



A retrospective study of indications and consequences of monitoring direct oral anticoagulant plasma concentrations on patient care in a university hospital: The Retro-AOD study

Thibaud Cavaillez^a, Laurent Weinmann^b, Christine Mouton^b, Céline Delassasseigne^b,
Musa Sesay^a, Matthieu Biais^{a,c}, Chloé James^{b,c}, Stéphanie Roulet^{a,c,*}

^a CHU Bordeaux, Service d'Anesthésie-Réanimation Tripode, F-33000 Bordeaux, France

^b CHU Bordeaux, Laboratoire d'hématologie, F-33000 Bordeaux, France

^c Univ. Bordeaux, INSERM, Biologie des maladies cardiovasculaire, U1034, F-33600 Pessac, France

ARTICLE INFO

Keywords:

Direct oral anticoagulant
Pharmacology
Anti-Xa activity
Anti-IIa activity

ABSTRACT

Introduction: The use of direct oral anticoagulants (DOAC) is increasing. Specific concentrations are available and have been proven to be reliable and reproducible in optimising patient care. This retrospective, monocentric study aimed to describe the indications and consequences of monitoring DOAC plasma levels on patient care.

Materials and methods: We collected data of patients hospitalised at the Bordeaux University Hospital between January 2017 and December 2018. These included demographics, indications, type, dose of DOAC, standard coagulation tests, creatinine clearance and DOAC plasma concentration using specifically calibrated rivaroxaban and apixaban anti-Xa and dabigatran anti-IIa assays. The date of last DOAC intake, the time between intake and plasma level measurement were also collected and analysed.

Results: A total of 2197 DOAC assays in 1488 patients were obtained in various clinical situations: urgent or elective procedures, context of acute renal failure, suspicion or occurrence of ischemic strokes, intra-cranial and other bleeding sites. Interpretation of these assays led physicians to maintain, postpone or cancel invasive and high haemorrhagic risk procedures in 757, 261 and 56 cases respectively. The remaining 1123 assays were associated with no significant modification of patient care. DOAC plasma concentration was ≤ 30 ng ml⁻¹ (sensitivity 85.4%, specificity 73.6%, positive predictive value 71.1%, negative predictive value 86.7%, AUC 0.81) after a last intake of at least 2 days.

Conclusions: Our study is, to date, the largest report of real-life measurement of specific DOAC plasma level at a single institution. Patient care was not modified in more than half of the assays.

1. Introduction

Since their introduction in 2008, indications for direct oral anticoagulants (DOACs) are increasing world-wide [1–3]. Three DOACs are currently available in France: two direct factor Xa inhibitors (rivaroxaban and apixaban) and one direct factor IIa inhibitor (dabigatran). They are considered to be equal or more effective than vitamin K antagonists (VKA) in those indications, with a reduction of mortality and risk of major or intra-cranial bleedings [1,3]. DOAC treatments have fixed doses, fewer interactions, without the need to check the anticoagulant plasma level in daily clinical practice. The lack of laboratory testing requirement is attributed to a more predictable bioavailability.

However, this low variability is subject to debate. Gulilat et al. measured DOAC concentration in 243 patients and found a variation of over 50-fold in plasma concentration for both apixaban et rivaroxaban, and over 16% and 40% of patients outside the predicted concentration, respectively [4]. Hence, in some clinical situations, routine measurement of DOAC concentration could be useful [5,6].

The French proposals, from the Groupe d'Intérêt en Hémostase Périopératoire (GIHP) did not recommend the routine use of these tests in patients treated with DOAC undergoing elective surgery but only in serious and life-threatening bleedings and emergency surgeries [7]. Other situations (i.e. intoxication, acute renal failure, acute episode of thrombosis, etc.) have also been identified in which anticoagulant assay

* Corresponding author at: Service d'Anesthésie-Réanimation Tripode, CHU Bordeaux, Place Amélie Raba-Léon, 33000 Bordeaux, France.

E-mail address: stephanie.roulet@chu-bordeaux.fr (S. Roulet).

<https://doi.org/10.1016/j.thromres.2021.08.010>

Received 9 May 2021; Received in revised form 31 July 2021; Accepted 11 August 2021

Available online 18 August 2021

0049-3848/© 2021 Elsevier Ltd. All rights reserved.

can be helpful in patient care [8,9]. However, some of these indications are controversial [10].

Specific measurements of anti-Xa and anti-IIa activity have proven to provide reliable and reproducible results across various concentrations tested. The most commonly used tests are diluted thrombin time for dabigatran, and specific anti-Xa levels for apixaban and rivaroxaban [11], with studies raising doubts on low accuracy for low drug-concentration [12,13]. The coagulation tests routinely used in clinical practice such as Quick time (QT), prothrombin ratio (PT), INR and activated partial thromboplastin time (aPTT) are poorly correlated with specific anti-Xa and anti-IIa activity [11,14,15].

Whereas possible indications for DOAC plasma level measurements have been described [16,17], little is known about the actual use of laboratory measurement of specific anti-Xa and anti-IIa in daily clinical routine and the impact of the results on clinical management of patients.

We conducted a retrospective, observational, monocentric study of all plasma levels of rivaroxaban and apixaban anti-Xa and dabigatran anti-IIa activity performed at the Bordeaux University Hospital, between the 1st of January 2017 and the 31st of December 2018: the Rétro-AOD study. The primary aim was to describe the indications of laboratory testing of the three DOAC and their adequacy with the GIHP proposals. The secondary objectives were to describe the results of these DOAC plasma concentrations in elective and urgent clinical cases, and to compare the results with standard coagulation tests.

2. Methods

2.1. Inclusion and exclusion criteria

All patients hospitalised at the Bordeaux University Hospital between the 1st of January 2017 and the 31st of December 2018 and who had at least one DOAC assay were eligible. Exclusion criteria were patients <18 years-old during the study period, non-hospitalised patients and refusal to participate. A standard information letter was sent to patients at their last known addresses. The study was approved by the Comité d'éthique pour la recherche en Anesthésie-Réanimation (French Committee for Research in Anaesthesia and Intensive Care: IRB 00010254-2019-104, 06-24-2019, Pr. JE. BAZIN) and followed the rules for computer data management of the Commission National Informatique et Liberté (National Commission on Informatics and Liberty).

