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Intravenous thrombolysis for acute ischaemic stroke in patients on direct oral anticoagulants

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Abstract

Background and purpose

Whereas intravenous thrombolysis (IVT) is allowed for acute ischaemic stroke in patients on vitamin K antagonists with international normalized ratio ≤ 1.7 , there are 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 of 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 joint position paper to provide a practical position regarding the emergency management of ischaemic stroke in patients on DOACs.

Method

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 h, the management should not differ from that in patients without oral anticoagulant. In patients who are still on DOACs, mechanical thrombectomy is encouraged 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 tests, standard tests (thrombin 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, it is suggested 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'Etudes sur l'Hémostase et la Thrombose (GFHT) (French Study Group on Haemostasis and Thrombosis). Because the literature is relatively scarce, essentially based on small case series and retrospective studies, high-level recommendations cannot be given. Nevertheless, it is important to take a position regarding the emergency management of ischaemic stroke (IS) in a patient treated with a direct oral anticoagulant (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 the 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 in 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 years¹. Several DOACs have recently been approved for use, namely anti-IIa (dabigatran) or anti-Xa drugs ('xabans' rivaroxaban, apixaban, edoxaban), providing alternatives to VKAs for non-valvular AF and venous thrombosis²⁻⁴.

Oral anticoagulants significantly reduce the risk of cerebral ischaemic events in the case of AF, but each year 1%–2% of patients will have an ischaemic cerebral event despite being on anticoagulants⁵. Moreover, anticoagulant therapy is theoretically a relative contraindication for intravenous thrombolysis (IVT) of IS. In clinical trials demonstrating the efficacy of recombinant tissue plasminogen activator (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 the international normalized ratio (INR) is ≤ 1.7 ^{6, 7}, and several international guidelines allow thrombolysis in this situation⁸.

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 patients⁴. However, they were all developed without the need for 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 pretreated with dabigatran 12. However, there are no similar guidelines for other DOACs. This statement relies on recent data with the aim of providing a sensible decision algorithm until better established clinical data become available.

Direct oral anticoagulant pharmacology

As shown in 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 factors (age, sex, renal and liver functions, genetic polymorphisms) but also extrinsic factors (interactions with inductive drugs, inhibitors or permeability glycoprotein transporter and/or CYP3A4 cytochrome substrates) 10, 11, 13.

Table 1. Pharmacology of direct oral anticoagulants (based on 49)

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3%–7%	52%	67%	66% without food 100% with food
Half-life	12–17 h	12 h	9–11 h	5–9 h (young subject) 11–13 h (elderly subject)
Onset of action	2 h	1–4 h	1–2 h	2–4 h
Pro-drug	Yes	No	No	No
Non-renal/renal elimination	20%/80%	73%/27%	50%/50%	65%/35%
Transport via permeability glycoprotein	Yes	Yes	Yes	Yes
Liver metabolism (CYP3A4)	No	Yes	Yes	Yes
Absorption with food	No effect	No effect	+6% to 22%	+39%
Recommended to be taken with food	No	No	No	Yes
Normal plasma concentrations, ng/ml				
C_{\max} (2–4 h)	175 (117–275)a	171 (91–321)b	294(116)c	249 (184–343)a
C_{\min} (12 h)	91 (61–143)a	103 (41–	ND	ND

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
C_{\min} (24 h)	ND	230) ^b ND	ND	44 (12–137) ^a

- ND, not determined.
- ^a 10th–90th percentiles; ^b5th–95th percentiles; ^cmean (SD).

Bioassays

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

Table 2. Effects of direct oral anticoagulants 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.

Prothrombin time and activated partial thromboplastin time

Activated partial thromboplastin time 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 the case of an overdose, for which there is a plateau effect. PT (expressed as PT or INR) is less sensitive to dabigatran than APTT 10, 11, 16.

Activated partial thromboplastin time 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 APTT, 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 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 for excluding dabigatran concentrations below 30 ng/ml 16.

Thrombin time and anti-Xa activity

The two tests TT and anti-Xa activity are useful to rule out the presence of dabigatran (TT) or xabans (anti-Xa activity). The TT is very sensitive to dabigatran, being unmeasurable in most patients on treatment, and is moderately prolonged even when the plasmatic concentration of dabigatran is low (≤ 30 ng/ml). Thus, a normal TT reliably rules out the presence of dabigatran, and for $TT \leq 60$ s dabigatran levels are low (<30 ng/ml) 10, 16. A similar reasoning applies when measuring anti-Xa activity, calibrated in heparin/low-molecular-weight heparin (heparin/LMWH) anti-Xa units. Anti-Xa activity is very xaban-sensitive, with values generally beyond the upper measurement limit ($>>1$ U/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.

