



# Clinical use and laboratory testing of oral anticoagulation therapy: experience from Finland

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**Abstract:** Anticoagulation therapy has been undergoing a transition during the last decade with the progressive availability of direct oral anticoagulants (DOACs). While DOACs are increasingly used in common indications for anticoagulation, including non-valvular atrial fibrillation (AF), deep vein thrombosis (DVT) and pulmonary embolism (PE), traditional anticoagulants, either warfarin or heparins, remain the primary choice for patients with cardiac valvular replacement, severe thrombophilia, pediatric, pregnant and many cancer patients. Laboratory monitoring of warfarin and heparins are well established, while under specific emergency conditions DOACs require specific assays, the availability of which may be limited. Finland benefits from centralized laboratory networks, offering harmonized services throughout our rather sparsely populated country. Specific assays for all DOACs are available 24/7 in the core laboratory (Southern Finland). Interaction, collaboration and continuous education between clinic and laboratory is increasingly needed, under the era of rapid change of traditions in anticoagulation management.

**Keywords:** Anticoagulation; coagulation testing; Finland; direct oral anticoagulants (DOACs)

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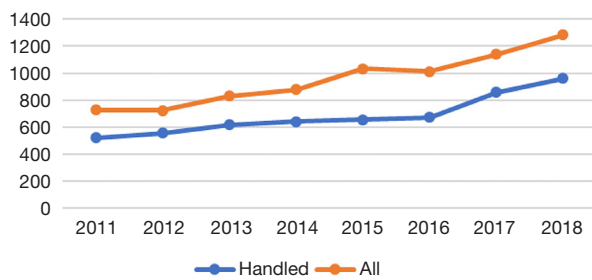
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## Introduction

Our Coagulation Disorders Unit was founded 20 years ago. The unit is a tertiary care center within the Helsinki University Hospital, combining clinical and coagulation laboratory services and serving the Helsinki and Uusimaa Hospital District. The unit handles consultation cases for severe thrombosis and/or bleeding tendency, also offering consultation services nationwide. While hemophilias, von Willebrand disease and other bleeding disorders constitute the major part of patient visits to the clinic, thrombosis and consultations regarding the safe use of anticoagulants are frequent and increasing (*Figure 1*). In a population of around 2 million inhabitants, more than 900,000 coagulation

tests, of which 60% represent INR, were performed in our laboratories (HUSLAB) in 2018.

When the direct oral anticoagulants (DOACs) became available from 2008 onwards, initially, we were not confident on the overall safety of these new drugs, in the absence of the monitoring of the drug effect. In the phase III trials of the DOACs, relevant patient groups, such as patients with kidney or liver failure, patients having antiplatelet therapy, patients encountering bleeds and patients with active malignancy were excluded (1). Nevertheless, questions regarding anticoagulation of these vulnerable patients are often encountered, and we could not recommend DOACs for these patients at this early stage. We also, to increase the national awareness, authored an



**Figure 1** The increasing (55%/5 years) number of consultations to the clinical Coagulation Disorders Unit, Department of Hematology and Comprehensive Cancer Centre, Helsinki University Hospital. The Unit was established in year 2000. The majority of the increased number of consultations are due to problems related to anticoagulation. ‘All’ consultations refer to the ones received to our unit, while ‘handled’ consultations refer to the online performed consultations, most urgent being the phone call consultations. The European Association of Haemophilia and Allied Disorders EUHANET project assigned the European Haemophilia Comprehensive Care Centre, EHCCC status to the Unit in 2014. Three to four doctors and 3–4 nurses work at the Unit. The Unit collaborates with the laboratory at multiple levels on daily basis.

article in the Finnish Medical Society Journal to encourage rational introduction of these new drugs (2), and national web-based guidelines have been gathered (accessible at [www.hematology.fi](http://www.hematology.fi), in Finnish). We were the first to set up specific laboratory assays for DOACs in our country, for dabigatran in 2011, for rivaroxaban in 2012 and for apixaban in 2015. In original studies, we have found that dabigatran may even paradoxically increase thrombin generation (TG) in certain situations, while rivaroxaban and apixaban differ in their TG response, mirroring the increasing DOAC concentration—i.e., once- *vs.* twice-daily dosing (3,4).

