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Measurement of plasma direct oral anticoagulants concentrations in real-world clinical and laboratory settings on a 24/7 basis: a 10-year experience

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Abstract

Routine direct oral anticoagulant (DOAC) measurements are not recommended; however, they may be useful in some clinical situations. We sought to evaluate the everyday practice in DOAC measurements on a 24/7 basis including the number of tests over 10 years, indications in out- and inpatients, and turnaround time (TAT) in our tertiary center. From 2013 to 2023, we evaluated all consecutive 758 DOAC measurements performed in 628 patients, aged 61.9 ± 17.6 years mostly with venous thromboembolism (n = 211, 33.5%) and atrial fibrillation (n = 207, 33%) using chromogenic methods. The median number of tests was 6 per month (interquartile range (IQR) 3–9). There were parabolic trend lines for rivaroxaban (n = 308, 40.6%) and dabigatran (n = 241, 32.1%) measurements with a peak in 2017, while apixaban (n = 209, 27.3%) measurements were stable over the study period. The most common indications for DOAC measurements were drug-drug interactions (n = 92, 24.2%) and questionable adherence (n = 60, 15.9%) for outpatients (n = 380, 50.1%), while the assessment of residual DOAC concentrations before invasive procedures (n = 98, 28%) and in embolic stroke of undetermined source (n = 74, 19.6%) were for inpatients (n = 378, 49.9%) including 91 (12%) urgent samples. The median TAT was 89 min (63–126 min) and was shorter by 30 min at the night shifts (n = 256, 33.8%). For emergencies in 2023, TAT reached 42 min (34–54 min). To our knowledge, this is the longest study on how often, in whom, and for which reason DOAC measurements were requested over the last 10 years if a 24/7 service is available. We showed that DOAC measurements are stably requested in inpatients and outpatients but obtaining the results within 30 min is hardly feasible.

Graphical Abstract

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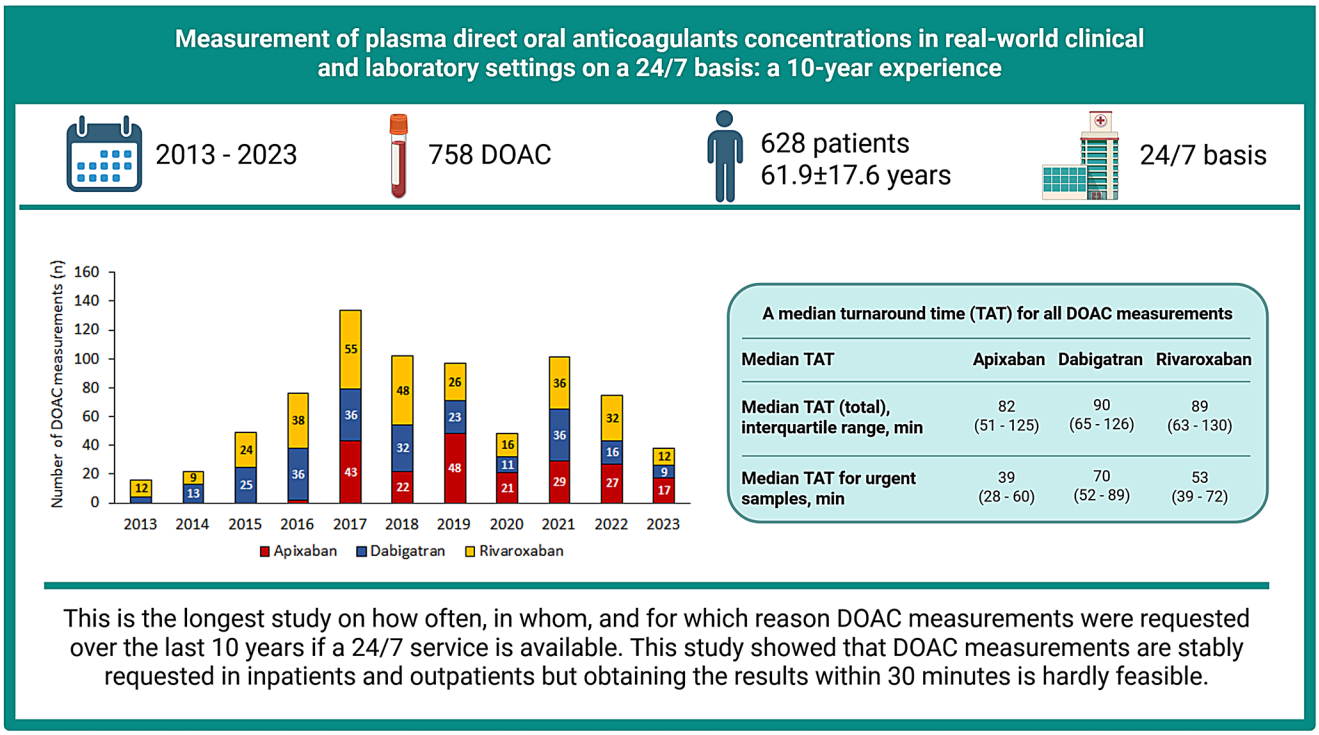

Keywords Apixaban · Dabigatran · Rivaroxaban · Turnaround time

Introduction

Direct oral anticoagulants (DOACs), including oral direct thrombin inhibitors (i.e., dabigatran) and direct factor Xa inhibitors (i.e., apixaban, rivaroxaban, edoxaban), are increasingly used in the last ten years, replacing vitamin K antagonists (VKAs) in most indications [1–3]. DOACs are widely used for stroke prevention in patients with atrial fibrillation (AF) and for the treatment of venous thromboembolism (VTE) [4–6] as well as to prevent postoperative VTE following elective knee or hip replacement surgery [7]. DOACs have few drug interactions and do not require routine monitoring of any coagulation variables due to their more predictable pharmacokinetic and pharmacodynamics profiles than VKAs [4]. Seminal phase III randomized controlled trials (RCTs) comparing DOACs to VKAs have been conducted without dose adjustments based on plasma level measurements. However, DOAC measurements may be required in some emergent (e.g., serious bleeding, urgent surgery, acute ischemic stroke in case of thrombolysis consideration, DOAC reversal) or elective (e.g., obesity, renal hypo- or hyperfunction, serious liver disease, suspected drug-drug interactions or gastrointestinal malabsorption) indications [4, 5, 8, 9, 10]. Of note, in appropriately selected patients, it would be ideal to perform DOAC measurements before the administration of antidote (such as idarucizumab or andexanet al.fa), which could prevent unnecessary prescription of expensive molecules [6].