2.2. Data collection

Demographic data were collected from computerised medical files, and the following data when available: type of DOACs, aPTT ratio, PT, weight, creatinine clearance assessed by the CKD-EPI formula and the Cockcroft and Gault formula, indication for treatment, indication for DOAC plasma measurement, date of last drug intake, time between intake and laboratory measurement, and follow-up assays. Comedication of interest were recorded (antiplatelet drug, antiarrhythmic drugs or proton-pump inhibitor [18]) as well as the use of idarucizumab, prothrombin complex concentrate (PCC, inactivated or activated), the clinical consequence of DOAC plasma concentration on patient management (either invasive procedure was carried out, postponed, cancelled or no incidence on the management).

Several concentration thresholds were used to interpret the results: <30 ng ml⁻¹ (the minimal result given by the assays and threshold proposed for high-bleeding risk surgery by French and international guidelines), 30-50 ng ml⁻¹ (the range under which haemorrhage is not supposed to be worsened by the drug effect), 51-100 ng ml⁻¹ (the range used for allowing use of intravenous thrombolysis for stroke in DOACs-treated patients is <100 ng ml⁻¹), 101-200 ng ml⁻¹ (the range associated with consistent worsening of perioperative haemorrhage), 201-400 ng ml⁻¹ and > 400 ng ml⁻¹ (the threshold of overdosing in drug medication) [18].

2.3. Assays

Dabigatran was measured using the HEMOSIL® DTI ASSAY (Werfen, Le Pré-Saint-Gervais, France) ACL TOP 700 (Werfen, Le Pré-Saint-Gervais, France) calibrated with HEMOSIL® Dabigatran Calibrator and HEMOSIL® Dabigatran Control provided by the same company. From December 2017 to March 2018, apixaban and rivaroxaban were measured using Coamatic® Heparin kit (Werfen). Since April 2018, Apixaban and rivaroxaban were measured using the HEMOSIL® Liquid Anti-Xa calibrated by the HEMOSIL® Apixaban Calibrator and HEMOSIL® Apixaban Control; and the HEMOSIL® Rivaroxaban Calibrator and HEMOSIL® Rivaroxaban Control, respectively. Routine tests (PT, QT, INR, aPTT) were performed using an ACL TOP 700 device (Werfen) using routine reagents from Werfen (Recombiplastin, aPTT SP).

2.4. Statistical analysis

Quantitative data are expressed as mean ± SD or median (interquartile range (IQR) 25 to 75) and qualitative data as number and percentage. Normality of distribution for continuous variables was assessed with a Shapiro-Wilk test. Quantitative data were compared with a Student-t-test and or a Mann-Whitney test as appropriate. Qualitative data were compared with a X² test or a Fisher exact test as appropriate. Spearman correlation coefficients were searched between DOAC concentrations and usual coagulations tests. Performance of coagulation tests to predict a DOAC concentration <30 ng ml⁻¹ and determination of the date of last intake to predict a DOAC concentration <30 ng ml⁻¹ were assessed with a ROC curve analysis. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed with the XLSTAT software (Addinsoft, Paris, France, 2020).

3. Results

3.1. Patients' characteristics and DOAC plasma assays

Two thousand three hundred and eight DOAC plasma assays were performed between the 1st of January 2017 and the 31st of December 2018. Fig. 1 represents the flow chart of the study. Eighty-three patients were not hospitalised at the time of at least one of their blood tests (103 assays were excluded), 3 patients were minors (3 assays excluded) and 3 patients refused to participate in the study (5 assays excluded), leaving a total of 2197 assays in 1488 patients for analysis.

The DOAC were distributed as follows: 1068 assays in 716 patients for apixaban, 880 assays in 622 patients for rivaroxaban and 249 assays in 173 patients for dabigatran. The number of assays varied between 1 and 13 in each patient, with a mean of 1.48 assays per patient; 1070 patient had only one assay.

Table 1 shows patients' data, characteristics of DOAC treatment and other medications of interest. The date for the last intake of the drug was available in 1000 patients.

Creatinine clearance according to CKD-EPI formula and Cockcroft and Gault formula was available in 1336 patients: 67 (IQR 46 to 84) and 60 (IQR 42 to 87) ml min⁻¹, respectively (*P* = 0.17). In acute situations, where acute renal failure is most likely to occur, measurement of creatinine was available in 217 out of 236 cases of ischemic stroke (91.9%), 530 out of 770 cases of urgent procedure (68.8%), 118 out of 146 cases of extra-cranial bleeding (80.8%), 135 out of 151 cases of intra-cranial bleeding (89.4%) and 69 out of 76 cases of overdosing (90.8%).

3.2. Indications for DOAC treatment and laboratory measurement

Indications for treatment were grouped as: non-embolic atrial fibrillation, embolic atrial fibrillation, VTE treatment, thromboprophylaxis, other, unknown and error when patients had testing for anti-Xa or anti-IIa specific activity for a treatment they did not received. The

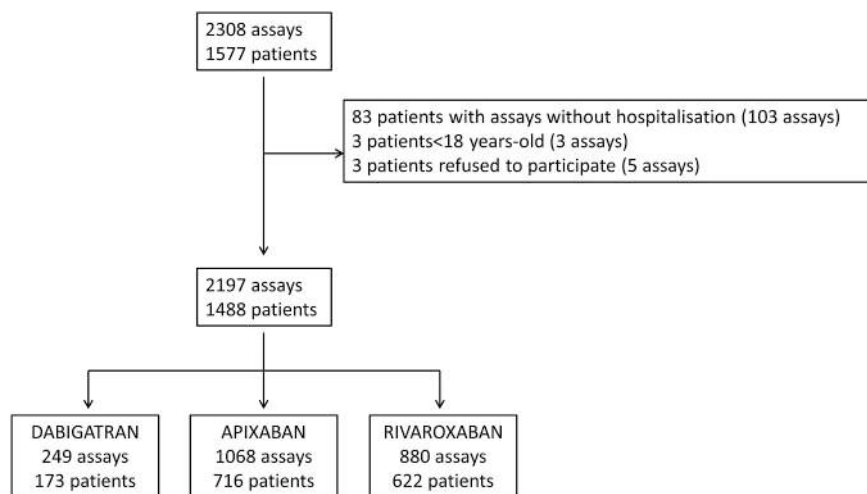


Fig. 1. Flow chart of the study.

Table 1

Description of the study population, demographic, drug tested and other drug of interest, indication for DOAC treatment and treatment regimen^a.

