The Influence of Direct Oral Anticoagulants on Coagulation Assays

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1. Introduction

Anticoagulants are used for prevention and treatment of thromboembolic disorders. Thromboprophylaxis is warranted in a wide variety of clinical conditions and procedures, such as atrial fibrillation and hip replacement surgery. Prior to the introduction of direct oral anticoagulants (DOACs), vitamin K antagonists such as warfarin, unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH) were (and still are) used for this purpose.

The disadvantages of these classic agents are well-documented. Warfarin has numerous interactions with diet and other medications, requires complex individualized dosing, and has a delayed onset of action. Unfractionated heparins and low-molecular-weight heparins both require parenteral administration and may cause heparin-induced thrombocytopenia, osteoporosis, and hemorrhage, which makes them problematic and inconvenient agents for both clinicians and patients.

The side effects of conventional anticoagulants have prompted research into novel drugs that offer such advantages as oral mode of administration, more predictable anticoagulant response, greater specificity with no requirement for antithrombin action, and no need for routine patient monitoring.

The direct FIIa-inhibitor dabigatran, as well as the direct FXa-inhibitors rivaroxaban, apixaban, and edoxaban, belong to this new generation of oral anticoagulants, which have been in clinical use for more than a decade. Their primary indications are for prevention of venous thromboembolism (VTE) and prevention of stroke and systemic embolism in patients with atrial fibrillation. Depending on the drug, additional specific clinical indications have been approved by authorities around the globe.

As shown in Figure 1, which depicts a portion of the coagulation cascade, the DOACs directly inhibit central clotting factors within the clotting pathway, such as thrombin (FIIa) or activated factor X (FXa).

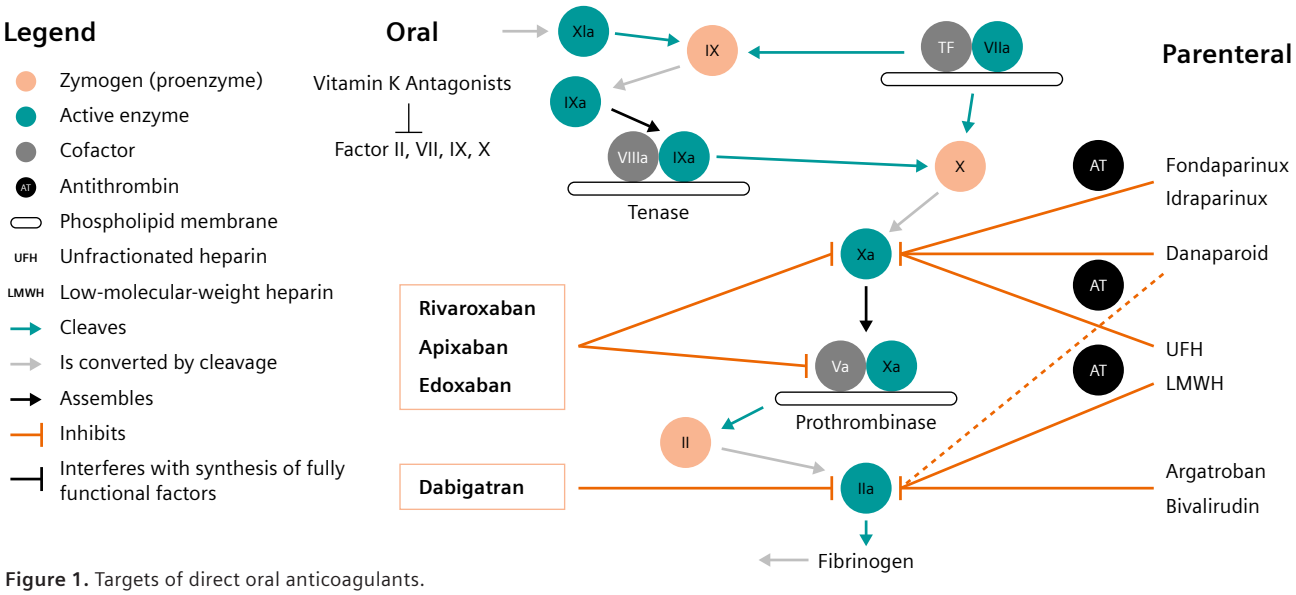

Figure 1. Targets of direct oral anticoagulants.

