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► To cite this version:

Nicolas Gendron, Paul Billoir, Virginie Siguret, Véronique Le Cam Duchez, Valerie Proulle, et al.. Is there a role for the laboratory monitoring in the management of specific antidotes of direct oral anticoagulants?. *Thrombosis Research*, 2024, 237, pp.171-180. 10.1016/j.thromres.2024.04.005 . hal-04567586

HAL Id: hal-04567586

<https://hal.science/hal-04567586>

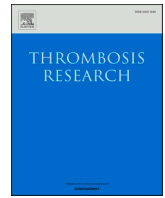
Submitted on 16 May 2024

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Is there a role for the laboratory monitoring in the management of specific antidotes of direct oral anticoagulants?

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ARTICLE INFO

Keywords:

Andexanet alfa
Antidote
Ciraparantag
Direct oral anticoagulant
Idarucizumab
Laboratory monitoring

ABSTRACT

Given the growing number of patients receiving direct oral anticoagulant (DOAC), patients requiring rapid neutralization is also increasing in case of major bleedings or urgent surgery/procedures. Idarucizumab is commercialized as a specific antidote to dabigatran while andexanet alfa has gained the Food and Drug Administration and the European Medicines Agency approval as an oral anti-factor Xa inhibitors antidote. Other antidotes or hemostatic agents are still under preclinical or clinical development, the most advanced being ciraparantag. DOAC plasma levels measurement allows to appropriately select patient for antidote administration and may prevent unnecessary prescription of expensive molecules in some acute clinical settings. However, these tests might be inconclusive after some antidote administration, namely andexanet alfa and ciraparantag. The benefit of laboratory monitoring following DOAC reversal remains unclear. Here, we sought to provide an overview of the key studies evaluating the safety and efficacy of DOAC reversal using the most developed/commercialized specific antidotes, to discuss the potential role of the laboratory monitoring in the management of patients receiving DOAC specific antidotes and to highlight the areas that deserve further investigations in order to establish the exact role of laboratory monitoring in the appropriate management of DOAC specific antidotes.

1. Introduction

Direct oral anticoagulants (DOACs) have been gradually introduced

in clinical practice worldwide [1,2] for more than a decade, with comparable or better efficacy and safety profiles than vitamin K antagonist (VKA). DOACs are prescribed for the prevention of stroke and systemic

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<https://doi.org/10.1016/j.thromres.2024.04.005>

Received 3 January 2024; Received in revised form 4 April 2024; Accepted 8 April 2024

Available online 10 April 2024

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thromboembolic events in non-valvular atrial fibrillation (NVAF) [3], for the treatment and secondary prevention of venous thromboembolic events (VTE) [4] and at lower doses for the primary VTE prevention following orthopedic surgeries [5,6] or in patients with symptomatic peripheral artery disease following recent lower-extremity revascularization [7]. DOACs inhibit directly, specifically and reversibly activated factor X (FXa, rivaroxaban, apixaban and edoxaban) or thrombin (dabigatran). In contrast to VKA, DOACs have predictable pharmacokinetic and pharmacodynamic profiles, wide therapeutic index and limited drug-drug and food-drug interactions [8]: laboratory monitoring is thus not needed. In real-world setting, clinicians encounter many challenges in DOAC-treated patients, above all the management of acute major bleeding events or urgent surgeries. Assessment of DOAC plasma concentrations is of interest in such clinical situations and when the use of specific antidotes are considered. In emergency situations, measuring DOAC levels might not be readily available, and the turnaround time for test results can be up to one hour. Hence, it is crucial to take into account the clinical context when considering DOAC-specific antidote, including the severity of bleeding, the risk associated with the surgery, and the timing of the last DOAC dose. Idarucizumab is commercialized as a specific antidote to dabigatran while andexanet alfa has gained the Food and Drug Administration and the European Medicines Agency approval as an oral anti-factor Xa inhibitors antidote. Other antidotes are still under preclinical or clinical development, the most advanced being ciraparantag. Yet, it remains unclear whether laboratory monitoring is mandatory, might be useful in some cases or has no role following specific antidotes administration. On behalf of the French Society on Thrombosis and Haemostasis (SFTH, previously named the French Study Group on Hemostasis and Thrombosis or GFHT), we analyzed the current available data for laboratory monitoring in the management of specific antidotes of DOACs and provided an overview of the available methods for DOAC measurement and of reversal thresholds, a brief summary of the key studies evaluating the safety and efficacy of DOAC reversal using the most developed/commercialized specific antidotes (Table 1), to discuss the potential role of the laboratory monitoring in the management of patients receiving DOAC specific antidotes and to highlight the areas that deserve further investigations in order to establish the exact role of laboratory monitoring in the appropriate management of DOAC specific antidotes.

2. Methods

We performed a literature review in PubMed using the terms “dabigatran reversal”, “DOAC reversal”, “apixaban reversal”, “rivaroxaban reversal”, “edoxaban reversal” covering the period of January 1st 2015 to December 31th 2023. Three investigators assessed the articles for eligibility and data extraction (NG, PB and GJ). First, we excluded articles based on titles and abstracts in order to select eligible articles for full text review. We notably included an article matching the inclusion criteria but presenting missing data thanks to the author who responded favorably to complete data.

2.1. Commercialized laboratory assays for DOAC measurement

Recommendations on the measurement of DOAC levels were issued by the International Council for Standardization in Hematology in 2018 [9] and updated in 2021 [10]. It is worth mentioning that routine coagulation assays, namely prothrombin time (PT) and activated partial thrombin time (aPTT), are inappropriate to monitor DOAC levels or even to exclude clinically relevant plasma levels of any of the DOACs [9,11–13]. Normal thrombin time (TT) and low-molecular weight heparin (LMWH) anti-Xa value below a cut-off that varies among reagents, can be used to exclude clinically relevant dabigatran and oral FXa inhibitors plasma levels, respectively [14–18]. Moreover, an easy-to-use nomogram was developed to accurately predict oral FXa inhibitors levels based on LMWH-anti-Xa results, in emergency situations such as

Table 1
Description and comparison of the different antidote in clinical development in 2023.