Specific tests measuring the plasma level of the drug

The reference technique is 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 h a day, serves as the most easily usable haemostatic technique comparator.

Different tests on the market allow the plasma drug levels, expressed as nanograms per millilitre of plasma, to be specifically measured 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. The 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 min 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 IS in mice (using monofilaments) has shown that an rtPA/warfarin combination increased the risk of haemorrhagic transformation, whilst an rtPA/dabigatran combination, at a dose assumed to be equivalent to that 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 ischaemia and not treated with rtPA suggested that dabigatran did not increase the 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 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 the risk of haemorrhagic transformation after thrombolysis. A similar dose–effect relation is likely with DOACs.

Clinical data on cerebral thrombolysis with DOACs

Data on IVT in patients taking DOACs remain limited. A series of 28 patients (Table 3) (compiled in the recent review by Cappellari and Bovi), three cases published in 2015 23, 24, a multicentre study 25 and a retrospective analysis of 251 patients on DOACs from a registry of consecutive patients who had IS in the USA 26 have been identified. In the review by Cappellari and Bovi, 18 patients received dabigatran, 12 received rivaroxaban and one received apixaban. In most cases, the indication for anticoagulant treatment was high-risk AF. In some cases, whether the patient was on DOACs 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 five patients taking dabigatran and a specific anti-Xa test in four patients taking rivaroxaban. The APTT was normal or slightly prolonged in most patients. Two patients on dabigatran had fatal intracranial haemorrhage (ICH). No major bleeding was observed in the other patients. A case series of five other patients, taking dabigatran and treated with rtPA, was recently published with no details about individual characteristics, and no patient had symptomatic ICH 24. However, given the small numbers of cases, uncertainty remains about the risk of intracranial bleeding in this situation.

Table 3. Review of intravenous thrombolysis cases in patients on direct oral anticoagulants (without antidote)

References	Age/sex	Time from symptom onset to thrombolysis	NIHSS	DOAC (dosage, mg), <i>n</i> times taken	Time since last taken – thrombolysis	PTA (s)	PT/INR	TT (s)	Specific test	Haemorrhagic complication
De Smedt <i>et al.</i> 50	46/F	4 h:30	19	D (NR) × 2	7 h	34.8	87%/1.2	NR	NR	No
Casado-Naranjo <i>et al.</i> 51	62/M	3 h	18	D (110) × 2	6 h	37.1	NR/1.3	14.6	NR	ICH and death
Matute <i>et al.</i> 52	76/F	2 h	4	D (220) × 1	15 h	30.6	11.4s/1.0	NR	NR	No
Marrone <i>et al.</i> 53	73/M	2 h	14	D (110) × 2	9 h	38.0	NR/1.1	NR	NR	No
Lee <i>et al.</i> 54	64/M	3 h:30	8	D (150) × 2	NR	37.6	NR/1.1	NR	NR	No
Sangha <i>et al.</i> 55	51/M	2 h:30	15	D (150) × 2	16 h	30.7	NR/1.1	26.4	NR	No
Pfeilschifter <i>et al.</i> 18	77/F	1 h:30	15	D (150) × 2	Unknown	20.0	NR/1.1	20	NR	No

References	Age/sex	Time from symptom onset to thrombolysis	NIHSS	DOAC (dosage, mg), <i>n</i> times taken	Time since last taken – thrombolysis	PTA (s)	PT/INR	TT (s)	Specific test	Haemorrhagic complication
Jayathissa <i>et al.</i> 56	67/M	2 h	NR	D (150) × 2	Unknown	28.0	NR/NR	NR	NR	ICH and death
Fluri <i>et al.</i> 57	83/M	3 h:30	9	R (15) × 1	21 h	41.9	NR/1.4	18.9	<Threshold	No
Breuer <i>et al.</i> 58	48/M	1 h:10	NR	D (150) × 2	9 h	NR	NR	NR	0 ng/ml	No
Kawiorski <i>et al.</i> 59	83/F	4 h	18	R (15) × 1	22 h	36.9	10.7/0.9	NR	NR	No
van Hooff <i>et al.</i> 60	80/M	2 h:15	19	R (20) × 1	24 h	29.4	44%/1.8	NR	NR	Minor haematuria
Kate <i>et al.</i> 47	61/M	2 h	2	D (150) × 2	10 h	N	N	N	NR	No
Tabata <i>et al.</i> 61	79/M	1 h:45	10	D (110) × 2		37	1.3	NR	NR	No
Seiffge <i>et al.</i> 62	74	NR	12	R (20) × 1	18 h	25.0	83%/1.1	15	10 ng/ml	No

