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Cerebrovascular Disorders (D Jamieson, Section Editor)

Acute Stroke Treatment in an Anticoagulated Patient: When Is Thrombolysis an Option?

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Abstract

Purpose of Review Direct oral anticoagulants (DOACs: the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban and the direct thrombin inhibitor dabigatran) are the mainstay of stroke prevention in patients with non-valvular atrial fibrillation (AF). Nevertheless, there is a residual stroke risk of 1–2% per year despite DOAC therapy. Intravenous thrombolysis (IVT) reduces morbidity in patients with ischemic stroke and improves functional outcome. Prior DOAC therapy is a (relative) contraindication for IVT but emerging evidence supports its use in selected patients.

Recent Findings Recent observational studies highlighted that IVT in patients on prior DOAC therapy seems feasible and did not yield major safety issues. Different selection criteria and approaches have been studied including selection by DOAC plasma levels, non-specific coagulation assays, time since last intake, and prior reversal agent use. The optimal selection process is however not clear and most studies comprised few patients.

Summary IVT in patients taking DOAC is a clinically challenging scenario. Several approaches have been proposed without major safety issues but current evidence is weak.

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A patient-oriented approach balancing potential benefits of IVT (i.e., amount of salvageable penumbra) against expected bleeding risk including appropriate monitoring of anticoagulant activity seem justified.

Introduction

Atrial fibrillation (AF) is a significant stroke risk factor, responsible for about 20–30% of all ischemic strokes [1]. There is agreement on the basic indication regarding oral anticoagulation for cardioembolism prophylaxis in patients with AF [2–4]. There are now two main oral anticoagulant drug classes [5]: on the one hand Warfarin and phenprocoumon as vitamin K antagonists (VKAs) and on the other hand direct oral anticoagulants (DOACs), which were approved in Europe in 2011 (Rivaroxaban, Dabigatran), respectively, 2012 (Apixaban) and 2015 (Edoxaban) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation [6]. International guidelines favor the use of DOACs over VKAs in most cases [7–10]. The main reason for this is the higher safety profile in terms of cerebral hemorrhage with similar thromboembolic prevention efficacy.

Nevertheless, ischemic stroke occurs despite oral anticoagulation [11–13••] with rates of 1–2% annually in large randomized controlled trials [4] and real-world observational data [14, 15]. A recent (2014–2019) Swiss cohort study showed that 18% of all AF patients with ischemic stroke had been on prior VKA therapy and 20% on orior DOAC therapy [16••]. Reasons for ischemic stroke despite anticoagulation include competing stroke etiology or mechanisms (e.g., large-artery atherosclerosis, small-vessel disease, active malignancy [17–21], medication error (e.g., non-adherence, inappropriate DOAC dosage, or subtherapeutic INR) as well as cardioembolism despite anticoagulant therapy. However, recent studies found that prior therapeutic anticoagulation with VKA or DOAC was associated with lower stroke severity [16••, 22••] and less large-vessel occlusion related ischemic stroke [16••]. Intravenous thrombolysis with alteplase is the gold standard in the treatment of acute ischemic stroke with significant improvement in functional outcome [23–26]. Prior anticoagulation at stroke onset remains a relative contraindication for IVT (according to the American heart Association [26] and European Stroke Organization [27••]). However, recent observational data, summarized below, provide reassuring results regarding the use of IVT in selected patients on VKA and DOAC with safety profiles comparable to patients without prior anticoagulation. For vitamin K antagonists, large observational data found that a cut-off of INR < 1.7 was associated with a reasonable safety profile; current guidelines recommend IVT in patients taking vitamin K antagonists and low INR [27••, 28, 29]. However, there is still great uncertainty regarding the use of IVT in patients taking DOACs at the time of acute ischemic stroke onset [30••, 31•, 32•, 33••]. Thus, it is not surprising that a recent Swiss study found a significantly lower IVT rate in potentially eligible patients taking a DOAC (15%) than in those taking VKA (63%) or controls not taking an oral anticoagulant (74%) [16••]. A German study showed an even lower 6% IVT rate among DOAC patients [34•]. Interestingly, symptomatic intracranial hemorrhage (sICH) was not more frequent in patients on prior DOAC therapy than in controls (sICH in patients without any anticoagulation: 3.6%, sICH in patients on VKA: 4.6%, and sICH in patients on DOAC therapy: 3.1%).

Current Guideline Recommendations

Physicians have an ethical obligation not to exclude potentially eligible patients (within a 4.5-h time window with National Institutes of Health Stroke Scale (NIHSS) ≥ 4) from acute IVT recanalization therapy [26, 27••].

