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CLINICAL RESEARCH
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Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study

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Aims Patients receiving direct oral anticoagulants (DOACs) frequently undergo elective invasive procedures. Their management is challenging. We aimed to determine the optimal duration of DOAC discontinuation that ensures a minimal anticoagulant effect during the procedure.

Methods and results This prospective multicentre study included 422 DOAC-treated patients requiring an invasive procedure. Pre-procedural DOAC concentration ([DOAC]) and routine haemostasis assays were performed to determine i/the proportion of patients who achieved a minimal pre-procedural [DOAC] (≤30 ng/mL) according to the duration of DOAC discontinuation, ii/the predictors of minimal [DOAC] and, iii/the ability of routine assays to predict minimal [DOAC]. Lastly, we assessed the predictors of peri-procedural bleeding events. The duration of DOAC discontinuation ranged from 1 to 218 h and pre-procedural [DOAC] from ≤30 to 527 ng/mL. After a 49–72-h discontinuation, 95% of the [DOAC] were ≤30 ng/mL. A 72-h discontinuation predicted concentrations ≤30 ng/mL with 91% specificity. In multivariable analysis, duration of DOAC discontinuation, creatinine clearance <50 mL/min and antiarrhythmics were independent predictors of minimal pre-procedural [DOAC] (concordance statistic 0.869; 95% confidence interval: 0.829–0.912). Conversely, routine haemostasis assays were poor predictors. Last, creatinine clearance <50 mL/min, antiplatelets and high-bleeding risk procedures were predictors of bleeding events.

Conclusion A last DOAC intake 3 days before a procedure resulted in minimal pre-procedural anticoagulant effect for almost all patients. Moderate renal impairment, especially in dabigatran-treated patients, and antiarrhythmics in anti-Xa-treated patients should result in a longer DOAC interruption. In situations requiring testing, routine assays should not replace DOAC concentration measurement.

Keywords Direct oral anticoagulant • Invasive procedure • Renal • Antiarrhythmic • Blood coagulation tests • Bleeding

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Introduction

Direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, are authorized for prevention and treatment of venous thromboembolism (VTE) and recommended in first intention for stroke prevention in patients with non-valvular atrial fibrillation (NVAF).[1] Each year, approximately 1 in 10 DOAC-treated patients requires a planned invasive procedure.[2,3] However, the pre-procedural management of DOACs is a complex challenge and the optimal duration of DOAC discontinuation remains uncertain.

Temporary interruption of DOACs is typically individualized according to the procedure-associated bleeding risk. Low-bleeding risk procedures can be safely undertaken while a patient is on DOAC or after a 24-h discontinuation. High-bleeding risk procedures require temporary discontinuation to ensure a minimal anticoagulant effect at the time of surgery, i.e. compatible with procedural management without increasing the bleeding risk. For these high-bleeding risk procedures, the duration of DOAC discontinuation proposed in current publications and practical guidelines is based on pharmacokinetic approaches and predicted by the elimination half-life, which is strongly influenced by renal function in DOACs with predominant renal excretion. However, these proposals provide a wide range of recommendations regarding the optimal duration of DOAC discontinuation before a high-bleeding risk procedure, from 2 to 7 days for dabigatran and from 2 to 5 days for apixaban or rivaroxaban.[4–7] In a previous pilot study, we reported that a 2-day discontinuation does not guarantee a minimal anticoagulant effect at the time of surgery.[8]

The COncentration of RIvaroxaban, Dabigatran and Apixaban (CORIDA) study was designed to address a simple question: what is the optimal duration of DOAC discontinuation to ensure a minimal anticoagulant effect at the time of a planned invasive procedure? To answer this question, we performed a multicentre prospective observational study which included a large number of dabigatran-, apixaban-, or rivaroxaban-treated patients slated for an invasive procedure irrespective of their duration of DOAC discontinuation. In these patients, we investigated the factors, and specifically the duration of DOAC discontinuation, influencing pre-procedural DOAC concentrations. In addition, we evaluated the ability of routine haemostasis assays to predict minimal anticoagulant effect. Lastly, we assessed the factors associated with peri-procedural bleeding events.

Methods

The CORIDA study was a multicentre, prospective, observational study conducted from June 2013 to December 2015 in six centres in France and Belgium (Fondation Rothschild, Hôpital Cochin, Hôpital du Val-de-Grâce, Hôpital Foch, Institut Mutualiste Montsouris and CHU UCL Namur). The study was approved by the research ethics boards (Comité de Protection des Personnes Ile de France 1, ref. 2013-13272 and Comité interne CHU UCL NAMUR 09/2014, ref. B039201422406). All patients were informed before inclusion and the physician in charge of the patient signed the non-opposition form (the research ethics board waived the need for patient signatures on informed consent forms since this was an observational study). This study was registered at ClinicalTrials.gov, number NCT02643992.

