Direct Oral Anticoagulants: Laboratory Challenges and Antidotes

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Abstract

The use of direct oral anticoagulants (DOACs) is increasing in patients needing treatment of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation (SPAF). This is due to the net clinical benefit in comparison to vitamin K antagonists (VKAs). The rise in DOAC use is accompanied by a remarkable reduction in heparin and VKA prescriptions. However, this rapid change in anticoagulation patterns brought new challenges to patients, prescribers, laboratories, and emergency physicians. Patients have new liberties concerning nutritional habits and comedication and no longer need frequent monitoring or dose adjustments. Still, they have to comprehend that DOACs are potent anticoagulants that may cause or contribute to bleeding. Challenges for the prescriber include decision pathways for choosing the right anticoagulant and dosage for a specific patient and to change bridging practice in case of invasive procedures. Laboratory personnel are challenged by DOAC due to limited 24/7 availability of specific DOAC quantification tests and by the impact of DOAC on routine coagulation assays and thrombophilia tests. Challenges for the emergency physician result from the increasing age of DOAC anticoagulated patients, the difficulties to establish last intake of DOAC type and dosage, to interpret coagulation test results in emergency situations, and to make decisions for or against DOAC reversal strategies in acute bleeding or urgent surgery. In conclusion, although DOACs make long-term anticoagulation safer and more convenient for patients, DOACs pose challenge to all healthcare providers involved in anticoagulation decisions. The key to correct patient management and optimal outcome therefore lies in education.

Keywords

- DOAC
- anticoagulation reversal
- laboratory testing

Introduction

After decades of using vitamin K antagonists (VKAs) for oral anticoagulation, direct oral anticoagulants (DOACs) have taken over in the majority of anticoagulated patients needing treatment of venous thromboembolism (VTE) or stroke prevention in atrial fibrillation (SPAF). Currently, there are two DOAC classes approved for use in these indications: the direct factor Xa inhibitors (DXI) comprising apixaban, betrixaban (approved by FDA but not by EMA), edoxaban, rivaroxaban, and the direct thrombin inhibitor (DTI) dabigatran.

Globally, the use of DOAC is increasing due to the net clinical benefit in comparison to VKA with similar efficacy but at the same time lower rates of major hemorrhages as well as a risk reduction in fatal bleeding and intracranial hemorrhage (ICH).[1] In Germany, the medical prescription report in outpatients 2021 ("Arzneimittelverordnungsreport") attested a nearly linear increase of DOAC prescriptions since 2012 with about 717 million defined daily dosages

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(DDD) in 2020[2] which was accompanied by an impressive reduction in heparin and VKA prescriptions.

However, as one can expect from such an overwhelming change in treatment patterns, new challenges arise: for patients, for prescribers, for laboratories, and for emergency physicians. This review article will discuss some of these challenges and aims to provide insights into problem-solving strategies.

Challenges for the Anticoagulated Patient

Most SPAF patients, but also a large proportion of VTE patients, are in need for long-term anticoagulation. In the VKA era, treatment was complicated due to the pronounced variability of dose–response effects. Some patients needed half a tablet of VKA every other day and other patients needed three tablets per day. As nutritional vitamin K intake may change, VKA dosages were never fix but needed adjustments according to the prothrombin time (PT) or the derived international normalized ratio (INR). Similarly, changes in liver function or drug interactions from concomitant medications often lead to dose adjustments. As a consequence, VKA-treated patients were told not to change their nutritional habits, to be careful with comedications, and to come to their physicians at least every 4 weeks for an INR check and dose adjustments.[3,4] As an alternative, compliant and capable patients were prescribed point-of-care (POC) devices for INR home testing and were trained to adjust their VKA dosages according to the INR test result.

With DOAC, all of this has changed. Patients no longer need to follow nutritional restrictions, frequent laboratory testing is no longer needed, and the predictable dose–response from DOAC allows prescribing a fixed-dose regimen, making life of anticoagulated patients much easier.

