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.
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 prior 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 any anticoagulation (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
| 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 ofandexanet and IVT with alteplase over no IVT |
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 Thrombin Time, PT prothrombin time, TT thrombin time, VKA vitamin K antagonist

### 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

77 year old female; AF on rivaroxaban 20mg/day. Rivaroxaban paused 50 hours before onset (prior to surgery)  
Acute onset with aphasia (NIHSS 2 points)

**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 < 0.5 U/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

![Image](https://example.com/image)

**Fig. 2** Patient selection using DOAC monitoring — avoid IVT if calibrated anti-Xa activity is too high.
71 year old male; AF on rivaroxaban 15mg/day, last intake 10 hours before stroke onset. Admission 2 hours after stroke onset with severe left side upper limb paresis (NIHSS 3 points)

Admission perfusion-CT

Follow-up MRI

POC-INR 1.0, calibrated anti-Xa activity level: 75ng/ml

Treatment decision: intravenous thrombolysis 157 minutes after onset (37 minutes after admission)

Outcome: no bleeding, NIHSS 0, mRS 0 at 3 months

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].

69 year old male; AF on rivaroxaban 20mg/day, last intake on the morning before. Admission 3 hours and 44 minutes after stroke onset with mild left side upper limb paresis (NIHSS 2 points)

Admission CT

POC-INR 1.03, Creatinine Clearance 78ml/min

Treatment decision: avoid intravenous thrombolysis (no results for calibrated anti-Xa level activity available

Follow-up MRI

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 thromboembolic 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 idarucizumab 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
84 year old male; AF on dabigatran 2x150mg/day, last intake 8 hours before stroke onset. Admission 1 hours after stroke onset with severe right side hemiparesis and aphasia (NIHSS 18 points)

Thrombin time 25sec (range 16-19sec)
Treatment decision: dabigatran reversal with idarucizumab 2x5mg followed by intravenous thrombolysis 107 minutes after onset (47 minutes after admission)
Outcome: no bleeding, NIHSS 0, mRS 1 at 3 months

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

still lacking. It also remains open whether reversal therapy with idarucizumab 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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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Eckardt L, Denene T, Diener HC, Hindricks G, Hoffmeister HM, Hohnloser SH, et al. Kommentar zu den 2016 Leitlinien der Europäischen Gesellschaft für Kardiologie (ESC) zum Management von Vorhofflimmern Comments on the 2016 guidelines of the European Society of Cardiology (ESC) for the management of atrial fibrillation. Der Kardiologe. 2017;11(3): p. 193–204.

2. Salazar CA, del Aguila D, Cordova EG. Direct thrombin inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in people with non-valvular atrial fibrillation. Cochrane Database Syst Rev. 2014(3):CD009893.

3. Saxena R, Koudstaal P. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. Cochrane Database Syst Rev. 2004(4):CD000187.

4. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.

5. Mader FM, Schwenke R. DEGAM Leitlinie-S3: Schlagenfall https://www.awmf.org/uploads/tx_szleitlinien/053-011_S3_Schlagenfall_2020-11.pdf; Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM); 2020 [cited 2021 20 Mar 2021].

6. Schott G, Bräutigam K, Ludwig W-D. Orale Antikoagulation bei nicht valvulärem Vorhofflimmern Empfehlungen zum Einsatz der direkten oralen Antikoagulanzien Dabigatran, Apixaban, Edoxaban und Rivaroxaban https://www.akdae.de/Arzneimitteltherapie/EF/PDF/OAKVHF.pdf Arzneimittelkommission der deutschen Ärzteschaft (AkDÄ); 2019 [cited 2021 19 Mar 2021].

7. Coutts SB, Wein TH, Lindsay MP, Buck B, Cote R, Ellis P, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014. Int J Stroke. 2015;10(3):282–91.

8. Foundation S. Clinical guidelines for stroke management 2017 https://informmne.org.au/Guidelines/Clinical-Guidelines-for-Stroke-Management: Australian Stroke Foundation; 2017 [cited 2021 19 Mar 2021].

9. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S – e184.

10. Culebras A, Messe SR. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;83(13):1220.

11. Rizos T, Horstmann S, Jenetzky E, Spindler M, Gumbinger C, Mohlenbruch M, et al. Oral
anticoagulants—a frequent challenge for the emergency management of acute ischemic stroke. Cerebrovasc Dis. 2012;34(5–6):411–8.

12. Auer E, Frey S, Kaesmacher J, Hakim A, Seiffge DJ, Goedlind M, et al. Stroke severity in patients with preceding direct oral anticoagulant therapy as compared to vitamin K antagonists. J Neurol. 2019;266(9):2263–72.

13. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, et al. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. Ann Neurol. 2020. (First and largest study to demonstrate the increased risk of recurrent stroke in patients who had ischemic stroke despite anticoagulant therapy.)

14. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Eur Heart J. 2016;37(38):2882–9.

15. Bassand JP, Virdone S, Goldhaber SZ, Camm AJ, Fitzmaurice DA, Fox KAA, et al. Early risks of death, stroke/systemic embolism, and major bleeding in patients with newly diagnosed atrial fibrillation. Circulation. 2019;139(6):787–98.

16. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, et al. Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. Annals of neurology. 2021;89(1):42–53. (Data from a national stroke registry that found 20% of patients with AF who had a stroke to be on prior DOAC therapy — a major challenge for acute treatment.)

17. Sakamoto Y, Okubo S, Nito C, Suda S, Matsumoto N, Abe A, et al. The relationship between stroke severity and prior direct oral anticoagulant therapy in patients with acute ischemic stroke and non-valvular atrial fibrillation. Eur J Neurol. 2017;24(11):1399–406.

18. Cappellari M, Bovi P. Continuation of direct oral anticoagulants in the acute phase of ischemic stroke. A case series J Thromb Thrombolysis. 2017;43(2):248–51.

19. Kim BJ, Kang HG, Lee DH, Kang DW, Kim JS, Kwon SU. Ischemic stroke on optimal anticoagulation with novel-oral anticoagulants compared with warfarin. Int J Stroke. 2015;10(6):E68.

20. Meinel TR, Frey S, Arnold M, Kendrout S, Fischer U, Kaesmacher J, et al. Clinical presentation, diagnostic findings and management of cerebral ischemic events in patients on treatment with non-vitamin K antagonist oral anticoagulants — a systematic review. PLoS One. 2019;14(3):e0213379.

21. Purrucker JC, Hölscher K, Kollmer J, Ringleb PA. Etiology of ischemic strokes of patients with atrial fibrillation and therapy with anticoagulants. Journal of clinical medicine. 2020;9(9). (Etiology and causes of stroke despite anticoagulant therapy are heterogenous and warrant thorough work-up.)

22. Xian Y, O’Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. JAMA : the journal of the American Medical Association. 2017;317(10):1057–67. (Large study from the US to demonstrate that prior DOAC therapy seems protective and was associated with lower stroke severity in case of stroke despite anticoagulation.)

23. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29.

24. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet. 1998;352(9136):1245–51.

25. group ISTc, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352–63.

26. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–418. (Most recent IVT guidelines including dedicated recommendations for IVT in patients on DOAC.)

27. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. 2021;6(1):I-lxii.

28. Xian Y, O’Brien EC, Liang L, Xu H, Schwamm LH, Bhatt DL, et al. Use of intravenous thrombolytic therapy with recombinant tissue plasminogen activator within 6 h of acute ischemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352–63.

29. Frank B, Grotta JC, Alexandrov AV, Bluhmki E, Lyden P, Meretoja A, et al. Thrombolysis in stroke despite contraindications or warnings? Stroke. 2013;44(3):727–33.

30. Xian Y, Federspiel JJ, Hernandez AF, Laskowitz DT, Schwamm LH, Bhatt DL, et al. Use of intravenous recombinant tissue plasminogen activator in patients with acute ischemic stroke who take non-vitamin K antagonist oral anticoagulants before stroke. Circulation. 2017;135(11):1024–35. (Data from the US get-with-the guidelines registry that found low bleeding risk in patients with ischemic stroke despite DOAC therapy receiving IVT.)
31. Shahjouei S, Tsivgoulis G, Goyal N, Sadighi A, Mowla A, Wang M, et al. Safety of intravenous thrombolysis among patients taking direct oral anticoagulants: a systematic review and meta-analysis. Stroke. 2020;51(2):533–41. (Systematic review and meta-analysis of published data on IVT in patients on DOAC.)

32. Seiffge DJ, Traenka C, Polymeris AA, Thilemann S, Wagner B, Hert L, et al. Intravenous thrombolysis in patients with stroke taking rivaroxaban using drug specific plasma levels: experience with a standard operation procedure in clinical practice. J Stroke. 2017;19(3):347–55. (Focused study on the use of DOAC plasma levels to guide IVT in patients on rivaroxaban.)

33. Seiffge DJ, Meinel T, Purrucker JC, Kaesmacher J, Fischer U, Wilson D, et al. Recanalisation therapies for acute ischaemic stroke in patients on direct oral anticoagulants. J Neurol Neurosurg Psychiatry. 2021. (Review paper summarizing current evidence and selection criteria of patients with DOAC receiving IVT.)

34. Purrucker JC, Haas K, Rizos T, Khan S, Poli S, Kraft P, et al. Coagulation testing in acute ischemic stroke patients taking non-vitamin K antagonist oral anticoagulants. Stroke. 2017;48(1):152–8. (Important review to guide interpretation of coagulation testing in patients treated with DOAC and stroke.)