Pharmacological properties	Idarucizumab	Andexanet alfa	Ciraparantag (aripazine, PER977)
Structure	Humanized monoclonal antibody fragment (Fab)	Human recombinant FXa variant	Synthetic cationic small molecule
Target	Dabigatran	Oral factor Xa inhibitors and heparin derivatives	Oral factor Xa and thrombin inhibitors
Administration	Intravenous	Intravenous	Intravenous
Half-life	47 min	5–7 h	12–19 min
Elimination	Renal	Unknown	Renal
Indication	Adult patients treated with dabigatran and: • requiring urgent surgery/invasive procedures • suffering from life-threatening or uncontrolled bleeding	Adult patients treated with oral factor Xa inhibitor (apixaban or rivaroxaban) and: • suffering from life-threatening or uncontrolled bleeding. • requiring urgent surgery/invasive procedures (under investigation)	–
DOAC plasma concentration measurement after reversal	dTT, ECA or ECT	Commercialized anti-Xa based assay are not suitable	Whole blood clotting time
Trials/ study in progress	Completed Phase III REVERSE-AD	Completed Phase III ANNEXA-4	Ongoing Phase II: NCT03288454 and NCT03172910
Authorization	FDA, EMA	FDA, EMA	–

DOAC: direct oral anticoagulant; dTT: diluted thrombin time; ECA: ecarin chromogenic assay; ECT: ecarin clotting time; FDA: Food and Drug Administration; EMA: European Medicines Agency.

in acute ischemic stroke patients when drug-specific assessments are not rapidly available [15]. Specific commercial anti-IIa and anti-Xa assays (approx. 16 € per test in France) including dedicated calibrators and controls are available in clinical laboratories to quantify DOAC levels. In contrast, the use of high-performance liquid chromatography/mass spectrometry (HPLC-MS/MS), considered as the gold-standard method, is currently limited to research laboratories [9]. A French academic study, performed in 30 clinical hemostasis laboratories, using spiked plasma concentrations (measured with HPLC-MS/MS) and 4 dabigatran and 5 rivaroxaban/apixaban calibrated assays on 3 different coagulation instruments, revealed an inter-laboratory coefficient of variation below 18 % for levels above 100 ng/mL and higher for levels around 40 ng/mL [19]. Therefore, commercialized calibrated DOAC assays allow measurement of anticoagulant plasma levels with a relatively good between-laboratory agreement, even though improvement of their performances could be made especially for low concentrations assessment. Besides, a point-of-care (POC) has recently been developed assessing the presence of DOACs in urine [20]. This easy-to-use bedside tool is positive whenever plasma DOAC levels are above 30 ng/mL. It has a good sensitivity (97.1 %) but a low specificity (20 %) and does not allow quantification of DOAC. A time to thrombolysis saving of 30 min was associated with the use of this POC in stroke patients with a false negative rate of 8 % [21]. Further studies are needed to confirm the clinical utility of this urine POC in acute settings.

2.2. Proposed laboratory thresholds for DOAC clinical management

Bleeding during DOAC therapy is a crucial issue. The risk of major bleeding while on DOACs therapy is estimated around 2 % per year [1,3]

in which case the fatality rate is about 8% [22,23]. Optimal management of these bleeding events is still poorly defined [24,25]. In the study of Testa et al. [26] only 23 % of the 117 patients with major bleeding under DOACs, had a specific measurement of DOAC for bleeding management suggesting that treatments were administered blind to hemostatic assessment. However, measuring DOAC levels is useful to consider reversal and to assess the anticoagulant's potential role in the severity of bleeding. A threshold of 50 ng/mL has been proposed by the subcommittee on control of anticoagulation of the International Society on Thrombosis and Hemostasis (ISTH) and the French Working group on perioperative hemostasis (GIHP) to warrant specific antidote administration in case of uncontrolled severe bleeding in DOAC-treated patients [27,28]. Besides, every year, 10 to 15 % of patients on anticoagulant require emergency surgery or invasive procedure [29]. Algorithms for the management of DOACs patients were proposed by the GIHP and the European Heart Rhythm Association (EHRA) [30]. The GIHP also suggested using specific antidotes, or at least procoagulant agents such as prothrombin complex concentrate (PCC) for DOAC reversal [27] in case of unknown DOAC plasma level with a time since the last drug intake of less than 24 h or a creatinine clearance (CrCl) of <50 mL/min. A safety hemostatic threshold of 30 ng/mL is suggested in case of very high bleeding risk urgent surgery (i.e., neurosurgery) [27,30]. DOAC neutralization should also be considered in case of per- or postoperative bleeding attributable to DOACs with a plasma level above 50 ng/mL as measured in preoperative of urgent high bleeding risk invasive procedure [27]. It is to mention that pre-operative DOAC levels <30 ng/mL or between 30 and 50 ng/mL were not associated with an increased risk for perioperative bleeding in the post-hoc analysis of the PAUSE study [31]. As for intravenous thrombolysis for acute ischemic stroke in patients on DOACs, joint propositions from the French Vascular Neurology Society and the SFTH based on plasma DOAC levels were also issued in 2018 [32].

2.3. Idarucizumab

2.3.1. Pharmacological characteristics

Idarucizumab is a humanized monoclonal antibody fragment (Fab) directed against dabigatran with a very high affinity approximately 300 times greater than that of dabigatran from thrombin. It potently and specifically neutralizes dabigatran and its active metabolite in a stoichiometric way [33,34]. The complexes idarucizumab-dabigatran and idarucizumab-dabigatran metabolites are thereafter excreted into the urine. Idarucizumab administration results in redistribution of dabigatran from the extravascular compartment to the plasma, where it is bound and inactivated by idarucizumab. Being a small protein with a molecular weight < 60 kDa, idarucizumab undergoes a glomerular filtration. It is subsequently reuptaken in the proximal renal tubular cells [35]. Therefore, its elimination is largely controlled by the rate of glomerular filtration. Urinary excretion of idarucizumab increases with its dose, suggesting saturation of renal tubular reuptake processes at higher doses. Renal impairment increases idarucizumab exposure and initial half-life but does not affect its terminal half-life of 74 minutes [35]. Idarucizumab pharmacokinetics is unaffected by the presence of dabigatran [35].