DOACs are gaining new indications, rivaroxaban for prevention of atherothrombosis in coronary artery disease, and several DOACs are being considered in cancer patients as well (5–7). While the use of DOACs is increasing, clinicians will encounter many patients switching from traditional vitamin K antagonists (VKAs) to DOACs, and broad education is required (8). To respond to the challenge of increased repertoire of anticoagulants in patients with risk factors for both thrombosis and bleeding, e.g., elderly patients undergoing vascular surgery, a special anticoagulation clinic was launched in conjunction with the Coagulation Disorders Unit in 2015. One physician and a registered nurse have the primary responsibility of

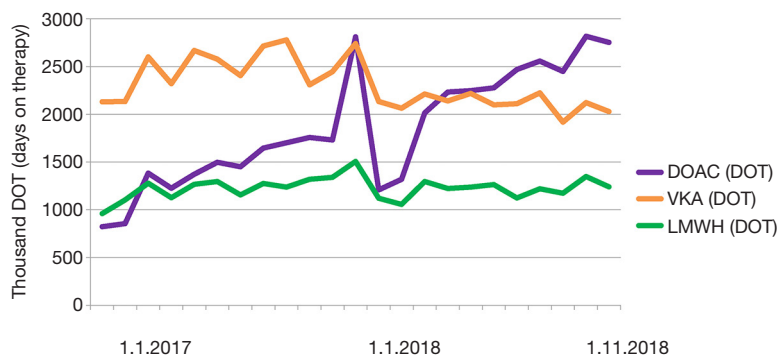
responding to clinical consultations in anticoagulation-related questions in both in- and out-patient settings. A warfarin self-management program was launched as well in collaboration with the laboratory at that time, to provide warfarin guidance and establishing safe therapy in patients with mechanical valvular replacement.

## Oral anticoagulants

### Direct oral anticoagulants

Dabigatran was the first DOAC to come on market, for thromboprophylaxis after orthopedic surgery with European Medicines Agency (EMA) approval in 2008. Orally administered direct factor Xa inhibitors (FXaI) include rivaroxaban, apixaban, edoxaban and betrixaban (but not in the EU for the last agent). At present, the indications for DOACs dabigatran, rivaroxaban and apixaban include thromboprophylaxis after knee and hip replacement orthopedic surgery, stroke prevention in conjunction with non-valvular atrial fibrillation (AF), treatment of deep venous thrombosis (DVT) or uncomplicated, hemodynamically stable pulmonary embolism (PE) (9). Uniquely for rivaroxaban, prevention of atherothrombotic events in coronary artery disease or peripheral arterial occlusive disease in conjunction with acetylsalicylic acid (ASA) is also recently indicated (5,10). Edoxaban was approved by the EMA for stroke prevention with AF and treatment of DVT and uncomplicated PE in 2015 (11). Betrixaban is not currently available in the European market, but is the sole DOAC with the indication of thromboprophylaxis for medically ill patients (12). The distribution of anticoagulation use is presented in *Figure 2*. Rivaroxaban is the most used DOAC in Finland at the moment. Recently dabigatran was found to be non-inferior to warfarin in the treatment of cerebral sinus venous thrombosis (RESPECT\_CVT, submitted 2019).

Monitoring of DOAC anticoagulation effect is not recommended for routine use, while liver or kidney dysfunction, thrombosis or bleeding breakthrough during treatment, extremes in body weight, suspicion of non-compliance or overdose are situations where measurement is useful. Routine coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) are unreliable in assessment of DOAC effect, and their sensitivity depends on laboratory and reagents used (13–16). However, the baseline assessment of PT and APTT are valuable screening tests to obtain an understanding of the



Data Source: IQVIA 12/2018.

**Figure 2** The use of oral anticoagulants in Finland, data source IQVIA 12/2018. The use of warfarin is decreasing and DOACs increasing. DOAC purchase peak in the turn of the years 2017–2018 due to stock replenishment of the pharmacies (IQVIA Finland, The Human Data Science Company<sup>TM</sup>).

liver function prior to initiation of DOACs. Also, in case of severe accumulation of DOAC, both tests depict prolonged coagulation times. The effect and interference of DOACs on the other coagulation factor testing is under continuous discussion and education between clinic and laboratory. Some neutralization strategies to better interpret laboratory tests may be needed.

Specific assays for DOACs are available and in regular use nowadays (*Table 1*). Thrombin time (TT) is extremely sensitive to dabigatran and can be diluted and calibrated with known drug concentrations, one modification of such is used in our laboratory. Ecarin clotting assay (ECA) based methods have also proven to be accurate (14).

Chromogenic anti-FXa assay can be calibrated with known concentrations of FXa inhibitors (FXaI) to provide a functional assay for estimating concentration. However, all FXa-inhibiting drugs, including indirect FXa inhibitors, such as heparin, elicit a response. A calibrated assay is said to be specific for the given FXaI, and the clinician must ask for the specific assay compatible with the current FXaI in use (not just request a FXa assay). This is important as anti-FXa sensitivities to different FXaIs vary. As an example, edoxaban amounts to the strongest anti-FXa inhibition in the low molecular weight heparin (LMWH) calibrated assays. On the other hand FXaIs can be quite reliably traced and excluded with LMWH assay (11,17,18), which is particularly relevant where the specific assay is not available for 24/7.