Still, the challenge is in education: patients have to understand that DOACs are still potent anticoagulants that may cause or contribute to significant bleeding. Regular intake is even more important than with VKA since half-lives of DOAC are considerably shorter (8–12 hours) so that the antithrombotic protection is lost if intake is skipped. Drug interactions—although far less frequent compared with VKA—may also increase or decrease the anticoagulation intensity of DOAC. Finally, VKA patients using POC devices for INR monitoring are often adverse to the idea that anticoagulation intensity is no longer monitored. They need to be told that they should not use their POC device to test INR during DOAC therapy. DOAC can affect INR, but the patient has to understand that the "INR" provided by the POC device has nothing to do with the INR from VKA and does not correlate to anticoagulant activity. It is a lab artifact that should not lead to any action. Hence, such testing should be strongly discouraged.

Finally, many patients were told that DOACs are much safer than VKA (which is true), but patients may misinterpret this and may be less inclined to avoid occupational or leisure-related bleeding risks. Therefore, education about bleeding risks, preventive measures, and the need to seek medical attention in case of atypical bleeding signs remains important also for a DOAC-treated patient.

Challenges for the Prescriber

The first challenge for the prescriber is to identify which patient may benefit from a DOAC and which patient needs to be treated with VKA. As a first step in this decision pathway,

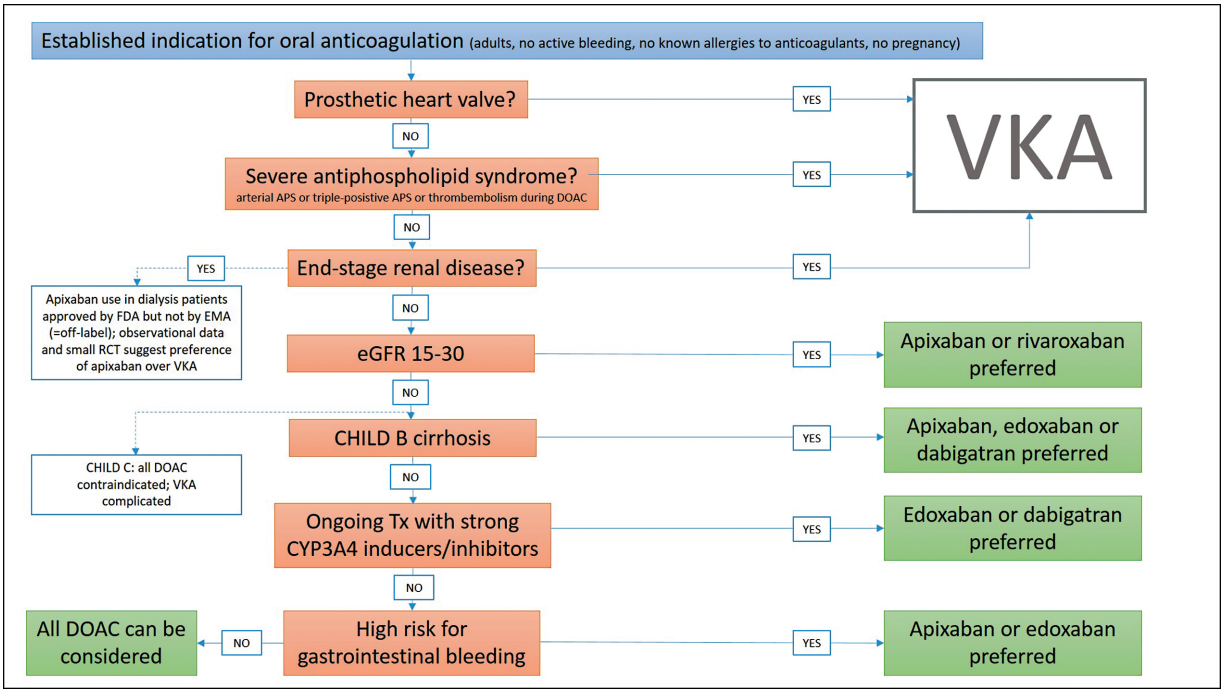

Fig. 1 Decision points for choosing anticoagulant drugs in VTE treatment and stroke prevention in atrial fibrillation. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.

contraindications for each drug class must be evaluated. Next, the choice of DOAC depends on the individual patient profile (bleeding risks, liver and renal function, comedication), but the preference and experience of the prescriber with each DOAC should also be taken into account.[5,6]

►Fig. 1 depicts some decision points that can guide the choice of anticoagulant drug. Of note, this list of frequent clinical scenarios serves as an example only and many more decision points could be implemented.