In the 2021 European Heart Rhythm Association Practical Guide on the use of DOACs, it has been stated that: "DOAC anticoagulant activity can be measured via specific coagulation tests developed for the quantification of DOAC plasma levels; institutions should strongly consider 24/7 availability of these tests for emergency situations" [4]. The update of the International Council for Standardization in Haematology (ICSH) from 2021 recognized that there are insufficient data for providing dose-adjustment recommendations based on DOAC levels alone, however, their measurements may identify potential excessive clearance or drug accumulation and could be used in situations where the benefit of such measurement is likely to outweigh the risk [11]. In the latest 2023 ACC/AHA/ACCP/HRS guidelines for the diagnosis and management of AF, the experts do not recommend the routine measurement of DOAC concentrations, allowing for such testing "when clinicians assess DOAC adherence for potentially noncompliant patients, quantify residual anticoagulation levels before emergency invasive procedures/surgeries, or evaluate the absorption of DOAC after bariatric surgery" [12].

The largest study on the experience of DOAC measurements in everyday practice was conducted by Cavaillez et al. [13] with 2,197 assays from the Bordeaux University

Hospital performed over two years. Two other reports based on analysis of 292 and 604 blood samples of in- and outpatients from medical centers in Israel and the Netherlands, respectively, did not contain a clear statement on whether DOAC measurements were performed on a 24/7 basis or not [14, 15]. There were also several small-sized studies, all without data on changes in the number of DOAC measurements during the COVID-19 pandemic [16–21]. The first Polish experience from our center with rivaroxaban and dabigatran measurements was reported in patients with DVT and AF in 2014, respectively [22, 23], and then with apixaban in 2018 [24].

Given a paucity of real-life experience with DOAC measurements on a 24/7 basis, we sought to evaluate everyday practice in such investigations from laboratory and clinical perspectives, including the number of DOAC measurements, indications in out- and inpatients, and turnaround time (TAT) in our tertiary center which has the longest experience in the measurement of plasma DOAC concentrations in Poland including the COVID-19 pandemic.

Materials and methods

The DOACs levels were measured in blood samples from all 628 consecutive hospitalized or ambulatory patients in whom physicians requested such investigations in the Saint John Paul II Hospital, Krakow, Poland. We assessed plasma rivaroxaban and dabigatran levels measured since their initiation in May 2013 to April 30, 2023 and apixaban levels from December 2016 to April 30, 2023. The DOAC measurements performed for scientific purposes were excluded. From the very beginning, DOAC measurements were available on a 24/7 basis in our center, which is a 576-bed high tertiary care hospital with 26 departments, that offer a wide range of medical services mainly in the field of cardiology, heart and vascular surgery, lung diseases, and thoracic surgery, including diagnostic evaluation and therapy in emergent coronary interventions, and acute stroke. The total number of admissions in 2023 was 149,152, including 119,692 outpatient admissions and 29,460 hospital admissions.

Demographic and clinical data of all the patients tested for DOAC levels were collected using a questionnaire. The current retrospective study was part of a routine clinical diagnostic evaluation; therefore, the approval of the Bioethical Committee was not required.

Indications for DOAC measurements

The indications for DOAC measurements in outpatients were categorized as follows: suspected clinically relevant drug-drug interactions e.g., anticancer agents, carbamazepine, rifampicin, amiodarone, verapamil, and others; questionable adherence; obesity defined as a body mass index (BMI)$\geq$35 kg/m^2, or >120 kg; a very low weight (BMI<18 kg/m^2) in particular in elderly patients; history of recurrent minor or any clinically relevant bleeding reported by patients at visit when were not explained by his/her comorbidities and/or concomitant treatment; liver cirrhosis; chronic kidney disease defined as an estimated glomerular filtration rate of <60 mL/minutes/1.73 m^2; thromboembolic events under controlled anticoagulation; prior bariatric surgery; and gastrointestinal malabsorption.

In inpatients the indications were as follows

before planned or urgent surgery or invasive procedure if there was a suspicion that the drug had not been appropriately stopped as recommended by a physician (e.g., arrhythmia ablation, transbronchial biopsy, cardioverter defibrillator implantation, cardiovascular surgery); suspicion/signs of embolic stroke of undetermined source (ESUS) if a patient was considered for thrombolytic therapy; severe liver injury or kidney dysfunction; morbid obesity or low body weight (see indications for outpatients); suspected clinically relevant drug-drug interactions; and DOAC reversal.

Laboratory investigations

DOAC measurements were performed in citrated plasma samples. Blood samples were drawn from an antecubital vein with minimal stasis and transferred to the central hospital laboratory within 10 min in special transport containers. Blood samples were collected into citrated tubes (9:1 of 0.106 M sodium citrate; Monovette, Sarstedt, Nümbrecht, Germany), centrifuged at 2500 g and 20 °C for 10 min to obtain platelet-poor plasma, and then tested as soon as possible. The assays used to measure DOACs are shown in Table 1. DOAC measurements were performed on the BCS-XP automated analyzer (Siemens Healthcare, Marburg, Germany) from 2013 to mid-2022, while from July 2022 to April 2023 on the Atellica COAG 360 System (Siemens Healthcare, Marburg, Germany). When a higher working range of DOACs was required e.g., for samples>500 ng/mL, the samples were diluted with standard human plasma (1:1). For DOAC concentrations below the detection threshold, i.e., <30 ng/mL, lower concentration calibrators were used, especially in patients undergoing surgery or with ESUS while using DOACs.

TAT was calculated as the time from the test request to the final report of its results. The data were analyzed separately for the day shift (from 7:00 a.m. to 2:35 p.m.) when the laboratory was fully staffed and on duty (from 2:35 p.m. to

Table 1 The assays used to determine concentrations of direct oral anticoagulants (DOACs)

DOAC	Introduction of DOAC measurements	Name of test	Analytical ranges of measurement*	Detection threshold (ng/mL)	References ranges for DOACs**		
					Indications	C_{max}, ng/mL	C_{min}, ng/mL
Apixaban	December 2016 - June 2019	Chromogenic Biophen DiXaI test (Hyphen BioMed, Neuville-Sur-Oise, France)	50–350 ng/mL from December 2016	50 20	VTE AF	59–302 69–321	22–177 34–230
	July 2019 -present	Chromogenic Innovation Anti-Xa Test (Siemens Healthineers, Erlangen, Germany)	0–350 ng/mL from July 2019 till present				
Dabigatran	July 2013 - June 2019	Hemoclot thrombin inhibitor test (Hyphen BioMed, Neuville-sur-Oise, France)	35–500 ng/mL from July 2013 till December 2016	35 20	VTE AF	117–275 64–443	61–143 31–225
	July 2019 - present	Innovance DTI Test (Siemens Healthineers, Erlangen, Germany)	0–500 ng/mL from January 2017 till present				
Rivaroxaban	May 2013 - June 2019	Chromogenic Biophen DiXaI test (Hyphen BioMed, Neuville-Sur-Oise, France)	50–500 ng/mL from May 2013	50 20	VTE AF	22–535 184–343	6–239 12–137
	July 2019 - present	Chromogenic Innovation Anti-Xa Test (Siemens Healthineers, Erlangen, Germany)	0–500 ng/mL from March 2018 till present				

* samples with the DOAC levels above 500 ng/mL were diluted; ** the reference values were provided with the information about DOAC concentrations with the therapeutic effect. AF, atrial fibrillation; C_{max}, maximal concentration after 2–4 h from the last dose of DOAC; C_{min}, minimal concentration before the next dose; PE, pulmonary embolism; VTE, venous thromboembolism

7:00 a.m.) when only 3 employees worked (the night shift) based on the hospital regulations. In addition, we assessed TAT for each DOAC according to the priority (urgent versus non-urgent) or the category of patients (inpatients versus outpatients).