Patients and study design

The methodology was described in detail in a previous pilot study.[8] In each participating centre, the physicians in charge of the study prospectively enrolled consecutive patients who were taking dabigatran, apixaban, or rivaroxaban for NVAF or VTE treatment and required any invasive procedure. Invasive procedure was defined as any elective or urgent surgery, endoscopy, and cardiac catheterization. Urgent procedure was defined as a procedure required within 48 h. Patients were managed according to local practice and the study had no impact on procedures. For the study, patients had one blood sample taken in the operating room just before the beginning of the invasive procedure (pre-procedural blood sampling). Blood was collected into 109 mM citrate tubes and was centrifuged within 2 h to obtain plasma for coagulation testing.

Coagulation testing

Coagulation testing included DOAC concentration measurement and routine haemostasis assays, namely prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) (in plasma of dabigatran-treated patients), and low-molecular-weight heparin (LMWH) anti-Xa activity (in plasma of apixaban and rivaroxaban-treated patients) (details presented in the Supplementary material online).

Data collection

For each patient, demographic, clinical, and biological data were collected: age, gender, weight, history of stroke, and creatinine clearance calculated using the Cockcroft and Gault formula (moderate and severe renal impairments were defined as clearance lower than 50 and 30 mL/min, respectively). Relevant comedications were also recorded. They included P-glycoprotein and/or CYP 3A4 inhibitors that interact with DOAC metabolism and potentially increase DOAC concentrations, including antiarrhythmic drugs such as amiodarone, dronedarone, verapamil, diltiazem and quinidine, and antifungal agents;[3] proton-pump inhibitors that decrease the gastro-intestinal absorption of dabigatran and non-steroidal anti-inflammatory drugs and antiplatelet agents, which could potentiate the bleeding risk.[3]

The following characteristics of peri-procedural DOAC management were recorded: DOAC type and indication, duration of discontinuation, use of pre-procedural and/or post-procedural bridging (LMWH or unfractionated heparin), and finally coagulation test results at the beginning of the procedure. The duration of DOAC discontinuation was recorded as the exact time from the last drug intake to the invasive procedure and classified according to predefined 24-h intervals.

Pre-procedural DOAC concentrations were interpreted according to different thresholds: 30, 50, 100, and 200 ng/mL. First, 30 ng/mL was selected since it is the safety haemostatic threshold proposed for high-bleeding risk surgery by the subcommittee on control of anticoagulation of the ISTH and the French Working Group on perioperative haemostasis (GIHP).[9,10] We then considered the 50 ng/mL threshold proposed by the subcommittee on control of anticoagulation in patients with serious bleeding since concentrations below this threshold might not exacerbate ongoing haemorrhage.[9] We also chose 100 ng/mL which has been proposed as the maximal cut-off for the use of intravenous thrombolysis in rivaroxaban treated-patients with stroke.[11,12] Lastly, we selected 200 ng/mL which has been described as a DOAC concentration associated with a consistent peri-procedural bleeding risk.[10]

The types, dates, and outcomes of the invasive procedures were noted (details presented in the Supplementary material online).

Statistical analysis

The study sample size was estimated to test the hypothesis that creatinine clearance would be a predictive factor of pre-procedural DOAC

concentration ≤30 ng/mL. Calculations were based on data from our pilot study: observed creatinine clearances were 75 ± 25 mL/min and 83 ± 33 mL/min in patients with pre-procedural DOAC concentrations below and over 30 ng/mL, respectively, and the sample size ratio between the two groups was 1.4.[8] Using a test with a first order risk of 0.05, the total number of subjects needed to reach a 0.80 power is 417.

Descriptive statistics used median (minimum–maximum) for quantitative variables and numbers (percentages) for qualitative ones. A non-parametric regression curve of the DOAC concentration value vs. duration of DOAC discontinuation was estimated by the loess method. In order to define the best duration of DOAC discontinuation, we constructed a receiver operating characteristic (ROC) curve relating duration of DOAC discontinuation with DOAC concentrations ≤30 ng/mL at the time of the invasive procedure. The best duration was defined as the minimum duration with a specificity higher than 90% in order to optimize the proportion of false positive i.e. patients with DOAC concentrations >30 g/mL wrongly predicted to be ≤30 ng/mL. We used Wilcoxon tests for quantitative variables and χ^2 tests or Fisher's exact tests for qualitative variables to compare groups of individuals with DOAC concentrations ≤30 ng/mL and individuals with DOAC concentrations >30 ng/mL. Among factors associated with concentrations ≤30 ng/mL, the quantitative variables tested were age, weight, duration of DOAC discontinuation whereas the qualitative variables were gender, creatinine clearance lower than 50 mL/min, DOAC type and indication, history of stroke, concomitant intake of interfering drugs, pre-procedural bridging, procedure-associated bleeding risk, and elective characteristics. In a second step, a stepwise logistic regression was performed to predict DOAC concentrations ≤30 ng/mL. Variables entered in the stepwise regression had a *P*-value lower than 0.10 in the univariate analysis whereas variables retained in the final model had a *P*-value lower than 0.05 by the Wald test. The performance of the predictive model was assessed by both the concordance statistic (area under the ROC curve) and the optimism-corrected value of Harrell's concordance statistic. Similar comparisons were performed for the threshold of 50 ng/mL.