Population (number)	1488
Age (year)	75.3 ± 13.0
Weight (kg)	75.7 ± 19.2
Assays (number)	2197
Number of assays per DOAC	
Dabigatran	249 (11.3)
Rivaroxaban	880 (40.1)
Apixaban	1068 (48.6)
Other medication	
Antiplatelet drug	369 (16.8)
Antiarrhythmic drug	767 (34.9)
Proton pump inhibitor	765 (34.8)
Indication for DOAC treatment	
Non embolic atrial fibrillation	1342 (61.1)
Embolic atrial fibrillation	104 (18.3)
VTE	348 (15.8)
Preventive	12 (0.5)
Other	67 (3.0)
Unknown	76 (3.5)
None or error	14 (0.6)
Treatment regimen (missing data = 159)	
Apixaban (n = 644)	
2.5 mg od	10 (1.6)
2.5 mg bid	260 (40.4)
5 mg od	6 (0.9)
5 mg bid	362 (56.2)
10 mg bid	6 (0.9)
Dabigatran (n = 143)	
110 mg od	1 (0.7)
110 mg bid	83 (60.1)
150 mg od	1 (0.7)
150 mg bid	55 (38.5)
Rivaroxaban (n = 542)	
10 mg od	27 (5.0)
10 mg bid	1 (0.2)
15 mg od	156 (28.8)
15 mg bid	26 (4.8)
20 mg od	331 (61)
30 mg od	1 (0.2)

bid: twice a day; DOAC, direct oral anticoagulant; od: once a day; VTE, venous thromboembolism.

^a Values are expressed as mean ± SD or number (percentage).

respective numbers of assays per group of treatment indications were: 1342, 401, 348, 12, 67, 76 and 14.

Clinical situations requiring DOAC assays were: 770 emergency procedures (31.9%), 367 elective procedures (16.7%), 282 in a context of acute or acute-on-chronic renal failure (12.8%), 236 ischemic strokes

or suspicion of such (10.7%), 151 intra-cranial bleedings (6.9%), 146 bleedings other than intra-cranial (6.6%), 76 overdoses (3.5%), 26 self-induced intoxications (1.2%), 2 incident of venous thrombosis (0.1%), 2 for doubt on prescription of the drug (0.1%) and 446 for other reasons (20.3%). This last category regrouped mostly patients hospitalised or consulting in medical ward with chronic pathology who did not required specific intervention.

3.3. Results of DOAC assays

Fig. 2 represents the results (in terms of frequency) of each DOAC assays in the six most frequent situations where a DOAC assay was prescribed. Among the 150 first assays for each individual cases of proven ischemic stroke, 36 (24%) were <30 ng ml⁻¹ and 16 (11%) were between 30 and 50 ng ml⁻¹, leaving 98 (65%) >50 ng ml⁻¹. Twenty-eight patients (19%) underwent mechanical thrombectomy and 13 (9%) had an intra-venous thrombolysis. The remaining patients had no specific treatment because of either efficient anticoagulation or too long delay between the onset of stroke and hospitalisation or unknown reason.

In the cases of elective invasive procedures, 68% of the assays were <30 ng ml⁻¹ (60% for apixaban, 74% for dabigatran and 75% for rivaroxaban).

3.4. Coagulation assays

Values for concomitant determination of aPTT ratio and PT were available in 1585 and 1546 cases, respectively. Fig. 3 shows the scatter plots of each DOAC concentration with aPTT ratio and PT. Correlation between standard coagulation tests and specific DOAC measurement were rather poor and below statistical significance.

Table 2 represents the performance of standard coagulation tests aPTT ratio and PT to predict a DOAC concentration ≤30 ng ml⁻¹, the threshold mostly accepted to safely perform an elective invasive procedure. For dabigatran, the most predictive coagulation test was aPTT ratio with an area under the ROC (AUROC) of about 0.90. For rivaroxaban, it was PT, with an AUROC of 0.82. For apixaban none of the standard coagulation tests emerged.

3.5. Impact of the DOAC assay on patient care

Among the 2197 DOAC assays performed, 1074 (49%) led to clinical decisions: 757 dosages allowed the physician to perform the invasive or with high haemorrhagic risk procedure as planned, 261 led to postpone such an intervention (most of the time with repeated assays and procedure performed after a suitable drug-concentration was achieved) and

