DR. EMMANUEL TOUZÉ (Orcid ID : 0000-0002-7254-2162)

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INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE IN PATIENTS ON DIRECT ORAL ANTICOAGULANTS

EXPERT OPINION OF THE SOCIETE FRANCAISE DE NEUROLOGIE VASCULAIRE (SFNV) [*FRENCH VASCULAR NEUROLOGY SOCIETY*] AND THE GROUPE FRANCAIS D'ETUDES SUR L'HEMOSTASE ET LA THROMBOSE (GFHT) [*FRENCH STUDY GROUP ON HAEMOSTASISAND THROMBOSIS*]

Emmanuel Touzé,[1] Yves Gruel,[2] Isabelle Gouin-Thibault,[3] Emmanuel De Maistre,[4] Sophie Susen,[5] Pierre Sie,[6] Laurent Derex.[7]

[1] Normandie Université, UNICAEN, Unité Neurovasculaire, CHU Caen, 14000, Caen

[2] Service d'Hématologie-Hémostase, Centre Régional de Traitement de l'Hémophilie

UMR CNRS 7292, Hôpital Trousseau, CHRU de Tours et Université François Rabelais, Tours

[3] Laboratoire d'Hématologie, Hôpital Cochin, UMR_S1140, Université Paris Descartes, Paris

[4] Laboratoire d'Hématologie – Hémostase, CHU Dijon Bourgogne 21079 Dijon cedex

[5] Département d'Hématologie et Transfusion, CHRU, Cedex 59037 Lille, France.

[6] Laboratoire d'hématologie, hôpital Rangueil, CHU de Toulouse, TSA 50032, Toulouse

[7] Unité Neurovasculaire, Hôpital Neurologique, Hospices Civils, Lyon

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Corresponding author :

Emmanuel Touzé, Normandie Université, Unicaen, CHU Caen, Service de

Neurologie, Avenue de la Côte de Nacre, 14000 Caen, France -

emmanuel.touze@unicaen.fr

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ABSTRACT

Background and Purpose

Whereas intravenous thrombolysis (IVT) is allowed in acute ischaemic stroke (IS) in patients on vitamin K antagonists if INR≤1.7, there is no similar recommendations for patients on direct oral anticoagulants (DOACs), notably due to the lack of coagulation tests to assess the therapeutic effects. Although the literature is scarce, consisting in small case series and retrospective studies, considering the frequency of this situation, the French Vascular Neurology Society and the French study Group on Haemostasis and Thrombosis have worked on a joined position paper to provide a practical position regarding emergency management of IS in patients on DOACs.

Methods

Based on a review of the literature, the authors wrote a first text that was submitted to a broad panel of members from the two societies. The text was then amended by the authors to address experts' comments and to reach a consensus.

Results

In patients with normal renal function and who stopped the DOAC for at least 48 hours, the management should not differ from that in patients without oral anticoagulant. In patients who are still on DOAC, we encourage mechanical thrombectomy preferentially when applicable in

first line. Otherwise, when specific tests are available, values <50 ng/mL indicate that IVT is allowed. In the absence of specific test, standard tests (thrombine time, prothrombin time, and activated partial thromboplastin time) can be used for dabigatran and rivaroxaban, although interpretation of these tests may be less reliable. In some patients on dabigatran, idarucizumab may be used before IVT.

Conclusions

In this expert opinion paper, we suggest that IVT can be performed in patients selected according to the time elapsed since the drug was last taken, renal function, type of hospital where the patient is admitted and plasma concentration of DOAC.

FOREWORD

This document is a joint initiative of the Société Française de Neurologie Vasculaire (SFNV) [*French Vascular Neurology Society*] and the Groupe Français d'études sur l'Hémostase et la Thrombose (GFHT) [*French study Group on Haemostasis and Thrombosis*]. Because literature is relatively scarce, essentially based on small case series and retrospective studies, high-level recommendations cannot be given. Nevertheless, we have considered it important to take a position regarding emergency management of ischaemic stroke in a patient treated with DOAC, an increasingly common situation. The proposals in this text are to be considered as an expert opinion (level C). Based on a review of the literature, the authors wrote a first text that was submitted to a broad panel of members from the two societies (see Appendix). The text was then amended by the authors to address experts' comments and to reach a consensus.