Comparisons of groups of individuals with bleeding events and individuals without bleeding events were performed using Student's *t*-tests. Among factors associated with bleeding events, the quantitative variables tested were age, weight, duration of DOAC discontinuation, and pre-procedural DOAC concentration and the qualitative variables were gender, creatinine clearance lower than 50 mL/min, DOAC type and indication, history of stroke, concomitant intake of interfering drugs, pre-procedural bridging, procedure-associated bleeding risk, and elective characteristics. In a second step, a stepwise logistic regression was performed in order to predict bleeding events. Variables entered in the stepwise regression had a *P*-value lower than 0.10 in the univariate analysis whereas the variables retained in the final model had a *P*-value lower than 0.05 by the Wald test. The effect of an antiarrhythmic drug, defined as administration of either amiodarone or verapamil or diltiazem, was analysed as well as the effect of each antiarrhythmic drug.

In order to evaluate the ability of the combination of a normal PT and a normal aPTT to predict minimal pre-procedural DOAC concentrations, we determined the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the combination of a normal PT and a normal aPTT to predict a concentration ≤30 ng/mL. Thus, PPV is the probability that patients with a combination of a normal PT and a normal aPTT have a concentration ≤30 ng/mL whereas NPV is the probability that patients with a PT and/or an aPTT above the normal value do not have concentration ≤30 ng/mL. We also evaluated the ability of a normal TT and the ability of LMWH anti-Xa activity ≤0.1 IU/mL to predict a concentration ≤30 ng/mL. The 95% confidence intervals (CIs) of the sensitivity, specificity, PPV and NPV have been computed using the Agresti–Coull method.

All tests were two-sided, with a *P*-value of 0.05 considered as significant. The computations were performed using the SAS V9.3 statistical package (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Between June 2013 and December 2015, 422 DOAC-treated patients slated for invasive procedures were included in the study. Their characteristics are shown in the Supplementary material online. More than half of the patients were treated with rivaroxaban (55%), followed by dabigatran (31%) and apixaban (14%). Non-valvular atrial fibrillation was the most common indication for DOAC therapy (95%). One-fourth of the patients had a history of stroke and 14% of the patients had a creatinine clearance lower than 50 mL/min. Fifty-nine percent of the procedures were classified as having a high-bleeding risk and 92% were elective procedures.

Pre-procedural direct oral anticoagulant management

The median duration of DOAC discontinuation was 66 h (range: 1–218 h). Pre-procedural bridging was performed in 35% of the patients scheduled for elective procedures.

Pre-procedural direct oral anticoagulant concentrations and duration of direct oral anticoagulant discontinuation

Direct oral anticoagulant concentrations measured at the time of the invasive procedure ranged from ≤30 to 527 ng/mL; 77% of the measurements were ≤30 ng/mL and 86% of the measurements were ≤50 ng/mL. The relationship between duration of DOAC discontinuation and concentrations is illustrated in *Figure 1*.

The proportion of patients with pre-procedural DOAC concentrations below the four pre-defined thresholds according to the duration of DOAC discontinuation is illustrated in *Figure 2*. As expected, more concentrations were ≤ 30 ng/mL after 48-h discontinuation than after a shorter period ($P = 0.0001$). Indeed, a 25 to 48-h discontinuation resulted in 38% of the DOAC concentrations >30 ng/mL and 7% of the measurements remained >100 ng/mL. On the contrary, after a 49 to 72-h discontinuation, only 5% of the DOAC concentrations remained >30 ng/mL and none was >50 ng/mL.

The ROC curve analysis (*Figure 3*) demonstrated that 54 h was the best duration of DOAC discontinuation to predict a DOAC concentration ≤30 ng/mL with a specificity of 91% (95% CI: 85–97) and a sensitivity of 68% (95% CI: 63–73). The PPV of the 54-h discontinuation was 96% (95% CI: 93–99). A last intake 54 h before an invasive procedure cannot be easily applied in clinical practice but this exact duration is included in the predefined interval of 49–72 h with the following performances: a 49-h discontinuation has a specificity of 89% (95% CI: 83–95) which is less accurate than a 54-h discontinuation, and a sensitivity of 72% (95% CI: 67–77). A 72-h discontinuation has a specificity of 91% (95% CI: 85–97), similar to a 54-h discontinuation, and a sensitivity of 60% (95% CI: 55–66).