35. Touze E, Gritel N, Gouin-Thibault I, De Maistre E, Mowla A, Wang M, et al. Safety of intravenous thrombolysis among patients taking direct oral anticoagulants: a systematic review and meta-analysis. Stroke. 2020;51(2):533–41. (Systematic review and meta-analysis of published data on IVT in patients on DOAC.)

36. Toyoda K, Koga M, Iguchi Y, Ibashi R, Inoue M, Okada Y, et al. Guidelines for intravenous thrombolysis (recombinant tissue-type plasminogen activator), the third edition, March 2019: a guideline from the Japan Stroke Society. Neurol Med Chir (Tokyo). 2019;59(12):449–91. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

37. Toyoda K, Yamagami H, Koga M. Consensus guides on stroke thrombolysis for anticoagulated patients from Japan: application to other populations. J Stroke. 2018;20(3):321–31. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

38. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373–498. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

39. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J. 2013;34(27):2094–106. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

40. Ozaki AF, Choi AS, Le QT, Ko DT, Han JK, Park SS, et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2020;13(3):e005969. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

41. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. Chest. 2017;151(1):127–38. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

42. Gong Y, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Can J Cardiol. 2013;29(7 Suppl):S24-33. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

43. Seiffge DJ, Kagi G, Michel P, Fischer U, Bejot Y, Wegener S, et al. Rivaroxaban plasma levels in acute ischemic stroke and intracerebral hemorrhage. Ann Neurol. 2018;83(3):451–9. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

44. Scheitz JF, Gensicke H, Zinkstok SM, Curtze S, Arnold M, Hametner C, et al. Cohort profile: Thrombolysis in Ischemic Stroke Patients (TRISP): a multicentre research collaboration. BMJ Open. 2018;8(9):e023265. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

45. Mazya MV, Lees KR, Markus R, Roine R, Seet RCS, Wahlgren N, et al. Safety of intravenous thrombolysis for acute ischaemic stroke in patients treated with warfarin. Cerebrovascular Diseases. 2013;35:567–72. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

46. Drouet L, Bal Dit Sollier C, Steiner T, Purrucker J. Measuring non-vitamin K antagonist oral anticoagulant levels: when is it appropriate and which methods should be used? Int J Stroke. 2016;11(7):748–58. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

47. Steiner T, Bohm M, Dichiens M, Diener HC, Ell C, Endres M, et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. Clin Res Cardiol. 2013;102(6):399–412. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

48. Seiffge DJ, Traenka C, Gensicke H, Tsakiris DA, Bonati LH, Peters N, et al. Intravenous thrombolysis in stroke patients receiving rivaroxaban. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2014;21(1):e3-4. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

49. Zantek ND, Hayward CP, Simcox TG, Smock KJ, Hsu P, Van Cott EM. An assessment of the state of current practice in coagulation laboratories. Am J Clin Pathol. 2016;146(3):378–83. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

50. Favaloro EJ, Porter K, Butler barJ, Marsden K. Laboratory testing for the new oral anticoagulants: a review of current practice. Pathology. 2013;45(4):435–7. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

51. Marsch A, Macha K, Siedler G, Breuer L, Strasser EF, Engelhorn T, et al. Direct Oral anticoagulant plasma levels for the management of acute ischemic stroke. Cerebrovasc Dis. 2019;48(1–2):17–25. (Important study to highlight importance of coagulation testing in patients on stroke and DOACs.)

52. Seiffge DJ, Traenka C, Polymeris A, Hert L, Fisch U, Peters N, et al. Feasibility of rapid measurement of Rivaroxaban plasma levels in patients with acute stroke. J Thromb Thrombolysis. 2017;43(1):112–6. (Single center study demonstrating the feasibility of rapid central-lab DOAC level testing for IVT.)

53. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Destege L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in
patients with atrial fibrillation: executive summary. Europace. 2018;20(8):1231–42.

54. • Rizos T, Herweh C, Jenetzky E, Lichy C, Ringleb PA, Hacke W, et al. Point-of-care international normalized ratio testing accelerates thrombolysis in patients with acute ischemic stroke using oral anticoagulants. Stroke. 2009;40(11):3547–51.

(Important study to demonstrate the utility of POC testing to facilitate IVT in patients taking vitamin K antagonists.)

55. • Ebner M, Peter A, Spencer C, Hartig F, Birschmann I, Kuhn J, et al. Point-of-care testing of coagulation in patients treated with non-vitamin K antagonists oral anticoagulants. Stroke. 2015;46(10):2741–7.

(This study investigates the correlation between POC testing and DOAC activity.)

