Preprocedural DOAC plasma levels and to which extend they predict the risk of periprocedural blood loss

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Abstract

Background

Currently, Direct oral anticoagulants (DOACs) users undergoing elective procedures interrupt therapy according to a standard perioperative protocol. However, patients may benefit from preprocedural DOAC monitoring to reduce the bleeding risk during the surgery, since in ~ 9 – 23% of patients DOAC levels are still elevated before surgery.

Aim

To determine preprocedural DOAC levels and to which extend residual DOAC levels predict the risk of periprocedural blood loss.

Methods

The DALI study is a cohort study including patients who interrupted apixaban, dabigatran or rivaroxaban for an elective surgery. Before procedure, a blood sample was drawn to measure DOAC levels, which were categorized, and the percentage of patients in each category was calculated. Further, this data was stratified for bleeding risk of the procedure, sex, age, and renal function. In addition, linear regression was conducted between DOAC levels and perioperative blood loss. Similarly, linear regression was carried out between albumin levels and perioperative blood loss. Post procedure, patients were followed up for 30 days to assess perioperative blood loss, major and minor bleeding events.

Results

The preoperative DOAC level was measured for 178 patients of whom 99 apixaban, 45 rivaroxaban, and 34 dabigatran users. For apixaban, 13 (13,2%) had elevated levels. For rivaroxaban, 2 patients (4.4%) had elevated levels. None of the dabigatran users had elevated levels. Only in the apixaban cohort, a higher risk of elevated levels was found for females, <75 years and estimated glomerular filtration rate (eGFR) < 50 mL/min. However, none were significant. Further, there was no association between preoperative DOAC levels and periprocedural blood loss. Similarly, no correlation was found for albumin levels and blood loss. During follow up, there were 9 (5.1%) major bleeds with DOAC levels < 30 ng/mL, and 14 (7.9%) minor bleeds of which 13 (92.9%) with DOAC levels < 30 ng/mL.

Conclusions

The residual DOAC level before surgery was minor and the occurrence of perioperative blood loss, major or minor bleeding events was unrelated to the preprocedural DOAC concentration. Therefore, there seems to be no need to consider monitoring DOAC levels before an elective procedure.

Background

Oral anticoagulants (OACs) are used for prevention and treatment of thromboembolic events in patients with indications such as venous thrombosis and non-valvular atrial fibrillation (1, 2). OACs include vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), which consists of apixaban, rivaroxaban, edoxaban (factor Xa inhibitors) and dabigatran (thrombin inhibitor) (2). In the Netherlands only one third of all 570.00 OAC users used a DOAC in 2017, whereas this was increased to two third in 2021 (3). The advantage of DOACs is that they have a more predictable and stable pharmacodynamics and pharmacokinetics compared to the VKAs. Therefore, DOACs have a fixed dose and obviate the need for routine monitoring. As a result, DOAC therapy is more simple in comparison to VKAs (4, 5).

DOAC users who need to undergo an elective procedure need to interrupt therapy to prevent excess bleeding during and after surgery. This requires perioperative DOAC management (1, 6). The standard management protocol used worldwide takes into account the following aspects: bleeding risk of the procedure, estimated glomerular filtration rate (eGFR) and the average half-life of the DOAC. Based on these, the protocol states to interrupt the DOAC for a fixed period of time, which makes it a simple policy (1, 7). Even though the study of Douketis et al. showed that this standard protocol was safe, the rates of major bleedings were still ~3% for apixaban, ~1% for dabigatran and ~3% for rivaroxaban for procedures with a high

bleeding risk (1). This could be due to the procedure itself or the periprocedural protocol could be improved. Moreover, the protocol is based on the average half-life of DOACs, while this differs for the individual patient (8). For instance, the half-life of rivaroxaban is between 5 to 9 hours for adults and 11 to 13 hours for elderly (9). Consequently, the individual patient might still have elevated DOAC levels during a procedure when following the standard protocol. This was confirmed in recent studies, Douketis et al. showed that 8.8% of dabigatran users had increased levels just before surgery (> 50 ng/mL) (8). Additionally, Shaw et al. showed that 4.9% of dabigatran users (≥ 50 ng/mL) and ~23% of apixaban and rivaroxaban users had elevated levels (≥ 30 ng/mL) (10). Moreover, Shaw et al. showed that specific patient groups are more likely to have elevated periprocedural DOAC levels, such as elderly, patients with impaired renal function, and women (10). Furthermore, patients with low albumin might have an increased periprocedural bleeding risk, because the study of Chaussade et al. found a correlation between low albumin levels and haemorrhagic events in dabigatran users (11). One possible explanation could be that low albumin increases the unbound fraction of the DOAC. Consequently, this might increase the anticoagulant effect. However, this has no influence on the total DOAC level. Dabigatran only binds approximately 35% to plasma proteins, whereas rivaroxaban approximately 92 – 95% and apixaban approximately 87% and both are predominately bound to albumin (9, 12, 13). Therefore, this effect might be even stronger in apixaban and rivaroxaban.

In conclusion, patients with elevated levels or low albumin might have an increased bleeding risk during and after the surgery. However, the aforementioned studies did not investigate the association between DOAC levels and periprocedural risk of bleeding (8, 10). Including monitoring DOAC levels into the protocol could potentially decrease the risk of bleeding. Nonetheless, there is limited data available of which DOAC ranges are truly elevated before a procedure (14-16). For this reason, the main aim is to determine DOAC levels in patients before elective surgery following the standard perioperative protocol and to which extent they predict blood loss during the procedure. Furthermore, we will determine if there are specific subgroups at higher risk of elevated DOAC levels. Lastly, we will also assess to which extend albumin levels are associated with periprocedural blood loss.

Method

Study design and population

The DOAC Levels prior to Incision (DALI) study was a cohort study, which included all patients above 18 years that used either apixaban, dabigatran, rivaroxaban who underwent an elective procedure in either the Leiden University Medical Centre (LUMC) or Haga Teaching Hospital between 2019-2024. Patients were included when they met the following inclusion criteria: the use of the DOAC was initiated for at least one week before the procedure, temporary interruption of the DOAC was required and was according to the standard perioperative anticoagulation protocol. They were excluded from participation if they were intellectually disabled. Edoxaban users were not included, because of the low prescription rate in the Netherlands (17).

This study was approved by the medical ethical committee of the LUMC. Screening for eligible patients was done via the preoperative screening (POS) outpatient clinic. Eligible patients were asked to participate and to fill out a written informed consent.

Perioperative DOAC management

DOAC therapy was interrupted and resumed according to the standard perioperative anticoagulation protocol which was according to the Dutch guidelines and based on the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study (1, 6, 7). This management strategy was designed to minimize the risks of bleeding and thromboembolisms around the procedure/surgery (1). The management protocol is summarized below.

Preprocedural DOAC interruption

The DOAC interruption time was based on the bleeding risk of the procedure and the estimated eGFR of the patients (Table 1) (7).

		Time before last dose of procedure	
DOAC	eGFR (mL/min)	Intermediate bleeding risk	High bleeding risk
Apixaban	> 30	24 hours	48 hours
	< 30	36 hours	48 hours
Rivaroxaban	> 30	24 hours	48 hours
	< 30	36 hours	48 hours
Dabigatran	> 80	24 hours	48 hours
	50 – 80	36 hours	72 hours
	30 – 50	48 hours	96 hours

Table 1: Interruption time for each DOAC before the procedure/surgery (7).