LITERATURE REVIEW AND ARGUMENT

Introduction

Oral anticoagulants are currently used in a wide range of clinical conditions, either for a predetermined period (e.g., venous thromboembolic disease) or on the long-term, especially for the prevention of arterial embolic events in atrial fibrillation (AF) patients or in patients with prosthetic valves. Vitamin K antagonists (VKAs) have been used for over 60 years.[1] Several direct oral anticoagulants (DOACs) have been recently approved for use, namely anti-IIa (dabigatran) or anti-Xa drugs ("xabans" rivaroxaban, apixaban, edoxaban), providing alternatives to VKA for non-valvular AF (NVAF) and venous thrombosis.[2-4]

Oral anticoagulants significantly reduce the risk of cerebral ischaemic events in case of AF, but each year, 1 to 2% of patients will have with an ischemic cerebral event, despite being on anticoagulant.[5] Moreover, anticoagulant therapy is theoretically a relative contraindication for intravenous thrombolysis (IVT) of ischaemic stroke (IS). In clinical trials demonstrating the efficacy of rtPA, patients on VKA (the only oral anticoagulant available, until recently) were not included. However, several observational studies have shown that rtPA could be administered without major risk in IS when INR is ≤ 1.7,[6, 7] and several international guidelines allow thrombolysis in this situation.[8]

In terms of efficacy, DOACs have been shown to be non-inferior, or even superior in some subgroups, compared to VKAs for the prevention of IS in AF patients.[4] However, they were all developed without need of monitoring via coagulation tests to assess the therapeutic effects or to adjust the dose. This lack of biological monitoring of the anticoagulant effects may complicate management of patients with haemorrhagic or thrombotic events. Thus, in the context of an IS, the decision to perform IVT on a patient taking DOACs is problematic.[6, 9]

Nevertheless, our knowledge of the effects of DOACs on biological tests has improved, and specific dosages of plasma concentration are now available for all drugs.[10, 11] The emergence of specific antidotes should also improve patient management during bleeding or in situations at high risk of haemorrhage. A recent expert opinion provides guidance on the use of the specific reversal agent idarucizumab followed by IVT and/or mechanical thrombectomy (MT) in patients with IS pre-treated with dabigatran.[12] However, there are no similar guidelines for other DOACs. This statement relies on recent data with the aim to provide a sensible decision algorithm until better-established clinical data becomes available.

DOAC pharmacology

As shown in supplemental table 1, half-life and onset of action are relatively similar across DOACs whereas other characteristics differ, notably elimination pathway, which is much more renal function-dependent for dabigatran than for xabans. Interindividual variability of DOAC plasma concentrations is huge, whatever the drug or the dosage. This variability depends on numerous intrinsic (age, sex, renal and liver functions, genetic polymorphisms), but also extrinsic factors (interactions with inductive drugs, inhibitors, or Pgp transporter and/or CYP3A4 cytochrome substrates).[10, 11, 13]

Bioassays

There is no test equivalent to the INR for VKAs allowing a reliable assessment of DOAC anticoagulant activity. Prothrombin time (PT), expressed as international normalized ratio (INR), and activated partial thromboplastin time (APTT) are both modified on DOAC. However, for a same DOAC changes in PT an APTT vary widely depending on the type of test, reagent, and patient haemostasis. Moreover, there are differences according to the DOAC (supplemental table 2).[14, 15] These tests have not been standardized to assess the anticoagulant effects of DOACs and are thus unsuitable for biological monitoring.

1) Prothrombin time (PT) and activated partial thromboplastin time (APTT)

APTT provides a semi-quantitative indication of dabigatran levels. Depending on the reagent and the patient, a normal APTT can correspond to a dabigatran level between 0 and 100 ng/ml. Beyond this level, APTT is prolonged without close correlation with concentration of the drug, particularly in case of an overdosage, for which there is a plateau effect. PT (expressed as PT or INR) is less sensitive to dabigatran than APTT.[10, 11, 16]

APTT and PT are variably modified by the xabans, and the sensitivity of these tests, particularly PT, strongly depends on the reagents used. For rivaroxaban and edoxaban, PT is more sensitive than APTT. However, a normal PT, even if combined with a normal APT, does not rule out the presence of low residual concentration (<50 ng/mL) of rivaroxaban or edoxaban.[17] Thus, the use of PT and APTT is thus not the best option to determine whether the patient is anticoagulated or not. Finally, with most reagents, apixaban has a significant effect on these tests when present in plasma at supratherapeutic plasma concentrations.