However, only vague and imprecise international recommendations (American Heart Association [26], European Stroke Organization [27••], French Society of Vascular Neurology [35], Japan Stroke Society [36, 37], and European Society of Cardiology [38]) are currently available (Table 1). Various selection criteria (time since last intake, drug monitoring, use of specific reversal agents) for potentially eligible IVT patients under existing DOAC therapy have been proposed [33••], but currently without consensus.

Current Approaches for Patient Selection

Here, we provide an overview and available evidence for different current approaches to select appropriate patients taking a DOAC for IVT, together with illustrative case reports.

Selection of Patients by Time Since last DOAC Intake

International consensus is that patients on DOAC therapy with last dose intake > 48 h (or 4 half-lives) and creatinine clearance > 50 ml/min (Cockcroft-Gault formula) can be offered IVT without delay [26, 39]. However, frequently patients are either compliant (so have had taken the drug within the last 48 h) [40] or cannot provide information on timing of their last DOAC intake. Unfortunately, anticoagulant activity in patients taking DOACs has a high interpersonal variability making the prediction of DOAC levels < 48 h after last intake challenging [32•]. Both intrinsic (age, renal function, genetic polymorphisms) and extrinsic factors (drug interactions and metabolism) as well as dosing and dosing frequency (once or twice a day) may influence DOAC levels and time since last intake is a poor surrogate for anticoagulant activity [33••,41–43].

Illustrative case "time since last intake" selection strategy: A 77 year old patient was taking 20 mg of rivaroxaban per day for permanent atrial fibrillation. Rivaroxaban was paused 3 days prior to planned surgery. On the day of surgery, the patient developed severe aphasia. On neurological examination, the patient had persistent aphasia (NIHSS of 2 points). Based on the severity of symptoms and the known last intake (50 h before imaging; Fig. 1), decision for IVT was made 180 min after symptom onset. Central lab-calibrated anti-Xa activity was < 30 ng/ml (below detection level). The patient improved slightly to an NIHSS of 1 point and follow-up MRI showed no bleeding complications (Fig. 1). At 90 days, the patient had mild disability (modified Rankin scale score 1).

Selection of Patients by Drug Monitoring

Monitoring anticoagulant activity in patients with VKA is easy and feasible using International Normalized Ratio (INR). The cut-off of INR < 1.7 to select patients suitable for thrombolysis has long been proposed, although

Table 1 Summary of current national and international guideline recommendations

Organization	Recommendation
American Heart/Stroke Association [26]	-Intravenous alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or -The patient has not received a dose of these agents for > 48 h (assuming normal renal metabolizing function)
Japanese consensus statement [36, 37]	For dabigatran: -IVT can be considered if the time of the last dose is ≥ 4 h and the level of aPTT is ≤ 1.5 times the baseline value -If aPTT is > 1.5 times baseline value (≥ 40 s only as a guide) or last dose is < 4 h IVT can be considered after intravenous administration of idarucizumab. However, this recommendation lacks sufficient supporting evidence. Thus, direct mechanical thrombectomy without idarucizumab and without bridging IVT may be reasonable to be considered in institutes capable of performing endovascular stroke treatment For factor Xa inhibitors: -IVT is not recommended if INR exceeds at least 1.7 or if the time of the last dose is < 4 h (direct mechanical thrombectomy can be considered for such patients in institutes capable of performing endovascular stroke treatment -IVT after emergent reversal of prolonged INR using antidotes for other anticoagulants is not recommended It should be considered if potential benefits outweigh the possible risks, especially when the time of the last dose of dabigatran or Xa inhibitor is < 12 h, because these anticoagulants have a half-life of approximately 12 h
European Stroke Organisation (ESO) Update 2021 [27••]	-For patients with acute ischemic stroke of < 4.5-h duration, who used a DOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e., calibrated anti-Xa activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), IVT is not suggested Expert consensus statements for patients with acute ischemic stroke of < 4.5-h duration, who used -A NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity < 0.5 U/ml (for factor Xa inhibitors) or thrombin time < 60 s (for direct thrombin inhibitors), 7 of 9 group members suggest IVT with alteplase -Dabigatran during the last 48 h before stroke onset, 8/9 group members suggest the combination of idarucizumab and IVT with alteplase over no IVT -Factor Xa inhibitors during the last 48 h before stroke onset, 9/9 group members suggest against the combination of andexanet and IVT with alteplase over no IVT

Table 1 (continued)