References	Age/sex	Time from symptom onset to thrombolysis	NIHSS	DOAC (dosage, mg), <i>n</i> times taken	Time since last taken – thrombolysis	PTA (s)	PT/INR	TT (s)	Specific test	Haemorrhagic complication
	78	NR	8	R (20) × 1	22 h	29.0	62%/1.3	18	67 ng/ml	No
Bornkamm and Harloff 63	81/M	3 h:15	19	R (20) × 1	24–26 h	N	N		NR	No
Ishihara <i>et al.</i> 64	80/M	2 h	10	R (10) × 1	6 h	46.0	22.6s/2.0	NR	NR	No
Korya <i>et al.</i> 65	71/M	NR	7	R (NR)	>4 h	31.6	15.1s/1.2	NR	NR	No
Neal <i>et al.</i> 66	79/F	3 h:05	27	R (20) × 1	15–17 h	23	NR/1.1	NR	25 ng/ml	No
Inaishi <i>et al.</i> 67	72/M	2 h:40	11	D (110) × 2	7 h:10	39.1	NR/NR	NR	NR	No
Govindarajan and Galvez 68	59/M	NR	9	D (150) × 2	10 h	30	NR/1.0	NR	NR	No
De Smedt <i>et al.</i> 69	74/M	4 h:30	8	A (5) × 2	8 h:30	N	N/NR	NR	NR	No
Landais and Ginoux 70	76/F	3 h:30	4	R (15) × 1	5 h:45	NR	55%/1.5	NR	NR	No
Cappellari and Bovi 23	72/F	NR	20	D (150) × 2	13 h	N	NR/1.15	NR	NR	No
Nardetto <i>et al.</i> 71	78/M	3 h:30	21	R	26 h	N	N	NR	NR	No

References	Age/sex	Time from symptom onset to thrombolysis	NIHSS	DOAC (dosage, mg), <i>n</i> times taken	Time since last taken – thrombolysis	PTA (s)	PT/INR	TT (s)	Specific test	Haemorrhagic complication
Berrouschot <i>et al.</i> 35	76/M	2 h:30	11	(15) × 1 D (110) × 2	3 h:30	73.3	NR	218	NR	No
Schäfer <i>et al.</i> [36]	67/F	NR	10	D (150) × 2	NR	NR	NR	130	NR	No

- A, apixaban; APTT, activated partial thromboplastin time; D, dabigatran; DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; INR, international normalized ratio; N, normal; NR, not reported; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; R, rivaroxaban; TT, thrombin time.

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 IVT combined, in six cases, with endovascular treatment, and the others received endovascular treatment only. The symptomatic ICH rate was 2.6% using ECASS-II criteria (any ICH with neurological deterioration, as indicated by a National Institutes of Health Stroke Scale 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 National Institute of Neurological Disorders and Stroke 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, the unadjusted rate of symptomatic ICH 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 the three 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 also applies for patients on DOACs. However, specific antidotes of DOACs, recently developed, may have a role in the management of acute IS patients on DOACs 30.

Patients treated with dabigatran

Idarucizumab, the first specific DOAC antidote, is a monoclonal antibody, the affinity of which 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 were reported 33, 34. Depending on the criteria used, complete biological reversal was obtained in 88%–98% of patients within a few minutes after infusion. The median time before bleeding was stopped was 11 h, and in the 36 patients requiring surgery haemostasis was deemed normal in 92%. 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 require biological monitoring of haemostasis within 24 h after administration of the antidote.

Idarucizumab (Praxbind[®]) has recently been 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 seems valid 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 the dabigatran plasma level is high enough to contraindicate IVT 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 rtPA 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 the 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 proved, 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. It is considered that every hospital performing IVT should be able to assess blood levels of DOACs, with a result given in 30 min. In patients on DOAC treatment and having an acute IS, several factors need to be considered before treatment:

- the last time the medication was taken;
- renal function;
- the type of hospital where the patient is admitted;
- the presence of proximal intracranial arterial occlusion;
- the 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/unfractionated heparin 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 Fig. 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.