For instance, the predictive value of the combination PT plus aPTT, performed with sensitive reagents to exclude DOAC concentrations below 30 ng/mL is lower than 80% for rivaroxaban, 50% for apixaban and 95% for dabigatran. The thrombin time (TT) is the only test that is highly reliable to exclude dabigatran concentration below 30 ng/mL.[16]

2) Thrombin time (TT) and anti-Xa activity

These two tests are useful to rule out the presence of for dabigatran (TT) or xabans (anti-Xa activity). The thrombin time (TT) is very sensitive to dabigatran, being unmeasurable in most patients on treatment, and is moderately prolonged even when plasmatic concentration of

dabigatran is low (≤30 ng/mL). Thus, a normal TT reliably rules out the presence of dabigatran, and if TT≤60 sec, dabigatran levels are low (<30 ng/mL).[10, 16] A similar reasoning applies when measuring anti-Xa activity, calibrated in heparin/LMWH anti-Xa units. Anti-Xa activity is very xaban-sensitive, with values generally beyond the upper measurement limit (>> 1U/mL) for the usual concentrations observed in patients treated with xabans. A value at the lower quantification limit (≤0.1 U/mL) indicates the absence of the drug, and a low value (0.1-0.5 U/mL) corresponds to low xaban concentrations (<50-100 ng/mL).[10, 16]

3) Specific tests measuring the plasma level of the drug

The reference technique is a high-performance liquid chromatography that is coupled with mass spectrometry and calibrated with plasmas specifically supplemented with the drug to be dosed. This technique, not readily available 24 hours a day, serves as the most easily usable haemostatic technique comparator.

Different tests on the market allow to specifically measure the plasma drug levels, expressed as ng/mL of plasma, using dedicated calibrants and controls. These tests are derived from the TT and ecarin test for dabigatran, and specific anti-Xa activity tests are also available for xabans.[10] These tests are performed quickly in an automated manner, thus allowing a quantitative result in a measuring range corresponding to concentrations measured in most patients (50-500 ng/mL). Their analytical reliability is acceptable for values > 30 ng/mL. These assays should be widely available in laboratories of centres that receive patients in critical condition, and the result is available within 30 minutes after the laboratory has registered the sample.

Experimental data on thrombolysis on DOACs.

In the absence of large clinical studies, analysis of experimental animal studies may be helpful. A study performed in a model of ischaemic stroke in mice (using monofilament) has shown that rtPA/warfarin combination increased the risk of haemorrhagic transformation, while rtPA/dabigatran combination, at a dose assumed equivalent to the one used in the clinical setting, did not increase the risk of haemorrhage.[18] However, higher doses of dabigatran increased the risk. Likewise, data obtained from mice with brain ischemia and not treated with rtPA suggested that dabigatran did not increase risk of haemorrhagic transformation.[19] In another experimental study led by the same group, reversion of VKA effects by prothrombin

complex concentrates eliminated the excess in risk of bleeding after rtPA use.[20] Similar experiments conducted with apixaban showed that the risk of haemorrhagic transformation was lower with DOACs than with VKAs after thrombolysis.[21, 22]

Although it is unknown how these results could be translated in human subjects, it seems clear that, beyond a certain threshold, VKAs increase risk of haemorrhagic transformation after thrombolysis. A similar dose-effect relation is likely with DOACs.