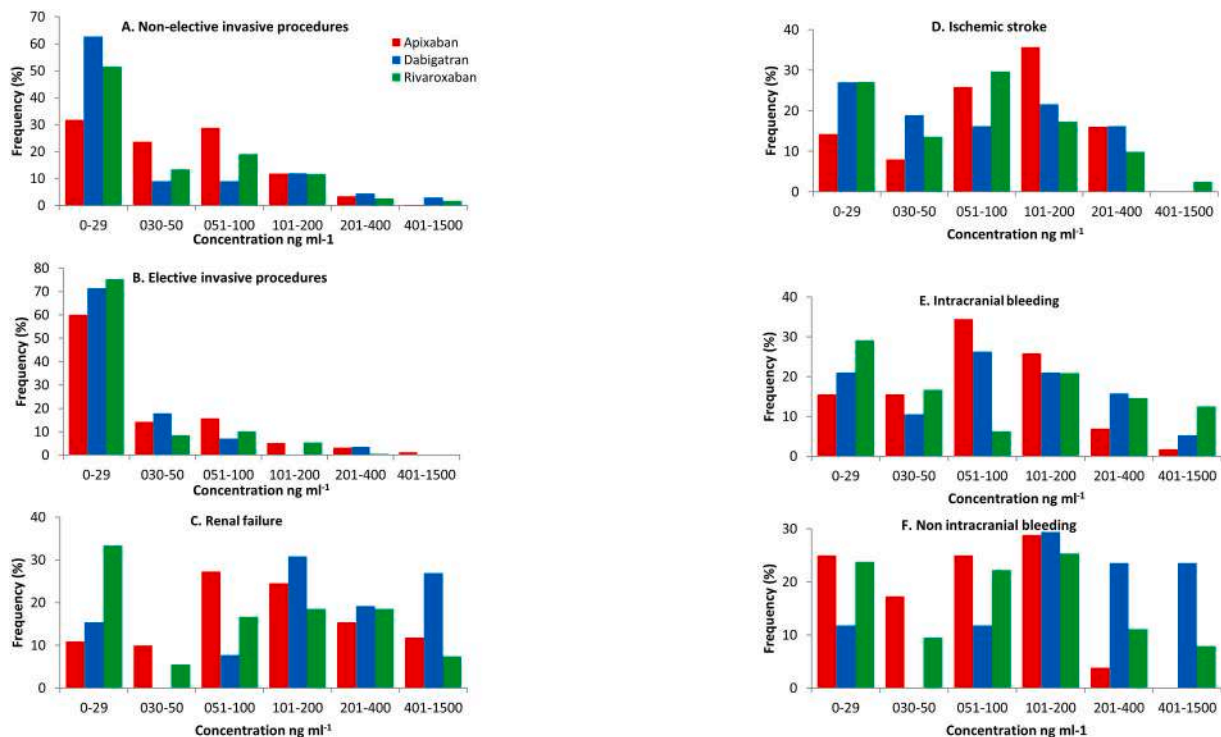


Fig. 2. Results of dosage by assays for each DOAC in the six most frequent situations where a DOAC concentration measurement was prescribed. A. non-elective invasive procedures; B. elective invasive procedures; C. renal failure; D. ischemic stroke; E. intra-cranial bleeding; F. non intra-cranial bleeding. Results for apixaban are in red, for dabigatran in blue and for rivaroxaban in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

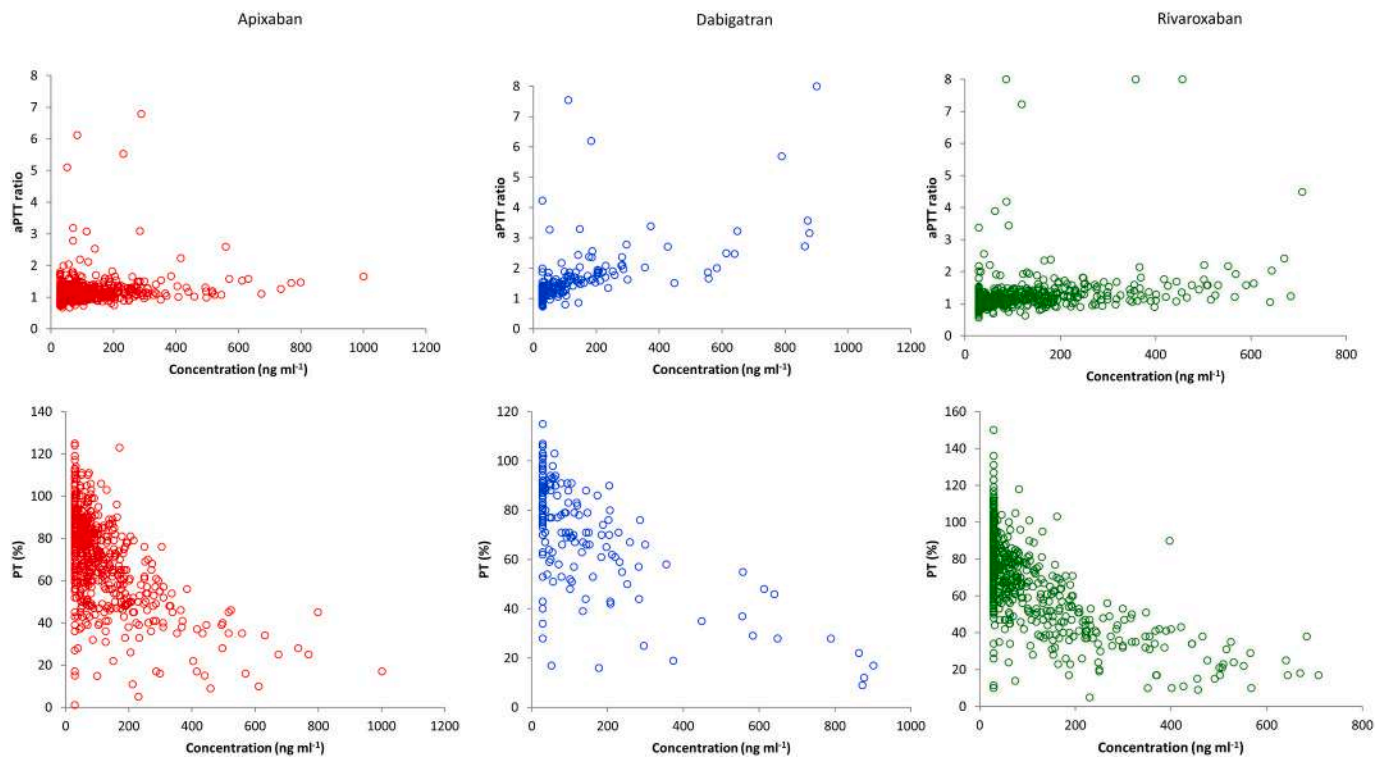


Fig. 3. Scatter plots of each DOAC concentration with aPTT ratio and PT for apixaban (red), dabigatran (blue) and rivaroxaban (green). Concentrations below 30 ng ml⁻¹ are represented as 29 ng ml⁻¹. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) of aPTT and PT tests to predict a DOAC concentration ≤ 30 ng ml⁻¹.

DOAC		aPTT ratio	PT (%)
Dabigatran	Threshold	≤ 1.31	≥ 73
	Sensitivity	84.4 (95% CI 74.5 to 91.0)	85.9 (95% CI 75.1 to 92.6)
	Specificity	79.6 (95% CI 71.2 to 81.6)	63.1 (95% CI 53.4 to 71.8)
	PPV	73.9	59.1
	NPV	88.2	87.8
	AUC	0.88 (95% CI 0.83 to 0.93), $P < 0.0001$	0.78 (95% CI 0.70 to 0.85), $P < 0.0001$
	Threshold	≤ 1.12	≥ 74
Apixaban	Sensitivity	79.7 (95% CI 73.9 to 84.5)	79.6 (95% CI 73.5 to 84.6)
	Specificity	46.5 (95% CI 42.4 to 50.7)	57.6 (95% CI 53.1 to 61.9)
	PPV	37.7	43.8
	NPV	85.0	87.1
	AUC	0.66 (95% CI 0.62 to 0.71), $P < 0.0001$	0.73 (95% CI 0.69 to 0.77), $P < 0.0001$
	Threshold	≤ 1.10	≥ 72
	Rivaroxaban	Sensitivity	70.1 (95% CI 64.6 to 75.0)
Specificity		64.2 (95% CI 59.5 to 68.7)	69.7 (95% CI 64.6 to 74.3)
PPV		58.4	66.8
NPV		75.0	82.5
AUC		0.73 (95% CI 0.69 to 0.76), $P < 0.0001$	0.82 (95% CI 0.79 to 0.85), $P < 0.0001$

aPTT, activated partial thromboplastin time; PT, prothrombin ratio.