Commercialized product characteristics

Idarucizumab (marketed under the trade name Praxbind in the US and in European Union, Boehringer Ingelheim, Deutschland) was granted an accelerated approval in the US (October 2015) and marketing authorization in the European Union (December 2015) for use in patients treated with dabigatran who require rapid reversal of the anticoagulant effects for urgent procedures or suffer from life-threatening or uncontrolled bleeding. Idarucizumab is commercialized as two separate single use vials each containing 2.5 g/50 mL and stored in the refrigerator at 2 °C to 8 °C. Prior to use, the unopened vial may be kept at room temperature for up to 48 h, if stored in the original package

in order to protect from light, or up to 6 h when exposed to light. The recommended dose of idarucizumab is 5 g given as 2 consecutive intravenous infusions (2.5 g/50 mL) administered over 5–10 min (min) within 15 min of each other. This dose of 5 g was calculated to reverse in a stoichiometric way the total body load of dabigatran that was associated with the 99th percentile of the dabigatran levels measured in the phase III study RE-LY [36] (dabigatran 110 mg BID with 65.9 ng/mL and 28.2–155.0 ng/mL and dabigatran 150 mg BID with 93.0 ng/mL and 39.8–215.0 ng/mL as median concentrations and 10th–90th interquartile ranges, respectively) [37].

2.3.2. Efficacy and safety

The efficacy and safety of idarucizumab in the reversal of dabigatran anticoagulant effects were demonstrated in studies in healthy volunteers, in subjects with mild to moderate renal impairment [34,35,38–40]. Idarucizumab has not been shown to have procoagulant properties [34,38]. Its efficacy and safety were demonstrated in patients with serious bleeding or those in need of emergency procedures [41,42] and confirmed in Japanese patients in a post-marketing surveillance study [43]. The full cohort analysis of the RE-VERSE AD trial [42] evaluated the efficacy and safety of idarucizumab in 503 dabigatran patients who experienced serious bleeding (group A, $n = 301$) or required urgent invasive procedures (group B, $n = 202$). In the efficacy analysis, the primary outcome was a laboratory parameter, the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 h after the administration of idarucizumab. The median baseline level of dabigatran was 110 ng/mL in group A and 73.6 ng/mL in group B. A median maximum percent reversal of 100 % was observed within 4 h in both groups as assessed by diluted TT (dTT) or ecarin clotting time (ECT) [42]. Although hemostatic efficacy was included as an outcome in group A, the clinical assessment of hemostasis can be subjective, and cessation of bleeding is often difficult to ascertain, depending on the site of bleeding. Hemostatic efficacy could not be assessed in patients presenting with intracranial hemorrhage (ICH), as not all patients underwent scheduled follow-up cranial imaging to assess for hematoma expansion. After exclusion of patients with ICH, cessation of bleeding was observed within 24 h for 67.7 % of patients, with a median time of 2.5 h. Among group B patients, normal hemostasis during the procedure was obtained for the majority of the patients (93.4 %). Of note, the relationship between reduction in plasma dabigatran levels and hemostatic efficacy was not evaluated. The 30-day mortality rate was 13.5 % in group A and 12.6 % in group B. The corresponding 90-day mortality rate was 18.8 and 18.9 %, respectively. Thrombotic events occurred in 24 participants and included VTE, myocardial infarction, and ischemic stroke. Most deaths that occurred within 5 days after reversal appeared to be related the severity of the index event and/or to coexisting conditions.

Idarucizumab use allows dabigatran-treated patients with acute ischemic stroke to regain eligibility for intravenous thrombolysis [32]. Kermer et al. showed that treatment with rt-PA following idarucizumab injection is feasible and seems to be safe and effective [44]. These results were confirmed by a systematic review that found decreased but not statistically significant rates of ICH (4.5 % versus 7.4 %) and death (4.5 % versus 12.0 %) [45], and statistically significant more favorable outcomes (79.1 % versus 39.2 %) in dabigatran-treated patients who received rt-PA with or without prior administration of idarucizumab, respectively. Idarucizumab was also shown to be both effective and safe in case of NVAf patients treated with dabigatran and awaiting heart transplantation [46–48].

In a large retrospective cohort study across 217 hospitals in the United States, Singh et al. [49] found no difference in in-hospital mortality among adult patients with dabigatran associated gastrointestinal bleeding exposed or not to idarucizumab. The authors observed an excess risk of in-hospital mortality associated with idarucizumab exposure among participants with intracranial bleeding (11.6 % versus 2.8 %, $p = 0.0011$). However, patients receiving idarucizumab had more

comorbidities, particularly more brain compression at baseline. Recently, van der Host et al. [50] performed a systematic literature review including thirty studies with 3602 patients who received idarucizumab and evaluated prescription indications, haemostatic efficacy and/or the occurrence of adverse events. The authors observed that idarucizumab was prescribed for bleeding (63.1 %), invasive procedures (30.5 %), thrombolysis (14.7 %), dabigatran intoxication without bleeding (4.7 %) or unspecified reasons (7.1 %) [50]. Hemostatic effectiveness was achieved in 77.7 % and peri-procedural hemostasis was normal in 98.5 % of patients. The pooled incidences of all-cause mortality ($n = 11$ studies included) and thromboembolic events ($n = 18$ studies included) at any follow-up duration were 13.6 % and 2.0 % respectively [50].

2.3.3. Laboratory role in idarucizumab management

The reversal effect of idarucizumab can be monitored by measuring patient’s dabigatran plasma levels through the determination of its anti-IIa activity, expressed in ng/mL. Such assays are based on the inhibition of thrombin activity with chromometric (dTT, ECT) or chromogenic measurement (ecarin chromogenic assay, ECA) [12,51,52]. Given its high sensitivity, TT could be useful for detecting dabigatran plasma rebound in emergency situations when specific methods are unavailable or their turnaround time is too long. However, TT does not allow the quantification of dabigatran plasma concentration.

2.3.4. Does one dose of idarucizumab fit all patients: is dabigatran level measurement useful?

Since the commercialization of idarucizumab, several studies have been conducted to describe its efficacy and safety in reversing dabigatran effects. However, many studies did not report any laboratory data before and after reversal. Consequently, contrasting results have been reported, suggesting that the effect of idarucizumab may be transitory. Indeed, several patients experienced plasma dabigatran rebound, defined as a re-elevation of dabigatran level after a successful idarucizumab reversal [53–55], especially in case of high levels of dabigatran to be neutralized at baseline: levels of unbound dabigatran were superior to the detection threshold in 23 % of the cases 24 h after administration of the antidote. Dabigatran rebound is thought to occur as a result of the redistribution in plasma of unbound dabigatran, from the peripheral (i.e., extravascular) tissues to the intravascular compartment over time after idarucizumab clearance, in response to the concentration gradient occurring after neutralization (Fig. 1) as previously observed in healthy volunteers [56]. In contrast to dabigatran’s molecular weight of 472 Da and large volume distribution of 50–70 L, idarucizumab has a molecular weight of 47.8 kDa and remains in the vascular compartment [56]. After elimination or saturation of idarucizumab, dabigatran can move freely from the extra- to the intravascular compartments in order to re-establish the equilibrium [57]. This difference in pharmacokinetic properties probably explains the rebound