Antidotes for DOACs have been launched with a delay. Idarucizumab, a monoclonal antibody against dabigatran without any influence on thrombin, was licensed by the

EMA and was available in Finland in late 2015 when we nationally launched web-based practical guidance to clinicians to approach problematic emergency cases (19). FXaI antidote andexanet alpha, effective against all the FXaIs, became available in EU only recently (20). The pricing will be unfortunately very high, so a rapid nation-specific health economic analysis will be needed prior the potential use of andexanet. Until now, the reversal of the FXaIs has been successfully performed with 4-factor prothrombin complex concentrates (PCC) (21).

DOAC reversal is indicated under acute situations, where it is not feasible to wait for drug elimination. These include drug overdose, acute kidney or liver failure, major bleed, trauma or urgent procedure with significant bleeding risk. Approximately 2–4% of patients on anticoagulation therapy encounter a major bleed and a further 2% require urgent procedure(s) while anticoagulated (22). In 2018, in the Helsinki and Uusimaa Hospital District, idarucizumab was used 120 times. More detailed analyses of these cases revealed that laboratory analyses (blood count, DOAC concentrations) were assessed only in a third of the patients, despite national guidelines from 2015 on DOAC on reversal, as idarucizumab is directly available to clinicians from the hospital pharmacy.

While typical DOAC concentrations during treatment are known, based on previous patient studies, actual concentrations observed in real-life patients may widely vary, 10- or even 100-fold at both peak and trough. Peak and trough levels for DOACs dabigatran, rivaroxaban and apixaban obtained in selected patient sample studies are

**Table 1** The commonly used anticoagulants available in Finland

Anticoagulant	Indication	Advantages	Disadvantages	Laboratory measurement
Unfractionated heparin, UFH	Anticoagulation during surgical procedures, intensive care, resolution of hemodynamically unstable pulmonary embolism	High therapeutic doses possible, antidote protamine sulfate available	Intravenous or subcutaneous dosing, highest risk of heparin-induced thrombocytopenia (HIT)	APTT, TT, Anti-Xa, ACT
Low-molecular weight heparin, LMWH	Anticoagulation during hospitalization, in active cancer, bridging treatment with warfarin, thrombophilias	Dosed subcutaneously, easier to use than unfractionated heparin, lower risk of HIT, antidote protamine sulfate available, although less effective than for UFH	Parenteral subcutaneous dosing	Anti-Xa
Warfarin, VKA	Almost all long-term situations requiring anticoagulation, including artificial heart valve, thrombophilia and cancer	Long experience on clinical use, readily monitored with INR, vitamin K readily available as antidote, for urgent reversal, PCC	Regular visits to the laboratory required for INR checks	INR
Dabigatran	Non-valvular AF, treatment of PE, DVT	No routine laboratory monitoring, fixed dose	Antidote idarucizumab expensive and not always available, PCC as an alternative, dabigatran cannot be used in kidney failure	diluted thrombin time (dTT) calibrated for dabigatran, ecarin clotting assay (ECA)
Rivaroxaban	Non-valvular AF, treatment of PE, DVT, prevention of atherothrombosis	No routine laboratory monitoring, fixed dose, once-daily dosing	Antidote andexanet alpha, expensive and not readily available, PCC as an alternative	Anti-Xa calibrated for rivaroxaban
Apixaban	Non-valvular AF, treatment of PE, DVT	No routine laboratory monitoring, fixed dose	Antidote andexanet alpha expensive and not readily available, PCC as an alternative	Anti-Xa calibrated for apixaban
Edoxaban	Non-valvular AF	No routine laboratory monitoring, fixed dose, once-daily dosing	Antidote andexanet alpha expensive and not readily available, PCC as an alternative	Anti-Xa calibrated for edoxaban

ACT, activated clotting time; AF, atrial fibrillation; Anti-Xa, anti-factor Xa assay; APTT, activated partial thromboplastin time; dTT, diluted thrombin time; DVT, deep vein thrombosis; ECA, ecarin clotting assay; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low molecular weight heparin; PCC, prothrombin complex concentrate; PE, pulmonary embolism; TT, thrombin time; UFH, unfractionated heparin.

shown in *Tables 2-4*. In a recent study, the mean peak level of edoxaban was 301 ng/mL (range, 60–569 ng/mL) and trough level was 39 ng/mL (range, 13–110 ng/mL) in 48 AF patients with an edoxaban OD dose of 60 mg (37).