Once the decision was made to treat the patient with a DOAC, several clinical factors can influence dose selection: age, renal impairment, low body weight, and comedications among them. It is important to know that these factors differ between the individual DOAC summaries of product characteristics (SmPC),[7–10] since they were based on pharmacological considerations and preclinical modeling and later tested as prespecified dosing criteria in clinical trials.[11–16] Although the criteria for dose reduction are well-defined for each DOAC, observational studies indicate that DOAC dosing outside of trials often deviates from the label which may affect the effectiveness of anticoagulant protection.[17–21]

Differently to VKA, there are no known direct interactions between food and DOAC absorption or metabolism, but DOAC intake without food may reduce DOAC absorption. Although the package inserts recommend DOAC intake with food for some but not all DOACs, it should be acknowledged that drug absorption studies are usually performed in preclinical settings involving short-term exposures to healthy volunteers. As a consequence, the clinical relevance of fasting status on DOAC absorption may be underestimated and it should be recommended to all patients to take their specific DOAC together with a meal.

Similar to selection of DOAC type and dosage, the management of DOAC poses new challenges for the prescriber, especially if patients need to undergo elective surgical or interventional procedures. In the VKA era, oral anticoagulation was stopped 1 to 2 weeks prior to such interventions and short-term bridging anticoagulation was performed using heparins. With the short half-life and rapid onset of action of DOAC, minor procedures can be performed with skipping only one dose of DOAC, whereas, for major procedures, short DOAC interruptions for up to 72 hours are often sufficient without a need for parenteral bridging.[22] The challenge here is again educational: surgeons and interventionalists need to learn that stopping periods differ between DOAC and VKA and that the need to provide heparin bridging is much less important (and may even be harmful) for DOAC patients. Healthcare providers should adapt their patient counseling accordingly. If DOAC is not stopped, timing of minor interventions should avoid peak DOAC concentrations (2–6 hours after last intake). Finally, surgeons, anesthetists, and interventionalists need to understand that global coagulation parameters such as PT, INR, or the activated partial thromboplastin time (aPTT) may or may not show the absence or presence of a DOAC, which will be discussed in the next section.

Challenges for the Laboratory

In the VKA era, time between last VKA intake and blood sampling was irrelevant: coagulation parameters would mostly be comparable in samples taken 2 or 12 hours after last VKA intake. In contrast, DOACs reach peak levels approximately 2 to 4 hours after intake and show a plasma half-life of approximately 8 to 12 hours (up to 17 hours for betrixaban) with rapid decline due to metabolism and elimination.[23] Consequently, the impact of DOAC on coagulation assays and their interpretation strongly depend on the knowledge of type, dose, and time of last drug intake—all of which can affect DOAC peak and trough plasma levels (►Table 1).

However, even if no dedicated DOAC quantification tests are ordered from the laboratory, "routine coagulation tests" such as PT, INR, or aPTT are also difficult to interpret in a

Table 1 Impact of DOAC on routine coagulation assays and DOAC quantification tests

Coagulation test		Availability	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Global routine test	Activated partial thromboplastin time	Usually within 1 h and 24/7	(↑)-↑	(↑)	(↑)	(↑)
	Prothrombin time INR	Usually within 1 h and 24/7	(↑)	(↑)	↑-↑↑	↑-↑↑
Unspecific sensitive tests	TT	Usually within 1 h and 24/7	↑↑↑	Not applicable		
	Ecarin clotting time	Within hours but rarely 24/7	↑↑↑	Not applicable		
Specific sensitive tests	Diluted TT or direct thrombin inhibitor assay	Within hours but rarely 24/7	↑↑↑	Not applicable		
	Anti-FXa activity with DOAC-specific calibrator curves	Within hours but rarely 24/7	Not applicable		↑↑↑	

Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio; TT, thrombin time.
Source: Modified from Steiner et al[25] and Drouet et al.[37]

DOAC patient. DOAC may interfere with several coagulation assays, but only some of these effects could be helpful to estimate DOAC activity in the sample and others are simply artifacts or not sensitive enough to identify the presence of DOAC.[24,25] Furthermore, the amount of DOAC interference with PT, INR, or aPTT strongly depends on the test assay used, so that the same DOAC type and concentration may result in false-negative and false-positive tests, depending on the specific assay used to test.

Direct Thrombin-Inhibitor Dabigatran

Activated Partial Thromboplastin Time

The aPTT is a measure of the intrinsic pathway and becomes prolonged in patients taking dabigatran with a nonlinear but curvilinear dose–response relationship that flattens at high dabigatran levels. Consequently, aPTT cannot be used to monitor the anticoagulation effect of DTI. At dabigatran trough levels, sensitive assays such as actin FS may still detect the presence of dabigatran, whereas SnythasIL and others may not.[24,26–30]

Prothrombin Time and International Normalized Ratio

PT and INR reflect the extrinsic coagulation pathway and dabigatran at therapeutic concentrations can elevate the INR. However, the overall sensitivity of PT assays toward dabigatran is low and INR values do not correlate to dabigatran plasma activity.[31,32]

Thrombin Time

A systematic review reported that normal TT excluded the presence of dabigatran plasma concentration in all 11 studies. However, without adjustments, standard TT cannot be used for dabigatran quantification.[31]

Diluted Thrombin Time

With adjustments, the sensitivity of TT toward thrombin inhibitors can be used to quantify dabigatran in plasma: diluted thrombin time (dTT) shows a linear relationship to dabigatran plasma concentration in ranges of 50 to 500 ng/mL and allows to distinguish between clinically relevant and insignificant dabigatran levels.[33] Some dTT assays (such as Hemoclot Thrombin Inhibitor LOW, Hyphen BioMed, Neuville-sur-Oise, France) require specific calibration for dabigatran levels lower than 50 ng/mL.[29,34–37]

Ecarin Clotting Time

For monitoring dabigatran at low plasma concentrations, ECT offers a favorable sensitivity for ECT 97/96% (for the clinically important threshold of 30 and 50 ng/mL) in comparison to the Hemoclot direct thrombin inhibitor assay (HTI; sensitivity: 86/89%, respectively). In a direct comparison of methods, ECT demonstrated a very strong correlation over the entire range of concentrations, whereas HTI showed only a moderate correlation at low dabigatran concentrations.[36,38] Although ECT is routinely used as a point-of-care test in centers for cardiovascular interventions where close monitoring of parenteral thrombin inhibitors is essential, outside of such settings, ECT may not be available 24/7.

• Anti-Xa Inhibitors (DXI, Apixaban, Edoxaban, Rivaroxaban)

Activated Partial Thromboplastin Time and Thrombin Time

At standard concentrations, DXI will not affect aPTT or TT but at extremely high plasma concentrations, some deviation can be observed. As a general rule, a normal aPTT or TT does not exclude the presence of DXI in a patient's blood sample.