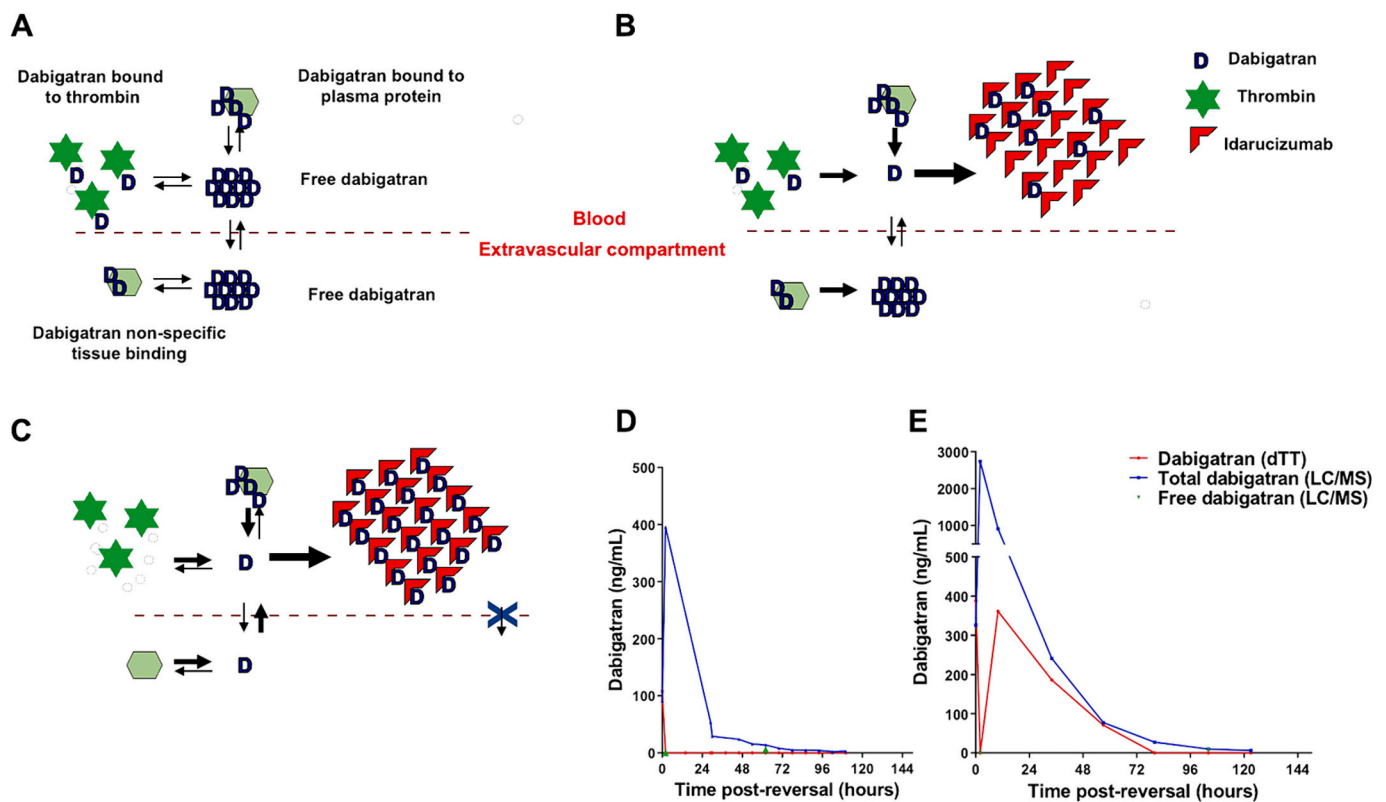


Fig. 1. Evolution of dabigatran levels in blood and extravascular compartment following idarucizumab injection. A, In patients taking dabigatran, equilibrium between circulating dabigatran, free or bound to thrombin in blood and extravascular compartments. B, After injection, idarucizumab rapidly binds free dabigatran in the plasma and dissociates dabigatran from thrombin because of the high affinity of dabigatran to idarucizumab. Idarucizumab binds all of the dabigatran in plasma and that drawn from the extravascular compartment within minutes, as evidenced by the rapid reduction in unbound dabigatran plasma levels (i.e., dabigatran and its conjugates that are not bound to plasma proteins or to idarucizumab) and the parallel reduction in the anticoagulant effects of dabigatran. C, Dabigatran presents a larger distribution volume and a longer elimination half-life than idarucizumab. After elimination or saturation of idarucizumab, dabigatran can freely move from the extra-vascular compartment to the plasma compartment to re-establish equilibrium. D, example of complete dabigatran reversal after idarucizumab administration. Unbound dabigatran levels remain low because the idarucizumab binds dabigatran so tightly that the complex is almost irreversible. E, example of complete dabigatran reversal after idarucizumab in patient with baseline dabigatran level above 200 ng/mL following by plasma dabigatran rebound (personal data). This rapid movement of dabigatran from the extravascular compartment into the plasma results in a paradoxical increase in plasma levels of total dabigatran, which includes inactive plasma protein-bound dabigatran (and metabolites), idarucizumab-bound dabigatran, and residual active dabigatran (measured by diluted thrombin time), dTT, and high-performance liquid chromatography/mass spectrometry (HPLC-MS/MS) as previously described [62].