Coagulation testing in the presence of anticoagulants is often performed as a routine postoperative laboratory control, to determine the cause of thrombosis in thrombophilia patients, or in case of an emergency. Many studies have assessed the ex vivo and in vitro dose-dependent effect of the DOACs in healthy individuals and patients.

This paper summarizes the pharmacology of the DOACs and describes their influence on coagulation tests based on peer-reviewed publications and in-house studies.

2. Direct Oral Anticoagulants

2.1 Direct thrombin inhibitors

Because of its key role in the coagulation cascade, thrombin (FIIa) is one of the main targets in the development of direct-acting anticoagulants. Unlike heparins, direct thrombin inhibitors (DTIs) are small molecules that inhibit thrombin directly, with no need for a cofactor like antithrombin. DTI action results in specific binding of free and fibrin-bound thrombin, thereby preventing fibrin formation, thrombin-mediated activation of FV, FVIII, FXI, and FXIII, and thrombin-induced platelet aggregation. Since their chemical structure differs completely from that of heparin, DTIs do not interfere with heparin-induced thrombocytopenia type II (HIT-II) antibodies.

For years, three parenteral DTIs were available: lepirudin (REFLUDAN), bivalirudin (ANGIOX), and argatroban (NOVASTAN). REFLUDAN has been withdrawn from use in the European Union.

The first oral DTI, ximelagatran (EXANTA), was taken off the market in February 2006, only 1.5 years after approval, because of side effects.

2.1.1 Dabigatran (PRADAXA)

Today, dabigatran (PRADAXA) is the only orally administered direct thrombin inhibitor available.

2.1.2. Antidote for direct factor IIa inhibitors

In 2015, the FDA approved idarucizumab (PRAXBIND), a specific reversal agent for dabigatran, to be used in emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding for patients on dabigatran therapy.[1]

2.2 Direct factor Xa inhibitors

Coagulation factor Xa is the other main target of direct-acting anticoagulants. Like thrombin, factor Xa is at the convergence point of the intrinsic and extrinsic pathways in the blood coagulation system.

2.2.1 Rivaroxaban (XARELTO)

Rivaroxaban is the first orally administered direct factor Xa inhibitor. It selectively and reversibly inhibits free and clot-associated factor Xa activity. Rivaroxaban provides concentration-dependent inhibition of factor Xa with high potency and selectivity.

2.2.2. Apixaban (ELIQUIS)

Apixaban is the second orally administered direct inhibitor of coagulation factor Xa (FXa) to be introduced. It selectively and reversibly inhibits free and clot-bound FXa and prothrombinase activity. Apixaban shows moderate selectivity for clot-bound factor Xa versus free factor Xa and also inhibits thrombin generation.

2.2.3. Edoxaban (SAVAYSA, LIXIANA)

A third substance, edoxaban, is an orally administered, selective, and reversible inhibitor of coagulation factor Xa (FXa). It inhibits free and clot-bound FXa and consequently prothrombinase activity.

2.2.4. Antidote for direct factor Xa inhibitors

In 2019, andexanet alfa (ANDEXXA) was approved as an antidote to direct factor Xa (FXa) inhibitors when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexanet alfa is currently approved only for the reversal of rivaroxaban and apixaban.[1]

3. Indirect FXa Inhibitors

Indirect factor Xa inhibitors exert their antithrombotic effect by binding to antithrombin, the natural antidote of thrombin, and strongly enhancing its inhibitory properties. Therefore, their efficacy depends on the circulating level of antithrombin. They are parenteral agents and cannot be administered orally.