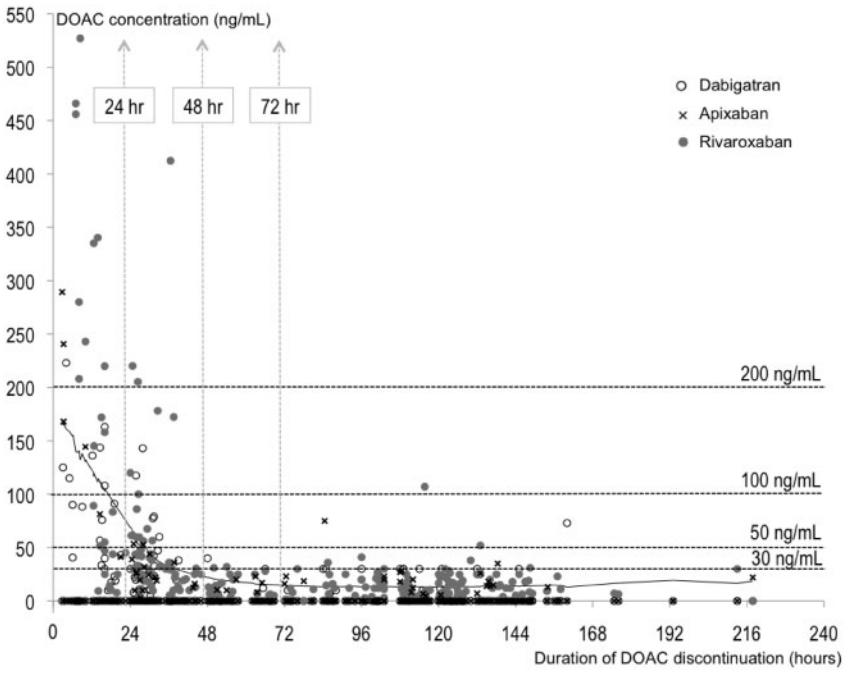

Figure 1 Fit plot of DOAC concentrations measured at the time of invasive procedure according to the duration of DOAC discontinuation. DOAC, direct oral anticoagulant.

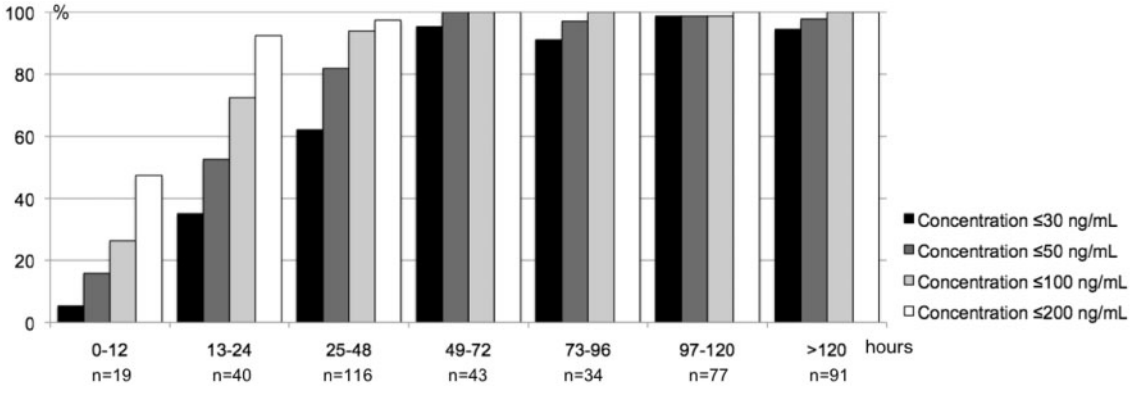

Figure 2 Proportion of patients with DOAC concentrations below various threshold values (30; 50; 100, and 200 ng/mL) at the time of the invasive procedure according to the duration of DOAC discontinuation. *n*: the number of patients with measured concentrations by duration of DOAC discontinuation. Each patient had a single blood sample taken in the operating room just before the beginning of the invasive procedure.

Factors associated with minimal pre-procedural direct oral anticoagulant concentrations

Multivariable analysis highlighted four independent predictors of DOAC concentration ≤30 ng/mL (*Table 1*): duration of DOAC discontinuation was highly associated with DOAC concentration ≤30 ng/mL, whereas creatinine clearance <50 mL/min, antiarrhythmic treatment and pre-procedural bridging were negatively associated with DOAC concentration ≤30 ng/mL. In contrast, the type of DOAC treatment was not associated with a