phenomenon. Recently, Eikelboom et al [58] evaluated the impact of renal impairment on the effect of dabigatran reversal by idarucizumab in RE-VERSE AD. They showed that dabigatran rebound within 12 to 24 h was more common in patients with renal impairment (median CrCl 32.7 mL/min versus 57.8 mL/min in patients without dabigatran rebound), whereas time to bleeding cessation and extent of hemostasis during procedures were similar to as patients without renal impairment. Retrospective French study confirmed that hemostatic effectiveness after idarucizumab injection did not correlate with renal function [59]. Moreover, it is important to consider that renal function may vary over time: in both RE-VERSE AD and the French study, renal function was only assessed before dabigatran reversal. Moreover, no significant difference between plasma creatinine level or clearance (Cockcroft and Gault formula) was found in patients with or without plasma dabigatran rebound after reversal [59]. Furthermore, Glund et al. [60] showed that subjects with mild or moderate renal impairment had an increased exposure with a decreased clearance and a prolonged half-life of idarucizumab compared to healthy subjects. Overall, hemostatic efficacy and dabigatran plasma rebound would be driven by a balance between dabigatran extravascular accumulation/redistribution and the neutralization capacity of circulating idarucizumab over time. In brief, dabigatran plasma levels before reversal appear to be more predictive of the outcomes of reversal. Indeed, previous studies showed that baseline dabigatran level (before reversal) above 200 ng/mL [54,59] could predict the apparition of dabigatran rebound (defined as a re-elevation of dabigatran level after a successful idarucizumab reversal) and was associated with less hemostasis effectiveness [59]. Of note, around 75 % of dabigatran levels in the two group of patients included in REVERSE-AD were below 200 ng/mL [42]. In REVERSE-AD [61], dabigatran rebound was observed in 23.0 % and 13.5 % of patients after 12-h and 24-h idarucizumab administration, respectively. In our two retrospective case studies [59,62], a median time-period rebound was observed 22 h (IQR 7–42) post-idarucizumab injection in 15 out of 22 evaluable patients. In addition, idarucizumab appears to be limited to achieve a complete reversal in patients suffering from important dabigatran overdose and/or renal impairment [62]. Indeed, a dose-response relation between dabigatran level at baseline and the capacity of idarucizumab to achieve a complete reversal was observed [63]. In a recent meta-analysis, Melicene et al [62] suggested that idarucizumab failure (defined as a detectable dabigatran level despite idarucizumab administration) could be suspected in patients with dabigatran level > 1000 ng/mL at baseline but this risk may include dabigatran plasma accumulation and the state of renal function. In case of baseline dabigatran level > 1000 ng/mL, an additional idarucizumab dose might be proposed, especially in case of persistent uncontrolled bleeding or need for an urgent invasive procedure. Based on spontaneous case reports, idarucizumab reversal failure appears to be rare. Estimating the exact frequency is difficult due to the absence of prospective large-scale studies. In our bicentric study [62], we reported a reversal failure frequency of 4.3 % out of 46 patients, which is comparable to the 4.2 % out of 24 patients described in a Danish study by Haastrup et al. [64] Consequently, initial dabigatran assessment is of interest to predict biological and clinical outcomes of idarucizumab as suggested recently by the International Council for Standardization in Hematology [10]. Levy et al [65] showed in the RE-VERSE AD trial that the median time from the first vial of idarucizumab to surgery or procedures was <2 h in all groups except neurosurgery, where it was 3.3 h. Idarucizumab should be injected without awaiting the laboratory results, but dabigatran level at admission could help in anticipating dabigatran-reversal failure and/or rebound, thus predicting the need for subsequent injections. A closed monitoring of dabigatran level could be performed in order to prevent the risk of recurrent bleeding or postoperative bleeding.

2.3.5. Perspective or areas that deserve further investigation

Data concerning idarucizumab use in real-life clinical scenarios are increasing world-wide but are limited to case reports, small case series

or retrospective data with a lack of standardized clinical description, biological monitoring and follow-up. It could be due to the low frequency of use of this antidote as dabigatran is the less prescribed DOAC and of situations requiring reversal. In a prospective Japanese study including 5436 dabigatran-naïve patients with NVAf who received dabigatran and were followed for up to 52 weeks, the rate of major bleeding was low (1.1 %/year) and idarucizumab was required for 12 (0.2 %) patients [66]. One retrospective study in New Zealand evaluated the efficacy and safety of half-dose of idarucizumab (a single injection of 2.5 g) [67]. Approximately 20 % of the patients had dabigatran levels measured at baseline and laboratory monitoring was performed around 24 h after reversal in <20 % of the cases. The median baseline dabigatran level was 43 ng/mL in the 2.5 g dose group (range: <10 to >500 ng/mL), and 68 ng/mL in the 5 g dose group (range: <10 to 370 ng/mL). Initial 2.5 g dose was not associated with an increased rate of receiving a second dose, death, thrombosis or bleeding compared with the 5 g dose group. Of note, 2 (0.97 %) patients in the 2.5 g dose group experienced dabigatran rebound (dTT >80 s) that prevented procedural intervention for ongoing bleeding control. Inappropriate or excessive antidote utilization would have significant healthcare costs [68]. Indeed, dabigatran reversal is a costly therapy, with a current estimated US price of \$3880 [69] (1530 € in France) to treat a single patient, which is an additional reason to use it wisely. Moreover, Fanikos et al. reported in the RE-VECTO surveillance program [70] only minimal off-label dosing (e.g., use of only 2.5 g in 12 patients) and 7 patients without on-going dabigatran treatment among 359 idarucizumab-treated patients. In the systematic literature review of van der Host et al. [50], 2.8 % of prescription indications were reported to be inappropriate [50].

In each institution, guidelines on the appropriate use of idarucizumab should be available with the detailed recommended dosing regimen (2.5 g x2) and patient's management. Further prospective studies are needed to confirm the place of baseline and post-reversal monitoring of dabigatran level to predict dabigatran reversal failure or rebound.

2.4. Andexanet alfa

2.4.1. Pharmacological characteristics

Andexanet alfa is a human recombinant FXa produced in Chinese hamster ovary. It is catalytically inactive (substitution of the active-site serine to alanine, S419A) and lacks the membrane-binding γ -carboxyglutamic acid domain (i.e., the 11 GLA residues) thus preventing competitive formation of the prothrombinase complex [71]. However, it retains the ability of native FXa to bind oral FXa inhibitors as well as heparin-activated antithrombin (AT). It works as a decoy for both oral and injectable FXa inhibitors resulting in a temporary delay of their renal elimination [72]. Its elimination half-life is 5 to 7 h while it has a pharmacodynamic half-life of one hour and a volume of distribution of 5 L [73]. Andexanet alfa is not detected in urine and the exact mechanism of its elimination remains to be established.

Andexanet alfa binds each oral FXa inhibitor with a nanomolar affinity with the binding to rivaroxaban being the tightest ($K_d = 0.9$ nM) [74]. Its relative potencies of binding FXa inhibitors are in line with the inhibition constants (K_i) found in the literature for oral FXa inhibitors to FXa [75]. Unlike the relatively weak direct binding to unfractionated heparin (UFH), LMWH or fondaparinux, andexanet alfa binds tightly to heparinoid-AT complex which primarily leads to the neutralization of their anticoagulant effects [74].