3.1 Danaparoid (ORGARAN)

The indirect factor Xa inhibitor danaparoid sodium is a mixture of partially depolymerized glucosaminoglycans. Antithrombin-mediated danaparoid catalyzes the inactivation of factor Xa.

There is also an antithrombin and heparin cofactor II-mediated inhibition of thrombin. However, the ratio of anti-Xa to anti-IIa activity is more than 22:1. The substance is in clinical use for thrombosis prophylaxis, and, because of its low cross-reactivity with heparin-platelet factor 4, it is also suitable for treatment of immune HIT-II.

3.2 Fondaparinux (ARIXTRA)

The synthetic pentasaccharide fondaparinux, an indirect factor Xa inhibitor, acts by specific binding to antithrombin; it has no effect on thrombin or nonspecific plasma protein binding. It exhibits almost 100% bioavailability after subcutaneous application. The drug is eliminated via renal filtration, and its half-life is about 17 hours. In vitro studies show no cross-reactivity with HIT antibodies.

3.3 Idraparinux

Due to its irreversible binding to antithrombin, the highly sulfated pentasaccharide idraparinux is characterized by a long half-life of approximately 80 hours. This is very convenient for patients, because a once-weekly subcutaneous administration is sufficient. A biotinylated form of the drug, currently in clinical trials, allows inactivation by avidin (a tetrameric biotin-binding protein).

3.4 Antidote for indirect factor Xa inhibitors

No specific antidotes are available for indirect FXa inhibitors.

4. Pharmacological Profiles of Anticoagulants

Table 1 lists brief pharmacological profiles of different anticoagulants distinguished mainly by their bioavailability and metabolism. The clinical indication may vary among countries outside the EU.

Table 1. Overview of approved anticoagulants (EU; May 2022).

Anticoagulation	Substance (drug)	Application	Half-life Time (time to peak concentration)	Elimination	Monitoring
Direct thrombin inhibitors	Dabigatran (PRADAXA)	Oral, twice daily	14–17 h (2–4 h)	Renal	**Not required** Options: Diluted thrombin time, ecarin clotting time, anti-FIIa assay (requires calibration with dabigatran)
	Argatroban (ARGATRA)	Intravenous	25 min	Hepatic	**Mandatory** APTT target: 1.5–3.0 fold Chromogenic ECT, anti-FIIa assay (requires calibration with argatroban)
	Bivalrudin (ANGIOX)	Intravenous	25 min	Renal	**ACT recommended** Target: ACT >115 seconds
Direct FXa inhibitors	Rivaroxaban (XARELTO)	Oral, once daily	7–11 h (2–4 h)	Renal and hepatic	**Not required** Option: Anti-FXa assay (requires calibration with rivaroxaban)
	Apixaban (ELIQUIS)	Oral, twice daily	8–15 h (0.5–2 h)	Renal and biliary	**Not required** Option: Anti-FXa assay (requires calibration with apixaban)
	Edoxaban (SAVAYSA, LIXIANA)	Oral, once daily	10–14 h (1–2 h)	Renal and hepatic	**Not required** Option: Anti-FXa assay (requires calibration with edoxaban)
Indirect FXa inhibitors (require antithrombin)	Fondaparinux (ARIXTRA)	Intravenous, subcutaneous, once daily	17 h (25 min)	Renal	**Not required** Option: Anti-FXa assay (requires calibration with fondaparinux)
	Danaparoid (ORGARAN)	Intravenous, subcutaneous, twice daily	7–8 h (4–5 h)	Renal	**Recommended** For patients with renal impairment who weigh >90 kg Anti-FXa assay (requires calibration with danaparoid)

5. Patient Groups Likely to Receive DOACs

Based on the range of clinical indications, the following patients are likely to receive DOACs if reliable patient information is missing:

- Age >75 years
- Atrial fibrillation
- Cardiovascular disease (may be treated with low-dose rivaroxaban)
- Recent surgery or trauma
- Recurrent stroke or VTE

6. Influence of Direct Oral Anticoagulants on Coagulation Assays: An Overview

6.1 Introduction

The stable and reproducible pharmacokinetics of the direct oral anticoagulants is an advantage over conventional agents, allowing them to be administered with fixed dosing and requiring no laboratory monitoring of drug levels or coagulation parameters. However, determination of plasma concentrations of DOACs may be helpful in certain circumstances, such as patients with an overdose, a hemorrhagic or thromboembolic event during treatment, deteriorating renal function, or those who require urgent surgery.