Organization	Recommendation
European Society of Cardiology (ESC) 2020 [38]	-IVT should not be performed in systemically anticoagulated patients taking DOACs (measurement of apTT or TT (for dabigatran), or antifactor Xa levels (for factor Xa inhibitors) is required) -IVT is considered to be safe in patients with last DOAC intake being > 48 h (assuming normal renal function) -In patients taking dabigatran, IVT may be performed after reversal of the dabigatran action by idarucizumab
French Society of Vascular Neurology [35]	-IVT if no intake > 48 h or -DOAC level < 50 ng/ml (if specific tests are available < 30 min) or -If specific tests are not available: TT < 60 s (in case of dabigatran) or anti-Xa < 0.5 U/ml (in case of factor Xa inhibitors) -In the case of dabigatran, reversal with idaracizumab may also be considered

aPTT activated partial thrombin time, ***DOAC*** direct oral anticoagulant, *INR* international normalized ratio, ***IVT*** intravenous thrombolysis, *PT* prothrombin time, ***TT*** thrombin time, *VKA* vitamin ***K*** antagonist

only in recent years data from large multicenter studies from Europe and the US found that this cut-off is safe with no increased risk of sICH [28, 44, 45]. Monitoring the anticoagulant activity in patients taking DOACs is more challenging [46••]. Nonspecific coagulation assays like INR, activated Partial

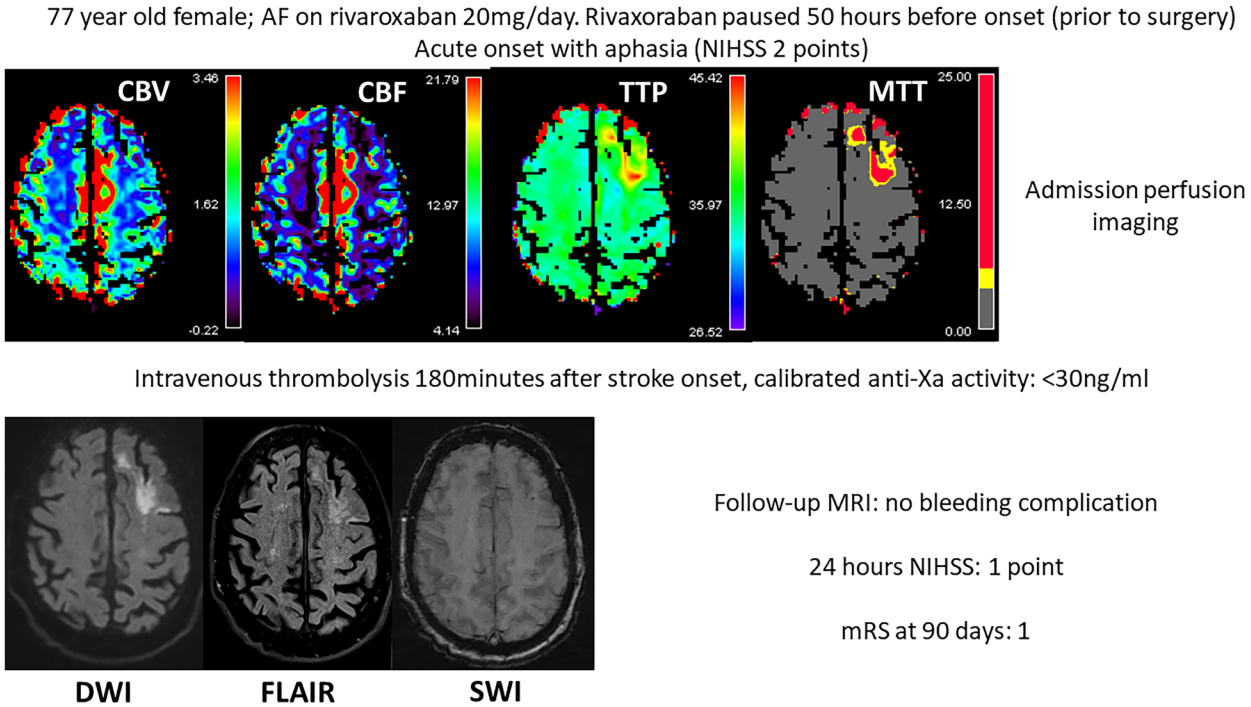

Fig. 1 Patient selection using time since last intake > 48 h.