Statistical analysis

Variables are presented as numbers and percentages, mean ± standard deviation (SD), or median and interquartile range (IQR), as appropriate. Normality was assessed by Shapiro-Wilk test. Mean times were compared between years with the Kruskal–Wallis ANOVA due to the small number of measurements in some cases. The comparison of the year and type of drug were done by the chi-square test. The post-hoc analysis was applied for both the Kruskal-Wallis ANOVA and the chi-square test as appropriate. The influence of years, the status (outpatients or inpatients), and time of day (the day shift or the night shift) on a mean TAT of DOAC measurements was assessed by the multivariable linear regression separately for apixaban, rivaroxaban, and dabigatran. The number of tests performed in 2023 was too small (the data were available till April) to include this year in the advanced statistical analysis so the regression models were built based on the number of tests available for all 12 months per year (2013–2022).

The normality of the models residues was verified by the Shapiro-Wilk test and normality plots. The Breusch-Pagan test was used for heteroscedasticity and the Durbin-Watson test was used to check autocorrelation in the regression models. A P-value < 0.05 was considered statistically significant. Statistical calculations were performed using STATISTICA Version 13.3 (StatSoft, Inc., Tulsa, Oklahoma, United States) and Rv.4.1.0 [25].

Results

Number of DOAC measurements

A total of 758 consecutive DOAC measurements, which represented as few as 0.0016% of all laboratory investigations performed between May 2013 and April 2023 in the hospital laboratory, were evaluated. DOAC measurements were requested in 628 patients aged 5–99 years, 61.9 ± 17.6 years (258 women, 45.4%). Blood samples for DOAC measurements were obtained from similar numbers of hospitalized patients ($n = 378$, 49.9%) and outpatients ($n = 380$, 50.1%).

As shown in Fig. 1A, in 2013 as few as 16 (2.1% of the total) DOAC measurements were performed with a tendency to increase in the following years and a peak was reached in 2017 ($n = 134$, 17.7%).

Then the number of DOAC measurements was rather constant over the study period for apixaban and dabigatran, while for rivaroxaban slightly fluctuations were observed, then declined by 50% during the COVID-19 pandemic in 2020; however, in 2021 and 2022, the number of tests increased, reaching pre-pandemic levels in the latter. To

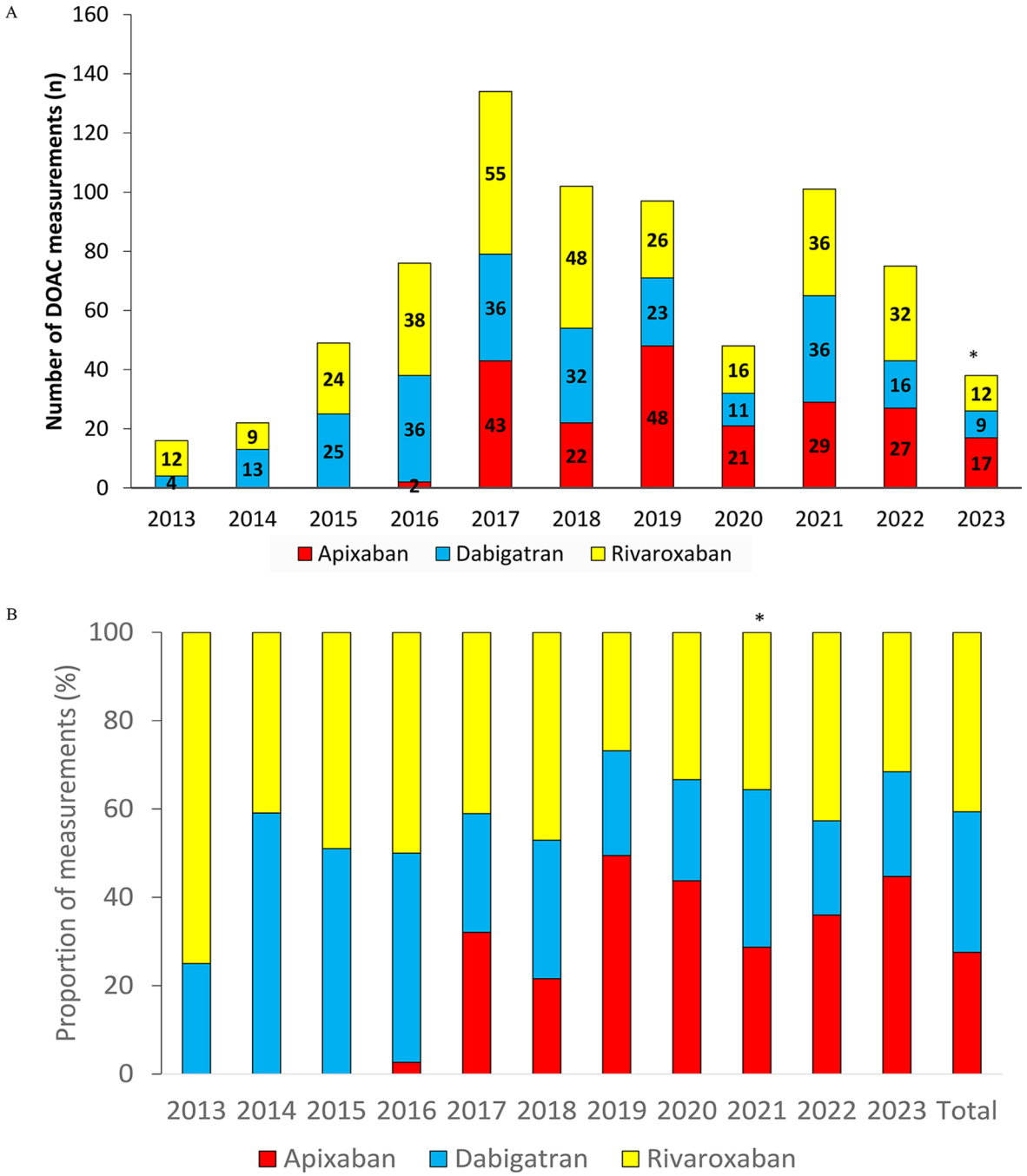

Fig. 1 Direct oral anticoagulant (DOAC) measurements between 2013 and 2023; a number (**A**) and a percentage (**B**) of measurements for individual drugs. *, data for 2023 were collected from January to April

sum up, the fewest tests were performed in the first year of measurements and during the COVID-19 pandemic in 2020 for all DOACs. From May 2013 to April 2023, plasma concentrations of rivaroxaban were determined in 308 samples (40.6%), followed by dabigatran 241 (32.1%) and from December 2016 to April 2023, apixaban 209 (27.3%) (Fig. 1B).