### VKAs (*warfarin*)

Warfarin is the traditional oral anticoagulant with decades

of experience for its use. The clinical indications of warfarin include: (I) stroke prevention in all forms of AF, including valvular and under mechanical valvular replacement, (II) treatment of DVT and PE (including complicated, hemodynamically unstable PE), and other rare locations of thrombosis (e.g., cerebral sinus and portal vein thrombosis), although initial heparin bridging is used when treating acute thrombosis, (III) secondary prevention of thrombotic events

**Table 2** Dabigatran levels in patient sample studies varied significantly interindividually

Study	Indication	Dose	Number of patients	Peak level (ng/mL)			Trough level (ng/mL)			Measurement method	Reference
				Mean	Median	Range	Mean	Median	Range		
Antovic <i>et al.</i> 2013	Atrial fibrillation	Not reported	70						<0.5–586	LC-MS/MS	(23)
Reilly <i>et al.</i> 2014	Atrial fibrillation	110 mg BID	4,583	126	133	1–745	65	66	1–608	LC-MS/MS	(24)
Reilly <i>et al.</i> 2014	Atrial fibrillation	150 mg BID	4,600	175	184	2–1,000	91	93	1–809	LC-MS/MS	(24)
Skeppholm <i>et al.</i> 2014	Atrial fibrillation	110 mg BID	17					60	23–168	LC-MS/MS	(25)
Skeppholm <i>et al.</i> 2014	Atrial fibrillation	150 mg BID	73					52	8–188	LC-MS/MS	(25)
Chan <i>et al.</i> 2015	Atrial fibrillation	110–150 mg BID	100		155				<30–722	dTT	(26)
Shimomura <i>et al.</i> 2015	Atrial fibrillation	110 mg BID	259		79					dTT	(27)
Shimomura <i>et al.</i> 2015	Atrial fibrillation	150 mg BID	57		128					dTT	(27)
Freyburger <i>et al.</i> 2011	Hip or knee replacement	150–220 mg OD	40	105						dTT	(28)
Herrmann <i>et al.</i> 2013	Hip or knee replacement	150 mg BID	17	129			68			dTT	(29)
Samama <i>et al.</i> 2013	Hip or knee replacement	150–220 mg OD	65	51		0–324				dTT	(30)
Schellings <i>et al.</i> 2016	Hip or knee replacement	220 mg OD	40		81			12		LC-MS/MS	(31)
Testa <i>et al.</i> 2016	Various	110 mg BID	90	170		30–650	120		10–400	dTT	(32)
Testa <i>et al.</i> 2016	Various	150 mg BID	70	180		30–550	120		10–500	dTT	(32)
Lin <i>et al.</i> 2018	Various	110 mg BID	38								(33)
Lin <i>et al.</i> 2018	Various	150 mg BID	8								(33)

BID, twice daily; dTT, diluted thrombin time; LC-MS/MS, liquid chromatography tandem mass spectrometry.

after myocardial infarction and (IV) prevention of DVT in the setting of surgery.

Warfarin has wide intra- and interindividual variation in its metabolism. The active S enantiomer of warfarin exhibits significant metabolic variation, the variants contributing to increased warfarin sensitivity, include CYP2C9\*2 (c.430C>T) and \*3 (c.1075A>C) and VKORC1 c.-1639G>A variant (38,39). In addition, the amount of vitamin K in the diet, cigarette smoking, alcohol consumption and many medications interact with warfarin effect, mandating regular laboratory monitoring upon warfarin use (40). The International Normalized Ratio (INR), derived from PT and standardized between laboratories using the

International Sensitivity Index (ISI), is used to monitor warfarin effect (41). The INR treatment target is usually 2.0–3.0, with higher treatment target of 2.5–3.5 used in patients with mechanical heart valve replacement, corresponding to higher warfarin dose in these patients (42). It is noteworthy that no DOACs have been approved for use with the mechanical heart valves, and we are not aware of any such ongoing studies.

Quality of warfarin anticoagulation for patients has been measured according to time in therapeutic range (TTR), especially in research settings for over two decades. In the Rosendaal method of calculating TTR, the INR is assumed to change linearly between dates of measurement and total

**Table 3** Rivaroxaban levels in patient sample studies

Study	Indication	Dose	Number of patients	Peak level (ng/mL)			Trough level (ng/mL)			Measurement method	Reference
				Mean	Median	Range	Mean	Median	Range		
Freyburger <i>et al.</i> 2011	Hip or knee replacement	10 mg OD	40	117					Anti-Xa	(28)	
Herrmann <i>et al.</i> 2013	Hip or knee replacement	10 mg OD	15	133			5		Anti-Xa	(29)	
Freyburger <i>et al.</i> 2015	Hip or knee replacement	10 mg OD	51		113		7		LC-MS/MS	(34)	
Samama <i>et al.</i> 2013	Hip or knee replacement	10 mg OD	41	142		0–412			Anti-Xa	(30)	
Schellings <i>et al.</i> 2016	Hip or knee replacement	10 mg OD	40		125		17		LC-MS/MS	(31)	
Arachillage <i>et al.</i> 2016	Thromboembolism	20 mg OD	105	280					Anti-Xa	(35)	
Testa <i>et al.</i> 2016	Various	20 mg OD	37	210		50–450	30	5–140	Anti-Xa	(32)	
Testa <i>et al.</i> 2016	Various	15 mg OD	34	180		60–410	20	5–120	Anti-Xa	(32)	
Suwa <i>et al.</i> 2019	Atrial fibrillation	15 mg OD	90		348	150–610	28	0–100	Anti-Xa	(36)	
Suwa <i>et al.</i> 2019	Atrial fibrillation	10 mg OD	46		270	120–480	26	0–120	Anti-Xa	(36)	

LC-MS/MS, liquid chromatography tandem mass spectrometry; OD, once daily.