Thromboplastin Time (aPTT), or prothrombin time (PT) are generally unsuitable to monitor DOAC activity as the results are difficult to interpret [27••]. Nevertheless, current AHA/ASA guidelines indicate that if the aforementioned assays are normal then patients taking a DOAC are potential candidates for IVT [26]. Specific assays to assess anticoagulant activity of DOACs include the ecarin clotting time (for dabigatran) and calibrated anti-Xa activity assays (for rivaroxaban, apixaban, edoxaban), both of which have linear correlations with the respective dose-dependent serum drug levels [41]. These assays are increasingly used in specialized centers, where results can be available within 30 min, making this a potentially suitable strategy to select patients for IVT [32•, 47, 48]. However, the availability of these coagulation tests varies widely internationally and nationally [16••, 49, 50]. Even in the case of available plasma levels in acute ischemic stroke cases, there is currently no uniform internationally agreed cut-off value for safe IVT implementation. Only small observational studies or case reports are available, with large multicenter studies mostly lacking. For example, a German study, including 261 patients with acute ischemic stroke taking a DOAC, suggested that a calibrated anti-Xa activity of < 50 ng/ml could support eligibility for safe IVT, since only one patient experienced sICH (4.2%) [51]. A Swiss study also observed no sICH or systemic bleeding events after IVT in patients taking rivaroxaban with low (< 20 ng/ml) or intermediate anti-Xa activity levels (20–100 ng/ml) [32•]. In both studies, the time to obtain anti-Xa levels was 37 [32•] and 39 min [51], so plasma level determination did not seem to add significant time delay to that of routine acute ischemic stroke diagnostics (NIHSS, CT/MRI, etc.). A lack of time loss prior to IVT administration has also been shown in other studies (door-to-needle-time between 37 and 48 min) [32•,48, 51, 52•]. A practical guideline from the European Heart and Rhythm Association instead suggested IVT in selected patients on rivaroxaban, apixaban, or edoxaban with a calibrated anti-Xa level of < 30 ng/ml [53]. The most recent European Stroke Organisation (ESO) guidelines 2021 suggested the following possible selection criteria for IVT [27••], based on the aforementioned evidence: for the direct thrombin inhibitor dabigatran, a normal thrombin time or < 60 s is recommended [35]; for patients taking rivaroxaban IVT is possible with (uncalibrated!) anti-Xa activity of < 0.5U/ml. However, this recommendation using (uncalibrated) anti-Xa activity has never been tested in any study, and there are no direct data to support it.

While point-of-care testing (POCT) of coagulation (especially prothrombin time/international normalized ratio) has already proven to be a time-saving diagnostic tool in emergency situations for patients on VKA [54••], POCT is not yet available for DOAC patients. However, recent studies have shown that relevant plasma concentrations of DOACs can be rapidly ruled out with POCT. While point-of-care INR/PT determination via CoaguChek® (Roche, Basel, Switzerland) is only applicable for rivaroxaban, Hemochron® Signature (ITC, Edison, NJ, USA) is used for both rivaroxaban and dabigatran via measuring activated partial thromboplastin time (aPTT) and activated clotting time (ACT) [55•, 56–60]. A recent study demonstrated that Rivaroxaban concentrations of < 30 and < 100 ng/ml were detected with > 95% specificity at PT/INR POCT ≤ 1.0 and ≤ 1.1, respectively, while dabigatran

concentrations of < 30 and < 50 ng/ml were detected with > 95% specificity at PT/INR POCT ≤ 1.1 and ≤ 1.2, respectively [61]. These results are promising and suggest that POCT can be used in the absence of specific tests to estimate anticoagulant activity in patients taking rivaroxaban or dabigatran.

Based on the available evidence we suggest that POCT (if suitable) together with calibrated anti-Xa activity is optimal, if available, to select patients suitable for IVT (and to avoid IVT in patients with high activity).

Illustrative case "DOAC monitoring — avoid IVT"*:* A 70-year-old female patient on apixaban 2 × 5 mg for permanent atrial fibrillation experienced left side weakness and speech disturbance 12 h after the last intake of apixaban. She was admitted 4 h after symptom onset. Neurological examination revealed moderate dysarthria and left side hemiparesis (NIHSS 5). On MRI, proximal M2 occlusion of the right middle cerebral artery was detected (Fig. 2), POC-INR (CoaguChek® Roche) was 1.2, and calibrated anti-Xa activity was 150 ng/ml. Based on these findings, IVT was not administered and direct mechanical thrombectomy was performed (TICI 2c). Follow-up MRI showed no bleeding complication (NIHSS 2) with good recovery at 3 months (modified Rankin scale 1).