Post procedure DOAC resumption

After procedure, DOAC therapy was resumed after 24 hours for intermediate bleeding risk procedures and after 48 – 72 hours for high bleeding risk procedures, provided that adequate hemostasis had been achieved (7).

Patient follow-up and data collecting

At the two hospitals, the baseline characteristics and the follow-up data were obtained from the electronic patient records. These included age, sex, type of DOAC, dose of the DOAC, indication for DOAC therapy, type of surgery, comorbidities, kidney failure, weight, height, hemoglobin, last creatinine and eGFR chronic kidney disease – epidemiology collaboration (CKD-EPI). The Body Mass Index (BMI) was calculated by weight (in kg)/ height2 (in m2) (18).

Patients were followed for 30 days after the procedure to assess the occurrence of major bleeding and minor bleeding events through the electronic patient records. A bleeding event was classified as a major if it was fatal, if it caused a fall in hemoglobin levels of 2.0 g/dL or more, if it led to a blood transfusion or if it was a symptomatic in a critical area or organ: intraspinal, intracranial, intraocular, intra-articular, retroperitoneal or intramuscular with compartment syndrome (19). Any other bleeding was classified as a minor bleeding.

Albumin levels were obtained from the electronic patients records if it was available. Further, if the patient had perioperative blood loss or received blood product during surgery, it was also acquired from the electronic patient records.

Blood collection and DOAC measurement

From the included patients, at least 12.5 mL of blood was collected by the anesthesiologist in two different vacutainer tubes from a venous or central line just before the surgery. One tube was used to determine creatinine levels and the eGFR was calculated with the CKD-EPI equation (20). The other (9 mL, with sodium citrate buffer 3,2%) was used to measure DOAC levels in plasma, which was centrifuged for 8 minutes at 3000 relative centrifugal force at 22 degrees °C. The plasma was then separated into Sarstedt tubes and stored at - 80 °C. The plasma DOAC levels were then measured by liquid chromatography-mass spectrometry (LC-MS).

Definition of elevated DOAC levels

It is unknown which DOAC levels need to be strived for before surgery. Therefore, there is little consensus on which plasma DOAC concentration is related with residual anticoagulant effect. In the study of Douketis et al., < 20 ng/mL was considered safe and ≥ 50 ng/mL was considered elevated for dabigatran (8). However, there is still discussion about the threshold for elevated levels for apixaban and rivaroxaban, since in the literature it is either ≥ 30 ng/mL or ≥ 50 ng/mL (10, 21). For the analysis, we considered ≥ 30 ng/mL elevated for apixaban and rivaroxaban and ≥ 50 ng/mL for dabigatran.

Statistical analyses

Sample size calculation

The sample size calculation was based on previous observations in the study of Douketis et al., where they showed that ~15% of the dabigatran users had increased levels (≥ 20 ng/mL) before surgery with the standard protocol (8). The calculated sample size consisted of 100 patients for each DOAC with power of 80% and p-value of 0.05. We would be able to observe 15% of patients with elevated levels with a 95% confidence interval (CI) of 9 – 23.

Primary outcome

For the primary outcome, DOAC levels were presented as a median with interquartile range (IQR) and in a categorical manner in percentages of patients within each category. These categories were ranges of DOAC levels in ng/mL: <30, 30 - 49 and ≥ 50. This outcome was stratified for each type of DOAC and the bleeding risk of the procedure, and we aimed to also stratify in combination with one of the following: sex, age(< 75 and ≥ 75) and eGFR (<30 mL/min, 30 – 50 mL/min, 50 – 70 mL/min and > 70 mL/min). Nevertheless, this was infeasible, owing to the small subgroups. Therefore, to identify specific patient

populations with increased risk of elevated levels, stratification was carried out for only the type of DOAC and one of the above characteristics. Moreover, for the eGFR stratification, considering the limited number of patients in some of the initial categories, the ranges were expanded for the stratification (<50 mL/min, 50 – 80 mL/min, and >80 mL/min).

Secondary outcome

For each type of DOAC, we performed linear regression to evaluate the association between DOAC levels and blood loss in mL during surgery adjusted for the bleeding risk of the procedure. Also, linear regression was carried out with stratification for the bleeding risk of the surgery. In addition, the 95% CI was estimated for both linear regression models. Besides, for patients with non-elevated levels and elevated levels, the percentage of patients with periprocedural blood loss was described. Further, we used linear regression to evaluate the association between albumin levels and periprocedural blood loss (in mL) adjusted for the procedure bleeding risk and DOAC type, and the 95% CI was estimated. We aimed to analyze this association for every DOAC separately, however this was unattainable due to albumin levels only measured in 63 patients (41 apixaban users, 15 rivaroxaban users, and 11 dabigatran users), therefore the DOAC users were grouped together. Additionally, there was a linear regression model plotted with stratification for the bleeding risk of the surgery, again with an estimated 95% CI. Also, for hypo albumin patients the median and category of the DOAC level was given. Lastly, for each DOAC there was described the number of major and minor bleeding events, and the rate of events was calculated for patients with safe and elevated preprocedural DOAC levels.

Results

Study population

A total of 259 patients were enrolled in the DALI study, 100 patients using apixaban, 100 using rivaroxaban and 56 using dabigatran. At the time the analysis was conducted, the data was completed for 178 patients (68.7%), DOAC measurement failed for 1 patient (0.3%) due to technical difficulties, and measurement had not been performed yet for 80 patients (30.9%). The baseline characteristics of the 178 patients are shown in Table 2, of whom 99 apixaban users, 45 rivaroxaban users and 34 dabigatran users. There was no lost to follow-up. In brief, most procedures had a high bleeding risk (78 for apixaban [78.8%], 42 for rivaroxaban [93.3%], and 26 [76.5%] for dabigatran). Also, patients were more frequently male than female (71 apixaban users [71.7%], 27 rivaroxaban users [60.0%], and 25 dabigatran users [73.5%]). Furthermore, the number of patients with an eGFR <30 mL/min was scarce (3 apixaban users [3.1%], 0 dabigatran users [0%], and 0 rivaroxaban users [0%]). Similarly, patients with an eGFR ≥30 - ≤50 were limited (12 for apixaban [12.2%], 1 for rivaroxaban [2.5%], and 3 for dabigatran [8.8%]).

Table 2: *Patients baseline characteristics*

		Type of DOAC		
Baseline characteristic	Overall, N = 1781	Apixaban, N = 991	Rivaroxaban, N = 451	Dabigatran, N = 341
Age				
<75	107 (60.1%)	56 (56.6%)	31 (68.9%)	20 (58.8%)
≥ 75	71 (39.9%)	43 (43.4%)	14 (31.1%)	14 (41.2%)
Sex				
Female	55 (30.9%)	28 (28.3%)	18 (40.0%)	9 (26.5%)
Male	123 (69.1%)	71 (71.7%)	27 (60.0%)	25 (73.5%)
Bleeding risk of the procedure				
High	146 (82.0%)	78 (78.8%)	42 (93.3%)	26 (76.5%)
Intermediate	32 (18.0%)	21 (21.2%)	3 (6.7%)	8 (23.5%)
eGFR				