**Table 4** Apixaban levels in patient sample studies

Study	Indication	Dose	Number of patients	Peak level (ng/mL)			Trough level (ng/mL)			Measurement method	Reference
				Mean	Median	Range	Mean	Median	Range		
Freyburger <i>et al.</i> 2015	Hip or knee replacement	2.5 mg BID	51		76		45		LC-MS/MS	(34)	
Testa <i>et al.</i> 2016	Various	5 mg BID	73	200		110–440	140	30–400	Anti-Xa	(32)	
Testa <i>et al.</i> 2016	Various	2.5 mg BID	26	160		50–300	100	20–280	Anti-Xa	(32)	
Suwa <i>et al.</i> 2019	Atrial fibrillation	5 mg BID	58		237	100–550	108	30–190	Anti-Xa	(36)	
Suwa <i>et al.</i> 2019	Atrial fibrillation	2.5 mg BID	61		157	60–480	68	10–170	Anti-Xa	(36)	

BID, twice daily; dTT, diluted thrombin time; LC-MS/MS, liquid chromatography tandem mass spectrometry.

number of days in the therapeutic range is then calculated as a percentage (43). TTR can be used to assess the quality of therapy at individual patient level or at treatment center's—typical TTRs in warfarin patients range from 55–60% in USA and central Europe to over 70% in Sweden (44–48). TTR should only be used for long-term warfarin treatment

when the patient is in a clinically stable condition, without interruptions in warfarin treatment. During acute illness or trauma, hospitalization with warfarin interruptions and heparin use, TTR is decreased, but this offers very limited information on warfarin suitability to a given patient. We offer a TTR calculator freely available on the Internet,



including guidance in its rational use. Patients benefit from well-performing centers overall, centers with higher TTR during warfarin fare better with DOAC anticoagulation as well (49). While transitioning from warfarin to DOACs, the challenge is maintaining the high quality and adequate frequency of clinical follow-ups, when laboratory monitoring is no longer necessary (i.e., when on DOACs).

INR self-testing and self-management of warfarin are suitable options for motivated patients; even in the era of DOACs there is a special need. Not surprisingly, TTR values are best in patients participating in the self-management programs (50). When of high quality, self-testing performs well and is reliable, safe and efficient, increases patient safety and satisfaction, and decreases complications and even mortality (51,52). Professional training for patient selection is crucial, as appropriate skills and the ability to commit to the program are needed. We have offered a patient self-monitoring service since 2015. The program includes patient selection and training by the anticoagulation nurse and a laboratory technician, so that the patient acquires competency in both warfarin dosing and point-of-care (POC) INR measurement. The demand to serve new patients is currently higher than our capacity, and some primary healthcare units are being trained for this purpose as well. At the moment, the remuneration of self-management (devices, test strips and lancets) varies according to the different municipalities, which limits the adoption of the model nationwide.

### *Heparins*

Heparins are of animal origin, from porcine and bovine gut mucosa, that is another reason why the synthetic anticoagulants appear important in the anticoagulation armamentarium. The unfractionated heparins (UFH) with chains of 10–20 kDa in molecular weight are administered in cardiac and vascular surgery setting and during plasma exchange. Therein contact activation demands an anticoagulant acting both at the level of thrombin and other coagulation factors. The development and subcutaneous administration of LMWH was a major milestone in the 1970s.

The strengths of heparin include its subcutaneous (sc) administration route, when oral route is not reliable; its anti-inflammatory actions and relatively short half-life, 90 min for UFH and 4–6 hours for LMWH depending on the dosing (53). Dabigatran and edoxaban when used to manage venous thromboembolism, requires use of LMWH first

for a few days, prior to their initiation. LMWH is the drug of choice for cancer patients at vulnerable phases of chemotherapies and surgery, including pathological fractures (54). Also, pediatric and pregnant patients continue to benefit from this safe strategy to manage and prevent thrombosis. For hospitalized medically ill patients, LMWH as a thromboprophylactic therapy has the most solid evidence of balanced safety and efficacy, while DOACs failed in this indication, with the exception of betrixaban. Also, high risk warfarin treated patients having cardiac valvular replacement need LMWH bridging. The limitation of heparin is its immunological side effects, including heparin-induced thrombocytopenia, with even paradoxical thrombosis. The smallest effective unit of heparin is pentasaccharide, fondaparinux, which binds to antithrombin and as a synthetic mode of parenteral FXa inhibition offers an option to some heparin-intolerant patients.