The median total number of DOAC measurements monthly was 6.0 (IQR:3.0–9.0) in the studied period of time. Most of the patients were tested once ($n=500$, 84.2%), while 74 (12.5%) patients had two measurements performed. Triple measurements were requested in 15 (2.5%) patients. Two patients were assessed 4 (0.3%) times, one subject 5 (0.2%) times, and two individuals as many as 7 (0.3%) times. Of note, following the introduction of

idarucizumab, a reversal agent for dabigatran in 2016, we tested the samples from 16 (2.1%) patients before or during the use of this antidote, despite the fact that such testing was not recommended by experts.

There was a relationship between the year in which the DOACs were measured and the type of the drug ($p<0.0001$). In the years 2016–2020 the number of apixaban measurements showed a polynominal trend (Fig. 2A) confirmed by nonlinear regression ($p=0.038$). The number of dabigatran and rivaroxaban measurements showed a parabolic trend line (Fig. 2B and C, respectively) with a peak value reached in 2016 and 2017 (in both years $n=36$) for dabigatran and in 2017 ($n=55$) for rivaroxaban. The post-hoc analysis showed that the number of tests per year for apixaban (19.2) is smaller than for dabigatran or rivaroxaban (23.2 and 29.6, respectively; for both comparisons, $p<0.0001$): there was no significant difference between the values for dabigatran and rivaroxaban ($p=0.29$).

Five hundred and two (66.2%) samples were measured during the day shift and 256 (33.8%) during the night shift. Ninety-one (12%) tests were urgent with similar percentages in consecutive years, whereas the remaining 667 samples (88%) were assessed as a regular investigation requested mostly in outpatients ($n=362$, 56.6%).

DOAC measurements were performed in patients with VTE ($n=211$, 33.5%), AF ($n=207$, 33.0%), ESUS ($n=109$, 17.3%), heart failure ($n=32$, 5.1%), acute myocardial infarction ($n=25$, 4.1%) and other ($n=44$, 7.0%). Of note, the youngest patient in whom the measurement was performed was a 5-year-old girl with Wilson's disease on dabigatran (150 mg, twice a day) despite no indication for its use in children at that time. The oldest patient tested was a 99-year-old woman with AF on rivaroxaban who was admitted to an emergency department with a suspicion of acute ischemic stroke, and the concentration of 12 ng/mL obtained within one hour enabled successful thrombolysis in this patient.

Indications for DOAC measurements

As shown in Fig. 3A, indications for DOAC measurements in outpatients ($n=380$, 50.1%) were as follows: drug-drug interactions ($n=92$, 24.2%) most commonly: anticancer medications ($n=48$, 52.2%), carbamazepine ($n=25$, 27.2%), rifampicin ($n=12$, 13%); questionable adherence ($n=60$, 15.8%); morbid/extreme obesity ($n=60$, 15.8%); bleeding episodes ($n=59$, 15.5%); chronic kidney disease ($n=38$, 10.0%); liver cirrhosis ($n=20$, 5.3%); bariatric surgery ($n=20$, 5.3%); low body weight ($n=13$, 3.4%); occurrence of thromboembolic events under correctly conducted anticoagulation ($n=12$, 3.1%; AF: $n=8$, 2%, VTE: $n=4$, 1%), and malabsorption ($n=6$, 1.6%).

The indications for DOAC measurements in inpatients ($n=378$, 49.9%) presented in Fig. 3B were: before invasive procedures such as coronary angiography, arrhythmia ablation, cardiac electronic device implantation ($n=98$, 25.9%);

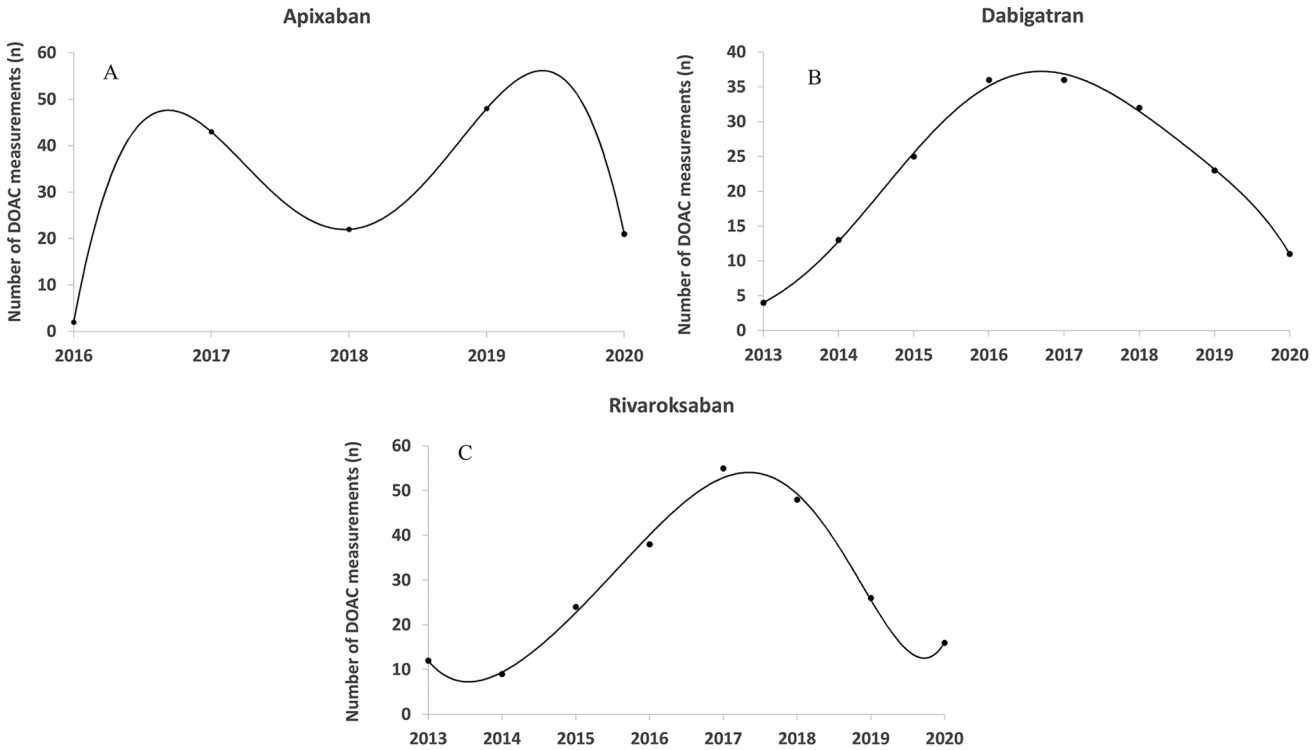

Fig. 2 Temporal trends in the number of direct oral anticoagulant (DOAC) measurements. (**A**) Apixaban; (**B**) Dabigatran; (**C**) Rivaroxaban