56 to cancel it. The 1123 others were not associated with a significant change in patient care.

We identified 367 cases of DOAC assays performed in the context of elective procedure. Two of these assays led to cancellation of the procedure (a patient was supposed to undergo electrical cardioversion for atrial fibrillation, the discovery of a ventricular thrombus led to two laboratory assessment of dabigatran concentration which were 232 and 86 ng ml⁻¹ and finally the procedure was cancelled). In 31 cases, the procedures were not carried out for reason other than the DOAC assay. In 47 cases, the procedure was postponed, sometimes after several assays were done (up to 5 tests that led to the postponement of the surgery before it was finally done). In the 287 other cases, the procedure was carried out, after one or several days of delay for drug testing or immediately as initially planned. Cardiac surgery and neurosurgery represented respectively 18.3% and 10.4% of the assays performed in the context of elective procedure.

3.6. Reversion

Some assays led to anticoagulation reversion, mainly for bleeding (69 cases), need for emergency surgery (24 cases), and overdosing (5 cases, all of them associated with a bleeding and/or a need for urgent surgery). Reversion drugs used were inactivated PCC in 73 cases (50 (IQR 45 to 51) IU kg⁻¹); activated PCC in 11 cases (50 (IQR 50 to 54) IU kg⁻¹) and specific reversal of dabigatran by idarucizumab in 11 cases (5 (IQR 5 to 5) g).

Four patients treated with dabigatran had renal replacement therapy (RRT) without any of them for the sole reason of lowering the concentration of dabigatran; no patient received oral activated carbon for dabigatran intoxication.

3.7. Relation between last-drug intake and DOAC concentration

Timing between last drug intake and concentration measured on admission to the hospital was available in 727 cases of elective or non-

elective invasive procedure, ischemic stroke, or another medical context. Acute renal failure and intoxications were excluded, as well as assays performed while DOAC was replaced by heparin (unfractionated or low weight molecular heparin), because of the effective interactions on anti-Xa results. Fig. 4 represents the DOAC concentration according to the day of last intake. Fig. 5 represents the ROC curve assessing the relationship between the number of days after the last intake and the probability of the DOAC concentration to be ≤ 30 ng ml⁻¹. A last intake of 2 days or more ensures a DOAC concentration ≤ 30 ng ml⁻¹ with a sensitivity of 85.4% (95% CI 81.2 to 88.8), a specificity of 73.6% (95% CI 69.3 to 77.5), a positive predictive value of 71.1% and a negative predictive value of 86.7% (AUC 0.81 (95% CI 0.78 to 0.84), $P < 0.0001$).

4. Discussion

For over two years, more than 2000 DOAC assays with specific anti-Xa or anti-IIa activity were performed in almost 1500 patients in a real-life setting. Analysed by the spectrum of the GIHP proposals, more than half of these assays were unnecessary, as they led to no modification in patient care. Moreover, creatinine clearance was available only in 77.5% of the cases even though it is strongly recommended.

One of the main advantages of DOAC over VKA is that they do not require monitoring of their efficacy by biological tests in routine, daily practice. However, variability in real-life is superior to what has been found on healthy volunteers in whom initial pharmacokinetic studies were carried out and in the clinical trial that allowed their prescription approval [4]. This real-life variability is expressed in the 238 (10.8%) cases in which the assays were performed in a context of suspicion or proven incident of thrombosis.

As previously identified in the literature, we found a poor correlation between DOAC concentration and standard coagulation tests, highlighting the necessity of specific assay to explore the pharmacological effect of those drugs [9].

Previous studies have aimed at analysing the indications of DOAC-concentration measurement in clinical practice, and the outcomes for patient care [19–21]. The first one included 113 patients and 169 assays over 2 years. The main reasons for DOAC testing were bleedings (32%), emergent surgeries or invasive procedures (25%, with 36 measures that guided clinical decision to postpone or carry out the intervention), search for biological efficacy in stable state (22%) and elective surgery (5.5%) [19]. Wright and al. studied 32 patients and 37 assays over a 30-months period; 62% did not lead to a change in patient care, 14% allowed a procedure to be carried out, and 11% lead to a postponement [20]. The last study comprised 48 assays among 28 patients over a 3-years period [21]. Three patients had one or several assays before an invasive procedure: one had the procedure done immediately; one was postponed until dabigatran level was low enough and one was finally cancelled entirely. Most of the other assays were done to check anticoagulation level on patient with extreme bodyweight or comedication that lead the physician to have doubt on the treatment efficacy.

In our study, several clinical situations that led the attending physician to prescribe the measurement of DOAC anticoagulant effect were identified. Firstly, to find out whether the medication is active during an emergency (recurrent thrombosis or ischemic stroke on a patient treated for VTE or AF, respectively, bleeding, or the need for surgery or a potentially haemorrhagic invasive procedure). These situations highlight importance of having at disposal a quick biological result which will enable the clinician in crucial decisions to carry out, postpone or cancel an urgent procedure. Drug reversion is also problematic in these cases, with pending questions about thresholds for the use of the different drugs in specific situations and the follow-up of the reversion [6,8]. In the case of elective surgery, there was a controversy on the best strategy to adopt: based on pharmacokinetic or drug measurement before surgery [22]. French proposals suggest that the second method should be preferred in the vast majority of cases [23] but other studies show that this strategy does not always yield the expected results