The presence of direct thrombin and FXa inhibitors causes a significant prolongation of the clotting reaction, which in turn can produce altered and potentially misleading results in routine coagulation tests. In contrast, indirect FXa inhibitors usually do not influence routine and special coagulation tests.

In hospitals, these alterations are observed during routine preoperative or postoperative laboratory coagulation testing, raising concerns about potential bleeding risk in patients.

Because of the possibility of altered, misleading results, clinicians must be able to accurately interpret coagulation parameters in patients taking, for example, rivaroxaban or dabigatran. Detailed knowledge about these drugs' effects on routine coagulation assays is critical and essential.

The routine coagulation assays prothrombin time (PT) and activated partial thromboplastin time (APTT) are affected differently by DOACs depending on the type of drug, drug concentration, and the reagent used for testing. Most PT and APTT reagents display a higher sensitivity for rivaroxaban and edoxaban than for apixaban.[2]

Recent guidelines recommend the use of mixing tests to differentiate factor deficiencies from inhibitor effects such as lupus anticoagulant.[3] In mixing tests using APTT or PT, DOACs will appear as nonspecific inhibitors, with the inhibitor effect most pronounced at higher drug concentrations.[3,4]

6.2 Clotting assays

Clotting tests are still the most often performed assays in the hemostasis laboratory. In clotting tests, the time between the addition of a thromboplastin reagent and the formation of the fibrin clot is measured. The increasing viscosity and turbidity of the sample allow the detection of clot formation using mechanical or optical end-point detection.

6.2.1 Prothrombin time

The prothrombin time clotting assay is a screening assay for the function of the extrinsic pathway. It is used to obtain an overview of factors VII, X, V, thrombin, and fibrinogen.

The PT is influenced with an increase in INR or seconds by direct thrombin and factor Xa inhibitors in a concentration-dependent manner, with the sensitivity dependent on the reagent being used. Rivaroxaban and edoxaban prolong PT at concentrations in their therapeutic range, while higher concentrations of apixaban and dabigatran are required to affect the assay, making PT relatively insensitive to those two drugs. Nevertheless, PT is not sensitive enough to detect clinically relevant changes in drug concentration of any DOAC.[2,5,6]

The PT reagents Dade® Innovin® and Thromborel® S show a higher sensitivity for edoxaban and rivaroxaban than for apixaban[2,5] and appear to be least sensitive to dabigatran in comparison to other PT reagents.[7]

Conversely, indirect factor Xa inhibitors such as LMWHs, which react via antithrombin/heparin complexes, do not influence the PT.

6.2.2. Activated partial thromboplastin time

In contrast to the PT assay, activated partial thromboplastin time is a screening test for the intrinsic system and its factors: kininogen, prekallikrein, factors XII, XI, IX, VIII, X, V, and thrombin. In the preincubation/preactivation phase of this test, antithrombin/heparin complexes can inactivate thrombin and its positive-feedback reactions.

In general, APTT may be prolonged with therapeutic drug levels of dabigatran, while it is usually less influenced by direct FXa inhibitors. But a normal APTT does not exclude the presence of dabigatran. Dade Actin® FSL Activated PTT Reagent was found less sensitive for dabigatran than Dade Actin FS Activated PTT Reagent and other APTT-reagents.[7]

The APTT reagents Dade Actin Activated Cephaloplastin Reagent, Dade Actin FS Activated PTT Reagent, and Dade Actin FSL Activated PTT Reagent are all more sensitive to rivaroxaban than to edoxaban, while none of them is sensitive to apixaban.[2,5] Again, Dade Actin FSL Activated PTT Reagent appears to be the least sensitive to the effect of FXa inhibitors.[7]

Indirect factor Xa inhibitors such as LMWHs, which react via antithrombin/heparin complexes, do not influence APTT.