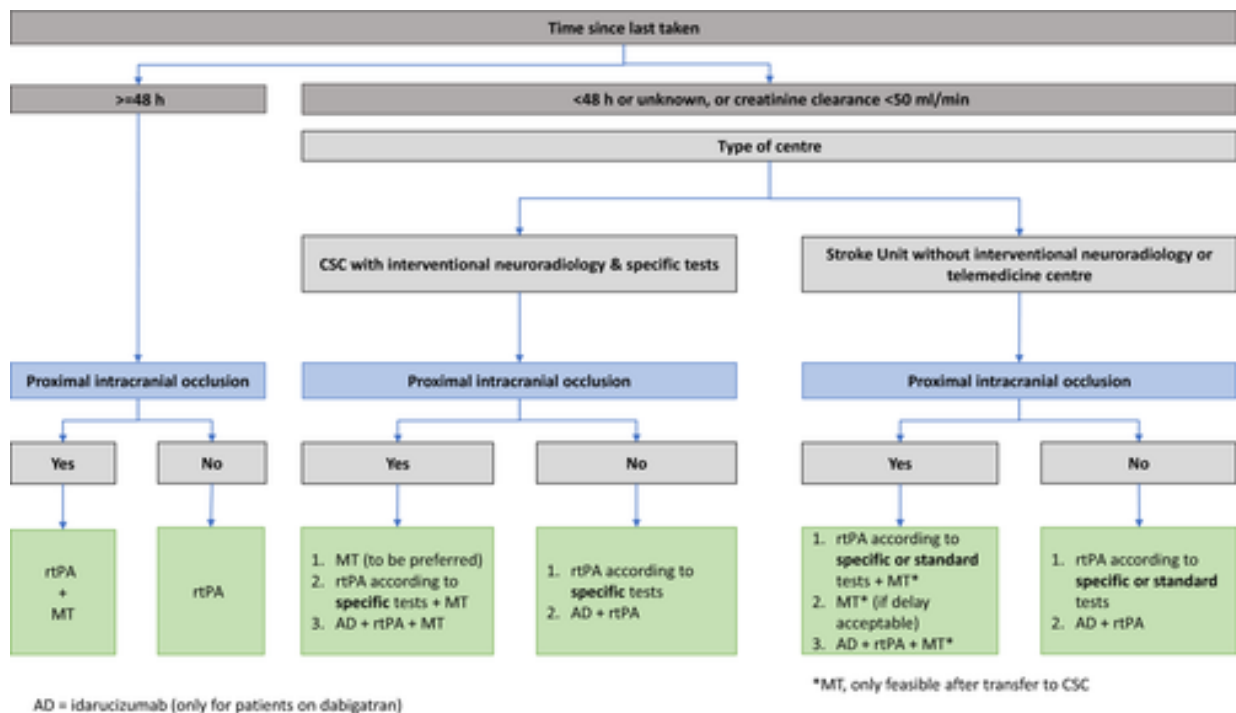


Figure 1

Open in figure viewerPowerPoint

Decision algorithm for recanalization in a cerebral infarction patient on a direct oral anticoagulant. In the case of idarucizumab use, it is important to proceed to intravenous thrombolysis immediately after antidote administration to prevent sudden anticoagulation correction from leading to prolonged thrombosis in the patient who has just experienced a thrombotic event. AD, antidote (to date, only idarucizumab is available); rtPA-intravenous thrombolysis (IV rtPA); MT, mechanical thrombectomy; creatinine clearance, Cockcroft formula. [Colour figure can be viewed at wileyonlinelibrary.com].

1. Regardless of the DOAC and regardless of the hospital where the patient is admitted, if the drug was last taken at least 48 h ago (or 4 half-lives, on average) and with creatinine clearance > 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 h, or if creatinine clearance is < 50 ml/min, the residual plasma concentration of the drug is not predictable. Immediate IVT is not possible.