Clinical data on cerebral thrombolysis on DOACs

Data on IV thrombolysis in patients taking DOACs remains limited. We have identified a series of 28 patients (supplemental table 3), compiled in the recent review by Cappellari and Bovi, 3 cases published in 2015,[23, 24] a multicenter study,[25] and a retrospective analysis of 251 patients on DOAC from a registry of consecutive patients who had ischemic stroke in the United States.[26] In the review by Cappellari and Bovi, 18 patients received dabigatran, 12 received rivaroxaban, and 1 received apixaban. In most cases, the indication for anticoagulant treatment was high-risk AF. In some cases, whether the patient was on DOAC or not at the time of the admission was unknown. Thus, thrombolysis was performed on the basis of apparently normal coagulation tests. However, in most cases, neither the arguments leading to initiation of thrombolysis, despite having recently taken the drug, nor results from the usual coagulation tests performed in the absence of results from specific tests were reported. A modified TT (Hemoclot®) was performed in 5 patients taking dabigatran, and a specific anti-Xa test in 4 patients taking rivaroxaban. The APTT was normal or slightly prolonged in most patients. Two patients on dabigatran had fatal intracranial haemorrhage. No major bleeding was observed in the other patients. A case series of 5 other patients, taking dabigatran and treated with rtPA, was recently published with no details about individual characteristics, and no patient had symptomatic intracranial hemorrhage.[24] However, given the small numbers of cases, uncertainty remains about the risk of intracranial bleeding in this situation.

In a collaborative retrospective study conducted in 9457 patients who received thrombolysis and/or endovascular treatment, 78 were treated with a DOAC (rivaroxaban: 47; dabigatran: 29; apixaban: 2) at the time of admission.[25] Fifty-one of them received IV thrombolysis combined, in 6 cases, with endovascular treatment, and the others received endovascular treatment only. The symptomatic intracranial haemorrhage rate was 2.6% using ECASS-II criteria (any ICH with

neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days, or any haemorrhage leading to death),[27] and 3.9% using NINDS criteria (any ICH on follow-up imaging with any decline in neurological status).[28] These rates were no different from those observed in patients taking VKAs, with a median INR of 1.3 (6.5% and 9.3%, respectively) and no different from those of patients without anticoagulant therapy (5.0% and 7.2%, respectively). However, the endovascular treatment rate was higher in patients taking DOACs. In 22 of the patients on rivaroxaban, a DOAC level of < 100 ng/mL (mean: 21 ng/mL, IQR 8-23 ng/mL) was used to allow thrombolysis.

In the US registry, unadjusted the rate of symptomatic intracranial haemorrhage was 4.8% in patients on DOAC, 4.9% in those on warfarin, and 3.9% in those without anticoagulant (P=0.11). No difference was found after adjustment for confounders. There were also no significant differences in the risk for life-threatening/serious systemic haemorrhage, any rt-PA complication, in-hospital mortality, and modified Rankin Scale at discharge across 3 groups.[26]

Antidotes

In patients on VKAs, attempting to restore normal coagulation with coagulation factors before thrombolysis is not recommended, as there is a potential thrombotic risk, although a few isolated cases have been reported.[29] This recommendation applies also for patients on DOACs. However, specific antidotes of DOACs, recently developed, may have a role in management of acute IS patients on DOACs.[30]

- Patients treated with dabigatran

Idarucizumab, the first specific DOAC antidote, is a monoclonal antibody, which affinity for dabigatran is 350 times greater than that for thrombin. This antidote immediately and completely neutralizes the action of dabigatran. Unlike prothrombin complex concentrates, idarucizumab has no pro-thrombotic effects. After first evaluations in healthy subjects,[31, 32] data for the first 90 patients treated with idarucizumab and having a major haemorrhage or requiring emergency surgery was reported.[33, 34] Depending on the criteria used, complete biological reversal was obtained in 88 to 98% of patients within a few minutes after infusion. The median time before bleeding was stopped was 11 hours, and in the 36 patients requiring surgery, haemostasis was deemed normal in 92% of them. Rebound in plasma concentration of the drug after a few hours was observed in patients whose plasma levels were very high before administration of the antidote. Although, in the case of cerebral infarction, lower anticoagulant plasma concentrations are expected, the use of idarucizumab in this condition would therefore

require biological monitoring of haemostasis within 24 hours after administration of the antidote.