6.2.3. Single-factor assays, one-stage clotting

As both PT and APTT clotting times are prolonged in the presence of DOACs, all one-stage clotting assays based on the same reagents for determination of single coagulation factor activity are also affected. Consequently, the presence of DOACs may lead to an underestimation of single coagulation factor activity. The extent of underestimation depends on drug concentration and the PT or APTT reagent used.

6.2.4. Thrombin time

Thrombin time (TT) is a clotting screening test for fibrinogen polymerization. It is performed by adding a low concentration of thrombin to plasma. This leads to formation of fibrin. The TT assay is a functional test of fibrinogen concentration and fibrin formation.

Not surprisingly, thrombin time is highly sensitive for dabigatran and can be used as a screening assay for the drug because it is not influenced by direct FXa inhibitors.[2] Diluted thrombin time is one of the recommended assays for the quantification of dabigatran in human plasma.[4, 9-11]

6.2.5. Fibrinogen (Clauss method)

The determination of fibrinogen is another routine parameter in coagulation testing. Frequently the method according to Clauss, which is based on the addition of an excess of thrombin to plasma, is used.

Using the Clauss method, fibrinogen activity tends to be unaffected by DOACs due to the relatively high sample dilution and the high concentration of thrombin used in reagents such as Multifibren® U or Dade Thrombin Reagent.[2,6] Decreased fibrinogen activity was reported only at high dabigatran concentrations.[8]

The determination of fibrinogen antigen is not influenced by DOACs (see also Immunoassays).

6.2.6. Derived fibrinogen

Table 2. Influence of anticoagulants on routine coagulation assays.

Assay	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Indirect FXa Inhibitors
PT sec and INR	↑	↑↑	↑	↑↑	↔
APTT	↑↑	↑	↑-↔	↑	↔
Thrombin time	↑↑↑	↔	↔	↔	↔
Fibrinogen (Clauss)	↔ - ↓*	↔	↔	↔	↔
Derived fibrinogen	↔	↔	↔	↔	↔
D-dimer	↔	↔	↔	↔	↔

*Only at very high dabigatran concentrations.

The total increase of turbidity during the prothrombin time measurement is directly proportional to the concentration of fibrinogen. Therefore, the PT-derived fibrinogen assay is widely used as an alternate method for measurement of fibrinogen.

Like the determination of fibrinogen by the Clauss method, derived fibrinogen is hardly affected by the presence of DOACs.[7]

6.2.7. Lupus anticoagulant (dilute Russell's viper venom time)

For determination of lupus anticoagulant (LA), the ratio between a dilute Russell's viper venom time (dRVVT) low in phospholipids (LA screen) and a dRVVT rich in phospholipids (LA confirm) is measured.

Lupus anticoagulant measurement or dilute Russell's viper venom time are strongly affected by the presence of DOACs, leading to false-positive results.

The clotting times of LA screen assays, LA confirmation assays, and the LA ratio are already prolonged or altered at low, sub-therapeutic plasma levels of FXa inhibitors. The sensitivity for rivaroxaban and edoxaban is higher than for apixaban.[2]

Dabigatran also prolongs and alters the clotting times of lupus anticoagulant assays already at sub-therapeutic plasma levels.[6]

6.2.8. Other clotting assays

The coagulometric **protein C** assay is based on an APTT reaction in which the activated protein C inactivates the accelerators FVa and FVIIIa, prolonging the clotting time with increasing protein C levels.

In the dRVVT-based coagulometric **protein S** assay, the clotting time recorded is proportional to the protein S activity.