In specific indications, LMWH and fondaparinux can be measured with the chromogenic anti-FXa assay. Like the FXaIs mentioned previously, the assay requires specific calibration. The aim of the monitoring of these drug effects is to acquire high enough dosing in thrombophilic patients and vice versa, in vulnerable organ-function compromised patients to avoid bleeding complications.

Summary of the anticoagulation options with their advantages and disadvantages are given in *Table 1*.

### **Clinical use of oral anticoagulation and laboratory testing in different clinical situations**

#### *Oral anticoagulation in cardiology*

In heart disease, the most common indications for anticoagulation are AF, mechanical heart valve replacement and severe mitral stenosis. A DOAC is the drug of choice in most new patients, except for those with a mechanical heart valve, moderate to severe mitral stenosis or advanced renal failure (55). Individual risk assessment for stroke (CHA<sub>2</sub>DS<sub>2</sub>VASc) and bleeding (HAS-BLED) are guiding the choice of anticoagulation. Yet, there are problems with these scores. At a broad level, some of the scores are semiquantitative, and more attention is needed for a comprehensive understanding of the individual patient's coagulation status. It is important to assess patient history on a prolonged time period, as limiting attention to only past six months has been shown to lead to underestimation of risk in CHA<sub>2</sub>DS<sub>2</sub>VASc score (56). Iron deficiency anemia is often overlooked, while it is a correctable risk

factor for bleeds. Hypertension predisposes to intracerebral hemorrhage, as well as other bleeds, and is commonly present in cardiac patients.

Clinical scoring systems account for patient age, frailty, renal and liver dysfunction to varying degrees, while all significantly affect DOAC response. In acute coronary syndrome, dual antithrombotic therapy seems to be as effective as triple antithrombotic therapy, but is not surprisingly associated with significantly lower major bleeding risk (57). Anticoagulants may also be used in cerebrovascular disorders unrelated to AF (e.g., in cerebral venous thrombosis, basilar artery occlusion, or carotid or vertebral artery dissection). However, evidence on the use of DOACs in these special circumstances is still relatively weak. Critical studies are underway (58), and first line drugs are LMWH and warfarin. Use of DOACs is likely to increase along with new evidence as it is gained.

#### *Oral anticoagulation and renal impairment*

The incidence of chronic renal disease is increasing along with the aging population. For many clinical situations, knowledge on safety and efficacy of medications is lacking. Renal insufficiency exposes the risk of both bleeding and thrombosis complications, and while anticoagulation appears indicated, it is simultaneously challenging. Risk assessment tools with CHA<sub>2</sub>DS<sub>2</sub>VASc and HAS-BLED are not validated in these patients, while renal impairment is a relevant concern in cardiac patients (57). Clinical decisions on anticoagulation should be individualized with the help of laboratory testing. In case of mild and moderate renal insufficiency, with glomerular filtration rate (GFR) less than 30 mL/min, the dose of DOAC must be lowered. Patients on anticoagulation should be followed regularly, and more frequently when renal function declines, as the safety, the choice of management (need of dialysis), the drug and the dose of anticoagulation therapy should be re-evaluated.

Dabigatran is 80% excreted by kidneys, and it is cumulating to extravascular tissues during renal dysfunction. If GFR is <30 mL/min, dabigatran is contraindicated. If GFR is 30–50 mL/min, a lower dose of 110 mg BID must be chosen. However, renal extraction is lower for FXaIs, for apixaban, 27%, rivaroxaban 50% and edoxaban 35%. In renal impairment, apixaban is currently preferred, with the lower dose of 2.5 mg BID recommended in case of creatinine >133 mmol/L, elderly patients (>80 yrs) and small weight (<60 kg) (59). Finally, renal patients are subjected to the most severe complications of drug interactions, which

tend to be increasingly identified (8).

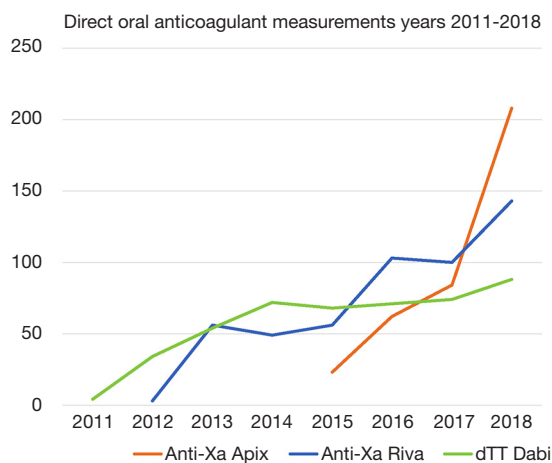
#### *Oral anticoagulation and surgery or invasive procedures and trauma*

