent thromboembolism exceeds the risk of hemorrhagic transformation of the acute brain infarct with anticoagulation is likely to vary among individual patients – this can be from 3 to 21 days after the stroke, depending on the size of the infarct (49,50) and the individual patient's risk factors for these events (49–51). Patients with small (vs. large) ischemic lesions, controlled blood pressure (systolic < 140 mmHg), and normal blood glucose and platelet counts are likely to be at a lower risk of hemorrhagic transformation of the brain infarct and might be considered for earlier initiation of anticoagulant therapy if they are deemed to be at high risk of recurrent stroke (49–51). Patients with transient ischemic attacks or minor ischemic stroke but without a visualized ischemic abnormality on magnetic resonance imaging (or on a computed tomography scan performed after a few days have elapsed) should be able to safely start anticoagulation without further delay.

Intracerebral haemorrhage

The occurrence of spontaneous ICH while a patient is taking anticoagulants requires prompt interruption of anticoagulation to minimize the risk of prolonging, expanding, or triggering further bleeding events, regardless of the degree of the patient's underlying risk of experiencing a thromboembolic event (31). Although the labels of the VKAs and the NOACs state that ICH constitutes a contraindication for oral anticoagulation (and therefore restarting anticoagulation after ICH would be off-label use), there are patients at high risk of ischemic stroke and systemic thromboembolism in whom the potential benefits of anticoagulation in reducing ischemic risk may be, or become, sufficient to offset the hemorrhagic risks of restarting anticoagulation.

There are two main stages when the risks of hemorrhage and thromboembolic ischemia are evolving at different rates or in different directions. The first of these is an acute phase in which the risk of hematoma expansion or recurrent ICH is higher than the risk of thromboembolic events. The second is a postacute phase in which the risk of hematoma expansion or recurrent ICH falls while thromboembolic risk increases, and may ultimately exceed the risk of recurrent bleeding (31). The acute phase may terminate when coagulation is normal, but may continue until the integrity of blood vessels within the hemorrhagic brain lesion has healed, which can take up to 14–30 days. The initiation and duration of the postacute phase are even less clear: some authors have suggested that this phase begins anywhere from approximately 10–14 days after the event (31), whereas others have proposed that it does not occur until 10 weeks or more have elapsed (52).

Acute treatment of ICH related to NOACs

The current concept of acute treatment of ICH occurring during treatment with NOACs is based on experience with ICH related to treatment with VKAs. Under the latter circumstances, hematoma expansion occurs in approximately 30–50% of patients (53–55).

Therefore, the goal of emergency treatment in such patients is to normalize coagulation by administration of coagulation factors

(53,56). However, in the event of ICH related to NOACs, it is unknown whether hematoma expansion does occur and, if so, to what extent. Additionally, there are no specific antidotes available to antagonize the effect of the NOACs. However, studies on antidotes for all three NOACs are currently being conducted (NCT01688830, NCT01758432, NCT01826266). Until these antidotes are available, the use of other approaches (e.g. factor concentrates) should be considered.

When to restart anticoagulation after ICH

The other question that arises is when, or even if, anticoagulation should be restarted after ICH; this will depend on when the post-acute phase is believed to start. A retrospective analysis was conducted for 177 patients with ICH who were followed for a median of 69 weeks (interquartile range: 19–144 weeks). Cox models based on results for the 59 patients who resumed warfarin after a median of 5·6 weeks (interquartile range: 2·6–17·0 weeks) indicated that restarting warfarin after ICH increased the risk of recurrent ICH approximately fivefold (hazard ratio: 5·57; 95% confidence interval: 1·80–17·25; $P = 0·0029$), compared with patients who did not restart warfarin. Conversely, restarting warfarin was associated with a ninefold lower risk of thromboembolism (hazard ratio: 0·11; 95% confidence interval: 0·14–0·87; $P = 0·036$) (52). The incidence of recurrent ICH was most common in the first 35 days after recommencing treatment with warfarin (0·75% per day; hazard ratio: 4·13), after which the incidence of recurrent ICH plateaued at a much lower rate. Among the 118 patients with ICH who did not restart warfarin during the follow-up period, recurrent ICH occurred at a rate of 0·18% per day in the first 35 days and ischemic stroke occurred at a rate of 0·068% per day in the first 77 days. The combined risk of recurrent ICH or ischemic stroke reached the lowest point if warfarin was resumed approximately 10–30 weeks after the initial ICH, suggesting that this timeframe may be optimal for the resumption of warfarin therapy after warfarin-related ICH (52); however, the retrospective nature of this study and the large confidence intervals associated with the findings make this an approximation at best. Other reports, highlighting that annual rates of ischemic events can be as high as 18% in patients with AF and additional risk factors for stroke (57), and as high as 10% in patients with recurrent VTE (58), advocate restarting anticoagulation earlier, at 1–3 weeks, particularly in patients with high thromboembolic risk (31,53,59,60).