ProC® Global is an APTT-based screening assay for the protein C system that determines the ratio of a diluted APTT in the presence of protein C activation versus no protein C activation. **ProC Ac R** is a similar, more specific assay for the determination of activated protein C resistance (APCR) to so-called **FV Leiden** using a dRVVT with FV-deficient plasma in the presence and absence of a protein C activator.

Clot-based assays for determination of protein C or protein S activity are affected by DOACs, resulting in falsely increased values.[2,5,12]

The falsely increased values caused by DOACs in clot-based, activated protein C resistance assays may result in a patient with factor V Leiden mutation being misdiagnosed as normal.[12]

The batroxobin or reptilase time is not influenced by DOACs.[13]

6.2.9. Mixing studies

In mixing studies for APTT, PT, and lupus anticoagulant, DOACs will appear as nonspecific inhibitors, with the inhibitor effect most pronounced at higher drug concentrations.[3,4]

6.3 Chromogenic assays

Chromogenic assays allow a direct determination of the activity of a coagulation factor by photometrically measuring the formation of a chromophore form of a specific substrate.

6.3.1. Influence of DOACs on factor X-based chromogenic assays

Factor X-based assays are used to determine antithrombin activity or to quantify the activity of heparins by measuring the inhibitory effect of those analytes on FXa. Chromogenic assays for the quantification of either coagulation factor VIII or coagulation factor IX typically also use chromogenic substrates for FXa.

Naturally, FX-based assays using a substrate for FXa are strongly influenced by the direct FXa inhibitors rivaroxaban, apixaban, and edoxaban, while direct thrombin inhibitors do not have any impact.[5-7,12,14] The presence of direct FXa inhibitors leads to falsely increased results in FX-based assays used for the quantification of antithrombin activity or the activity of indirect FXa inhibitors such as unfractionated and low-molecular-weight heparins.[2,5,6,12,13]

Consequently, FX-based assays are recommended for the quantification of rivaroxaban, apixaban, and edoxaban using drug-specific calibrators and controls.[4,9-11]

Chromogenic assays for the quantification of coagulation factors VIII and IX are also affected by direct FXa inhibitors, showing concentration- and drug-dependent decreasing results.[5,13]

6.3.2. Influence of DOACs on factor II-based chromogenic assays

A factor II-based assay can also be used to determine the activity of antithrombin. Not surprisingly, chromogenic assays using a substrate for thrombin (FIIa) are sensitive to dabigatran, resulting in a strong overestimation of, for instance, antithrombin activity.[5,13] Chromogenic FII-based assays using dabigatran calibrators and controls are therefore a recommended method to quantify dabigatran in human plasma.[4]

6.3.3. Influence on factor XIII activity assay

The chromogenic FXIII activity assay requires as a first step in the reaction the activation of FXIII to FXIIIa by thrombin. Hence, this assay is sensitive to the presence of dabigatran, which results in markedly decreased FXIII activity.[14]

6.3.4. Influence on activity assays for protein C, plasminogen, α2-antiplasmin, and C1 inhibitor

The different chromogenic assays allow a direct determination of the enzymatic activity of protein C, plasminogen, α2-antiplasmin, or C1 inhibitor and are not affected by the presence of DOACs.[2,4]

6.4 Immunoassays

In latex agglutination immunoassays, analyte-specific antibodies against the analyte (e.g., **D-dimer**, **free protein S**, **vWF:Ag**) bound to latex particles are used for quantification. The binding of the analyte to the antibodies results in an agglutination of the latex particles, which can be measured either turbidimetrically or nephelometrically.

6.4.1 Influence of DOACs on immunoassays

All variants of immunoassays such as protein S, VWF:Ag, and D-dimer immunoassays are not influenced by direct FXa or thrombin inhibitors.[13]

Table 3. Influence of anticoagulants on specialty coagulation assays.