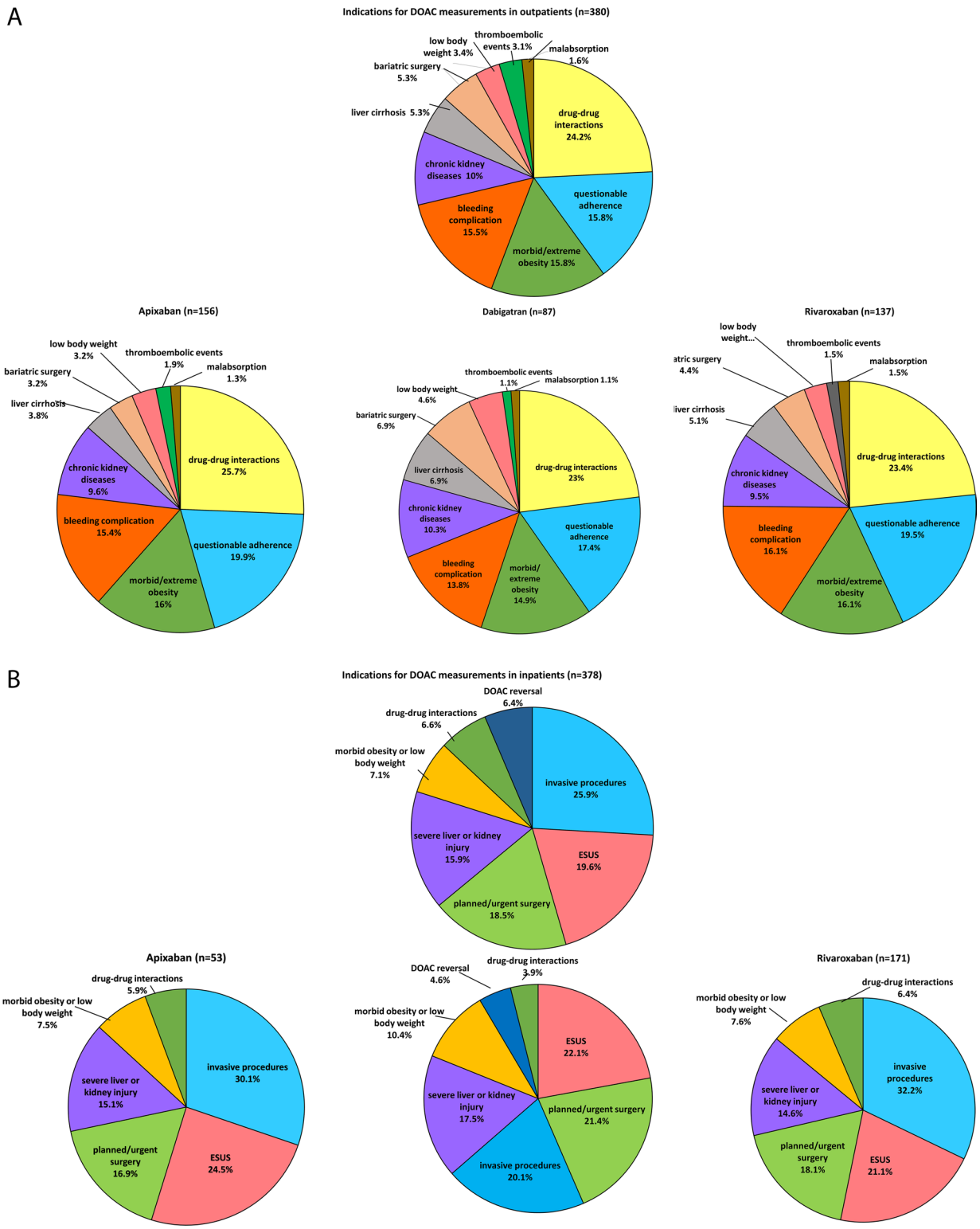

Fig. 3 Indications for direct oral anticoagulant (DOAC) measurements (%) in total and divided into individual DOAC: (**A**) in outpatients ($n=380$); (**B**) in inpatients ($n=378$)

with suspected ESUS before thrombolysis ($n=74$, 19.6%); before planned/urgent surgery ($n=70$, 18.5%); severe liver or kidney injury ($n=60$, 15.9%); morbid obesity or low body weight ($n=27$, 7.1%); suspected clinically relevant drug-drug interactions ($n=25$, 6.6%), and DOAC reversal ($n=24$, 6.%).

There were no significant changes in the indication profile in the years analysed for inpatients and outpatients. No differences between DOAC measurement indications and each specific DOAC were noted (Fig. 3).

TAT of DOAC measurements

A median TAT for all DOAC measurements in the study period was 89 min (63–126 min). TAT in non-urgent samples was 94 (67–133) minutes but in urgent samples it was 34 min shorter (60 [43–78] minutes, $p<0.001$). Importantly, a median TAT for the last 100 samples collected from February 2022 to April 2023 was 20 min shorter compared to the first 100 samples from May 2013 to March 2016 (80 [54–112] vs. 101 [69–134] minutes, respectively, $p=0.018$). For emergencies in 2023 ($n=10$, 26% of all samples analysed in this year) TAT reached 42 (34–54) minutes.

The TAT was shorter by 26 min during the night shift compared to the day shift (71 [52–109] vs. 97 [71–135] minutes, $p<0.0001$, respectively). Similar differences were observed in each year within the analysed period.

In each subsequent year, the median TAT for apixaban was shorter by 6 min ($p=0.042$) and by 31 min for inpatients compared to outpatients ($p=0.028$), with no effect of the time of day (the day/night shifts) the median TAT ($p=0.43$, Fig. 4A). For dabigatran the median TAT was shorter by 4 min ($p=0.004$) and tests performed during the night shift took 20 min less than during the day shift ($p=0.025$, Fig. 4B). There was no difference in median TAT between outpatients and inpatients receiving dabigatran ($p=0.3$). In the case of rivaroxaban, the tests performed by the night shift yielded results on average 27 min earlier compared to results during the day ($p=0.0013$). Neither a place of test request ($p=0.35$) nor year ($p=0.77$) influenced TAT for rivaroxaban (Fig. 4C). Data on the median TAT was presented in Table 2.