2.4.2. Commercialized product characteristics

Andexanet alfa (marketed under the trade names Andexxa in the US and Ondexxa in European Union, AstraZeneca, Cambridge, UK) was granted an accelerated approval in the US (May 2018) and Japan (March 2022) and a conditional marketing authorization in the European Union, Switzerland and UK (April 2019) for adult patients taking apixaban or rivaroxaban and suffering from life-threatening or uncontrolled

bleeding. The prescribing information carries a boxed warning regarding serious and life-threatening adverse events including thromboembolic/ischemic events, cardiac arrest and sudden deaths. Andexanet alfa is commercialized as 100 and 200 mg single-use vials with a shelf life of 24 months and a stability of 8 h at room temperature (around 25 °C) after reconstitution or 24 h at refrigerated temperature (2–8 °C) [24]. It is administered intravenously as an intravenous bolus (30 mg/h) followed by 2-h infusion. The dosing regimen (high- or low-dose) is determined by the FXa inhibitor, its dose and the time since the last administration (Table 2). Treatment with the high-dose would cost \$49,500 USD for the drug alone (\$5500 USD/200 mg vial) whereas the low-dose regimen would cost half as much [76,77].

2.4.3. Efficacy and safety

Andexanet alfa efficacy and safety were evaluated in a multicenter prospective open-label, single-group study (ANNEXA-4) performed in 352 patients (194 apixaban, 128 rivaroxaban, 10 edoxaban and 20 enoxaparin) who had acute major bleeding within the 18 h after administration of a FXa inhibitor [78]. Hemostatic efficacy was considered excellent or good when intracranial hemorrhage volume expanded <20 % or 35 % or when hemoglobin/hematocrit drop in gastrointestinal bleeding was <10 % or 20 %, respectively. A 92 % reduction of anti-Xa values was recorded along with an excellent to good hemostasis in 82 % of the cases (among 134 apixaban, 100 rivaroxaban and 4 edoxaban patients having a baseline anti-Xa level of a least 75 ng/mL and 16 enoxaparin patients having a baseline anti-Xa value ≥ 0.25 IU/mL). The mortality rate within 30 days was 14 % and that of thrombotic events of 10 % (encompassing 7 myocardial infarctions, 15 transient ischemic attacks/strokes and 18 VTE) [78]. Thrombotic risk may have been related to a delayed resumption of anticoagulation. ANNEXA-4 results were confirmed in the final study report recently published [79]. In total, 479 patients (245 apixaban, 176 rivaroxaban, 36 edoxaban and 22 enoxaparin) were included. The median decrease in anti-Xa activity was 94 to 95 % for apixaban and rivaroxaban, respectively. It was less effective in edoxaban and enoxaparin samples (71 % and 75 %, respectively). These heterogeneous results might be explained by the pharmacodynamic/pharmacokinetic differences between FXa inhibitors or different interactions between andexanet alfa and these various drugs. This remains to be appropriately addressed. After the end of the infusion, anti-Xa activity gradually increased back to anticipated normal clearance levels. In parallel, an excellent to good hemostasis was recorded in 80 % of the patients (among 172 apixaban and 132 rivaroxaban patients having a baseline anti-Xa level of a least 75 ng/mL, 28 edoxaban patients having a baseline anti-Xa level of a least 40 ng/mL and 17 enoxaparin patients having a baseline anti-Xa value ≥ 0.25 IU/mL). The mortality rate within 30 days was 15.7 % and that of thrombotic events of 10.4 % (encompassing 10 myocardial infarctions, 26 transient ischemic attacks/strokes and 22 VTE) [79]. Comparable results were observed in the sub-study of patients with major ICH [80]. That said, such designed study does not allow determining how many of the patients would have achieved hemostatic efficacy without andexanet alfa administration and assessing whether the frequency of thrombotic

events and mortality rate exceeded that expected in such patients.

Thereafter, many observational studies reported the successful results of andexanet alfa use in real-world scenarios [81–96] which sometimes fell outside of ANNEXA-4 eligible criteria such as in patients who require emergent procedures concurrently or soon after treatment with andexanet alfa as in trauma patients [83–85]. A recent observational cohort study from the United States using electronic health records of 4395 patients for oral FXa inhibitor-related major bleeding (andexanet alfa, $n = 2122$; 4 factors-PCC, $n = 2273$) showed that treatment with andexanet alfa was associated with 50 % lower odds of in-hospital mortality than 4F-PCC with similar magnitude in ICH and gastro-intestinal bleedings [96]. Hemostatic efficacy and thrombotic events were not reported in this study. Whereas no laboratory parameters were evaluated after andexanet alfa administration in the vast majority of the cases [81,82,84–90,92–96], anti-Xa activity (UFH/LMWH specific calibrated) was used to assess the decrease of the anti-coagulant activity in very rare studies [83,91].

A phase IV trial (ANNEXA-I, NCT03661528) assessing andexanet alfa safety and efficacy in comparison to the usual care in adult patients taking oral FXa inhibitors and suffering from ICH was prematurely stopped following the planned interim analysis. Pre-specified stopping criteria of superior efficacy (i.e., limited expansion of life-threatening brain bleeding) were attained; results are excitedly awaited. Another multicenter prospective open-label study (ANNEXA-S) is currently being conducted evaluating the efficacy and safety of andexanet alfa in patients requiring urgent surgery within 15 h following the last dose of FXa inhibitors. While the primary outcome consists on the effective hemostasis throughout the surgery, the secondary one is based on the percent change in anti-Xa activity from baseline to treatment nadir (NCT04233073). Recruitment is terminated and results are expected very shortly. A second open-label, randomized, controlled, prospective, multicenter study, ANNEXA-RS trial (NCT05926349) is yet to be opened. This study will include same patients as ANNEXA-S but it will compare the use of andexanet alfa to the usual care given at the study center.