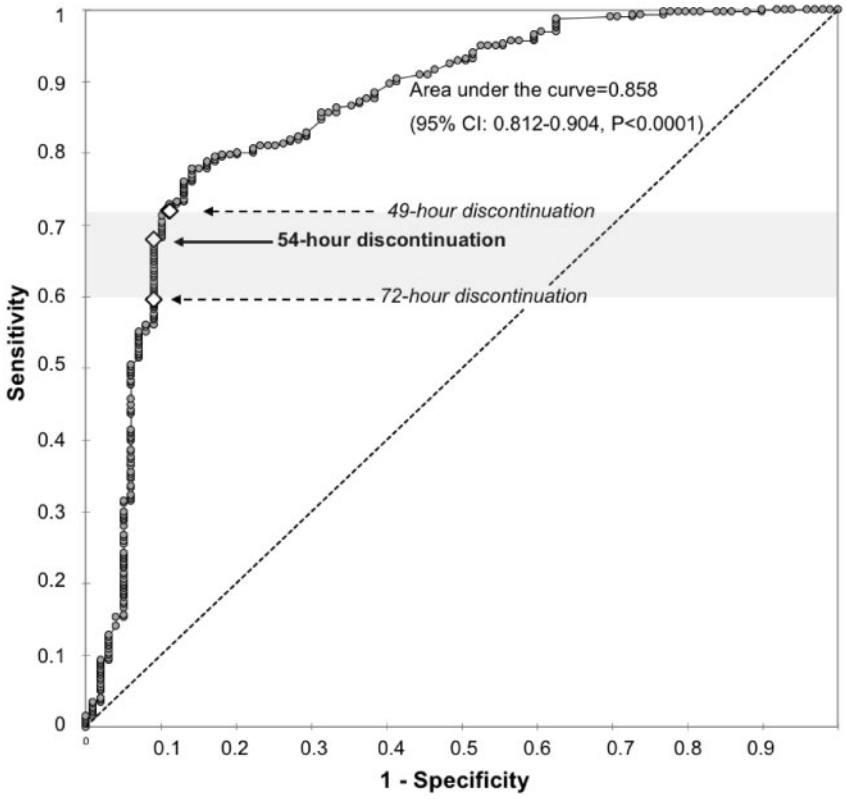

Figure 3 Receiver operating characteristic (ROC) curve relating duration of DOAC discontinuation with DOAC concentrations ≤30 ng/mL at the time of the invasive procedure. The diagonal line represents a hypothetical ROC curve from a test that yielded no diagnostic information. The bold arrow shows that a 54-h discontinuation is the shorter duration of DOAC discontinuation with a specificity higher than 90%. The dotted arrows show performance of the 49 to 72-h interval.

concentration ≤30 ng/mL. Noteworthy, when performing the multivariable logistic analysis without any variable selection, the results remained unchanged. Regarding performance of the predictive model, the concordance statistic was 0.869 (95% CI: 0.829–0.912, $P < 0.0001$; ROC curve in the Supplementary material online) and the optimism-corrected value of Harrell's concordance statistic was 0.849. When each antiarrhythmic drug was analysed separately, both amiodarone and verapamil were independent predictors of DOAC concentration ≤30 ng/mL [odds ratio (OR) 0.351; 95% CI 0.180–0.683; $P = 0.0021$ and OR 0.094; 95% CI 0.011–0.809; $P = 0.0313$, respectively].

When focusing on patients who stopped DOACs within 48 h before the invasive procedure, the independent predictors of DOAC concentration ≤ 30 ng/mL remained the duration of DOAC discontinuation (OR 8.991; 95% CI 3.499–23.102; $P < 0.0001$), creatinine clearance < 50 mL/min (OR 0.264; 95% CI 0.105–0.664; $P = 0.0046$), and antiarrhythmic treatment (OR 0.299; 95% CI 0.131–0.679; $P = 0.0039$).

Direct oral anticoagulants were also separately assessed. For dabigatran, the duration of DOAC discontinuation (OR 3.066; 95% CI 1.688–5.568; $P = 0.0002$) and creatinine clearance <50 mL/min (OR 0.212; 95% CI 0.052–0.855; $P = 0.0292$) were independent predictors of concentration ≤ 30 ng/mL. For rivaroxaban, the duration of DOAC discontinuation (OR 6.302; 95% CI 3.213–12.360; $P \leq 0.0001$), antiarrhythmic treatment (OR 0.375; 95% CI 0.148–0.947; $P = 0.0379$) and bridging (OR 0.03; 95% CI 0.004–0.248; $P = 0.0012$) were independent predictors of concentration ≤30 ng/mL whereas for apixaban, only the duration of DOAC discontinuation (OR 3.293; 95% CI 1.461–7.424; $P = 0.0041$) and antiarrhythmic treatment (OR 0.038; 95% CI 0.003–0.467; $P = 0.0105$) were independent predictors of concentration ≤30 ng/mL.

Moreover, the independent predictors of DOAC concentration ≤50 ng/mL in multivariable analysis performed in the overall population were the same as for the 30 ng/mL threshold (details presented in the Supplementary material online).

The ability of routine haemostasis assays to predict minimal pre-procedural direct oral anticoagulant concentrations

The combination of a normal PT and a normal aPTT measured at the same time as pre-procedural DOAC concentrations had good PPV (92%) and good specificity (81%) but limited NPV (45%) and sensitivity (69%) to predict a concentration ≤30 ng/mL in the overall population.