Idarucizumab (Praxbind®) has been recently allowed in two situations involving patients treated with dabigatran: major bleeding threatening the vital or functional prognosis, and as preparation for an emergency invasive procedure with high risk of haemorrhage. The need to use thrombolytic drugs in a patient with IS cannot be formally linked to any of these categories. However, regarding the risk of haemorrhagic transformation after thrombolysis, a complication that is more severe and frequent in patients with anticoagulant therapy, thrombolysis can be incorporated into an emergency invasive medical procedure with a high risk of haemorrhage threatening the vital or functional prognosis. Regarding the expected benefits of rapid reperfusion, it is lawful to suggest neutralizing the anticoagulant effect of the drug, as the effect is immediate and there is no thrombogenic effect. The use of idarucizumab may therefore be discussed if dabigatran has been taken recently and/or if dabigatran plasma level is high enough to contraindicate IV thrombolysis in the absence of any alternative. More recently, several observations of IVT following administration of idarucizumab have been reported, with no haemorrhagic or thrombotic complications.[35-44] A recent expert opinion statement has provided guidance on the use of the specific reversal agent idarucizumab followed by rt-PA and/or thrombectomy.[12]

- Patients treated with a xaban

Andexanet α, an inhibitor of direct anti-Xa (xabans) and indirect anti-Xa (LMWH, fondaparinux) is currently being assessed.[45] It could be suggested for pre-thrombolysis neutralization under the same conditions as idarucizumab for dabigatran, but this product is unavailable at the time of this writing. Administration of this drug in healthy volunteers is associated with a pro-thrombotic biological signal (transient increase in D-dimers and prothrombin activation peptide).[46] For this reason, simply incorporating its use into haemorrhagic event care in a patient suffering from cerebral infarction is inconceivable without any data specific to this situation. Until perfect tolerance of Andexanet α is proven, it is contraindicated in the same manner as pro-coagulant drugs (prothrombin complex concentrates, activated or non-activated).

DECISION ALGORITHM

Whereas IVT can be administered without waiting for the results of haemostasis tests in a patient not receiving oral anticoagulant, haemostasis tests are essential when no information on ongoing treatments can be obtained from the patient. This is particularly critical with DOACs as the usual coagulation tests can be minimally modified. A few expert recommendations have been published, but decision algorithms are rarely proposed.[6, 9, 12, 47, 48] We consider that every hospital performing IVT should be able to assess blood levels of DOACs, with a result given in 30 minutes. In patients on DOAC treatment and having an acute IS, several factors need to be considered before treatment:

- Last time the medication was taken;
- Renal function;
- Type of hospital where the patient is admitted;
- Presence of proximal intracranial arterial occlusion;
- Plasma concentration of the DOAC, measured with a specific test. Failing this, the combined results of commonly used bioassays, PT, APTT, and TT for dabigatran and PT, APTT, and LMWH/UFH anti-Xa activity for xabans, can be indicators of the presence of a DOAC that are more or less accurate depending on the DOAC.

The algorithm is shown in figure 1. If information on DOAC treatment can be obtained at the time of the emergency medical system call and if there is no major extension of the delay for acute management, it might be preferable to refer the patient to a comprehensive stroke centre (CSC) where interventional neuroradiology is available.

1) Regardless of the DOAC and regardless of the hospital where the patient is admitted, if the drug was last taken since **at least 48 hours** (or 4 half-lives, on average) and creatinine clearance of >50 mL/min (Cockcroft-Gault formula), the drug plasma level is probably very low, if not nil. There is no need to wait for haemostasis assays to decide. IVT can be performed, combined with MT if indicated.

2) Regardless of the DOAC, if the time since it was last taken is **unknown** or **less than 48 hours**, or if creatinine clearance is <50 mL/min, residual plasma concentration of the drug is not predictable. Immediate IVT is not possible.

a) The patient is admitted to a CSC

- In case of proximal occlusion, the 3 options are:

Immediate MT without IVT (to be preferred);

IVT based on DOAC levels (figure 2), combined with MT;

In case of dabigatran, reversal by idarucizumab (with or without bioassays beforehand), then IVT combined MT.

- In the absence of proximal arterial occlusion, the 2 options are:

IVT based on DOAC levels (figure 2);

In case of dabigatran, reversal by idarucizumab, then IVT;

If the antidote is administered without knowing the circulating level of dabigatran, there is a possibility of administering the antidote while the drug level is low or zero.

b) The patient is admitted to centre where an interventional neuroradiology platform is not available (local stroke unit or telemedicine site)

- In case of proximal occlusion, the 3 options are:

IVT based on haemostasis results (figure 2), then immediate transfer to CSC for MT;

In case of dabigatran, reversal by idarucizumab (with or without bioassays beforehand), then IVT, then immediate transfer to CSC for MT.