Illustrative case "DOAC monitoring — enable IVT"*:* A 71-year-old male patient with persistent AF receiving rivaroxaban 15 mg/day (last intake: 10 h before stroke onset) presented 2 h after symptom onset with severe left side upper limb paresis (NIHSS 3). Admission perfusion-CT showed a small hypoperfused area in the right parietal cortex, POC-INR (CoaguChek® Roche) was 1.0, and calibrated anti-Xa activity level was 75 ng/ml. IVT (alteplase 0.9-mg/kg bodyweight) was administered 37 min after admission. Follow-up MRI showed no bleeding complication; the NIHSS was 0 with excellent recovery (modified Rankin scale score of 0 at 3 months) (Fig. 3).

Illustrative case "DOAC monitoring — missed opportunity"*:* A 69-year-old male patient with paroxysmal AF and receiving treatment with rivaroxaban 20 mg (last intake on the morning before) experienced left side weakness at

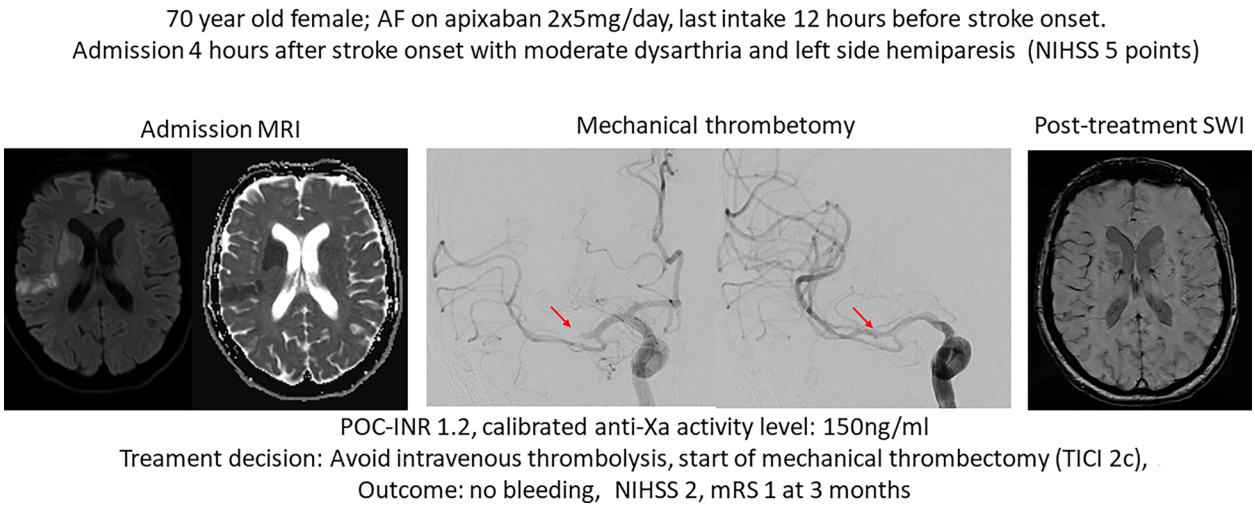

Fig. 2 Patient selection using DOAC monitoring — avoid IVT if calibrated anti-Xa activity is too high.

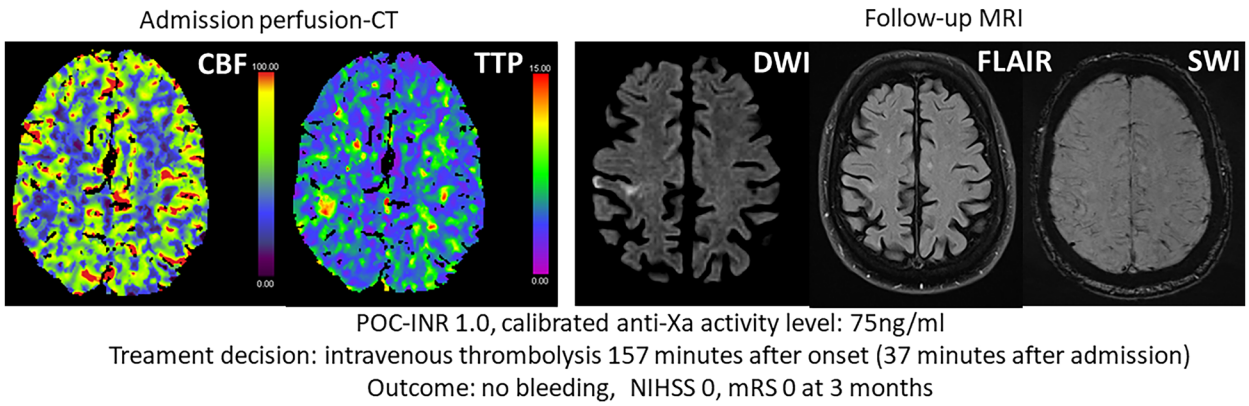

Fig. 3 Patient selection using DOAC monitoring — enable IVT if DOAC levels are low.