In 2023 the median TAT for apixaban, dabigatran, and rivaroxaban were 54 (37–74) minutes, 69 (57–91) minutes, and 64 (46–91) minutes, respectively. The corresponding values for samples received from the emergency department

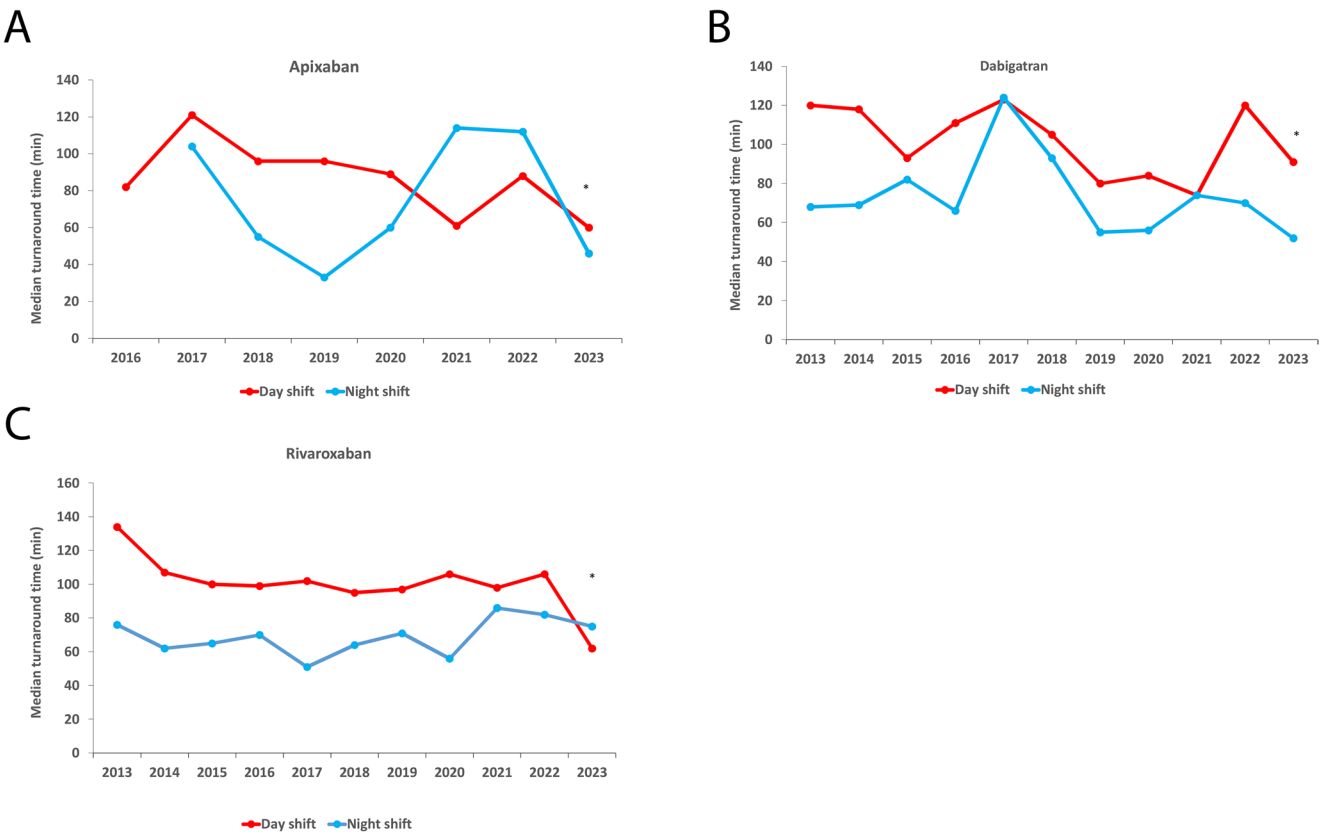

Fig. 4 Median turnaround time of direct oral anticoagulant (DOAC) measurements in relations to day and night shifts in total. (**A**) Apixaban; (**B**) Dabigatran; (**C**) Rivaroxaban. *, data for 2023 were collected from January to April

Table 2 Turnaround time (TAT) for all direct oral anticoagulant (DOAC) measurements in the study period

A median TAT for all DOAC measurements (minutes)			
Median TAT	Apixaban	Dabigatran	Rivaroxaban
Median TAT (total), interquartile range	82 (51–125)	90 (65–126)	89 (63–130)
Median TAT for urgent samples	39 (28–60)	70 (52–89)	53 (39–72)

were 29 (23–34) minutes, 60 (49–100) minutes, and 46 (36–57) minutes ($p=0.01$), respectively.

DOAC levels

All DOAC concentrations ranged from 0 to 846 ng/mL (median, 50.0 [32.9-109.9] ng/mL) and corresponding DOAC levels in subsequent years were shown in Fig. 5. Plasma apixaban concentrations ranged from 0 to 477.4 ng/mL (median, 87.3 [43.7-122.9] ng/mL). The absence of apixaban (0 ng/mL) was recorded in 4 (1.9%) samples. The concentration < 50 ng/mL was assessed in 57 (27.3%) samples. The concentration > 350 ng/mL was found in 4 samples (1.9%).

Plasma dabigatran concentrations ranged from 0 to 642.5 ng/mL (median, 35.8 [28.6–83.8] ng/mL). No dabigatran concentration was recorded in 7 (2.9%) samples. In 78 (32.3%) samples, the drug level was < 35 ng/mL, and in 2 (0.8%) samples it was > 500 ng/mL.

Plasma rivaroxaban concentrations ranged from 0 to 846.0 ng/mL (median 50 [35.5-112.3] ng/mL). In 4 samples (1.2%) absence (0 ng/mL) of rivaroxaban concentration was recorded. The concentration < 50 ng/mL was found in 91 (29.5%) and > 500 ng/mL in 4 (1.2%) samples.

No differences in DOAC levels in in-and out-patients as well as in normal and urgent admissions were found. The only difference noted were higher rivaroxaban levels in urgent compared to non-urgent samples (156.3 [41.8-255.6] ng/mL vs. 50 [35.1-104.2] ng/mL, $p=0.008$).

Discussion

To our knowledge, this is the longest study that shows a comprehensive analysis of the real-world scenarios when DOAC concentrations are measured 24/7, including changes with time in the number of tests requested over 10 years till 2023 (together with the COVID-19 pandemic), indications in out- and inpatients (including emergency settings), and time trends in TAT for dabigatran, rivaroxaban, and apixaban. Previous studies did not address such a broad spectrum of clinical and laboratory aspects in the years 2013–2023. Regarding the number of tests requested in a post-pandemic time (which to our knowledge, has not been specifically assessed in available papers) our observation on a stable number of DOAC measurements in every day practice is