Ultimately, the decision of if and when to restart anticoagulation will depend on the estimated risk of recurrent ICH and the risk of recurrent stroke or systemic embolism, without and with oral anticoagulation. The risk of recurrent ICH is likely to be greater in patients with lobar ICH than in those with deep hemispheric hemorrhage (61), or a history of previous ischemic stroke, diabetes mellitus, or ASA use. Conversely, the risk is likely to be lower if the patient has well-controlled hypertension (62–64). Others have noted that the decreased risk of ICH seen with the NOACs, relative to warfarin, may also influence consideration of the balance between recurrent ICH and recurrent thromboembolism (61), and that use of a NOAC might be considered when restarting anticoagulation in a patient who experienced an ICH while on warfarin therapy.

Other predictors of ICH may include the predictors of major bleeding (extra- and intracranial) that comprise the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or pre-disposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly). A HAS-BLED score of >3 is considered 'high risk', although it should be noted that because this scoring system was developed for use in AF, its applicability to other patient groups is unclear (65,66). The risk of recurrent stroke and systemic embolism is likely to be greater in patients with AF and a high $CHADS_2$ or CHA_2DS_2-VASc score, and transesophageal echocardiographic evidence of left ventricular dysfunction, left atrial enlargement, or left atrial thrombus (67,68).

Conclusions and recommendations

After an AIS

1. Thrombolysis should only be initiated in patients receiving one of the NOACs if the clinical history and a laboratory test reliably suggest the absence of an anticoagulant effect, or until at least two half-lives have elapsed since the most recent dose of the NOAC (in patients with normal renal function).
2. In patients taking dabigatran, thrombolysis should only be considered if there is no clinically relevant anticoagulant effect, as determined by one or more of the following assays (assessed ≥four-hours after the final dose of dabigatran has been administered):
   - A normal TT
   - A normal ECT
   - A normal Hemoclot result

   Note that a normal aPTT in isolation is not considered sufficient evidence of a lack of anticoagulation.
3. After an ischemic stroke in a patient receiving rivaroxaban or apixaban, we recommend that thrombolytic agents should not be administered, unless there is reliable information that the most recent dose was taken at least 24 h previously, or a chromogenic Factor Xa assay confirms no residual anticoagulant effect.

When restarting anticoagulant therapy with a NOAC after AIS

1. The optimal time at which to start/restart anticoagulation after a stroke should take into account the individual patient's risk factors for hemorrhagic transformation of the acute brain infarct, such as infarct size. Although pertinent clinical data regarding the timing of the reinstitution of anticoagulation are missing, some advocate as a rule of thumb, the 1–3–6–12 day rule, with reinstitution of anticoagulation in patients with a transient ischemic attack (TIA) after one-day, with small, nondisabling infarct after three-days, and with a moderate stroke after six-days; while large infarcts involving large parts of the arterial territory should not be treated before two (or even three) weeks have elapsed (31).
2. Reinitiating anticoagulant therapy earlier than recommended by the guidelines might be considered in patients with small ischemic lesions who are at high risk of recurrent stroke, if they are considered to be at a lower risk of hemorrhagic transformation, as evidenced by the following:
   - Controlled blood pressure (systolic <140 mmHg)
   - Normal platelet count

Patients without a visualized ischemic abnormality on magnetic resonance imaging (or on a computed tomography scan performed after a few days have elapsed) should be able to safely start anticoagulation without further delay.

After an ICH

1. The decision on whether or not to restart anticoagulation after an ICH will depend on the relative benefit–risk profile for each patient, which, in turn, will depend on the estimated risk of recurrent ICH and the risk of recurrent stroke or systemic embolism, without and with oral anticoagulation.
   - There are no reliable data to determine accurately the prognosis and prognostic factors for recurrent ICH among anticoagulated patients, however:
     (a) The risk of recurrent ICH is likely to be greater in patients with lobar ICH, or a history of previous ischemic stroke, diabetes mellitus, or ASA use
     (b) The risk of recurrent stroke and systemic embolism is likely to be greater in patients with AF and a high $CHADS_2$ or CHA_2DS_2-VASc score, and transesophageal echocardiographic evidence of left ventricular dysfunction, left atrial enlargement, or left atrial thrombus
     (c) The risk of recurrent ICH is likely to be lower if any hypertension that is present is well controlled
   - Some studies suggest that the optimal timing for the resumption of anticoagulation may be between 10 and 30 weeks after an ICH, but other publications advocate restarting anticoagulation earlier, at 1–3 weeks, in cases of high thromboembolic risk and low risk of ICH.

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