08:00 h in the morning. On presentation at 11.44 h, the patient had moderate left side upper limb paresis (NIHSS 2 points). Admission CT did not show bleeding or signs of infarction, POC-INR was 1.03, and renal function was normal (creatinine clearance 78 ml/min). At this time point, no information from specific DOAC assays was available, so the patient was denied thrombolysis. Later, results from calibrated anti-Xa level activity were 58 ng/ml but information arrived too late to allow thrombolysis. Follow-up MRI showed acute infarction without bleeding complications (Fig. 4).

Use of Specific Reversal Agents

Another potential way to facilitate IVT in orally anticoagulated patients is the use of reversal agents, though only limited data are available to support this approach [32•, 35, 62].

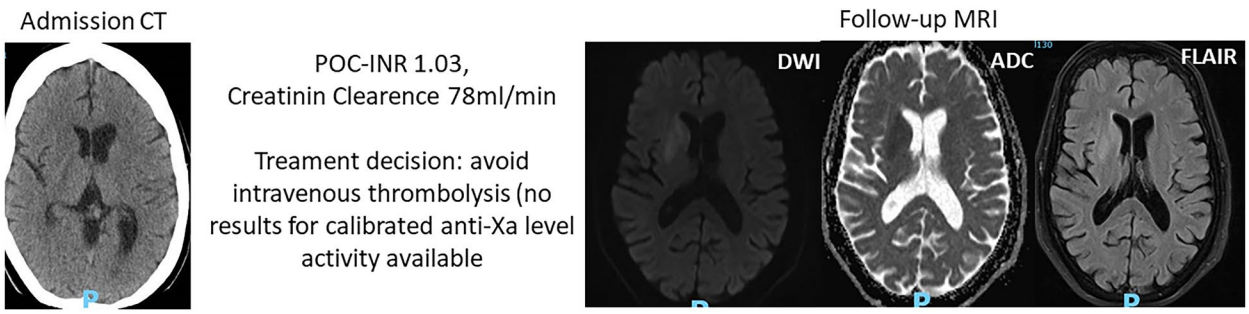

Fig. 4 Patient selection using DOAC-monitoring — missed opportunity due to delayed measurement of calibrated anti-Xa activity levels.

Andexanet alfa, a recombinant human factor Xa protein, is a FX fragment that carries a binding site for inhibitors and thus is a competitive substrate for DOACs. The compound has been modified to lack the enzymatic activity of FXa by replacing the amino acid serine with alanine in the active site. As a result, unlike FXa, andexanet alfa is unable to cleave and activate prothrombin. It has been approved by the US Food and Drug Administration (FDA) in 2018 and European Medicines Agency (EMA) in 2019 for the reversal of the anticoagulant effects of the factor Xa inhibitors (apixaban or rivaroxaban) due to life-threatening or uncontrolled bleeding. In contrast to idarucizumab in patients treated with dabigatran, andexanet alpha has not been approved for reversing factor Xa inhibitor activity in patients who require emergency surgery/urgent procedures like IVT after acute ischemic stroke. Andexanet alfa is administered intravenously as a bolus followed by a continuous infusion over 2 h. Since IVT is required in a 4.5-h time window, the duration of administration of andexanet alfa reduces its clinical practicability. In addition, the high cost (100 mg: 2750$) is another limiting factor [63]. Moreover, andexanet alfa is not approved for reversal of edoxaban [64], although promising data exist [65]. Disadvantages of using andexanet alfa include the potential rebound effect of anti-Xa activity and the occurrence of 40 thromboembolic events in 34 patients (10%) within 30 days in the ANNEXA-4 study [66]. Therefore, a warning notice regarding serious and life-threatening adverse events, including thrombo-embolic events, ischemic events, cardiac arrest, and sudden death, accompanies the prescribing information in the US [64]. Unfortunately, there is so far only one reported case of the use of andexanet alfa before thrombolysis in acute ischemic stroke [67•]. Consequently, the European Stroke Organisation (ESO) cautions against off-label use of andexanet alfa for reversal of anticoagulation with apixaban or rivaroxaban in acute ischemic stroke patients potentially eligible for IVT [27••].