The management of chronic anticoagulation therapy in patients undergoing surgical procedures or trauma needs careful planning. Surgery, invasive procedures and trauma all have associated bleeding risks that are increased by the anticoagulant administered for prevention of thromboembolism. At the same time, interrupting anticoagulation transiently increases the risk of thromboembolism at least due to surgery-triggered exposure of vascular collagen and tissue factor. Warfarin therapy may be continued if the bleeding risk is manageable. However, warfarin should be stopped during high bleeding risk procedures and the physicians should carefully consider the need for bridging with LMWH with either full or prophylactic dose. According to the latest findings, bridging anticoagulation may be of no benefit in preventing thromboembolism and may increase the incidence of bleeding in patients with moderate thrombotic risk. In the Bridge study, forgoing heparin bridging anticoagulation in AF patients was non-inferior to perioperative LMWH bridging (60). However, patients included were low risk and bridging is recommended in patients with mechanical heart valve or other high risk for thromboembolism (61). Thus, for patients with high thromboembolic risk, bridging with LMWHs remains a valid strategy. The use of DOACs, during perioperative situations, is increasing in clinical practice, although without evidence.

#### *Acute bleeding complication and oral anticoagulation*

During major bleeds, anticoagulation should be either stopped and/or reversed, depending on the severity and localization of the bleed and the half-life of the anticoagulant. The timing of the last intake of the anticoagulant is relevant information, especially in the case of DOACs. Warfarin may be reversed with vitamin K and PCC, dabigatran by idarucizumab, and FXaIs with andexanet alpha (19–21); however, a clearly limiting factor is that specific antidotes are available in the major hospitals only. PCC can be used if antidote is not available or cost constraints preclude its use. Supportive care includes single dose of iv tranexamic acid and replacement of appropriate blood products according to laboratory analysis. Regardless of the severity of bleeding, other risk factors should be





**Figure 3** The availability and use of DOAC laboratory tests at Helsinki and Uusimaa in 2011–2018. Apixaban is experiencing the fastest growth, although entering the market later than rivaroxaban or dabigatran. Apix, apixaban; Riva, rivaroxaban; Dabi, dabigatran.

treated, i.e., anemia, thrombocytopenia, and hypertension. Possible renal or liver dysfunction must also be assessed, since impairment of hemostasis and drug accumulation potentiates the worsening of hemostasis during acute bleed.

### *Oral anticoagulation and thrombophilia*

Currently for patients with hereditary thrombophilia, DOACs are not usually the primary anticoagulant recommended under these conditions (9–11,59). In the REMEDY trial, small subgroup analysis, dabigatran seemed noninferior to warfarin in thrombophilia patients (protein C or S deficiency, antithrombin deficiency, antiphospholipid antibodies, FV Leiden or prothrombin variant heterozygous mutation) (62). Rivaroxaban was assessed as noninferior to warfarin in phospholipid antibody syndrome (APS) in a phase III trial (63); however, the most severe APS patients did not benefit from rivaroxaban in comparison with warfarin (64). Overall, the evidence for use of DOACs in these rare conditions remains limited, with much of the data still based on case reports (65). For the time being, the EMA is evaluating APS data of DOAC treatments, and warfarin and heparin remain the mainstay.

### *Oral anticoagulation and laboratory testing*

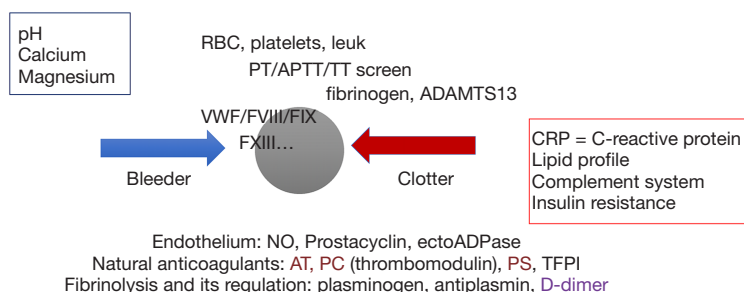
While anticoagulation therapy has changed dramatically, one of the major alterations is also the change in laboratory

practice. Although the number of DOAC users is steadily increasing, the remuneration policies in each country are the main limiting factor for more widespread use. Since 2–3% of the population is now using anticoagulation therapy, the impact on the laboratory is remarkable (66). Clinicians in the Northern countries are increasingly preferring DOACs over warfarin. However, when DOACs were launched a decade ago, one of the main requirements and concerns were how to measure the effect and level of anticoagulation (13). Clinicians were initially hesitant to start such a drug, the effect of which could not be assessed.