Transfer to CSC MT without IVT (if the delay is reasonable);

- In the absence of proximal arterial occlusion, the 2 options are:

IVT based on haemostasis results (figure 2);

In case of dabigatran, reversal by idarucizumab, then IVT;

The decision algorithm based on haemostasis results is shown in figure 2. Of note, if the drug was last taken since less than 12 hours, the plasma concentration is likely to be high and treatment option may be decided without waiting haemostasis results, *i.e.* MT in case of proximal artery occlusion or reversal by idarucizumab, then IVT, in case of dabigatran.

1) Specific dosages are available

Case reports (table 3 and Seiffge *et al*.[25]) suggest that when the drug level is < 50 ng/mL, the risk of intracranial haemorrhage after IVT is no greater than that observed in patients receiving no anticoagulant. No IVT was reported in patients with levels >100 ng/mL, and it seems wise, for the time being, to avoid IVT in this situation if there is no antidote available. Between 50 and 100 ng/mL, a very small number of patients underwent IVT without haemorrhagic complications. In this situation, the decision must be discussed in terms of the individual risk/benefit ratio and the possibility of a MT.

2) Specific dosages are not available

In the absence of any specific level measurements during the timeframes, the usual coagulation tests (PT, APTT) can be used, but this is a compromised solution (figure 2). Except for apixaban, which has no or little impact on PT or APTT measurements at normal concentration levels, a normal result of these tests rules out high-concentration dabigatran or rivaroxaban.

- If APTT and PT are both normal (generally defined as a ratio M/T <1.20 for APTT and PT ≥ 70%), the residual concentrations of rivaroxaban or dabigatran are likely to be very low. For apixaban, PT and APTT are not interpretable. For edoxaban, there is not enough data.
- A thrombin time (TT) for dabigatran, or the measurement of LMWH/UFH anti-Xa activity, for the xabans, should be systematically and simultaneously performed. If TT is normal, dabigatran plasma concentration is zero and if TT is measurable (<60 s), dabigatran plasma concentration is very low. Likewise, if anti-Xa activity is ≤0.1 UI/mL, xaban concentration is zero and is very low between 0.1 and 0.5 UI/mL. Under these conditions, IVT is conceivably possible.

- Beyond these thresholds (TT > 60 s, anti-Xa activity > 0.5 UI/mL) and/or if PT or APTT is abnormal, IVT is not recommended when the DOAC plasma level is unknown.

CONCLUSION

In a patient treated with a DOAC, IVT cannot be recommended with a sufficient level of evidence. However, available data suggest that in patients selected according to the time elapsed since the drug was last taken, and the concentration of the drug, IVT could be used. Although not formally validated, the use of antidotes, currently restricted to idarucizumab for dabigatran, might broad the scope of indications. We encourage to set up a local protocol involving haemostasis specialists for the treatment of ischemic stroke patients on DOAC. Finally, it is important to include all patients treated with a DOAC and a pharmacological or mechanical recanalization in a prospective registry.

Appendix

Special thanks to the reading group

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Members: S Alamowitch (SFN representative), JF Albucher, Y Béjot, C Cordonnier, S Debiais, S Deltour, M Giroud, M Hommel, B Lapergue, MH Mahagne, JL Mas, M Mazighi, T Moulin, JP Neau, M Obadia, T Ronzière, Y Samson, A Triquenot, F Woimant, V Wolf, M Zuber.