		Type of DOAC		
Baseline characteristic	Overall, N = 1781	Apixaban, N = 991	Rivaroxaban, N = 451	Dabigatran, N = 341
< 30	3 (1.7%)	3 (3.1%)	0 (0%)	0 (0%)
30 - 50	16 (9.3%)	12 (12.2%)	1 (2.5%)	3 (8.8%)
50 - 80	83 (48.3%)	42 (42.9%)	26 (65.0%)	15 (44.1%)
> 80	70 (40.7%)	41 (41.8%)	13 (32.5%)	16 (47.1%)
Unknown	6	1	5	0
BMI				
< 18	4 (2.2%)	3 (3.0%)	1 (2.2%)	0 (0.0%)
18 - 30	131 (73.6%)	71 (71.7%)	33 (73.3%)	27 (79.4%)
> 30	43 (24.2%)	25 (25.3%)	11 (24.4%)	7 (20.6%)
Hemoglobin levels*				
Below normal levels	64 (36.0%)	38 (38.4%)	14 (31.1%)	12 (35.3%)
Normal levels	97 (54.5%)	52 (52.5%)	25 (55.6%)	20 (58.8%)
Above normal levels	17 (9.6%)	9 (9.1%)	6 (13.3%)	2 (5.9%)
Indication DOAC treatment				
Atrial Fibrillation	137 (77.0%)	73 (73.7%)	31 (68.9%)	33 (97.1%)
Venous Thrombosis	23 (12.9%)	14 (14.1%)	9 (20.0%)	0 (0.0%)
Other	18 (10.1%)	12 (12.1%)	5 (11.1%)	1 (2.9%)
DOAC dose				
5 mg od	1 (0.6%)	1 (1.0%)	-	-
10 mg od	6 (3.4%)	-	6 (14.0%)	-
20 mg od	29 (16.5%)	-	29 (67.4%)	-
2.5 mg bid	14 (8.0%)	13 (13.1%)	1 (2.3%)	-
5 mg bid	92 (52.3%)	85 (85.9%)	7 (16.3%)	-
110 mg bid	12 (6.8%)	-	-	12 (35.3%)
150 mg bid	22 (12.5%)	-	-	22 (64.7%)
Unknown	2	0	2	0
Congestive Heart failure	2 (1.1%)	2 (2.0%)	0 (0%)	0 (0%)
Hypertension	25 (14.0%)	17 (17.2%)	4 (8.9%)	4 (11.8%)
Diabetes Mellitus	35 (19.7%)	22 (22.2%)	5 (11.1%)	8 (23.5%)
Prior stroke or transient ischemic attack	26 (14.6%)	16 (16.2%)	5 (11.1%)	5 (14.7%)
Atrial fibrillation	42 (23.6%)	17 (17.2%)	13 (28.9%)	12 (35.3%)

		Type of DOAC		
Baseline characteristic	Overall, N = 1781	Apixaban, N = 991	Rivaroxaban, N = 451	Dabigatran, N = 341
Venous Thromboembolism	37 (20.8%)	24 (24.2%)	12 (26.7%)	1 (2.9%)

1n (%)

DOAC: direct oral anticoagulant, eGFR: estimated glomerular filtration rate (mL/min), BMI: Body Mass Index (kg/m2), od: once daily, bid: twice daily.

* Normal hemoglobin levels for males 8.5 – 11.0 mmol/L, for females 7.5 – 10.0 mmol/L

Preoperative DOAC plasma levels

The median preoperative DOAC plasma levels of apixaban and dabigatran were both 7.5 ng/mL (IQR apixaban: 5.0 – 19.4, IQR dabigatran: 2.0 – 8.7) (Table 3). The median preoperative level of rivaroxaban was 4.3 ng/mL (IQR: 0 – 9.1). The majority of the patients had preprocedural levels < 30 ng/mL: 86 apixaban users (86.9%), 43 rivaroxaban users (95.6%), and 33 dabigatran users (97.1%) (Supplementary Figure 1). None of the dabigatran users (0%) had elevated preoperative levels (≥ 50 ng/mL). Of all the apixaban users, 13 (13.2%) had elevated levels, with 6 (6.1%) between 30 - 49 ng/mL, and 7 (7.1%) ≥ 50 ng/mL. For rivaroxaban, only 2 patients (4.4%) had elevated levels, with 1 (2.2%) 30 - 49 ng/mL, and 1 (2.2%) ≥ 50 ng/mL.

Table 3 *Preoperative DOAC plasma levels.*

	Total (n)	Median (ng/mL) (IQR)	< 30 ng/mL		30 - 49 ng/mL		≥ 50 ng/mL	
			n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
Apixaban	99	7.50 (5.0 – 19.4)	86	86.9 [80.2 - 93.5]	6	6.1 [1.4 – 10.8]	7	7.1 [2 – 12.1]
Rivaroxaban	45	4.3 (0 – 9.1)	43	95.6 [89.5 – 101.6]	1	2.2 [-2.1 – 6.5]	1	2.2 [-2.1 – 6.5]
Dabigatran	34	7.50 (2.0 – 8.7)	33	97.1 [91.4 – 102.7]	1	2.9 [-2.7 – 8.6]	0	0

Procedure bleeding risk

For all the DOACs, when stratified for the bleeding risk of the procedure, the median preprocedural DOAC level was higher within the group of intermediate bleeding risk procedures compared to the group with high bleeding risk procedures (Supplementary Table 1). None of the patients with a high bleeding risk procedure had preoperative DOAC levels ≥ 50 ng/mL. Only patients with an intermediate bleeding risk procedure had levels ≥ 50 ng/mL (7 [33.3%] apixaban users, and 1 (33.3%) rivaroxaban users) (Figure 1).

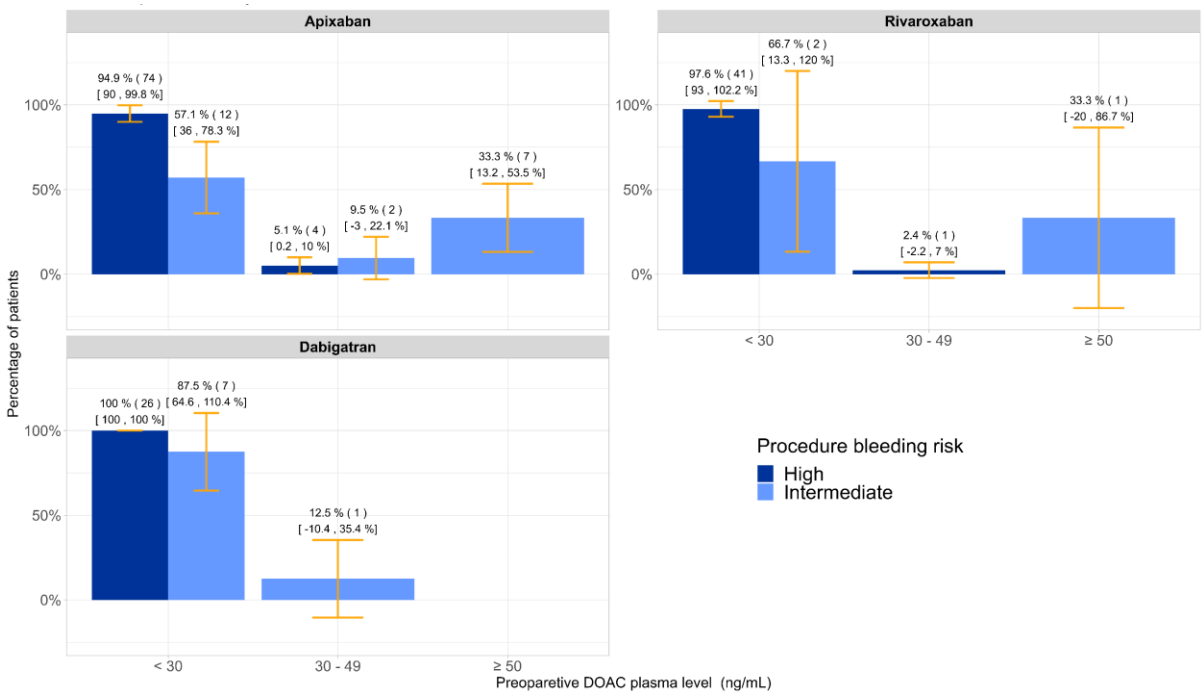

Figure 1 *Distribution of preprocedural DOAC plasma level (ng/mL), stratified for the procedure bleeding risk. The orange error bars represent the 95% CI. Statistics in the figure: % (n) [95% CI].*

Sex

When stratified for sex, there was no difference in the median preoperative DOAC level between males and females for each DOAC (Supplementary Table 2). Further, the percentage of the residual rivaroxaban and dabigatran levels for males and females were similar over the categories (Figure 2). Only for apixaban users, the percentage of females (4 [14.3%]) with levels ≥ 50 ng/mL was higher compared to the percentage of males (3 [4.2%]).