The patient is admitted to a CSC

In the case of proximal occlusion, the three options are

- immediate MT without IVT (to be preferred);

- IVT based on DOAC levels (Fig. 2), combined with MT;

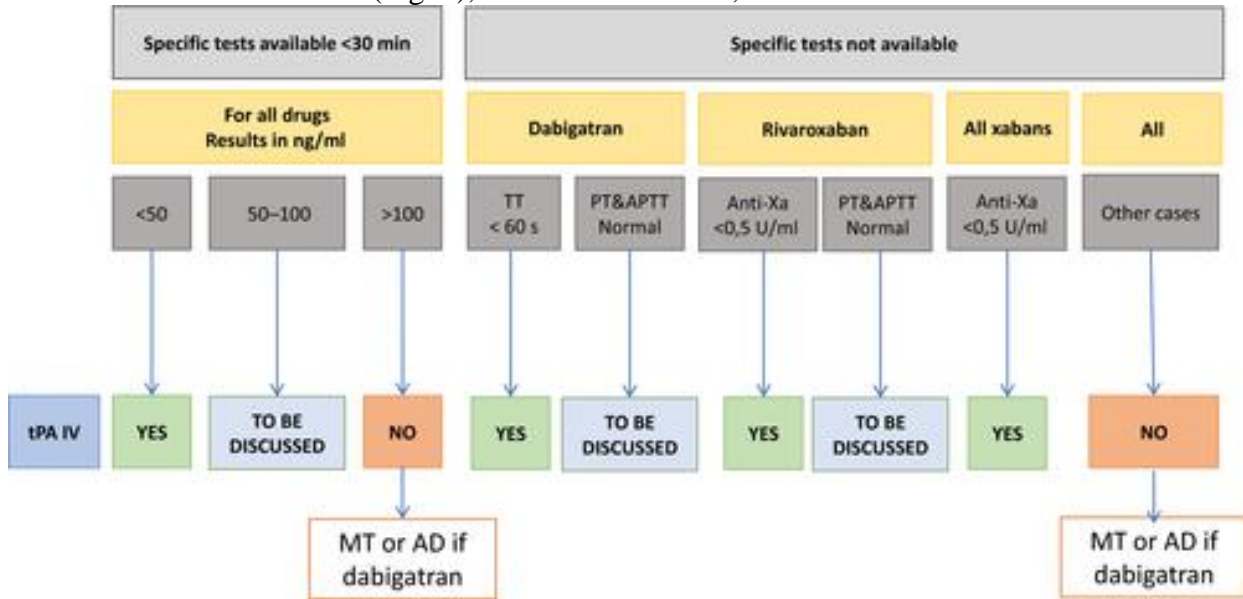


Figure 2

Open in figure viewerPowerPoint

Decision algorithm for thrombolysis in a cerebral infarction patient on direct oral anticoagulant, according to haemostasis tests. Anti-Xa, non-specific anti-Xa, as indicated in the text. [Colour figure can be viewed at wileyonlinelibrary.com].

- in the case of dabigatran, reversal by idarucizumab (with or without bioassays beforehand), and then IVT combined with MT.

In the absence of proximal arterial occlusion, the two options are

- IVT based on DOAC levels (Fig. 2);
- in the case of dabigatran, reversal by idarucizumab, and then IVT.

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

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

In the case of proximal occlusion, the three options are

- IVT based on haemostasis results (Fig. 2), and then immediate transfer to the CSC for MT;
- in the case of dabigatran, reversal by idarucizumab (with or without bioassays beforehand), then IVT, and then immediate transfer to the CSC for MT;
- transfer to the CSC MT without IVT (if the delay is reasonable).

In the absence of proximal arterial occlusion, the two options are

- IVT based on haemostasis results (Fig. 2);
- in the case of dabigatran, reversal by idarucizumab, and then IVT.

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

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 ICH 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 MT.

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 compromise solution (Fig. 2). Except for apixaban, which has little or no 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 (Patient/Control)<1.20 for APTT and PT \geq 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 are not enough data.
- A TT for dabigatran, or the measurement of LMWH/unfractionated heparin 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 \leq 0.1 U/ml, xaban concentration is zero or very low between 0.1 and 0.5 U/ml. Under these conditions, IVT is conceivably possible.
- Beyond these thresholds (TT >60 s, anti-Xa activity >0.5 U/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, the 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 broaden the scope of indications. It is encouraging that a local protocol is

set up involving haemostasis specialists for the treatment of IS patients on DOACs. Finally, it is important to include all patients treated with a DOAC and a pharmacological or mechanical recanalization in a prospective registry.

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A version in French of this expert opinion is available on www.societe-francaise-neurovasculaire.fr and on <http://site.geht.org/docutheque/>.

Appendix

Special thanks to the reading groups.

Société Française de Neuro-Vasculaire (SFNV)

Board of directors: S Timsit, H Chabriat, I Sibon, P Niclot, B Guillon, C Cognard.

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