Table 1 Univariate and multivariable analyses of predictors of direct oral anticoagulant concentrations ≤ 30 ng/mL

Variable	≤30 ng/mL *n* = 323	>30 ng/mL *n* = 99	*P*-value, univariate analysis	OR (95% CI)	*P*-value, multivariable analysis
Age, years	74 [40–96]	75 [44–95]	0.3060		
Male, %	187 (58)	49 (49)	0.1408		
Weight, kg	80 [43–185]	78 [40–165]	0.3477		
CrCL < 50 mL/min	32 (10)	24 (25)	0.0002	0.334 (0.160–0.695)	0.0034
NVAF/VTE	302 (94)/20 (6)	97 (98)/2 (2)	0.1013		
History of stroke	73 (24)	20 (23)	0.8725		
Dabigatran/apixaban/rivaroxaban	102 (32)/43 (13)/178 (55)	29 (29)/14 (14)/56 (57)	0.9071		
Antiarrhythmic drugs (A or V or D)	77 (24)	34 (34)	0.0378	0.334 (0.174–0.640)	0.001
PPI	101 (31)	32 (32)	0.8579		
NSAID	2 (1)	1 (1)	0.5526		
Antiplatelet agents	40 (12)	22 (22)	0.0156		
Elective procedure	305 (94)	84 (85)	0.0019		
High-bleeding risk	225 (70)	23 (23)	<0.0001		
Duration of DOAC discontinuation, h	97 [6–218]	26 [1–160]	<0.0001	4.652 (2.982–7.258)	<0.0001
Pre-procedural bridging	128 (40)	10 (10)	0.0001	0.078 (0.019–0.322)	0.0004

Values are given as median [min–max] or number (percentage).
CrCL, creatinine clearance; DOAC, direct oral anticoagulant; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitors; NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism; (A or V or D), amiodarone or verapamil or diltiazem; OR, odds ratio; CI, confidence interval.

Table 2 Performances of routine haemostasis assays to predict DOAC concentrations ≤ 30 ng/mL

Assays	DOAC	*n*	PPV	Specificity	NPV	Sensitivity
Normal aPTT and normal PT	dabigatran	108	44/46 = 96% [88–100]	24/26 = 92% [80–100]	24/62 = 39% [27–51]	44/82 = 54% [43–64]
	rivaroxaban	210	124/132 = 94% [90–98]	38/46 = 83% [72–94]	38/78 = 49% [38–60]	124/164 = 76% [70–82]
	apixaban	46	23/29 = 79% [65–94]	8/14 = 57% [34–80]	8/17 = 47% [26–68]	23/32 = 72% [57–87]
LMWH anti-Xa activity ≤ 0.1 IU/mL	rivaroxaban + apixaban	215	87/87 = 100% [97–100]	54/54 = 100% [95–100]	54/128 = 42% [34–51]	87/161 = 54% [46–62]
Normal thombin time	dabigatran	116	45/45 = 100% [95–100]	25/25 = 100% [91–100]	25/71 = 35% [24–46]	45/91 = 49% [39–60]

Data are presented as numerator/denominator = % and [95% CI].
DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; NPV, negative predictive value; PPV, positive predictive value; aPTT, activated partial thromboplastin time; PT, prothrombin time.

When focusing on patients treated with rivaroxaban or dabigatran, the PPV of this combination rose to 94% and 96%, respectively, whereas in apixaban-treated patients the PPV fell to 79% (*Table 2*).

Importantly, when considering only procedures performed within 48 h after DOAC discontinuation, the performance of the combination of a normal PT and a normal aPTT was poor: PPV was 80% for rivaroxaban and dabigatran-treated patients and dropped to 55% for apixaban-treated patients, with sensitivity remaining low at 58%.

Normal TT as well as LMWH anti-Xa activity ≤0.1 IU/mL were excellent to predict DOAC concentrations ≤30 ng/mL (*Table 2*). However, both had poor NPV.

Peri-procedural outcome

Thirty-one patients (7%) had peri-procedural bleeding events: 12 were major bleeds (including 10 events requiring blood transfusion) and 27 occurred after the procedure. In multivariable analysis,

Table 3 Uni- and multivariable analyses of risk factors for peri-procedural bleeding events

Factor	Patients with bleeding event $n = 31$	Patients without bleeding event $n = 391$	*P*-value	Multivariable odds ratio (95% CI)	*P*-value
Male	22 (71)	206 (55)	0.076		
CrCL < 50 mL/min	8 (27)	46 (13)	0.048	3.425 (1.364 - 8.621)	0.009
Dabigatran/apixaban/rivaroxaban	7 (23)/1 (3)/23 (74)	122 (32)/55 (15)/201 (53)	0.054		
Antiarrhythmic drugs (A or V or D)	12 (39)	94 (25)	0.090		
Antiplatelet agents	8 (26)	49 (13)	0.058	2.593 (1.004–6.696)	0.0491
High-bleeding risk	28 (90)	216 (57)	0.0003	7.610 (2.227 - 26.004)	0.001
General anaesthesia	22 (71)	191 (52)	0.038		
Duration of DOAC discontinuation, h, means (±SD)	98 (47)	72 (48)	0.003		
Pre-procedural bridging	15 (48)	121 (32)	0.063		
Post-procedural bridging	20 (67)	124 (33)	0.0002		

The table only shows variables with a *P*-value lower than 0.10 in the univariate analysis. Values are given as number (percentages), unless stated otherwise.
CrCL, creatinine clearance; DOAC, direct oral anticoagulant; (A or V or D), amiodarone or verapamil or diltiazem; SD, standard deviation; CI, confidence interval.

procedure-associated high-bleeding risk, antiplatelet therapy, and creatinine clearance lower than 50 mL/min were independent predictors of bleeding complications (*Table 3*). In contrast, pre-procedural DOAC concentration, duration of DOAC discontinuation, pre-procedural, or post-procedural bridging were not independent risk factors of bleeding events. No thromboembolic events, major cardiovascular events, or deaths were recorded.