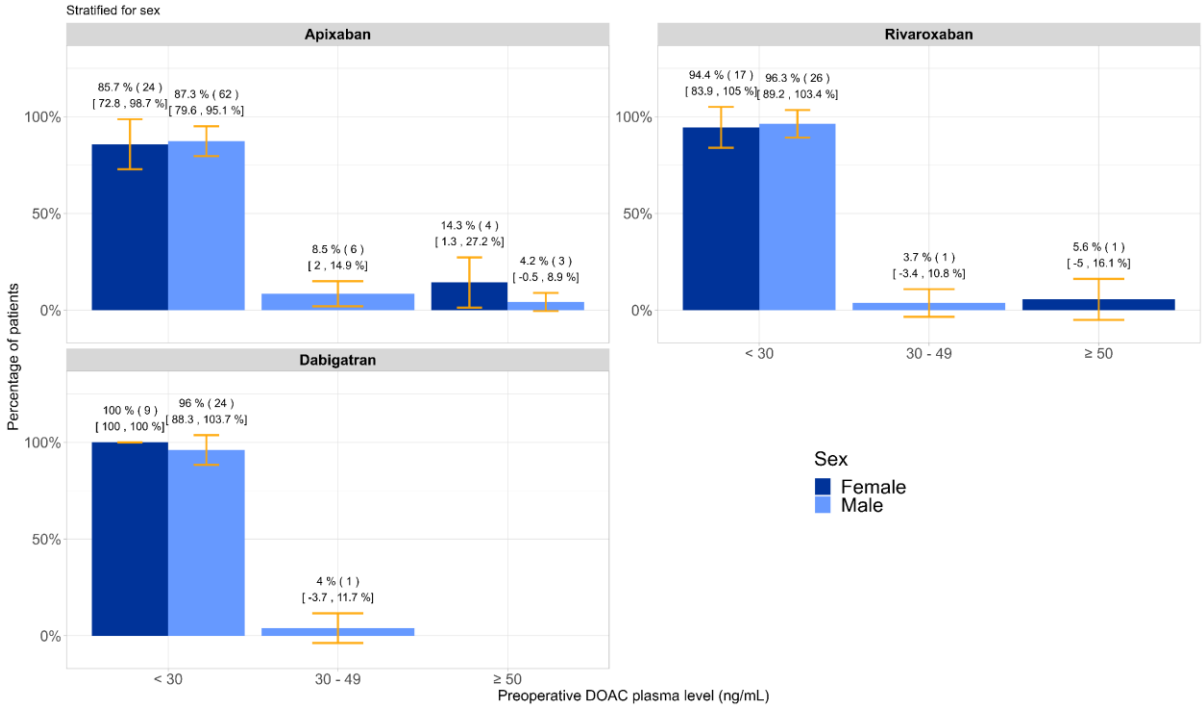

Figure 2 *Distribution of preprocedural DOAC plasma level (ng/mL), stratified for sex. The orange error bars represent the 95% CI. Statistics in the figure: % (n) [95% CI].*

Age

For each DOAC, patients < 75 years old had lower median preoperative levels compared to patients ≥ 75 years old (Supplementary Table 3). Nonetheless, for apixaban levels, patients < 75 age years old had more frequently elevated levels compared to patients ≥ 75 age years (9 [16.0%] versus 4 [9.4%] respectively). For rivaroxaban users, none of the patients ≥ 75 age years had elevated preoperative levels (Figure 3).

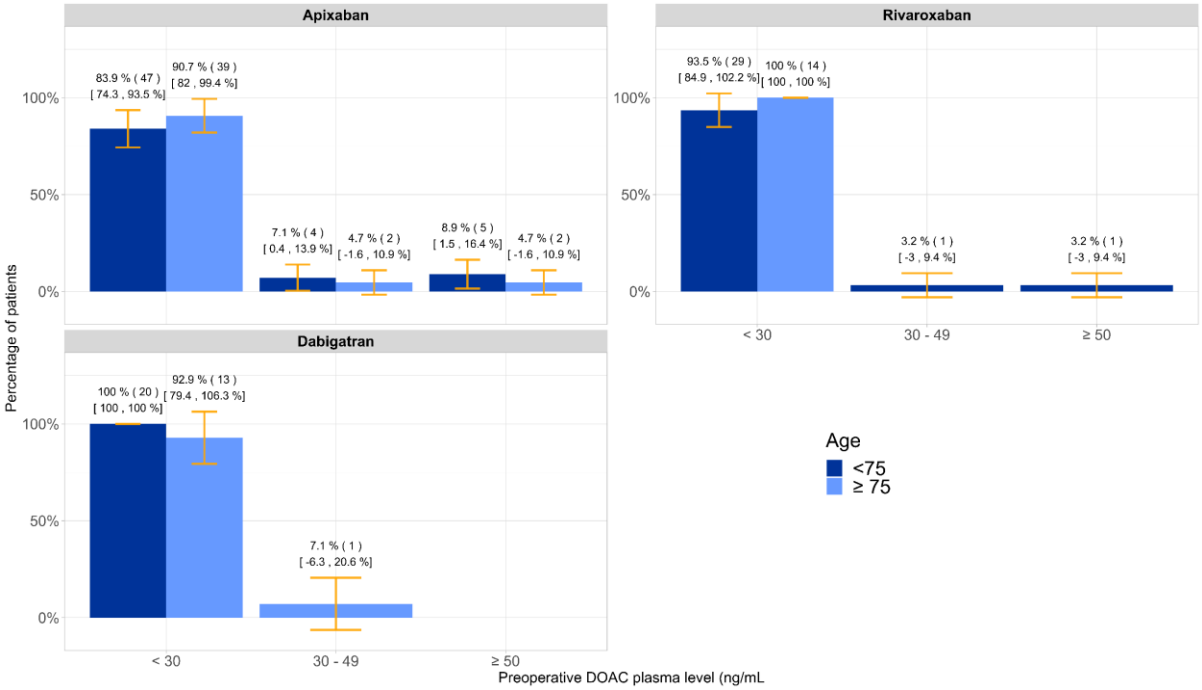

Figure 3 *Distribution of preprocedural DOAC plasma level (ng/mL), stratified for age. The orange error bars represent the 95% CI. Statistics in the figure: % (n) [95% CI].*

Renal function

Patients using apixaban with an eGFR < 50 mL/min had the highest median preoperative level compared to apixaban users with an eGFR 50 - 80 mL/min and > 80 mL/min (19.5 versus 7.5 versus 7.5 respectively) (Supplementary Table 4). Also, this group had a higher percentage with elevated levels in comparison to apixaban users with an eGFR 50 - 80 mL/min and > 80 mL/min (4 [36.4%] versus 6 [14%] versus 2 [4.5%] respectively). For dabigatran and rivaroxaban users, there was no difference in the percentage for the different eGFR categories (Figure 4).