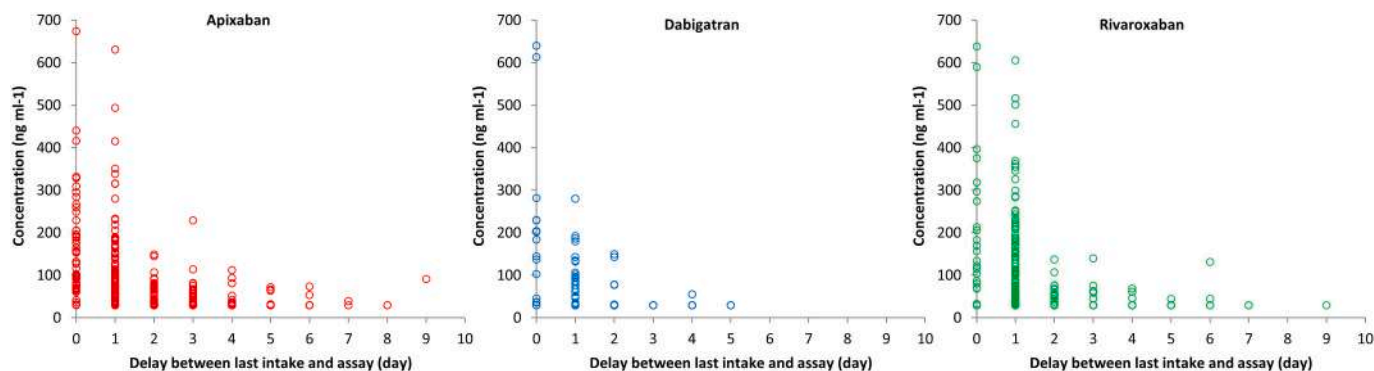
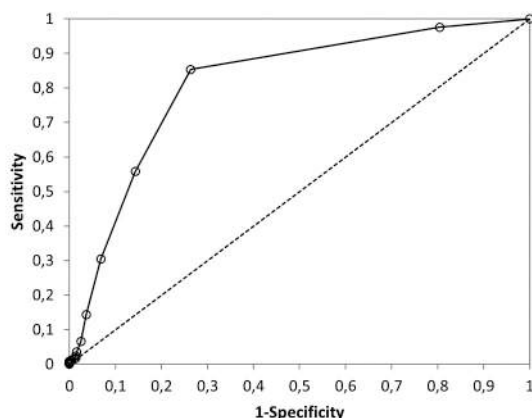


Fig. 4. Results of DOAC concentration according to the day of last intake (concentrations below 30 ng ml⁻¹ are represented as 29 ng ml⁻¹).



Last DOAC intake	Sensitivity	Specificity	PPV	NPV	AUC
≥ 1 day	97.6 (95.2-98.9)	19.5 (16.1-23.5)	48.0	91.5	0.81 (0.78-0.84), P<0.0001
≥ 2 days	85.4 (81.2-88.8)	73.6 (69.3-77.5)	71.1	86.7	
≥ 3 days	55.8 (50.5-61.0)	85.7 (82.1-88.7)	74.8	71.8	

Fig. 5. ROC curve analysis of assessing the relationship between the number of days after the last intake and the probability of the DOAC concentration to be ≤30 ng ml⁻¹.

[18,24,25]. The PAUSE study analysed a strategy of one to four days of DOAC withdrawal before surgery, depending on the post-operative bleeding risk, the DOAC considered and the renal function of the patient [25]. It resulted in less than 2% bleeding complications and less than 1% thrombotic complications despite concentration >50 ng ml⁻¹ in 6.2% of patients (1.2% for patients with a withdrawal of at least 2 days for high-risk surgeries). Unfortunately, the correlation between a DOAC concentration >50 ng ml⁻¹ at the time of surgery and bleeding complication was not reported. Another study by Douketis et al. found that in patients who discontinued dabigatran according to an equivalent protocol, 66.3% of patients had dabigatran level considered normal (84.1% for high bleeding-risk patients), and resulted in 0.6% of major bleedings, 5% of minor bleedings and 0.6% of ischemic events. Among the 10 patients with a bleeding complication, only 2 had a dabigatran level >50 ng ml⁻¹ (thigh ecchymosis after cardiac catheter and epistaxis after endoscopy) [24]. Finally, the CORIDA study analysed the immediate pre-procedural DOAC concentration of 422 patients according to the discontinuation period of their medication [18]. After a 49 to 72 h drug discontinuation, concentration was still >30 ng ml⁻¹ in 5% of the patients.

In our study, 367 DOAC assays were performed in the context of elective surgery or procedure. In these situations, DOAC testing could be needed if the drug discontinuation was not done accordingly to the guidelines, in case of subsisting doubt patient adherence to the prescription or in specific cases, such as extreme bodyweight, comedication that affect the clearance of the drug, or in renal-impaired patients, as identified by the CORIDA study [18].

The relatively high age of the patients in our cohort may be one of the explanatory factors of the observed variability, as well as the 1399 cases (63.7% overall) in which the DOAC-level measurement was done in an acute setting (laboratory testing before an emergency procedure, in case of acute bleeding, stroke or thrombosis or modification of pharmacokinetic parameters because of renal failure). With regard to this concern, variability and difficulty to predict peak and trough levels of the drugs have already been demonstrated [26].

Even though it goes against one of the major advantages of DOAC (i. e., no need for routine testing of drug efficacy), the individual variability observed in some patients (aged, renal impaired or with several treatments) leads, in some cases, to follow-up measurements (up to 13) of the anticoagulant effect among patients. However, the lack of data on the

targeted concentration in the most common indications impairs the development of this strategy [8].

Our study has several limitations. Firstly, it is a retrospective study, raising the concern for bias about the collection and analyse of data, as well as the study of the implication the result had on the patient's management. Data were extracted from the medical file of the patients who had at least one DOAC assay. It was sometimes difficult to trace back the thought process that led the physician to prescribe such an assay. Secondly, it is a monocentric study. Thirdly, the thresholds chosen in our study are widely accepted, but there is still a lack of clear data regarding correlation between DOAC-level and efficacy or complication risk [9,18,27].

5. Conclusion

Our study is the largest so far focusing on the clinical implications that DOAC-specific measurement had in everyday practice on the indication, patient management strategy, and follow-up. Many prescriptions were not in accordance with guidelines or did not lead to any modification in patient care.

More studies focusing on the outcomes of such laboratory testing in some specific clinical settings should be considered to improve knowledge on DOAC in real-life, and to focus on the search for concentration thresholds for decision making regarding patient's management, the need for anticoagulation reversion based on DOAC-specific measurement, the interest of an heparin-bridging in some situations, because of the interference it has on the results of the assay [28].

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements relating to this article

The authors gratefully thank Mrs. H el ene Lachat and Val erie Gauthier, medical secretaries, for their valuable help to inform the patients.