Discussion

In this prospective study which included a large number of patients, we found that a duration of DOAC discontinuation of 49–72 h resulted in pre-procedural DOAC concentrations ≤30 ng/mL for 95% of the patients. These data support that a last DOAC intake 3 days before an elective procedure with a high-bleeding risk is adequate to ensure a minimal pre-procedural DOAC concentration, irrespective of the DOAC or the dosing regimen (once or twice daily). The CORIDA study is the first large study to provide biological arguments to support the strategies currently proposed for the interruption of DOAC therapy before elective procedures. Indeed, these strategies are based on DOAC pharmacokinetic properties, assuming that an interruption of four to five DOAC half-lives would guarantee a minimal drug concentration compatible with a high-bleeding risk procedure.[5] This approach has been adopted in the three pivotal trials comparing DOACs with warfarin for NVAF and the resulting rates of major bleeding were low and similar in DOAC-treated and warfarin-treated patients.[2,3,13]

Our study provides evidence that renal impairment, even moderate, is an issue in the peri-operative setting, especially with dabigatran.[14] It supports the concept proposed by practical guidelines that dabigatran discontinuation should be based on patient renal function, with duration progressively prolonged according to creatinine clearance.[5,15,16] Thus, an additional 1–2 days of interruption, i.e. a total of 4 to 5 days, would ensure a minimal anticoagulant effect in patients receiving dabigatran with a clearance of 30–50 mL/min and slated for a high bleeding risk procedure.

In contrast, apixaban and rivaroxaban are less affected by renal function.[16] In our study, renal clearance of 30–50 mL/min was not associated to higher apixaban or rivaroxaban pre-procedural concentrations, which suggests that moderate renal impairment does not require an increased discontinuation duration for apixaban- or rivaroxaban-treated patients.

Drug–drug interactions may affect DOAC concentrations, especially concomitant use of P-glycoprotein inhibitors or CYP3A4 inhibitors.[4] The clinical relevance of these interactions has not been clearly defined, and has never been assessed in the perioperative setting. Our results showed that antiarrhythmic treatment was independently associated with higher DOAC pre-procedural concentrations. In particular, these drugs had a significant effect on apixaban and rivaroxaban, although this has been poorly reported.[4,17] In contrast, we found no effect of antiarrhythmic treatment on dabigatran although both amiodarone and verapamil are known to increase dabigatran plasma levels.[4] Physicians may consider adaptation of DOAC management before high-bleeding risk surgery in the presence of antiarrhythmic treatment.

The CORIDA study also assessed risk factors for peri-procedural bleeding complications and found that renal impairment was a major predictor. It is well known that patients with moderate to severe renal impairment are at increased risk of thromboembolism but also bleeding compared with patients with normal renal function.[18,19] However, the effect of renal impairment on peri-operative bleeding has been poorly assessed.[20,21] Our study demonstrated that patients with moderate renal dysfunction are at risk of peri-procedural bleeding events and supports the use of pre-operative calculation of creatinine clearance by the Cockcroft and Gault formula to identify patients at increased bleeding risk.[22] Lastly, the bleeding risk of the procedure and co-medication with antiplatelet therapy should also be considered during this pre-procedural assessment. Interestingly, duration of DOAC discontinuation and procedure-associated high-bleeding risk were both strongly associated with peri-procedural bleeding complications in univariate analysis, but since these co-variates are dependent, only bleeding risk remained an independent predictor of bleeding complications after multivariable analysis. Of note, our study was not

designed to assess the relationship between pre-procedural DOAC concentrations and bleeding events. Since a large proportion (88%) of patients had a pre-procedural DOAC concentration <50 ng/mL, no conclusion related to this issue can be drawn from our results.