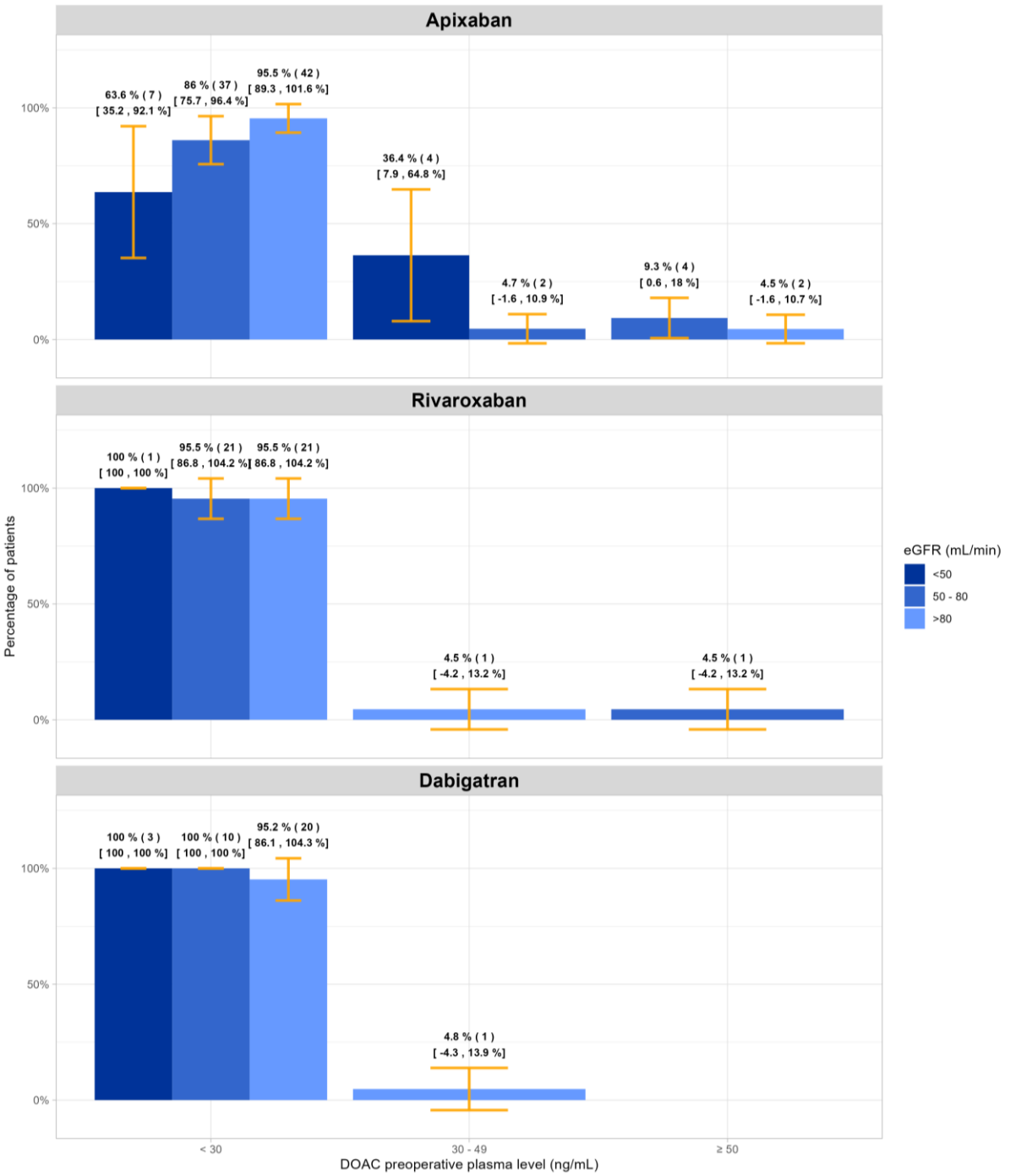

Figure 4 *Distribution of preprocedural DOAC plasma level (ng/mL), stratified for eGFR. The orange error bars represent the 95% CI. Statistics in the figure: % (n) [95% CI].*

Association between DOAC plasma level and perioperative blood loss

Apixaban

For every increase of 1 ng/mL in apixaban concentration, perioperative blood loss increased by 0.7 mL (95% CI: -3.5 – 4.9). For the high bleeding risk procedures, 74 patients (94.9%) had levels < 30 ng/mL of whom 30 (40.5%) experienced perioperative blood loss, whereas 4 patients (5.1%) with elevated levels experienced no perioperative blood loss (Figure 5). Within the group of intermediate bleeding risk procedures, 12 patients (57.1%) had levels < 30 ng/mL of whom 4 (33.3 %) experienced blood loss during surgery. In comparison, 9 patients (42.9%) had elevated levels, 2 of whom (22.2%) experienced periprocedural blood loss.

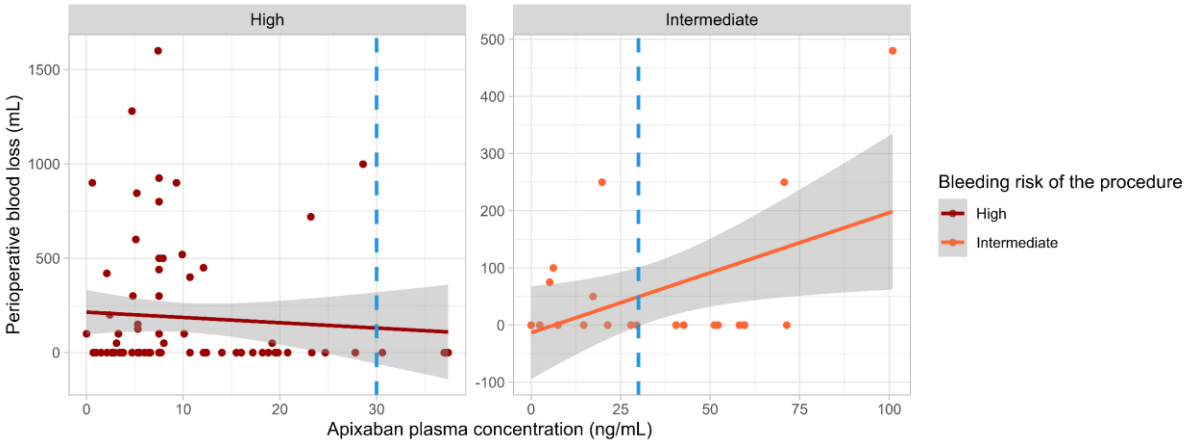

Figure 5 *Relation between residual apixaban plasma level (ng/mL) and perioperative blood loss (mL), stratified for procedure bleeding risk. The blue dashed line represents the rivaroxaban level < 30 ng/mL and the grey area represents the 95% CI.*

Rivaroxaban

For each increase of 1 ng/mL of rivaroxaban, the found decrease in blood loss was 2.2 mL (95% CI: -11.94 – 7.44). Furthermore, out of 41 patients (97.6%) with levels < 30 ng/mL who underwent a high bleeding risk procedure, 12 (29.3%) experienced periprocedural blood loss, whereas 1 patient (2.4%) with elevated levels did not experience blood loss (Figure 6). Within the group of intermediate bleeding risk procedures, 2 patients (66.7%) had levels < 30 ng/mL and none experienced blood loss during surgery. In contrast, 1 patient (33.3%) with elevated levels did experience blood loss.