Assay	Principle	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Indirect FXa Inhibitors
Unfractionated and low-molecular-weight heparin	FX-based assay	↔	↑↑	↑↑	↑↑	N/A
Antithrombin activity	FII-based assay	↑↑	↔	↔	↔	↔
	FX-based assay	↔	↑↑	↑↑	↑↑	↑↑*
Antithrombin, antigen	Immunoassay	↔	↔	↔	↔	↔
Protein C	Clotting	↑	↑	↑	↑	↔
	Chromogenic	↔	↔	↔	↔	↔
Protein S activity	Clotting	↑	↑	↑	↑	
Free Protein S, antigen	Latex-enhanced immunoassay	↔	↔	↔	↔	↔
Lupus anticoagulant (dRVVT)	Clotting	↑↑	↑↑	↑↑	↑↑	↔
Single coagulation factors, aPTT-based (FVIII, FIX, FXI, FXII)	Clotting	↓	↓	↓-↔	↓	↔
Single coagulation factors, PT-based (FII, FV, FVII, FX)	Clotting	↓	↓	↓-↔	↓	↔
Coagulation factor VIII	Chromogenic	↔	↓	↓	↓	↔
Coagulation factor IX	Chromogenic	↔	↓	↓	↓	↔
Coagulation factor XIII	Chromogenic	↓	↔	↔	↔	↔
Protein C activity (PCAT), factor V Leiden (APCR)	Clotting	↑	↑	↑	↑	↔
Batroxobin time	Clotting	↔	↔	↔	↔	↔
α2 Antiplasmin	Chromogenic	↔	↔	↔	↔	↔
Plasminogen activity	Chromogenic	↔	↔	↔	↔	↔
Plasminogen, antigen	Immunoassay	↔	↔	↔	↔	↔
Von Willebrand factor activity	Latex-enhanced immunoassay	↔	↔	↔	↔	↔
Von Willebrand factor, antigen	Latex-enhanced immunoassay	↔	↔	↔	↔	↔
Fibrinogen, antigen	Immunoassay	↔	↔	↔	↔	↔
C1 inhibitor activity	Chromogenic	↔	↔	↔	↔	↔
C1 inhibitor, antigen	Immunoassay	↔	↔	↔	↔	↔

*Only at very high dabigatran concentrations.

6.5 Summary

The influence of DOACs on commonly used coagulation assays as described in detail in section 6 are summarized in Tables 2 and 3.

This overview should enable coagulation laboratories to efficiently manage samples derived from patients on (unknown) DOAC therapy.

7. Neutralizing DOACs in Patient Samples

7.1 Neutralizing direct oral anticoagulants in patient samples

One option to accurately measure samples containing DOACs is the use of DOAC-neutralizing agents containing activated carbon. Currently available DOAC-neutralizing agents in tablet form include DOAC-Stop (Haematex Research) and DOAC-Remove (5-Diagnostics AG).[15] Both agents were shown to be effective in removing DOACs.[16,17]

7.2 Influence of DOAC reversal agents on coagulation assays

7.2.1. Idarucizumab

Idarucizumab is a specific and approved reversal agent for dabigatran when a rapid reversal of its anticoagulant effects is required due to an emergency surgery or life-threatening or uncontrolled bleeding. Idarucizumab by itself has no known impact on coagulation parameters.[18]

7.2.2. Andaxanet alfa

Andexanet alfa, a specific reversal agent, is approved for rivaroxaban and apixaban when the reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The drug must be applied intravenously, and anti-FXa activity returns to placebo concentrations about 2 hours after a bolus or infusion.[18] If chromogenic FXa assays are used to quantify the direct FXa inhibitor activity following an andaxanet alfa administration, caution is warranted, as the large sample dilution in the assay causes the dissociation of the drug-andexanet alfa complex, resulting in an erroneous elevation of the anti-FXa activity.[18]

8. Conclusion

Since their introduction more than a decade ago, direct oral anticoagulants are well-established and widely used in a broad range of patients. It is well-known that their presence in plasma samples can alter test results of several coagulation assays. Some strategies to overcome this interference in the lab have also been established.

This white paper summarizes the current knowledge on the influence of DOACs on coagulation tests, which must be considered in the coagulation lab when dealing with blood samples from patients on DOAC therapy.

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