While measuring DOAC concentration in elective surgery is not necessary, assessment of the anticoagulant effect may be required for patients requiring emergent procedures with a high-bleeding risk.[9] It has been proposed that patients may safely proceed to surgery if DOAC concentration is ≤30 ng/mL.[9,10] Above this threshold, if the procedure cannot be delayed to allow for DOAC clearance, reversal could be discussed, including idarucizumab for dabigatran, and prothrombin complex concentrates, although their efficacy and safety have been poorly assessed.[9] The wide range of DOAC concentrations observed in our study after a 0 to 48-h discontinuation, from <30 ng/mL to higher than up to 200 ng/mL, confirmed the need for an individual assessment of the anticoagulant effect. Since DOAC concentration measurement is not available in all centres, it has been proposed that routine haemostasis assays could be useful. Since normal PT or normal aPTT alone do not exclude the presence of clinically relevant concentrations of DOACs, it has been suggested that the combination of a normal PT and a normal aPTT indicates with relative reliability a DOAC concentration ≤30 ng/mL.[10] Nevertheless, this combination had poor performance when DOACs were interrupted in fewer than 48 h as in the case of emergency procedures. It is also ineffective for apixaban, which has little effect on the PT or aPTT.[23] Therefore, the combination of a normal PT and a normal aPTT could not accurately predict a DOAC concentration ≤30 ng/mL when DOACs are briefly interrupted. It should therefore not be used to guide the decision process in an emergency situation.

Finally, normal TT for dabigatran and LMWH anti-Xa activity ≤0.1 IU/mL for apixaban and rivaroxaban are highly reliable to exclude residual DOAC concentration. Nevertheless, more than half of the TT and LMWH anti-Xa activity increased even though concentrations were ≤ 30 ng/mL, confirming that they are too sensitive to the presence of DOACs and limit their use in the emergency setting. As for the combination of PT and aPTT, the poor NPV of normal TT and LMWH anti-Xa activity ≤0.1 IU/mL, i.e. increased TT and LMWH anti-Xa activity values despite concentrations ≤30 ng/mL, is an important limit, resulting potentially in incorrect peri-procedural management, including detrimental delay of a procedure or inadequate reversal. In the end, the measurement of DOAC plasma concentration appears to be the most accurate way to assess the residual anticoagulant effect and to manage emergency procedures.

There are several limitations to our study. First, pre-procedural DOAC management was not standardized and the duration of DOAC discontinuation was not predefined. However, our aim was not to evaluate a standardized DOAC-specific protocol as in other studies,[22,24] but to focus on the predictive factors of pre-procedural DOAC concentrations, which requires various types of DOAC management and different durations of DOAC discontinuation. Here, we reported the first available results regarding pre-procedural DOAC concentrations according to the exact duration of DOAC discontinuation and our findings provide relevant information to practicing clinicians.

Secondly, we used 30 ng/mL as a safety haemostatic threshold although this threshold has never been clinically validated. However, our study was not designed to assess the validity of this cut-off value. Above all, this threshold is increasingly proposed by experts and international societies.[9,10,15] Thirdly, bridging was widely used in our cohort since it was performed before 33% of the procedures, mainly in patients who interrupted DOAC for more than 72 h. This is in agreement with the findings from the prospective Dresden DOAC registry where bridging was performed for one in three patients.[25] Similarly more than one-fourth of American physicians involved in peri-procedural DOAC management indicated in a recent survey that a $CHADS_2$ score of two leads to prescribe bridging.[26] Bridging used to be recommended[6,27] until recent data revealed that bridging increased the risk of major bleeding with comparable rates of thromboembolism compared with no bridging.[27–29] In our study, pre-procedural bridging was not associated with an increased incidence of bleeding events compared with the 'no-bridging' approach, but our study was not designed to address this issue. Finally, multivariable analysis showed that pre-procedural bridging was statistically associated with a higher proportion of concentrations >30 ng/mL. This result was unexpected: since bridging is considered only in case of long duration of discontinuation, it was very unlikely that residual concentrations would be >30 ng/mL. We confirmed the negative interaction between duration of DOAC discontinuation and pre-procedural bridging using the Breslow Day test ($P = 0.0093$). The slight increase in DOAC concentration only observed in nine apixaban- or rivaroxaban-treated patients could be due to interferences of residual concentrations of LMWH with the DOAC dosage.[30] Additional research is needed to better assess this interaction.

In conclusion, our data provide the proof of concept for a pharmacokinetic strategy for peri-procedural DOAC management, based on DOAC elimination half-life, patient renal function and estimated procedure-associated bleeding risk. The main clinical implication of this study is that a last DOAC intakes 3 days before an elective high-bleeding risk procedure would ensure a minimal pre-procedural concentration for almost all patients, with no need for laboratory testing. Since moderate renal impairment, especially in dabigatran-treated patients, and antiarrhythmic treatment in apixaban- and rivaroxaban-treated patients were independent predictors for higher residual DOAC concentrations, a longer DOAC interruption should be considered in pre-procedural management of such patients. These data require confirmation in larger, prospective studies because of the implications of discontinuing DOAC too early (increased thrombosis risk) or too late (increased bleeding risk). The ongoing PAUSE trial (NCT02228798) is one such study that plans to assess the safety of standardized peri-operative DOAC management protocols according to clinical endpoints. In situations where pre-procedural coagulation testing is needed, including emergency procedures with a high-bleeding risk, routine haemostasis assays have had poor performances and the measurement of DOAC concentration is the only option to assess the residual anticoagulant effect.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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