2.4.4. Andexanet alfa and laboratory tests

Primary and secondary efficacy endpoints of phase II and III clinical studies consist on the evaluation of laboratory parameters such as the percent change in anti-Xa activities [78,97,98], in unbound inhibitor plasma concentrations [97], in endogenous thrombin potential of the thrombin generation assay [97], or in hemoglobin and hematocrit levels [98]. Andexanet alfa rapidly (≤ 2 min) reduced unbound FXa inhibitors levels (measured by equilibrium microdialysis followed by HPLC-MS/MS) [78,79,97], decreased anti-Xa activities [78,79,97] and restored thrombin generation [73,78,79,97,99]. The decrease of anti-Xa levels and unbound drug levels persisted during the continuous infusion and for 1 to 2 h afterwards before returning to placebo levels or even somewhat above. Unlikely, the restored thrombin generation was maintained up to 22 h after andexanet alfa administration which may reflect the reversible binding of this antidote to endogenous tissue factor pathway inhibitor (TFPI) and/or AT.

Anti-Xa activities reported in clinical studies [78,97,98] were assessed in a central laboratory using a modified chromogenic assay. Indeed, the standard commercialized anti-Xa assays cannot be used to measure the degree of reversal during or after andexanet alfa administration. The overall sample dilution in these assay set-up results in the dissociation of andexanet alfa from the anticoagulant drugs due to the reversible binding equilibrium of the complex. Consequently, andexanet alfa-FXa inhibitor binding-unbinding equilibrium shifts toward the unbound state in such case leading to an erroneous elevation of the anti-Xa activity which may impact treatment decision making [100]. The modified chromogenic assay used in the ANNEXA-4 study was adapted from a commercial kit (Coamatic Heparin, Diapharma, West Chester, OH) to minimize the sample dilution effect. Briefly, plasma (75 μ L) was diluted in assay buffer (25 μ L) and FXa substrate (i.e., S2732, 25 μ L) and

Table 2
Andexanet alfa dosing regimens according to oral factor Xa inhibitors.

Oral factor Xa inhibitors	Dose regimen per day	Time since last dose taken	
		<8 h or unknown	≥ 8 h
Rivaroxaban	≤ 10 mg	Low dose ^a	Low dose ^a
	>10 mg or unknown	High dose ^b	
Apixaban	≤ 5 mg	Low dose ^a	Low dose ^a
	>5 mg or unknown	High dose ^b	

^a Low dose: 400 mg IV at a target rate of 30 mg/min, followed by 4 mg/min continuous infusion for up to 2 h;

^b High dose: 800 mg at a target rate of 30 mg/min, followed by 8 mg/min continuous infusion for up to 2 h.

incubated 5 min at room temperature [73,74,97]. Bovine FXa (25 µL) was subsequently added and the reaction was quenched after 5 min by adding 20 % acetic acid (50 µL). Anti-Xa activity in plasma samples was then calculated by interpolation of the specific standard curves constructed with the inhibitor levels ranging from 0 to 100 ng/mL [73,74,97]. Samples with higher concentrations were reanalyzed following additional minimal sample dilution [73,97]. Similarly, Bourdin et al. [101] developed a modified automated STA-Liquid anti-Xa test (Diagnostica Stago, Asnières-sur-Seine, France) for accurately measuring anti-Xa activity after reversal with andexanet alfa. Plasma sample (125 µL) was incubated with STA-Liquid anti-Xa substrate (100 µL) for 4 min at 37 °C. Reaction was then triggered with prewarmed FXa (100 µL) at 37 °C resulting in a 1:2.6 final sample dilution. The optical density variation (at 405 nm) was measured between 1.33 and 2.50 min for rivaroxaban, 0.83 and 1.67 min for apixaban and 0.50 and 3.00 min for edoxaban [101]. HemosIL anti-Xa, with HemosIL apixaban or rivaroxaban calibrators and controls performed on ACL TOP 700 (Werfen, Barcelona, Spain), was also adapted to minimize the dilution effect seen with the standard assay for the andexanet alfa containing samples [100,102]. It is important to mention that oral FXa inhibitors plasma concentrations following andexanet alfa were not measured using HPLC-MS/MS in any of the previously mentioned studies thus the observed values with the modified functional assays were not validated.

That said, no significant relationship between the clinical hemostatic efficacy and the reduction in anti-Xa activity during andexanet alfa treatment was observed in ANNEXA-4 [78] which leads to conclude that monitoring anti-Xa activity in clinical practice is not likely to be useful for prediction of clinical response [78]. However, in patients with ICH, reduction of anti-Xa activity significantly predicted hemostatic efficacy of andexanet alfa (area under the receiver operating characteristic curve 0.62 (95%CI, 0.54–0.70)) and was significantly correlated with lower mortality in patients aged below 75 years old [79]. Results of the previously mentioned ANNEXA-I trial may confirm these findings.

All above led to the publication of a direct healthcare professional communication in June 2020 highlighting that treatment monitoring after the administration of andexanet alfa should not be performed using anti-Xa assay since the currently commercial assays are unsuitable (see above). Treatment monitoring should be based mainly on clinical parameters (achievement of hemostasis), lack of efficacy (re-bleeding) and adverse events (thromboembolic events). However, given that andexanet alfa effect begins to wane once the infusion is completed, the prospect of re-bleeding presents a potential concern, especially in patients with a residual high anti-Xa activity. Therefore, the assessment of the potential rebound effect of FXa inhibitors after administration of andexanet alfa is problematic. An administration of a second dose of andexanet alfa should only be considered when there is demonstration of persisting relevant anticoagulant plasma level of FXa inhibitors associated with clinically significant bleeding. Moreover, measuring residual FXa inhibitors level to guide the management of urgent procedure timing after andexanet alfa administration would also be critical. Not being able to use the widely commercialized specific anti-Xa assays in these different acute clinical scenarios is problematic and requires to be seriously addressed.

2.4.5. Procoagulant effect of andexanet alfa

Andexanet alfa induced a procoagulant state leading to a transient (≤ 72 h) but significant increase of the D-dimer and prothrombin fragments 1 and 2 levels as well as the endogenous thrombin potential (above the mean + 2 standard deviations) [72,73,103]. In ANNEXA I study, preliminary data revealed that thrombotic events incidence was increased in andexanet alfa group compared to the usual care group ($p = 0.048$) with higher rates of ischemic stroke and myocardial infarction [104]. This effect is most probably due to its binding to the TFPI [105]. As a matter of fact, no clinical thrombotic events were observed in healthy volunteers following andexanet alfa administration [73]. The procoagulant state following andexanet alfa injection could also be

linked to its binding to AT leaving more native FXa active and significantly compromising the efficacy of anticoagulation induced with heparin derivatives after the administration of andexanet alfa such as in patients requiring urgent cardiac or vascular surgery where UFH is routinely used. Indeed, the direct healthcare professional communication published in 2020 pointing out also the unresponsiveness to the heparin derivative after the administration of andexanet alfa. The extent and duration of such interaction have not been evaluated. Furthermore, monitoring anti-Xa activity in such case is very likely misleading. Since then, many case reports were published on andexanet-alfa associated heparin resistance or unresponsiveness [106–109]. Of note, these cases were off-label use of andexanet alfa for perioperative setting. Further studies, in particular, prospective registry are necessary to support this strategy. Monitoring the anticoagulant activity in these clinical settings would be of utmost importance yet could not be performed using standard anti-Xa activity (see above).