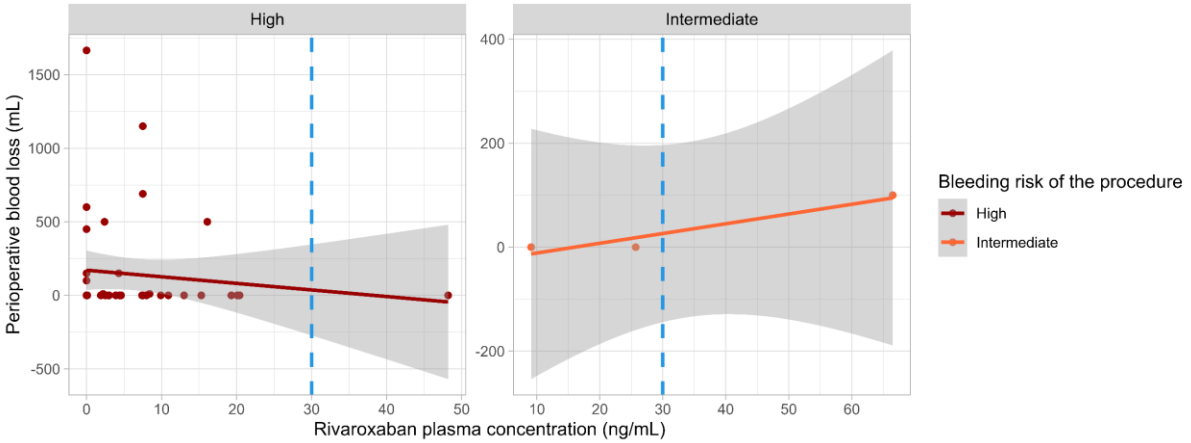

Figure 6 *Association between residual rivaroxaban plasma level (ng/mL) and perioperative blood loss (mL), stratified for procedure bleeding risk. The blue dashed line represents the rivaroxaban level < 30 ng/mL, and the grey area represents the 95% CI.*

Dabigatran

With every increase of 1 ng/mL dabigatran, the periprocedural blood loss increased by 0.2 mL (95% CI of -32.0 – 32.4). For high bleeding risk procedures, all patients had levels < 30 ng/mL, of whom 12 (46.2%) experienced periprocedural blood loss (Figure 7). Furthermore, all patients who underwent intermediate bleeding risk surgery had levels < 50 ng/mL, and among them, 2 (25%) experienced periprocedural blood loss.

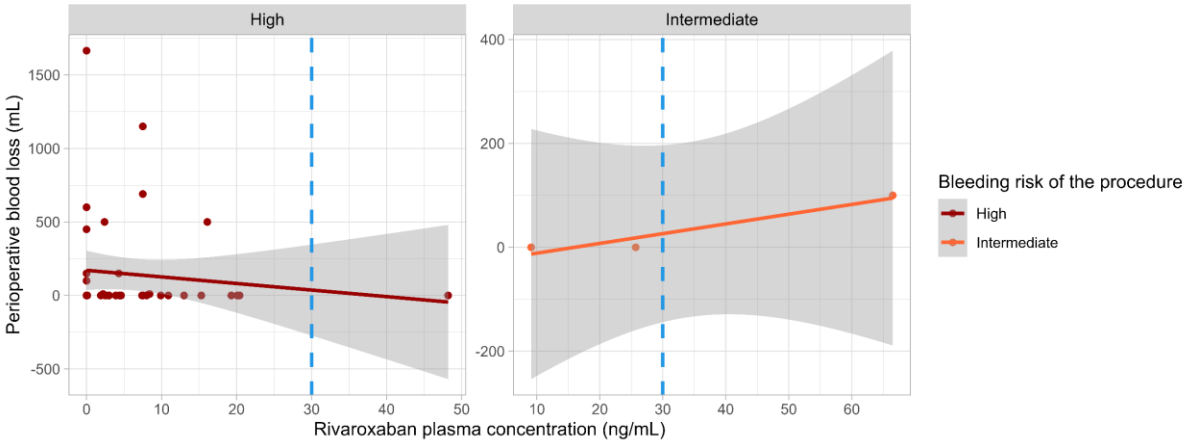

Figure 7 *Correlation between residual dabigatran plasma level (ng/mL) and perioperative blood loss (mL), stratified for procedure bleeding risk. The blue dashed line represents the rivaroxaban level < 50 ng/mL, and the grey area represents the 95% CI.*

Association between albumin level and perioperative blood loss

Albumin levels were measured in 63 patients (41 apixaban users, 15 rivaroxaban users, and 11 dabigatran users). The model suggested for each increase of 1 ng/mL of albumin, there was a corresponding increase in blood loss of 7.2 mL (95% CI: - 6.6 – 21).

All patients with hypo albumin (8) had no perioperative blood loss (Figure 8). The corresponding median DOAC level of these 8 patients was 10.30 ng/mL (7.5 – 15.2) and all had levels < 30 ng/mL.

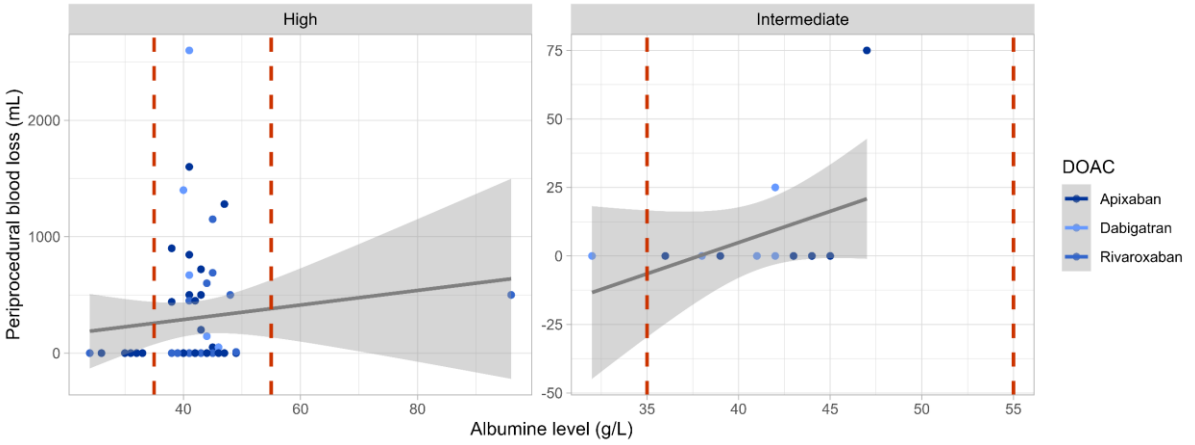

Figure 8 *Relation between albumin level and perioperative blood loss, stratified for the bleeding risk of the procedure: left for high bleeding risk procedures and right for intermediate bleeding risk procedures. The area between the red dashed lines represents the normal albumin range (35 - 55 g/L), and the grey area represents the 95% CI.*

Clinical outcomes

After 30 days of follow up, 9 patients (5.1%) had a major bleeding event. Among patients with elevated levels, none experienced a major bleeding event. In contrast to patients with safe levels, where 9 (5.6%) had a major bleeding event. Furthermore, in 14 patients (7.9%) a minor bleeding occurred. Similarly, patients with safe levels, 13 (8.0%) had a minor bleeding event. Whereas patients with elevated levels, only 1 (6.3%) experienced a minor bleeding event.