Declaration of competing interest

St ephane Roulet reports consulting fees from Bayer HealthCare. There are no other relationships or activities that could appear to have influenced the submitted work.

References

- [1] for the GARFIELD-AF Investigators, F. Cools, B. Wollaert, G. Vervoort, S. Verstraete, J. Voet, K. Hermans, A. Heyse, A. De Wolf, G. Hollanders, T. Boussy, W. Ann e, J. Vercammen, D. Faes, M. Beutels, G. Mairesse, P. Purnode, I. Blankoff, P. Vandergoten, L. Capi au, J. Allu, J.-P. Bassand, G. Kayani, Treatment patterns in anticoagulant therapy in patients with newly diagnosed atrial fibrillation in Belgium: results from the GARFIELD-AF registry, *Acta Cardiol.* 74 (2019) 309–318, <https://doi.org/10.1080/00015385.2018.1494089>.
- [2] B.A. Steinberg, H. Gao, P. Shrader, K. Pieper, L. Thomas, A.J. Camm, M. D. Ezekowitz, G.C. Fonarow, B.J. Gersh, S. Goldhaber, S. Haas, W. Hacke, P. R. Kowey, J. Ansell, K.W. Mahaffey, G. Naccarelli, J.A. Reiffel, A. Turpie, F. Verheugt, J.P. Piccini, A. Kakkar, E.D. Peterson, K.A.A. Fox, International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries, *Am. Heart J.* 194 (2017) 132–140, <https://doi.org/10.1016/j.ahj.2017.08.011>.
- [3] S.Y. Loo, S. Dell'Aniello, L. Huiart, C. Renoux, Trends in the prescription of novel oral anticoagulants in UK primary care: novel oral anticoagulant prescription trends, *Br. J. Clin. Pharmacol.* 83 (2017) 2096–2106, <https://doi.org/10.1111/bcp.13299>.
- [4] M. Gulilat, A. Tang, S.E. Gryn, P. Leong-Sit, A.C. Skanes, J.E. Alfonsi, G.K. Dresser, S.L. Henderson, R.V. Rose, D.J. Lizotte, W.A. Teft, U.I. Schwarz, R.G. Tirona, R. B. Kim, Interpatient variation in rivaroxaban and apixaban plasma concentrations in routine care, *Can. J. Cardiol.* 33 (2017) 1036–1043, <https://doi.org/10.1016/j.cjca.2017.04.008>.
- [5] I. Hegemann, C. Ganter, C.C. Widmer, M. Becker, D. M uller, D.R. Spahn, Ongoing redistribution of dabigatran necessitates repetitive application of idarucizumab, *Br. J. Anaesth.* 121 (2018) 505–508, <https://doi.org/10.1016/j.bja.2018.04.025>.
- [6] N. Gendron, R. Chocron, P. Billoir, J. Brunier, L. Camoin-Jau, M. Tuffigo, D. Faille, D. Teissandier, J. Gay, E. de Raucourt, L. Suner, C. Bonnet, A.-C. Martin, D. Lasne, C. Ladhari, A. Lebreton, L. Bertoletti, N. Ajzenberg, P. Gaussem, P.-E. Morange, V. Le Cam Duchez, A. Viallon, P.-M. Roy, A. Lillo-le Lou e, D.M. Smadja, Dabigatran level before reversal can predict hemostatic effectiveness of idarucizumab in a real-world setting, *Front. Med. (Lausanne)* 7 (2020), 599626, <https://doi.org/10.3389/fmed.2020.599626>.
- [7] P. Albaladejo, G. Pernod, A. Godier, E. de Maistre, N. Rosencher, J.L. Mas, P. Fontana, C.M. Samama, A. Steib, S. Schlumberger, E. Marret, S. Roulet, S. Susen, S. Madi-Jebara, P. Nguyen, J.F. Schved, F. Bonhomme, P. Si e, Management of bleeding and emergency invasive procedures in patients on dabigatran: updated guidelines from the French Working Group on Perioperative Haemostasis (GIHP) - September 2016, *Anaesth. Crit. Care Pain Med.* 37 (2018) 391–399, <https://doi.org/10.1016/j.accpm.2018.04.009>.
- [8] J. Douxfils, W. Ageno, C.-M. Samama, S. Lessire, H. ten Cate, P. Verhamme, J.-M. Dogn e, F. Mullier, Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians, *J. Thromb. Haemost.* 16 (2018) 209–219, <https://doi.org/10.1111/jth.13912>.
- [9] S.E. Conway, A.Y. Hwang, C.D. Ponte, J.G. Gums, Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know, *Pharmacotherapy* 37 (2017) 236–248, <https://doi.org/10.1002/phar.1884>.
- [10] A.C. Martin, W. Thomas, Z. Mahir, M.P. Crowley, T. Dowling, K. Breen, V. Collings, G.W. Moore, S. MacDonald, B.J. Hunt, A.T. Cohen, Direct oral anticoagulant concentrations in obese and high body weight patients: a cohort study, *Thromb. Haemost.* 121 (2021) 224–233, <https://doi.org/10.1055/s-0040-1715834>.
- [11] I. Gouin-Thibault, G. Freyburger, E. de Maistre, S. Susen, X. Delavenne, J.-L. Golmard, Y. Gruel, P. Si e, L. Abecassis, M.-F. Aillaud, N. Ajzenberg, M. Alhenc-Gelas, A.A. Flory, A. Bauters, C. Biron, M. Berruyer, F.B. Jouvan, M. Brionne-Fran ois, C. d'Audigier, B. Delahousse, M. Donnard, V. Eschwege, F. Fischer, C. Flaujac, P. Fontana, H. Galinat, N. H ezard, M.-G. Huisse, V. Le Cam-Duchez, L. Le Flem, A. Le Querrec, R. Marlu, I. Martin-Toutain, R. Meley, F. Menard-Deroure, G. M eraud-Vialon, G. Mourey, F. Pineau-Vincent, P. Saugot, M. Toussaint-Hacquard, C. Trichet, S. Voisin, Evaluation of dabigatran, rivaroxaban and apixaban target-specific assays in a multicenter french study, *Thromb. Res.* 158 (2017) 126–133, <https://doi.org/10.1016/j.thromres.2017.09.001>.
- [12] M. Ebner, I. Birschmann, A. Peter, F. H artig, C. Spencer, J. Kuhn, A. Rupp, G. Blumentstock, C.S. Zuern, U. Ziemann, S. Poli, Limitations of specific coagulation tests for direct oral anticoagulants: a critical analysis, *J. Am. Heart Assoc.* 7 (2018), e009807, <https://doi.org/10.1161/JAHA.118.009807>.
- [13] J.P. Antovic, M. Skeppholm, J. Eintrei, E.E. Boija, L. S oderblom, E.-M. Norberg, L. Onel ov, Y. R onquist-Nii, A. Pohanka, O. Beck, P. Hjemdahl, R.E. Malmstr om, Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma, *Eur. J. Clin. Pharmacol.* 69 (2013) 1875–1881, <https://doi.org/10.1007/s00228-013-1550-4>.
- [14] S. Testa, C. Legnani, A. Tripodi, O. Paoletti, V. Pengo, R. Abbate, L. Bassi, P. Carraro, M. Cini, R. Paniccio, D. Poli, G. Palareti, Poor comparability of coagulation screening test with specific measurement in patients receiving direct oral anticoagulants: results from a multicenter/multiplatform study, *J. Thromb. Haemost.* 14 (2016) 2194–2201, <https://doi.org/10.1111/jth.13486>.
- [15] G. Freyburger, G. Macouillard, S. Labrousche, F. Sztark, Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: two observational studies in patients undergoing total hip or total knee replacement, *Thromb. Res.* 127 (2011) 457–465, <https://doi.org/10.1016/j.thromres.2011.01.001>.
- [16] A. Tripodi, S. Braham, B. Scimeca, M. Moia, F. Peyvandini, How and when to measure anticoagulant effects of direct oral anticoagulants? Practical issues, *Pol. Arch. Intern. Med.* 128 (2018) 379–385, <https://doi.org/10.20452/pamw.4287>.
- [17] J.M. Connors, Testing and monitoring direct oral anticoagulants, *Blood* 132 (2018) 2009–2015, <https://doi.org/10.1182/blood-2018-04-791541>.
- [18] A. Godier, A.-S. Dincq, A.-C. Martin, A. Radu, I. Leblanc, M. Antona, M. Vasse, J.-L. Golmard, F. Mullier, I. Gouin-Thibault, Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study, *Eur. Heart J.* 38 (2017) 2431–2439, <https://doi.org/10.1093/eurheartj/ehx403>.
- [19] N.D.R. Denny, L. Keighley, Z. Siganporia, J. Thachil, M.J. Nash, A level-headed approach to measuring direct oral anticoagulants: a 2-year retrospective analysis of DOAC levels from a tertiary UK centre, *Int. J. Lab. Hematol.* 41 (2019) 200–207, <https://doi.org/10.1111/ijlh.12944>.
- [20] C. Wright, R. Brown, A. Cuker, Laboratory measurement of the direct oral anticoagulants: indications and impact on management in clinical practice, *Int. J. Lab. Hem.* 39 (2017) 31–36, <https://doi.org/10.1111/ijlh.12654>.
- [21] K. Martin, S. Moll, Direct oral anticoagulant drug level testing in clinical practice: a single institution experience, *Thromb. Res.* 143 (2016) 40–44, <https://doi.org/10.1016/j.thromres.2016.04.019>.
- [22] A. Tripodi, To measure or not to measure direct oral anticoagulants before surgery or invasive procedures, *J. Thromb. Haemost.* 14 (2016) 1325–1327, <https://doi.org/10.1111/jth.13344>.
- [23] P. Albaladejo, F. Bonhomme, N. Blais, J.-P. Collet, D. Faraoni, P. Fontana, A. Godier, J.V. Llau, D. Longrois, E. Marret, P. Mismetti, N. Rosencher, S. Roulet, C.-M. Samama, J.-F. Schved, P. Si e, A. Steib, S. Susen, GIHP, gestion des anticoagulants oraux directs pour la chirurgie et les actes invasifs programm es: propositions r actualis ees du Groupe d'int er et en h emostasie p eriop eratoire (GIHP)–septembre 2015, *Anesth Reanim.* 2 (2016) 414–420, <https://doi.org/10.1016/j.anrea.2016.08.016>.