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Table 1 – Pharmacology of DOACs (based on [49])

	Dabigatran	**Apixaban**	**Edoxaban**	**Rivaroxaban**
Bioavailability	3-7%	52%	67%	66% without food 100% with food
Half-life	12-17h	12h	9-11h	5-9h (young subject) 11-13h (elderly subject)
Onset of action	2h	1-4h	1-2h	2-4h
Pro-drug	Yes	No	No	No
Non-renal/renal elimination	20/80%	73/27%	50/50%	65/35%
Transport via Pgp	Yes	Yes	Yes	Yes
Liver metabolism (CYP3A4)	No	Yes	Yes	Yes
Absorption with food	No effect	No effect	+6-22%	+39%

Recommended to be taken with food		No	No	No	Yes
Normal plasma concentrations ng/mL					
	Cmax (2-4h)	175 (117-275)*	171 (91-321)**	294(116)***	249 (184-343)*
	Cmin (12 h)	91 (61-143)*	103 (41-230)**	ND	ND
	Cmin (24 h)	ND	ND	ND	44 (12-137)*

*10th-90th percentiles – ** 5th-95th percentiles – *** mean (SD) – ND: not determined

Figure 1 – Decision algorithm for recanalization in a cerebral infarction patient on DOAC.

In case of idaricizumab use, it is important to proceed to IVT immediately after antidote administration to prevent sudden anticoagulation correction from leading to prolonged thrombosis in the patient who has just experienced a thrombotic event.

Legend

AD=antidote (To date, only idarucizumab is available.)

rtPA-intravenous thrombolysis (IV rtPA)

MT=mechanical thrombectomy

Creatinine clearance (Cockroft formula)

Figure 2 – Decision algorithm for thrombolysis in a cerebral infarction patient on DOAC, according to haemostasis tests.

Anti-Xa = Non-specific anti-Xa, as indicated in the text

Table 2 – Effects of DOACs on coagulation tests[15, 17]

Test	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
APTT	↑↑	←→	↑	↑ to ←→
PT	↓	←→	↓	↓ to ↓↓
INR	↑	↑ to ←→	↑	↑ to ↑↑
TT and derivatives	↑↑↑↑	←→	←→	←→
Anti-Xa activity	←→	↑↑↑	↑↑↑	↑↑↑

←→ No effect ↑ increase ↓ decrease

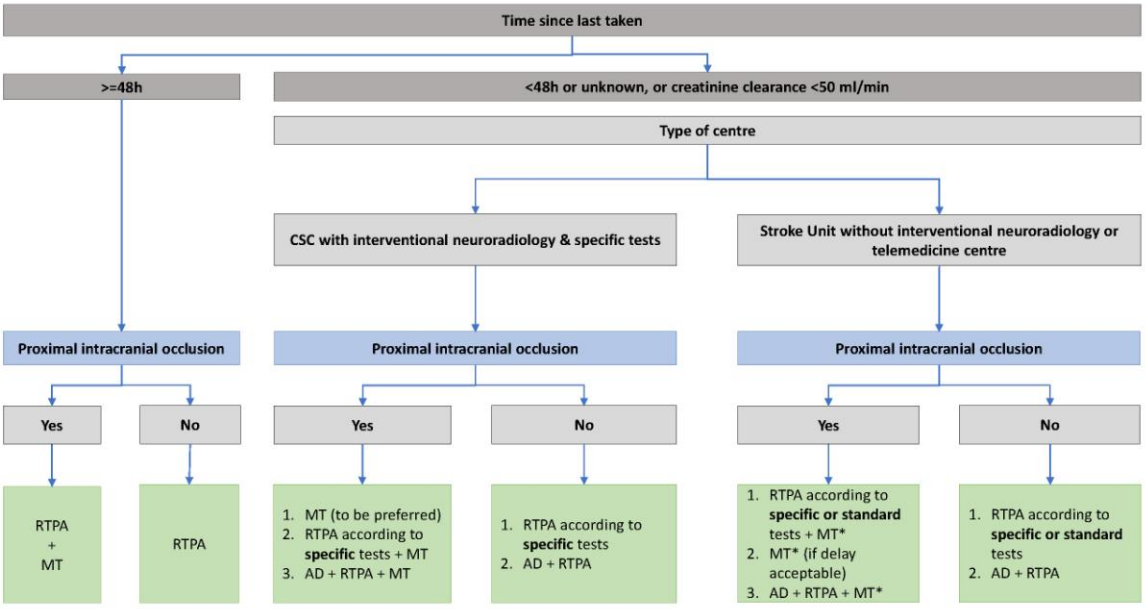
APTT=activated partial thromboplastin time – PT=prothrombin time – (%) – INR: International Normalized Ratio – TT=thrombin time

Table 3 – Review of IV thrombolysis cases in patients on DOACs (without antidote)