Prothrombin Time and International Normalized Ratio

Depending on type, dosage, and last intake, DXI can prolong PT and INR.[30] The strongest influence on PT shows rivaroxaban followed by edoxaban and apixaban, but different PT assays vary in their sensitivity toward DXI.[39,40]

PT assays using neoplastine demonstrate a high sensitivity toward DXI (so that even low DXI concentrations can increase PT and INR considerably).[24] Other PT assays such as Dade Innovin and HemosIL RecombiPlasTin 2G are less sensitive toward DXI (so that even higher DXI concentrations may not increase PT/INR).[39,41,42] The effects on PT and INR described earlier for rivaroxaban or edoxaban are much smaller for apixaban, so that PT could be normal despite high apixaban plasma levels ($\pm$ 200 ng/mL) due to low reactivity of all assays.[29,30]

Anti–Factor Xa Activity Assay

Anti-Xa activity levels can be measured not only for DOACs but also for heparin, low-molecular-weight heparin, and fondaparinux. With substrate-specific calibrators, anti-Xa chromogenic assays can quantitatively measure plasma concentrations of all DOACs within the whole range of their therapeutic levels. Though it is possible to dichotomize if direct FXa inhibitor activity is present or not, it is not recommended to perform quantitative DOAC measurement using non-dedicated anti-Xa chromogenic assays.[29,39]

Another challenge for the laboratory arises if thrombophilia testing is ordered for a DOAC patient. As with heparin, lupus anticoagulant assays such as dRVVT (dilute Russell's viper venom time) react highly sensitive to DOAC so that test results may be false positive. Furthermore, DOAC may interfere with clotting assays performed for protein C and S activities (false high results) and may interfere with single factor analyses of most clotting factors (usually false low results). The addition of in vitro DOAC adsorbent agents containing activated charcoal to the blood sample (DOAC-STOP Haematex Research, Hornsby, Australia; DOAC Remove 5 Diagnostics, Base, Switzerland) may reduce these artifacts.[43,44] However, the safest strategy might be not to perform such testing during active DOAC therapy when a short DOAC interruption can allow for a test in DOAC-free samples instead. Of note, antiphospholipid antibody assays and genetic testing (i.e., for prothrombin or factor V mutations) are not influenced by the presence of DOAC anticoagulation.

Finally, the most relevant challenge for a coagulation laboratory may arise from DOAC emergencies. In patients with acute trauma, emergency surgery, life-threatening

bleeding, or acute ischemic stroke emergency physicians will want to know about the anticoagulation status of the patient with as little delay and as high accuracy as possible. As pointed out earlier, dedicated tests are often not available 24/7. Therefore, emergency physicians, hemostasis experts, and laboratory personnel in each hospital need to establish standard operating procedures (SOPs) to define best management according to the setting of each specific hospital. The following section will provide some insights into emergency management of DOAC patients to guide such SOP developments.

Challenges for the Emergency Team

DOACs are potent anticoagulants that are prescribed to reduce the risk for arterial or VTE in high-risk patients. Since DOACs are not perfect, ischemic events may still occur—with potentially devastating outcomes. Similarly, in an aging population that exhibits complex comorbidities, nonischemic emergencies (i.e., acute abdomen, sepsis, major trauma) are also frequent and require urgent treatment, as major bleeding episodes do. As discussed earlier, the intensity of DOAC anticoagulation is not stable throughout the day, but presents different phases of activity. Theoretically, the pharmacodynamic profile of DOACs could allow to distinguish between phases of higher anticoagulation intensity (~2–6 hours after last intake), intermediate intensity (~7–12 hours after last intake), and low intensity (>12 hours after last intake). As a consequence, timing of emergency procedures and DOAC reversal strategies strongly depend on the knowledge of DOAC type, dosing, and last intake. However, to make things more complicated, chronic DOAC overdose, drug accumulation from acute kidney failure, or suicidal overdosing may lead to DOAC plasma levels far higher than those reported from healthy volunteer studies and clinical trials. Therefore, estimating plasma levels based on the knowledge of DOAC dosage and last intake may result in an underestimation of anticoagulation intensity. This has also been demonstrated in the German RADOA Registry, which collected blood samples from DOAC emergency patients and demonstrated that half-lives of DOACs are considerably prolonged both in bleeding and nonbleeding emergencies. Repeated testing demonstrated half-lives of 17.3 hours for rivaroxaban and 25.0 hours for apixaban emergencies.[45] Therefore, dedicated DOAC quantifications (dTT for dabigatran and anti-Xa measurements calibrated for the respective DXI) should be made available 24/7 and implemented into SOPs wherever possible.[29,46] If no such tests are available or if turnaround times are too long, alternatives could include POC devices to detect DOAC activity. For this, urine dipsticks are available and a negative DOAC urine test seems to safely rule out clinically relevant DOAC concentrations.[47,48] Still, urine may not be available and discolored urine makes assessment impossible. It is recommended to confirm urine POC test results by additional laboratory testing.