- [24] J.D. Douketis, G. Wang, N. Chan, J.W. Eikelboom, S. Syed, R. Barty, K.A. Moffat, F. A. Spencer, M. Blostein, S. Schulman, Effect of standardized perioperative dabigatran interruption on the residual anticoagulation effect at the time of surgery or procedure, *J. Thromb. Haemost.* 14 (2016) 89–97, <https://doi.org/10.1111/jth.13178>.
- [25] J.D. Douketis, A.C. Spyropoulos, J. Duncan, M. Carrier, G. Le Gal, A.J. Tafur, T. Vanassche, P. Verhamme, S. Shivakumar, P.L. Gross, A.Y.Y. Lee, E. Yeo, S. Solymoss, J. Kassis, G. Le Templier, S. Kowalski, M. Blostein, V. Shah, E. MacKay, C. Wu, N.P. Clark, S.M. Bates, F.A. Spencer, E. Arnaoutoglou, M. Coppens, D.M. Arnold, J.A. Caprini, N. Li, K.A. Moffat, S. Syed, S. Schulman, Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant, *JAMA Intern. Med.* 179 (2019) 1469–1478, <https://doi.org/10.1001/jamainternmed.2019.2431>.
- [26] M.M. Samama, C. Guinet, L. Le Flem, E. Ninin, J.-M. Debue, Measurement of dabigatran and rivaroxaban in primary prevention of venous thromboembolism in 106 patients, who have undergone major orthopedic surgery: an observational study, *J. Thromb. Thrombolysis* 35 (2013) 140–146, <https://doi.org/10.1007/s11239-012-0803-x>.
- [27] B.T. Samuelson, A. Cuker, Measurement and reversal of the direct oral anticoagulants, *Blood Rev.* 31 (2017) 77–84, <https://doi.org/10.1016/j.blre.2016.08.006>.
- [28] T. Eller, T. Flieder, V. Fox, T. Gripp, M. Dittrich, J. Kuhn, S. Alban, C. Knabbe, I. Birschmann, Direct oral anticoagulants and heparins: laboratory values and pitfalls in 'bridging therapy', *Eur. J. Cardiothorac. Surg.* 51 (2017) 624–632, <https://doi.org/10.1093/ejcts/ezw368>.