56. Baruch L, Sherman O. Potential inaccuracy of point-of-care INR in dabigatran-treated patients. Ann Pharmacother. 2011;45(7–8):e40.

57. van Ryn J, Baruch L, Clemens A. Interpretation of point-of-care INR results in patients treated with dabigatran. Am J Med. 2012;125(4):417–20.

58. Francart SJ, Hawes EM, Deal AM, Adcock DM, Gosselin R, Jeanneret C, et al. Performance of coagulation tests in patients on therapeutic doses of rivaroxaban. A cross-sectional pharmacodynamic study based on peak and trough plasma levels. Thromb Haemost. 2014;111(6):1133–40.

59. Hawes EM, Deal AM, Funk-Adcock D, Gosselin R, Jeanneret C, Cook AM, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: a cross-sectional pharmacodynamic study based on peak and trough plasma levels. J Thromb Haemost. 2013;11(8):1493–502.

60. Mani H, Herth N, Kasper A, Wendt T, Schuettfert G, Weil Y, et al. Point-of-care coagulation testing for assessment of the pharmacodynamic anticoagulant effect of direct oral anticoagulant. Ther Drug Monit. 2014;36(5):624–31.

61. Ebner M, Birschmann I, Peter A, Spencer C, Hartig F, Kuhn J, et al. Point-of-care testing for emergency assessment of coagulation in patients treated with direct oral anticoagulants. Critical care (London, England). 2017;21(1):32.

62. Diener HC, Bernstein R, Butcher K, Campbell B, Cloud C, Davalos A, et al. Thrombolysis and thrombectomy in patients treated with dabigatran with acute ischemic stroke: expert opinion. Int J Stroke. 2017;12(1):9–12.

63. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019;94(6):697–709.

64. (EMA) EMA. Andexanet alfa prescribing information https://www.ema.europa.eu/en/documents/product-information/ondexxya-epar-product-information_en.pdf; European Medicines Agency (EMA)

65. Lu G, Conley PB, Leeds JM, Karbarz MJ, Levy GG, Mathur VS, et al. A phase 2 PK/PD study of andexanet alfa for reversal of rivaroxaban and edoxaban anticoagulation in healthy volunteers. Blood Adv. 2020;4(4):728–39.

66. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019;380(14):1326–35.

67. • Kallmünzer B, Pott M, Schwab S. Letter by Kallmünzer et al Regarding Article, “Safety of intravenous thrombolysis among patients taking direct oral anticoagulants: a systematic review and meta-analysis”. Stroke. 2020;51(7):e130-e1.

(First case report to use andexanet alfa prior to IVT in a patient on factor Xa inhibitor)

68. Zhao H, Coote S, Pesavento L, Jones B, Rodrigues E, Ng JL, et al. Prehospital idarucizumab prior to intravenous thrombolysis in a mobile stroke unit. Int J Stroke. 2019;14(3):265–9.

69. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Abraham A, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany—updated series of 120 cases. Int J Stroke. 2020;15(6):609–18.

70. Giannandrea D, Caponi C, Mengoni A, Romoli M, Marando C, Gallina A, et al. Intravenous thrombolysis in stroke after dabigatran reversal with idarucizumab: case series and systematic review. J Neurol Neurosurg Psychiatry. 2019;90(5):619–23.

71. •• Barber PA, Wu TY, Ranta A. Stroke reperfusion therapy following dabigatran reversal with idarucizumab in a national cohort. Neurology. 2020;94(19):e1968-e72.

(Data from a national IVT registry that report safety results for the use of idarucizumab prior to IVT in patients on dabigatran.)

72. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511–20.

73. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, et al. A specific antidote for dabigatran: functional and structural characterization. Blood. 2013;121(18):3554–62.

74. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: functional and structural characterization. Blood Adv. 2020;4(4):1116–27.

75. {EMA} EMA. Summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/praxbind-epar-product-information_en.pdf; European Medicines Agency (EMA)

76. Pharmaceuticals BI. Idarucizumab prescribing information, https://docs.boehringer-ingelheim.com/Prescribing%20Information/Pls/Praxbind/Praxbind.pdf; Boehringer Ingelheim International GmbH; 2018 [ ]

77. Pikija S, Sztiriha LK, Sebastian Mutzenbach J, Golaszewski SM, Selinner J. Idarucizumab in dabigatran-treated patients with acute ischemic stroke
receiving alteplase: a systematic review of the available evidence. CNS Drugs. 2017;31(9):747–57.

78. Sanak D, Jakubicek S, Cernik D, Herzig R, Kunas Z, Mikulik R, et al. Intravenous thrombolysis in patients with acute ischemic stroke after a reversal of dabigatran anticoagulation with idarucizumab: a real-world clinical experience. J Stroke Cerebrovasc Dis. 2018;27(9):2479–83.

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