Another option would be to perform whole blood thrombelastography (TEG), for which several manufacturers provide more or less automated machines and variable test assays.[41] It should be noted that several manufacturers offer dedicated DOAC-specific cartridges to improve the reliability of DOAC detection in whole blood samples. If fully equipped and performed by trained personnel, TEG can be used not only to detect DOAC activity but also to detect hypercoagulation and impaired or accelerated fibrinolysis by evaluating mechanical properties of clot formation and lysis,[49–52] which will be relevant information for acute emergency management.

Once a clinically significant DOAC plasma concentration is suspected (or established), the next challenge for the emergency physician is the decision for or against reversal strategies which may include prothrombin complex factor concentrates (PCCs) or DOAC-specific antidotes. PCCs do not affect anti-Xa activity or DOAC plasma concentrations, but high doses of FII and FX contained in PCC aim to override the anticoagulatory DOAC effects. In vivo studies and observational data have demonstrated a reversing effect of PCC with up to 70% of DOAC patients achieving clinically effective hemostasis.[53,54] Of note, PCC should be the primary reversal strategy in emergencies with massive blood loss in whom coagulopathy requires factor repletion.

DOAC reversal can also be achieved by specific antidotes, which, compared with PCC, may act faster and more to the point of the DOAC-related coagulation disturbance. On the other hand, such antidotes may not be available in every hospital and they are considerably more expensive than PCC.

For dabigatran, the antibody fragment idarucizumab has been developed and approved in many countries. It is given at a dosage of 5 g intravenously, immediately binds dabigatran with high affinity and results in complete reversal of the anticoagulation effect of dabigatran.[55] After 6 hours, approximately one-third of the drug is cleared by the kidneys. For this reason in the case of continued bleeding, a second dose of idarucizumab may be needed. For the DXI apixaban and rivaroxaban, the reversal agent andexanet alfa is a modified human Xa protein very similar to endogenous activated factor X. The drug is administered intravenously, binds with high affinity to the DXI, and reaches its maximum effect within 2 minutes after initial bolus. Following this bolus, the short half-life requires an infusion for another 2 hours to stabilize primary hemostasis.[56] Depending on type, dosage, and the timing of the last dose of the DXI, andexanet alfa is given in a low dose (400 mg bolus + infusion of 4 mg/min for 2 hours) or a high dose (800 mg bolus + 8 mg/min over 2 hours). Andexanet alfa has become approved for major hemorrhage situations but not for emergency surgery. Andexanet alfa is also effective in reversing edoxaban,[57] but approval for this indication is still lacking.

Data from randomized controlled trials comparing PCC against specific antidotes such as idarucizumab or andexanet alfa are currently not available. Indirect comparisons and observational data suggest better outcomes from using specific antidotes.[58,59] These hypothesis-generating observations are currently being tested in the ANNEXA-I study—a randomized trial in DOAC-related ICH which compares andexanet alfa directly against standard of care including PCC.

Clinical challenges after idarucizumab or andexanet alfa reversal include a rebound of DOAC activity (especially in patients with high baseline plasma levels or chronic accumulation from impaired renal function when DOAC reflux from deep compartments may be pronounced).[60] Consequently, measuring DOAC plasma levels after specific reversal may lead to false high DOAC concentrations (if reflux occurred and antidote-bound DOAC dissolves during the sample processing). Another challenge that is specific for andexanet alfa reversal is the inactivation of heparins, which may be needed during emergency surgery.

Conflict of Interest

None declared.

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