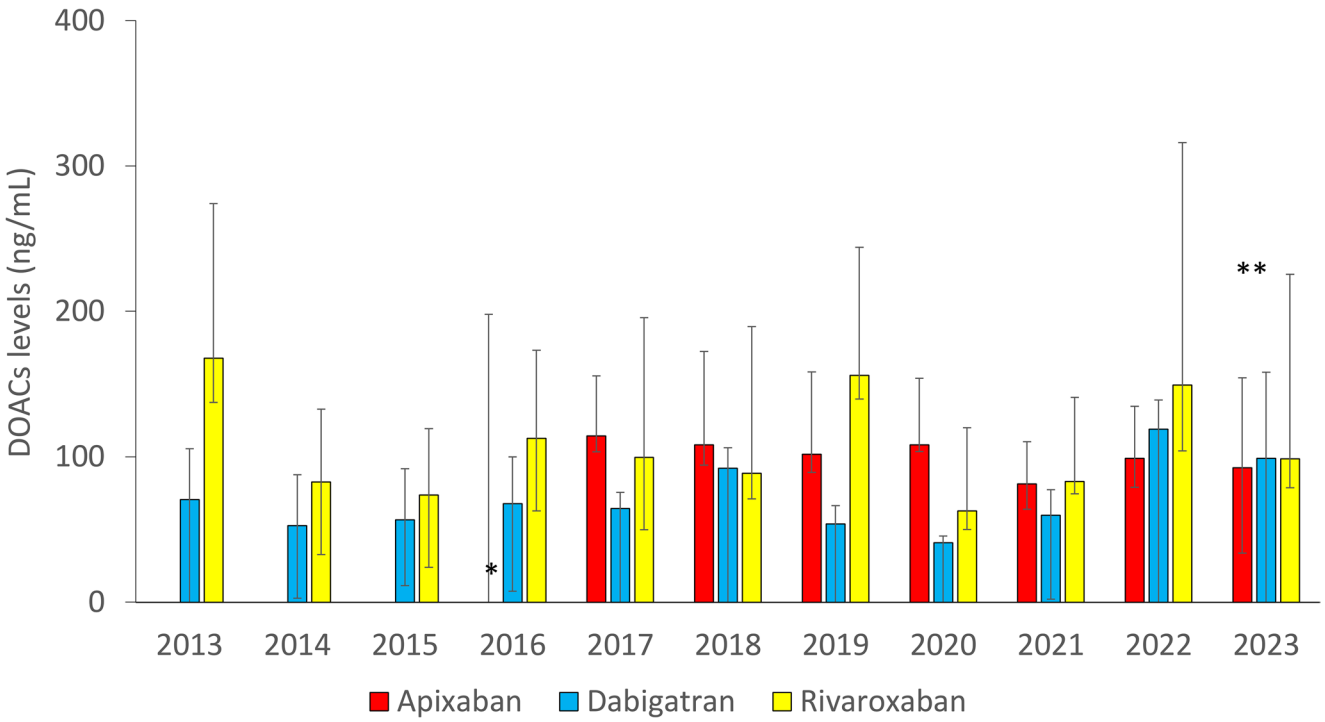

Fig. 5 The median levels (interquartile range as whiskers) of direct oral anticoagulant (DOAC) levels. *, Only two determinations were made for apixaban (197.9 and 255.1 ng/mL) in the first year of the test's introduction and they are not marked in the figure; **, data for 2023 were collected from January to April

of interest. Despite limited indications for the DOAC measurements, on average every week at least one test was performed in in- or outpatients mostly during the day shift. We observed that the total number of requested tests increased until 2017 and then remained constant until the pandemic, when it dropped by 50% and returned to the previous counts in 2022. The lack of an increase in DOAC testing may be related to increasing physicians' experience with the DOAC use and recommendations for DOAC testing solely in a few specific clinical situations; most physicians do not need the exact DOAC levels in everyday practice in non-emergency settings. Moreover, DOAC measurements are relatively expensive tests, which might also affect clinical decision making at least in some countries taking into account that no strong clinical guidelines support such testing. However, our study shows also the use of DOAC measurements in patients in whom DOACs are currently not recommended in particular, in patients with ESUS. It was hypothesized that oral anticoagulants may be more effective than antiplatelet therapy in preventing recurrence stroke in patients with ESUS [26, 27]. Observational studies indicated that the use of DOACs in ESUS patients may bring benefits as compared to aspirin [28, 29]. However, in the years 2018–2024, randomized trials with dabigatran, rivaroxaban, and apixaban showed that the DOACs were not superior to aspirin in reducing the risk of recurrent ESUS and were associated with a higher risk of bleeding [30–32]. Therefore, in the 2024 ESC guidelines for the management of AF, DOACs are not recommended instead of aspirin for the prevention of secondary stroke in patients with ESUS. Since our analysis covered 10 years of DOAC use, our study showed that physicians prescribed DOACs to a subset of ESUS patients, as reflected by the present results. In recent years the use of DOACs, in this indication has been reduced. To minimize the number of patients with ESUS on DOACs in our center, we conducted additional training for physicians. In our facility, a real-life TAT shorter than 60 min is hard to achieve, which in emergency situations could be suboptimal and thus encourages both the use of reversal agents in the case of bleeding and another treatment in acute ischemic stroke considered for thrombolysis. It should be noted however, that in acute stroke patients with normal renal function and who did not take the DOAC for at least 48 h, the management should not differ from that in non-anticoagulated individuals. In patients who are still on DOACs, mechanical thrombectomy is encouraged preferentially. Experts stated that if DOACs concentrations are <50 ng/ml thrombolysis is allowed [33].

Our findings indicate that DOAC measurements on a 24/7 basis should be available in tertiary centres to help guide the patient management and more intensive efforts are needed to ensure obtaining the results within 30 min, if necessary, in the case of routine coagulation parameters.

The indications for anticoagulation observed in our patients were mostly VTE (34%) and AF (33%), however, we showed a higher percentage of "other" indications (7%) compared to previous reports, e.g., 1%[15] or 4% [20]. The differences may be due at least in part to potential disease coding errors especially in complex cases. On the other hand, in everyday practice DOACs are increasingly used off-label in prevention of thromboembolism, which is also reflected in particular by a relatively large proportion of patients on DOACs for ESUS as it has been discussed above. Most likely, the off-label use of DOACs stimulates attending physicians to determine the levels of DOACs to optimize such a therapy despite no conclusive evidence that it is effective at all. Moreover, our data showed that DOAC measurements were requested in patients with left ventricular thrombus following acute myocardial infarction, which is another common off-label indication for these anticoagulants. However, given compelling data on similar therapeutic efficacy and safety of DOACs and VKA in such patients, now DOACs represent a reasonable alternative to VKA in this indication at least in patients in whom a therapeutic INR range is difficult to achieve consistently or in whom frequent INR checks are impossible [34].

Regarding reasons for requests to measure DOAC levels, we observed that in everyday ambulatory practice, drug-drug interactions, questionable adherence, extreme overweight, and persistent bleeding tendency were the most frequent indications for DOAC measurements while the assessment of residual DOAC concentrations before invasive procedures and in acute stroke were for inpatients. Bavalia et al. [15] presented a quite different pattern of indications for DOAC testing, since among patients with known indications the suspicion of accumulation, followed by bleeding or anaemia and yearly control were reported as most common. In our practice the indication "yearly control" was not used at all, while drug-drug interactions mostly antiepileptic agents prevailed which might only in part reflect the risk of accumulation [4]. Generally routine monitoring was not reported in our center as an indication if there was no increased risk of thromboembolism or bleeding, which is in disagreement with the study by Rottenstreich et al. [14] and Denny et al. [17] in which the majority of DOAC measurements for outpatients were routine follow-up/monitoring efficacy. Regarding obese patients, available data from RCTs and real-life studies on DOACs for the treatment of VTE suggest that in patients with BMI ≥ 40 kg/m^2 or weight ≥ 120 kg, apixaban and rivaroxaban appear to be effective and safe compared to VKAs. A switch to VKAs could be done in obese patients with low DOAC plasma level [35]. Of note, there are no recommendations on

reducing the DOAC dose in patients with very low body weight.