By contrast, there are more clinical data on the reversal agent idarucizumab [68–71••], a humanized monoclonal antibody fragment, which specifically binds to dabigatran, thereby inhibiting the drug in a dose-dependent manner. The substance has a 350-fold higher binding affinity to dabigatran than thrombin [72–74]. In contrast to andexanet alfa, idarucizumab is approved for patients who require emergency surgery or other urgent procedures and have prolonged clotting time [75, 76]. Another advantage, especially in emergency situations, is the duration of application: 5 g idarucizumab (2 vials of 2.5 g/50 ml) is administered intravenously as two consecutive infusions over 5 to 10 min each or as a bolus injection [75]. The theoretical concern that idarucizumab might have a prothrombotic effect in the acute stroke phase [62], leading to a worsening or recurrence of cerebral ischemia events, has not been confirmed in smaller studies from New Zealand and Germany [69, 71••]. However, no final statement can be made regarding the safety profile, especially since only a small number of patients were included in the studies. In most cases idarucizumab appeared to be safe with similar clinical outcomes to routinely managed patients [69–71••, 77, 78], despite an approximately 20-min door-to-needle time delay [71••]. Despite the high cost (5 g kit: $3500–4200) [62], the use of idaricuzumab reversal in stroke patients on dabigatran before IVT has increased in recent years (2017: 1.3% and 2018: 6%) [71••]. However, long-term data, e.g., outcome at 90 days, are

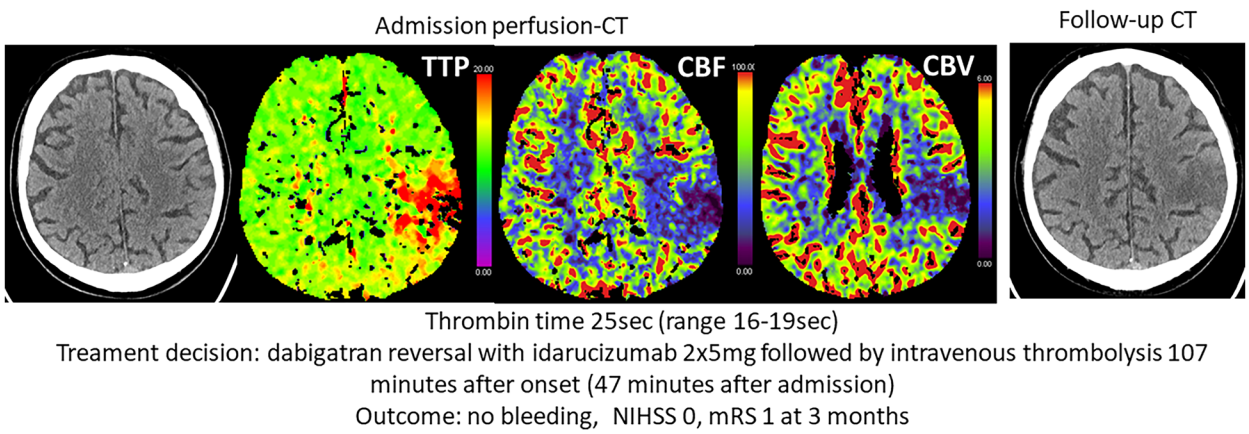

Fig. 5 Patient treatment using DOAC reversal prior to IVT.

still lacking. It also remains open whether reversal therapy with idaricuzumab should be offered only when there is no possibility of endovascular therapy [70]. Overall, the majority of ESO guideline authors favored IVT after idarucizumab in stroke patients anticoagulated with dabigatran in the case of stroke onset < 4.5 h and last dabigatran use < 48 h [27••].