Discussion

When following the standard perioperative anticoagulation protocol, the DOAC plasma levels before surgery were elevated for 13.2% of the apixaban users, 4.4% for rivaroxaban users, whereas no dabigatran users had elevated levels. Patients with an intermediate bleeding risk procedure were more likely to have elevated levels compared to patients with high bleeding risk procedures. This observation aligns with the shorter fixed interruption time of the DOAC. Furthermore, for apixaban

users, the subgroups females, < 75 years, or an eGFR < 50 mL/min were found to have higher likelihood of elevated residual DOAC levels. However, these findings were uncertain since the 95% CI were large and overlapped. There was no difference found in the analyzed subgroups for the other two DOACs. Moreover, there was no association observed between residual DOAC levels before surgery and periprocedural blood loss. In fact, only a minority of the patients with elevated DOAC levels experienced periprocedural blood loss, whereas a substantial proportion of patients with DOAC levels < 30 ng/mL did experience blood loss during surgery. Similarly, there was no association between albumin levels and periprocedural blood loss. At last, after 30 days of follow up, 5.1% of the patients had major bleeding event and 7.9% a minor bleeding event. The occurrences of the bleeding events seemed to be unrelated to the preprocedural DOAC level.

In the previous conducted studies, the observed residual dabigatran levels were elevated for 8.8% of the patients in the study of Douketis et al. (> 50 ng/mL), and 4.9% in the study of Shaw et al. (≥ 50 ng/mL) (8, 10). Moreover, the study of Shaw et al. observed ~23% patients with elevated levels (≥ 30 ng/mL) using either apixaban or rivaroxaban (10). In comparison, the DALI study observed fewer elevated levels for apixaban and rivaroxaban users and none for the dabigatran users. The differences between the observations of Douketis et al. and Shaw et al. compared to the DALI study could potentially be explained by the following variances. First of all, dabigatran (34 patients) and rivaroxaban (45 patients) did not reach the estimated sample size of 100 patients. By contrast, the studies of Douketis et al. (118 dabigatran patients) and Shaw et al. (1086 apixaban, 920 rivaroxaban, 535 dabigatran users) included larger study populations, potentially leading to differences due to statistical variation (8, 10). Moreover, baseline characteristics associated with a higher risk of elevated preprocedural DOAC level slightly differed between the DALI study, and the studies of Douketis et al. and Shaw et al (8, 10). For instance, in the study of Douketis et al. patients underwent more frequently a low/intermediate bleeding risk procedure than a high bleeding risk procedure, and had more patients with a low creatine clearance compared to the DALI study (8). Similarly, the study of Shaw et al. had more patients who underwent a low/intermediate bleeding risk procedure in contrast to patients with a high bleeding risk procedure (10). Therefore, the observed difference could be attributed to the variations in patient populations, since these demographics give a higher likelihood of elevated levels (10). Besides, at the LUMC, patients receive an additional telephonic consultation to be informed about the interruption of DOAC use. The communication to patients about the interruption time might have been less regulated in the other hospitals that participated in previous studies, potentially leading to lower adherence to the interruption protocol (8, 10). Consequently, this might have resulted in an increased rate of elevated levels in the aforementioned studies (8, 10).

Furthermore, while following the periprocedural protocol, another study of Douketis et al. observed less major bleeding events (1.35% for apixaban, 0.90% for dabigatran, and 1.85% for rivaroxaban) compared to our study (5.1%) (1). This higher rate of events could potentially be explained by the higher frequency of patients who underwent a high bleeding risk procedure (82.0%) compared to the study of Douketis et al. (~33%) (1).

In addition, the study of Shaw et al. found that low-intermediate bleeding risk procedures were associated with higher likelihood of elevated DOAC, similarly to our results (10). Moreover, Shaw et al. observed that females, age ≥75 years, creatine clearance of < 50 mL/min were associated with increased risk of elevated levels (10). In comparison, we only observed for apixaban a difference in the probability for elevated levels for the following subgroups: < 75 years, eGFR < 50 mL/min, females. Nonetheless, these findings came with uncertainties. These disparities could be attributed to the small sample size of the three DOAC cohorts compared to the cohorts of Shaw et al (10). Consequently, the subgroups were potentially too small to observe such a difference. Furthermore, we hypothesized that patients with hypo albumin might have an increased bleeding risk (11). However, we did not find an association, which may be attributed to the limited number of patients with hypo albumin and their concomitant low preprocedural DOAC levels. Therefore, the increased unbound fraction in hypo albumin patients in this study would exert a negligible anticoagulant effect.

The DALI study is the first study that investigated the association between residual DOAC levels and the periprocedural blood loss and between albumin levels an periprocedural blood loss. However, it was underpowered for these analyses, since it was not the primary outcome. Another strong point, it gives more insight in which residual DOAC levels are unacceptably high, since there was scarce data on this topic. Nonetheless, this study also had some limitations. First of all, the sample size was not reached for dabigatran and rivaroxaban. However, the DALI study will continue further to collect more patients for these two cohorts. Yet, regarding the calculated sample size, it should be noted that this was based on the study of Douketis et al. with ~15% of dabigatran users with elevated levels of ≥ 20 ng/mL. After the calculation, the defined elevated levels for the DALI study was raised to ≥ 50 ng/mL for dabigatran and ≥ 30 ng/mL for apixaban and rivaroxaban. Consequently, the estimated sample size might have been too small. Moreover, the cohorts were too small for stratification for the type of DOAC in combination with the procedure bleeding risk and one of the following: sex, age, or eGFR. In addition, the small

sample size could attribute to the non-significant findings. Another limitation, the albumin levels were only obtained when assessed during routine healthcare. Hence, the limited number of observations.

In conclusion, the observed elevated levels for each DOAC was minor. Moreover, the data implied that the periprocedural blood loss, major and minor bleeding events were unrelated to the residual DOAC concentration. Therefore, this indicates that the standard perioperative anticoagulation protocol is safe and that there may be no necessity to include monitoring the DOAC levels before surgery into the protocol.