For inpatients, emergency situations and perioperative evaluation were the most frequent indications in our study like in previous reports [14, 15, 17, 18, 19]. In contrast to the study by Bavalia et al. [15], in which 47% of patients had no specific indication for the requested DOAC measurements, in our study all DOAC measurements were performed with a specific indication which is undeniably an advantage despite the fact that some of them could be controversial. In our opinion, specific indications for DOAC measurements should be used to enhance the clinical impact of their results. Taken together, there is evidence that the patient profile treated in a given institution impacts the proportions of specific indications for DOACs measurements.

Emergency situations are largely considered by experts the indication of key importance, as evidenced for example by Winther-Larsen and Hvas [16], who reported that the majority of DOAC measurements (88%) were performed in an acute clinical situation predominantly acute ischemic stroke (53%). In our study, 72 patients (11.5%) with ESUS were checked for DOAC concentration before thrombolysis was administrated, which most likely resulted from a relatively lower number of acute stroke patients in our hospital in which cardiovascular diseases predominate among in- and outpatients. Nevertheless, DOAC measurements in acute stroke patients especially without access to mechanical thrombectomy is of vital therapeutic importance since prior anticoagulation with DOACs is a relative contraindication for intravenous thrombolysis [36]. It is estimated that among AF patients potentially eligible for thrombolysis, 18% had prior DOACs treatment with rapidly increasing numbers of DOAC pretreatment in recent years [37]. Even if access to thrombectomy is expected to rapidly grow worldwide, this indication for DOAC measurements is likely to remain valid in practice. Another emergency situation to determine DOAC levels is the use of reversal agents commonly associated with a few DOAC measurements [6], like in the case of idarucizumab administered in our hospital (including the first report in a patient with an acute aortic syndrome from 2016 [38] in whom dabigatran levels were determined before, during and after surgery). Such testing was not recommended by experts but our real-world data do demonstrate that in everyday practice DOACs measurements have been used more often in various clinical settings including the first months of the use of DOAC reversal agents, to help guide the therapy of patients at high bleeding risk. As suggested by van der Wall et al. [39], the decision to administer idarucizumab should be made by a multidisciplinary team and results of laboratory test may guide the decision whether or not to administer idarucizumab to avoid health care costs [39, 40]. Andexanet al.fa to reverse anticoagulant effects of FXa inhibitors has not been used in our center, but patients receiving this agent are likely to be tested in the future especially among subjects with intracranial bleeding [4, 41].

From a practical point of view, of key importance is the time from request for DOAC measurements to the final result, and this time was about 90 min in our study without significant differences between the anticoagulants, which was similar to a study by Denny et al. [17] but other real-world studies reported much shorter time [42, 43]. In general, it is difficult to achieve TAT shorter than 30 min mostly due to sample transport which takes an average of ~5–10 min even by tube, centrifugation and processing ~10 min, and test time 10–20 min. If reagents are refrigerated until use, additional time is required to warm, dissolve and mix them before use. In some situations, retesting of the sample is required, which further extending the TAT.

However, for emergencies (12% of tests) the TAT was shortened to 40 min in our center. The use of a pneumatic tube delivery system for transporting blood samples as well as point-of-care testing could significantly decrease TAT without a reduction in a sample quality [44, 45].

For emergency care and hospitals where specific DOAC determination is not available rapidly, the point of care testing with high negative predictive value may serve for exclusion of clinically relevant DOAC levels. As demonstrated in numerous studies, DOAC Dipstick tests for urine and plasma enable rapid DOAC measurements significantly reducing TAT which may help in immediate clinical decision-making [46–48].

Our analysis covered the COVID-19 pandemic, which has not been shown in other available studies on samples collected before 2020 [14–16], and we found that the fall by 50% occurred in 2020 compared to 2017–2019. This is mostly due to a dramatic decrease in the number of outpatients especially between March and June 2020, with a total shut down for a few weeks. Several wards at our hospital admitted solely COVID-19 patients including those previously using DOACs in secondary prevention of thromboembolism. At that time experts have recommended the use of low molecular weight heparin (LMWH) or unfractionated heparin in most COVID-19 patients in thrombosis prevention and therapy [49] as well as in patients requiring anticoagulation. Therefore, patients on DOACs were routinely switched to parenteral anticoagulants during hospitalization. Our single-center experience indicated that in hospitalized COVID-19 patients LMWH dosage regimens were routinely administered based in internal regulations which contributed to a reduction in DOAC measurements requested especially in 2020 [50].

In the current study we did not evaluate routinely APPT and PT in patients in whom DOAC measurements were

requested. At our hospital we have developed an approach in which, since 2013, DOAC measurements may be measured on a 24/7 basis and in practice, in emergency settings this test is largely ordered along with APTT and INR/PT. The prolonged APTT can be an indicator of the presence of dabigatran and prolonged PT can be used in the case of rivaroxaban, however, they have been reported of limited practical value in emergency settings, especially as compared to plasma DOAC measurements [51]. However, in an emergency setting when a clinical decision needs to be made before laboratory results are available, these screening tests can be used as first-line tests, especially when specific DOAC-concentration assays are not available or in situation when the TAT of DOACs measurements is prolonged. The standard procedures to ensure quick decision making in an emergency setting should be implemented in every hospital.

Limitations of the study

Firstly, this study was retrospective which is associated with inherent drawbacks. However, our tertiary center has the longest experience in the measurement of plasma DOAC concentrations in Poland. Secondly, the issue of whether the DOAC measurements lead to physicians' clinical decision-making e.g., changes in anticoagulant therapy as well as patient compliance was beyond the scope of the current study. Thirdly, our data cannot be extrapolated for hospitals with departments of general surgery, orthopaedics, or toxicology (e.g., taking DOACs for suicidal purposes) since our center is focused mainly on cardiology and neurology. Finally, information about co-morbidities or other drugs which might interfere with DOACs or data regarding solely liver disorders as well as association of clinical outcomes with specific DOAC levels were not investigated. Moreover, a detailed analysis the causes of a relatively long TAT was beyond the scope of the current study, however, certain pre- and analytical factors have been identified as responsible for prolonged TAT.

Finally, there was no data on edoxaban in our study since this agent is not available in Poland until now.

Conclusions

The study highlights the challenges of laboratory evaluation of DOACs levels and documents the feasibility of their determination on a 24/7 basis. The several challenges presented here could be similar to countries with low-to medium income in which DOACs are also commonly prescribed. We also showed that DOACs are often used off-label which prompts additional DOAC measurements in practice. Since generic DOACs are available in many countries and the number of patients on DOACs is expected to increase worldwide, there is a growing need for the availability of DOAC measurements 24 h a day, 7 days a week in hospitals with efforts to shorten the TAT especially in emergency cases. Standardization of DOAC measurements should be implemented to facilitate the interpretation of their results.

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Data availability Data available on request from the corresponding author.

Declarations

Competing interests A. Undas declares lecture honoraria from Bayer, Boehringer Ingelheim, and Pfizer and support for travel from Bayer and Pfizer. The other authors have no conflicts of interest to declare.

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