Quite quickly, we learned that routine coagulation tests PT and APTT were of little use in case of DOACs (13). There are large variations in sensitivity of different methods and reagents used. Owren type PT/INR, as used in the Nordic countries, is insensitive to DOACs and FV deficiency (impaired liver function), and this is still a matter of education for our clinicians (16). APTT may show an effect of dabigatran, whereas FXaIs affect the APTT less, or do not affect the APTT (15,16,67–69). More specific assays were quickly needed, and HUSLAB laboratory services was the first laboratory in Finland to set up the specific assays for dabigatran, rivaroxaban and apixaban, and offer them 24/7 for clinical use (since May 2017). The number of requested tests is still small, but increasing, the growth being fastest for apixaban, which came to the market later but is rapidly catching up (*Figure 3*). At the same time, number of INR tests has steadily declined annually by 10–15% since 2015. Yet, we also note that other coagulation testing, i.e., PT, APTT, fibrinogen, is increasing. In Finland, laboratory personnel, trained laboratory technicians, perform phlebotomy and take almost all the blood samples. The changes in coagulation test ordering practices widely impact on requirements of out-patient clinic blood sampling design also in the future.

Anticoagulation treatment increases the risk of bleeding complications, especially in the elderly, patients with cancer or with renal and liver dysfunction. To minimize the risk of bleeding, all anticoagulated patients should have regular follow-ups at minimum once, but in case of co-morbidities more frequently, at least 2–4 times annually (8,55).

Laboratory testing during such visits may help to assess the thrombotic burden, i.e., thrombophilia panel, high fibrinogen and FVIII, and elevated D-dimer (70–72) (*Figure 4*). Thrombotic and bleeding tendencies and complications, adverse effects, adherence, blood pressure, renal and liver function, comorbidities and drug interactions, possible anemia and thrombocytopenia, as well



**Figure 4** Grey zone of coagulation activity. The modern management of coagulation disorders, the subcutaneous non-factor therapies for haemophilia (emicizumab, fitusiran and concizumab) and DOACs, is initially assigned not to be monitored at all. Measurement of the status of the coagulation system, however, is important during trauma, bleeding episodes, breakthrough bleeds or thrombosis while on treatment and emergency surgery.

as the appropriateness (dose and product) of the current anticoagulation should be repeatedly addressed during regular follow-ups. This assessment should be repeated at each patient clinical visit.

Specific, calibrated anticoagulant measurement tests are needed in special clinical situations to capture the extent of anticoagulation, in terms of timing of the drug dosing and blood sampling. The effective levels vary widely, with overlapping peaks and troughs at a steady state. Under special complications, it is advisable to assess whether the level is on- or off-therapy range. The level of anticoagulation should be optimized where there is potential for over-anticoagulation: acute bleeding, preoperatively overdosing, renal failure, low BMI, acute medical illness, drug interactions and in the elderly patients, and in cases of under-anticoagulation: treatment failure, obesity, malabsorption and drug interactions (73,74).

In case of trauma, acute procedure and need of antidote, the test is requested to save time and help decision-making at critical moments (*Figure 4*). For many laboratories, it is difficult to keep up 24/7 services for few requests and the distances to the nearest laboratory will increase compared with standard INR availability. While point-of-care INR and activated clotting time (ACT) have some sensitivity to rivaroxaban, the authors opine that POC testing of DOACs is unlikely to offer solutions for the near future (75-78), although POC tests specifically targeted to DOACs are emerging (79,80). It is also noteworthy, that national and local conditions will dictate the access to (e.g., special) assays to measure DOAC effects, depending on the part of the Hospital District the patients reside in.

Novel global approaches for anticoagulation management

feasibly include viscoelastic testing and thrombin generation. Viscoelastic tests, the TEG<sup>®</sup> and ROTEM<sup>®</sup> are well suited for acute assessment of fibrin deficiency and massive bleeding complications in the emergency rooms or operating theaters. For both warfarin and DOACs, viscoelastic assays have shown conflicting data on detecting anticoagulation, and they are not recommended for monitoring (81,82). Thrombin generation assays have the potential to detect any anticoagulant, but their use is currently still limited to the research laboratory (83). Novel standardized methods, including the Stago ST Genesia<sup>®</sup> will probably become clinical routine in the near future (84).

## Conclusions

In the future of anticoagulation therapy, individual decisions and practices will be even more common. Basic laboratory testing, including blood cell counts with hematocrit, hemoglobin, leukocyte and platelet count, creatinine and estimated GFR and liver enzymes (ALT) as well as function tests (prealbumin, albumin, PT, lipids) and basic metabolic assays (pH, electrolytes and cations) are crucial in the risk assessment, but will also increasingly become a part of the regular follow-up of anticoagulated patients. The number of INR tests continues to decrease, as the usage of warfarin declines. DOACs will mainly replace warfarin, imposing additional requirements for specific testing under acute clinical situations, such as major bleeds, thrombosis and emergency surgery or trauma. Pediatric and pregnant populations as well as cancer patients will require the gathering of more evidence as to how to most optimally secure their anticoagulation management.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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