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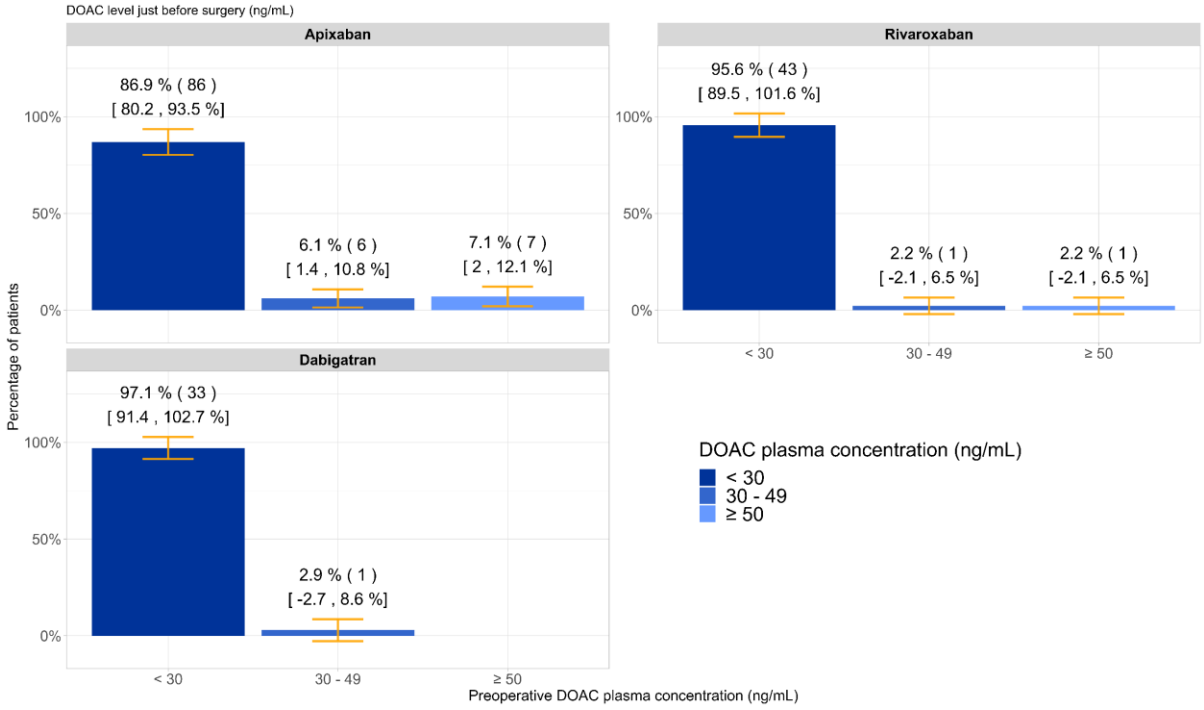
Supplementary



Supplementary Figure 1 *Distribution of DOAC plasma level just before surgery (ng/mL). The orange error bars represent the 95% CI. Statistics in the figure: % (n) [95% CI].*

Supplementary Table 1 *DOAC plasma levels before surgery stratified for procedure bleeding risk*

DOAC (n)	Bleeding risk of the procedure (n)	Median (ng/mL) (IQR)	< 30 ng/mL		30 - 49 ng/mL		≥ 50 ng/mL	
			n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
Apixaban (99)	High (78)	7.5 (4.0 – 12.3)	74	94.9 [90 – 99.8]	4	5.1[0.2 – 10]	0	0
	Intermediate (21)	27.9 (7.5 – 52.2)	12	57.1 [36 – 78.3]	2	9.5 [-3 – 22.1]	7	33.3 [13.2 – 53.5]
Rivaroxaban (45)	High (42)	3.45 (0 – 7.9)	41	97.6% [93 – 102.2]	1	2.4 [-2.2 – 7]	0	0
	Intermediate (3)	25.70 (17.4 – 46.1)	2	66.7 [13.3 – 120]	0	0	1	33.3 [-20 – 86.7]
Dabigatran (34)	High (26)	7.5 (1.6 – 7.5)	26	100	0	0	0	0
	Intermediate (8)	11.3 (7.5 – 22.9)	7	87.5 [64.6 – 110.4]	1	12.5 [-10.4 – 35.4]	0	0

Supplementary Table 2 *DOAC plasma levels just before surgery stratified for sex*

DOAC (n)	Sex (n)	Median (ng/mL) (IQR)	< 30 ng/mL n (%) [95% CI]		30 - 49 ng/mL n (%) [95% CI]		≥ 50 ng/mL n (%) [95% CI (%)]	
			n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
Apixaban (99)	Female (28)	7.5 (5.2 – 18.9)	24	85.7 [72.8 - 98.7]	0	0	4	14.3 [1.3 – 27.2]
	Male (71)	7.5 (4.8 – 19.4)	62	87.4 [79.6 - 95.1]	6	8.5 [2 – 14.9]	3	4.2 [-0.5 – 8.9]
Rivaroxaban (45)	Female (18)	4.15 (0 – 14.2)	17	94.4 [83.9 – 105]	0	0	1	5.6 [-5 – 16.1]
	Male (27)	4.3 (1 – 8.3)	26	96.3 [89.2 – 103.4]	1	3.7 [-3.4 – 10.8]	0	0
Dabigatran (34)	Female (9)	7.5 (7.5 – 7.5)	9	100	0	0	0	0
	Male (25)	7.5 (1.6 – 10.5)	24	96 [88.3 – 103.7]	1	4 [-3.7 – 11.7]	0	0

Supplementary Table 3 *DOAC plasma levels just before surgery stratified for age*

DOAC (n)	Age (n)	Median (ng/mL) (IQR)	< 30 ng/mL n (%) [95% CI]		30 - 49 ng/mL n (%) [95% CI]		≥ 50 ng/mL n (%) [95% CI]	
			n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
Apixaban (99)	< 75 (56)	7.5 (3.1 – 21.4)	47	83.9 [74.3 – 93.5]	4	7.1 [0.4 – 13.9]	5	8.9 [1.5 – 16.4]
	≥ 75 (43)	9.3 (6.2 – 18.1)	39	90.7 [82 – 99.4]	2	4.7 [-1.6 – 10.9]	2	4.7 [-1.6 – 10.9]
Rivaroxaban (45)	< 75 (31)	3 (0.1 – 8.8)	29	93.5 [84.9 – 102.2]	1	3.2 [-3.0 – 9.4]	1	3.2 [-3.0 – 9.4]
	≥ 75 (14)	6 (0.6 – 9.3)	14	100 [100 – 100]	0	0	0	0
Dabigatran (34)	< 75 (20)	7.1 (1.5 – 7.5)	20	100 [100 – 100]	0	0	0	0
	≥ 75 (14)	8.3 (6.9 – 11.7)	13	92.9 [79.4 – 106.3]	1	7.1 [-6.3 – 20.6]	0	0

Supplementary Table 4 *DOAC plasma levels just before surgery stratified for eGFR*

DOAC (n)	Renal function (mL/min) (n)	Median (ng/mL) (IQR)	< 30 ng/mL		30 - 49 ng/mL		≥ 50 ng/mL n (%) [95% CI]	
			n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
Apixaban (98*)	eGFR <50 (11)	19.5 (8.7 – 33.8)	7	63.6 [35.2 – 92.1]	4	36.4 [7.9 – 64.8]	0	0
	eGFR 50 - 80 (43)	7.5 (5.4 – 17.8)	37	86 [75.7 – 96.4]	2	4.7 [-1.6, 10.9]	4	9.3 [0.6 – 18]
	eGFR >80 (44)	7.5 (3.1 – 15.9)	42	95.5 [89.3 – 101.6]	0	0	2	4.5 [-1.6 – 10.7]
Rivaroxaban (45)	eGFR <50 (1)	7.5 (7.5 – 7.5)	1	100	0	0	0	0
	eGFR 50 - 80 (22)	4.5 (2.0 – 9.3)	21	95.5 [86.8 – 104.2]	0	0	1	4.5 [-4.2 – 13.2]
	eGFR >80 (22)	2.7 (0 – 8.9)	21	95.5 [86.8 – 104.2]	1	4.5 [-4.2 – 13.2]	0	0
Dabigatran (34)	eGFR <50 (3)	9.9 (6.1 – 10.3)	3	100	0	0	0	0
	eGFR 50 - 80 (10)	7.5 (3.3 – 8.7)	10	100	0	0	0	0
	eGFR >80 (21)	7.5 (1.6 – 7.5)	20	95.2 [86.1 – 104.3]	1	4.8 [-4.3 – 13.9]	0	0

*Within the apixaban group, 1 assessment of the eGFR failed due to technical difficulties and remained unknown, and was excluded from this analysis.