Reference	Age/Sex	Time of from symptom onset to thrombolysis	NIHSS	DOAC (dosage, mg), n times taken	Time since last taken – thrombolysis	PTA (s)	PT/INR	TT (s)	Specific test	Haemorrhagic complication
De Smedt, 2010[50]	46/F	4h30	19	D (?) x 2	7h	34.8	87%/1.2	NR	NR	No
Casado-Naranjo, 2011[51]	62/M	3h	18	D (110) x 2	6h	37.1	NR/1.3	14.6	NR	ICH and death
Matute, 2011[52]	76/F	2h	4	D (220) x 1	15h	30.6	11.4s/1.0	NR	NR	No
Marrone, 2012[53]	73/M	2h	14	D (110) x 2	9h	38.0	NR/1.1	NR	NR	No
Lee, 2012[54]	64/M	3h30	8	D (150) x 2	NR	37.6	NR/1.1	NR	NR	No
Sangha, 2012[55]	51/M	2h30	15	D (150) x 2	16h	30.7	NR/1.1	26.4	NR	No
Pfeilschifter, 2013[18]	77/F	1h30	15	D (150) x 2	Unknown	20.0	NR/1.1	20	NR	No
Jayathissa, 2013[56]	67/M	2h	NR	D (150) x 2	Unknown	28.0	NR/NR	NR	NR	ICH and death
Fluri, 2013[57]	83/M	3h30	9	R (15) x 1	21h	41.9	NR/1.4	18.9	<threshold	No
Breuer, 2013[58]	48/M	1h10	NR	D (150) x 2	9h	NR	NR	NR	0 ng/ml	No
Kawiorski, 2014[59]	83/F	4h	18	R (15) x 1	22h	36.9	10.7/0.9	NR	NR	No
Van Hooff, 2014[60]	80/M	2h15	19	R (20) x 1	24h	29.4	44%/1.8	NR	NR	Minor haematuria
Kate, 2014[47]	61/M	2h	2	D (150) x 2	10h	N	N	N	NR	No
Tabata, 2014[61]	79/M	1h45	10	D (110) x 2		37	1.3	NR	NR	No
Seiffge, 2014[62]	74	NR	12	R (20) x 1	18h	25.0	83%/1.1	15	10 ng/ml	No

	78	NR	8	R (20) x 1	22h	29.0	62%/1.3	18	67 ng/ml	No
Bornkamm, 2014[63]	81/M	3h15	19	R (20) x 1	24-26h	N	N		NR	No
Ishihara, 2014[64]	80/M	2h	10	R (10) x 1	6h	46.0	22.6s/2.0	NR	NR	No
Korya, 2014[65]	71/M	NR	7	R (?)	>4h	31.6	15.1s/1.2	NR	NR	No
Neal, 2014[66]	79/F	3h05	27	R (20) x 1	15-17h	23	NR/1.1	NR	25 ng/ml	No
Inaishi, 2014[67]	72/M	2h40	11	D (110) x 2	7h10	39.1	NR/NR	NR	NR	No
Govindarajan, 2014[68]	59/M	NR	9	D (150) x 2	10h	30	NR/1.0	NR	NR	No
De Smedt, 2014[69]	74/M	4h30	8	A (5) x 2	8h30	N	N/NR	NR	NR	No
Kawiorski, 2014[59]	83/F	3h15	18	R (15) x 1	22h	26.9	10.7/0.9	NR	NR	No
Landais, 2015[70]	76/F	3h30	4	R (15) x 1	5h45	NR	55%/1.5	NR	NR	No
Cappellari, 2015[23]	72/F	NR	20	D (150) x 2	13h	N	NR/1.15	NR	NR	No
Nardetto, 2015[71]	78/M	3h30	21	R (15) x 1	26h	N	N	NR	NR	No
Berrouschot, 2016	76/M	2h30	11	D (110) x 2	3h30	73.3	NR	218	NR	No
Schäfer, 2016	67/F	NR	10	D (150) x 2	NR	NR	NR	130	NR	No

D=dabigatran – R=rivaroxaban – A=apixaban – N=normal – NR=not reported.



AD=idarucizumab (only for patients on dabigatran)

*MT, only feasible after transfer to CSC