In conclusion, andexanet alfa administration remains a matter of debate in clinical practice because of the lack of direct comparison against the usual and local standard of care (involving PCC or aPCC), of its high cost and concerns about the potential risk of thromboembolic events. It is crucial that health professionals be aware of the pros and cons of such antidote. In the event of its commercialization worldwide, andexanet alfa should be prescribed in a manner that is cost-effective and that optimizes patient outcomes, keeping in mind that regular assays are not suitable for accurately monitoring the anti-Xa activity after its administration.

2.5. Ciraparantag

2.5.1. Pharmacological characteristics

Ciraparantag (PER977, arripazine) is a synthetic cationic small molecule, designed to bind DOACs through non-covalent hydrogen bond and charge-charge interactions [105]. Its elimination half-life is between 12 and 19 min. Ciraparantag is metabolized and excreted in urine within 24 h. In parallel, ciraparantag does not bind to various plasma proteins and several common cardiovascular and anesthetic drugs.

2.5.2. Ciraparantag and laboratory tests

The development of ciraparantag laboratory tests is not easy as it binds to contact pathway activators such as celite, kaolin and in vitro anticoagulants such as citrate, EDTA and heparin. Thus, it interferes with all assays available in laboratory to assess anticoagulant activity [110] (PT, aPTT, anti-Xa assay, thromboelastography reaction time (TEG 5000 thromboelastograph®) and activated clotting time). Consequently, ciraparantag cannot be studied in plasma from blood collected with sodium citrate. Citrate overpowers and disrupts the ciraparantag anticoagulant complex, thereby freeing the anticoagulant in the plasma and making plasma-based assays non-representative. Kaolin and celite activators also adsorb ciraparantag, significantly reducing its actual concentration in a blood sample and making kaolin and celite-based assays inadequate for the evaluation of DOAC reversal with ciraparantag. Only the measurement of the percent change from baseline of whole blood clotting time (WBCT) over time could be used for such purpose [111–113]. The WBCT is a glass-activated clotting time performed manually and reproducibly by trained technicians measuring clot size over time on photography [111]. WBCT appeared correlated with the PT in whole blood from placebo and edoxaban treated patients [111].

2.5.3. Efficacy and safety

In a phase 1 study, ciraparantag was administered as an IV bolus to healthy volunteers who previously received a single dose of 60 mg edoxaban. It restored baseline hemostasis assessed using the previously mentioned WBCT which decreased to within 10 % above the baseline value in 10 min or less and lasted for 24 hours [111]. Hemostasis was also assessed by clot structure evaluation (using scanning electron

microscopy) and was restored to baseline following a single 100 mg IV dose of ciraparantag. Scanning electron micrographs also demonstrated a dose-dependent increase in fibrin structure formation following ciraparantag administration. In a phase 1/2 clinical trial that evaluated the reversal of a single subcutaneous dose of enoxaparin (1.5 mg/kg) in 10 healthy volunteers, ciraparantag completely reversed the increase in WBCT within 20 min for subjects receiving a 100 mg dose and within 5 min for those given a 200 mg dose, with the effect lasting for 24 hours [112]. Phase 2 clinical trials are ongoing assessing ciraparantag efficacy and safety in apixaban- and rivaroxaban-treated patients (NCT03288454 and NCT03172910, respectively). In both phase 1 studies, there was no evidence of procoagulant activity after administration of ciraparantag, as assessed by measurement of D-dimer, prothrombin fragment 1 + 2, and TFPI levels [112]. However, in an in vitro study, ciraparantag did not reduce the anti-Xa activity of tested DOACs and bound weakly to UFH [74]. Additional clinical studies and technical assays are required to assess its ability to reverse anticoagulation and evaluate the performance of the new whole blood clotting time in clinical laboratories.

3. Conclusion

With the increasing number of anticoagulated patients, clinical settings requiring rapid DOAC neutralization is also increasing, such as in some major bleedings or urgent surgeries/procedures while on treatment. Commercialization of idarucizumab has led to significant changes in the reversal strategy of dabigatran. Andexanet alfa is not yet available worldwide. It has not been studied robustly in patients treated with oral FXa inhibitors and requiring urgent surgeries/procedures and is associated with a thrombotic risk. Ciraparantag was first described as a “universal” antidote to anticoagulant drugs although recent data did not show efficacy on UFH [74]. Ideally, patient selection for antidote administration requires measurement of baseline DOAC plasma concentration to prevent unnecessary prescription of expensive molecules, thereby ensuring timely and appropriate use of antidotes. However, in some emergent situations such as major uncontrolled or life-threatening bleeding, clinicians often do not have time to measure or get the laboratory result of DOAC plasma level. In such critical clinical settings, the context dictates the need and timing of antidote administration. Currently, only data supporting pre-reversal measurement of plasma dabigatran are available for idarucizumab, in order to assess the risk of anticoagulant plasma rebound, failure or hemostatic effectiveness, particularly in patients with renal failure and/or those with high risk of bleeding events. Moreover, available laboratory tests might be not suitable for post-reversal monitoring following some antidotes administration (namely andexanet alfa and ciraparantag). Future studies are still needed to establish the exact role of laboratory monitoring in the appropriate management of DOAC specific antidotes.

CRedit authorship contribution statement

Nicolas Gendron: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Paul Billoir:** Writing – original draft, Validation. **Virginie Siguret:** Writing – review & editing, Validation. **Véronique Le Cam-Duchez:** Writing – review & editing. **Valérie Proulle:** Writing – review & editing. **Laurent Macchi:** Writing – review & editing. **Elodie Boissier:** Writing – review & editing. **Christine Mouton:** Writing – review & editing. **Emmanuel De Maistre:** Writing – review & editing. **Isabelle Gouin-Thibault:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Georges Jourdi:** Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Cover figure was created with [BioRender.com](https://www.biorender.com).

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