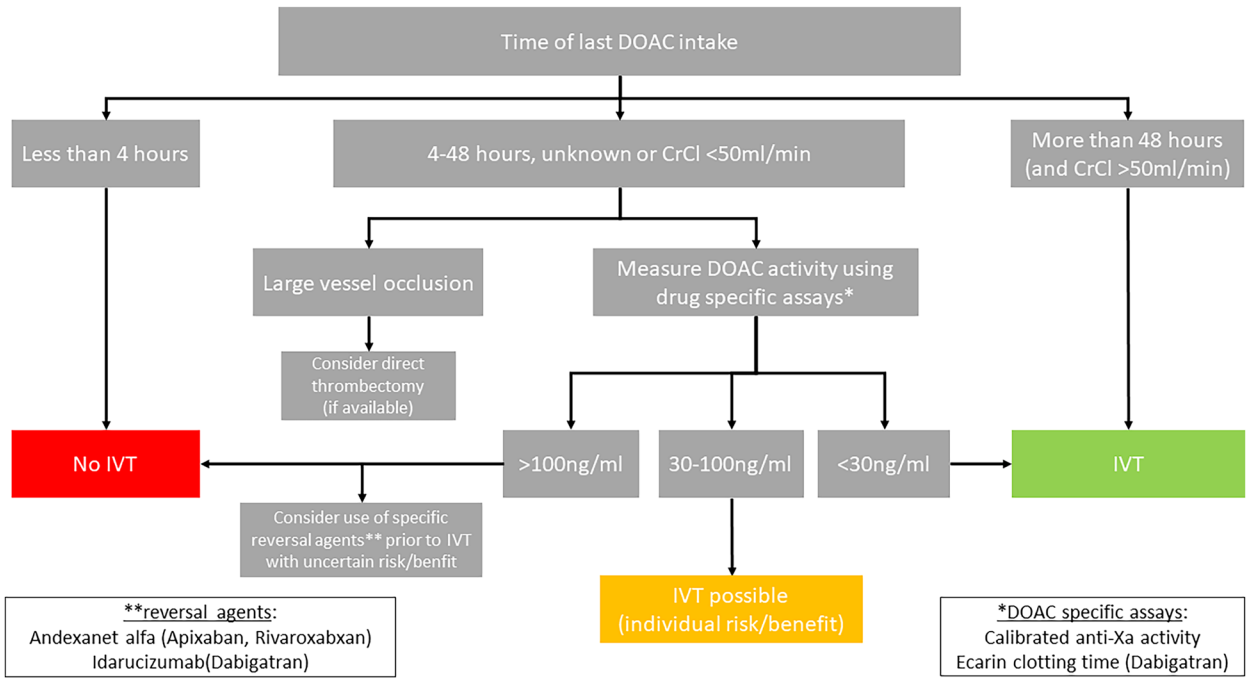

Fig. 6 Expert opinion pathway for IVT in patients on DOAC therapy. We recommend using drug-specific coagulation assays. Point-of-care devices to measure INR may however provide useful information in the absence of drug-specific coagulation assays and/or a first evaluation of the broader degree of anticoagulant activity.

Illustrative case "use of reversal agent prior to IVT": A 84-year-old male patient with paroxysmal AF on dabigatran 2 × 150 mg per day (not age-adjusted) presented with severe right side hemiparesis and aphasia (NIHSS 18 points) 1 h after symptom onset and 9 h after last dabigatran intake. Admission CT showed acute perfusion deficit in the left parietal region with corresponding M4 occlusion of the left middle cerebral artery. Thrombin time was slightly elevated and no dabigatran level was available. A decision to reversal dabigatran activity using idarucizumab (2 × 5 mg i.v.) directly followed by intravenous thrombolysis 47 min after hospital admission was made, taking into account the severe deficit and early presentation. Follow-up CT showed no bleeding complication; the patient recovered well (NIHSS 0, modified Rankin scale score 1 at 3 months) (Fig. 5).

Conclusion and Future Directions

Selecting appropriate patients who are taking oral anticoagulants at the time of acute ischemic stroke for IVT remains a clinical conundrum, although there is emerging evidence that this can be done safely if certain criteria are applied. While selection for IVT in patients taking VKA seems straightforward, prior DOAC therapy remains a major challenge. We have provided an overview about current selection criteria based on the available evidence from observational studies. In conclusion, a balanced approach seems most appropriate taking into account: (1) the stroke severity, (2) the amount of potentially salvageable tissue (e.g., large-vessel occlusion should undergo immediate mechanical thrombectomy without delay if the patient is a candidate), (3) an appropriate assessment of DOAC activity, and (4) the possible use of DOAC reversal agents in carefully selected patient cases. We compiled our expert opinion in Fig. 6.

Our review highlights also that there is remaining uncertainty even 10 years after introduction of DOACs. In theory, large multicenter randomized trials or prospective cohort studies are necessary to define reliable cut-off values for each DOAC and to evaluate the targeted use of reversal therapy prior to IVT. Although this would be desirable, the complexity and potential risks are likely to make such trials challenging. In the absence of randomized trial evidence, large prospective cohort studies could provide further evidence; even closer national and international collaboration is therefore inevitably needed to support the collection of large-scale, real-world evidence to develop rational criteria for patients taking DOACs and to implement cost-effective standard clinical pathways. In summary, an expansion of laboratory chemical point-of-care testing for drug monitoring besides the routine imaging and clinical findings in acute stroke patients and a good availability of reversal agents, especially at centers with a lack of availability of endovascular therapy, will become increasingly relevant in the future.

Compliance with Ethical Standards

Conflict of Interest

DJS: advisory board for Bayer and Portola/Alexion. All other authors have nothing to disclose.

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•• Of major importance

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