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Clinical impact of direct oral anticoagulant measuring in a real-life setting

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ABSTRACT

Introduction: Only sparse information exists on the use of direct oral anticoagulant (DOAC) testing and the impact on clinical management. Here, we evaluated the clinical impact of DOAC measurements in a real-life clinical setting. Moreover, number of tests performed in relation to number of DOAC-treated patients was evaluated.

Patients and methods: Clinical data was systematically retrieved from medical records on all patients who had undergone a DOAC testing at Aarhus University Hospital, Denmark from 2014 until March 2018. Data on consumption of DOACs and DOAC tests during 2012–2017 was retrieved from the MEDical STATistics database and from involved laboratories.

Results: A total of 241 DOAC measurements were performed in 234 patients from 2014 to 2018 at our institution. In 88% of patients, DOAC testing was performed in an acute clinical situation; most frequently in patients with acute stroke (53%) or bleedings (26%). Clinical management was explicitly affected by the DOAC testing in 77% of patients. Number of DOAC tests performed in relation to number of DOAC-treated patients in Denmark varied between 0.05% and 0.39% from 2012 to 2015. However, the number increased in 2017 to 2.10% for rivaroxaban-treated, 1.43% for apixaban-treated and 0.74% for dabigatran-treated patients.

Conclusion: DOAC testing had a significant impact on clinical management in the majority of patients. The study highlights the importance of availability to specific DOAC tests, especially in institutions handling emergent settings.

1. Introduction

Over the past decade, direct oral anticoagulants (DOACs) with inhibiting effect on either thrombin (dabigatran etexilate, hereafter dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban and betrixaban) have been approved as alternatives to treatment with vitamin K antagonists (VKA) [1–5]. DOACs are increasingly used in the clinic as they have several advantages over VKAs; DOACs have fewer drug-to-drug interactions and are not influenced by diet. They are given at fixed-dose regimes depending on the indication, patient characteristics (e.g. renal function and body weight) and the use of concomitant drugs; hence no routine laboratory testing is recommended for dose monitoring [6].

Yet, there are certain circumstances where laboratory testing of DOAC activity is necessary to guide clinical management including acute bleeding, before urgent surgery and identification of sub- or supra therapeutic levels e.g. in patients with extreme body weight or in patients with renal failure and therefore recommended by the International Society on Thrombosis and Haemostasis (ISTH) [7–9]. Widely available coagulation tests as activated partial thromboplastin time (APTT) and prothrombin/International Normalized Ratio (PT/INR) have shown lack of sensitivity in determination of DOAC activity as normal values can be found in DOAC-treated patients [10–12]. Therefore, specific tests for measuring DOAC activity have been developed showing greater sensitivity and these are consequently recommended for laboratory testing [9,13,14].

It is well known that a gap between recommendations and the clinical practice often exist [15,16]. Thus, it is of relevance to evaluate whether the aforementioned international clinical recommendations are followed in clinical practice. A recent multinational survey performed in a variety of physicians from Canada and US found a large knowledge gap with respect to the handling of DOAC-associated bleedings with < 50% indicating knowledge about specific DOAC tests [17]. Moreover, only very sparse information exists on the impact of laboratory testing of DOACs on the clinical management of patients in a real-life clinical setting [18–20]. In order to enlighten this area, we here evaluate indication and clinical consequence of DOAC drug measuring in a real-life setting. Moreover, number of tests performed in relation to number of DOAC-treated patients was evaluated.

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2. Materials and methods

2.1. Patients and data collection

DOAC plasma level measurements performed at Department of Clinical Biochemistry at Aarhus University Hospital, Denmark from 2014 until March 2018 were identified through the clinical laboratory information system (LABKA II). The DOAC assays became available at our laboratory in May 2014 (dabigatran), October 2014 (rivaroxaban) and December 2014 (apixaban). For each measurement, a personal identification number was identified and laboratory results (estimated glomerular filtration rate (eGFR), APTT and INR) performed simultaneously with the DOAC test were retrieved on each patient from the laboratory information system. eGFR was calculated using the CKD-EPI creatinine equation without any correction for race: $eGFR = 141 \times \min(\text{Serum Creatinine}/\kappa, 1)^{\alpha} \times \max(\text{Serum Creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female]. For the APTT measurement, the Dade Actin FS reagent on the Sysmex CS-2100i system was used, and the Medirox Owren's PT reagent on the Sysmex CS5100 was used for INR measurement. Medical records were systematically reviewed to achieve clinical data. Data collection was performed between March and August 2018 by one author (AWL).

The study was approved by the local institutional board. According to the Danish law on ethics, requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Number of patients treated with dabigatran, rivaroxaban and apixaban were achieved from the publicly accessible MEDical STATistics (Medstat) database [21] at the 16th of November 2018. Medstat has provided statistics on drug usage from the Danish primary sector since 1996. Data on the total number of drug level measurements was achieved by collecting data from each of the seven laboratories in Denmark performing the drug level testing. The first laboratory (Næstved, Zealand, Denmark) implemented the tests in 2012 while the remaining laboratories implemented the tests during the years 2013 to 2017.

2.2. Drug measurement

The DOAC measurements at Department of Clinical Biochemistry, Aarhus University Hospital, Denmark, were performed on plasma extracted from venous blood samples collected in tubes containing 3.2% sodium citrate (Terumo, Leuven, Belgium). Blood samples were centrifuged (3163 G in 25 min at 20–25 °C) within 60 min of collection and analyzed immediately thereafter. Plasma dabigatran activity was determined using a diluted thrombin time assay (Hemoclot® Thrombin Inhibitor assay, HYPHEN BioMed, Neuville-sur-Oise, France) with the Hyphen BioMed calibrator (ref 222801-RUO). The calibrator curve covered the range 35–400 μg/L. Plasma rivaroxaban and apixaban levels were determined by specifically calibrated anti-factor Xa activity assays (Biophen® Heparin LRT assay, HYPHEN BioMed, Neuville-sur-oise, France). The BIOPHEN Rivaroxaban® Plasma Calibrator (ref 222701-RUO) was used as calibrator for rivaroxaban measurement and the Technoview Apixaban Cal Set (Technoclone, Vienna, Austria) for apixaban quantification. Both calibrator curves covered the range 25–500 μg/L. Assays were performed on a Sysmex CS2100i or Sysmex CS5100. All assays are CE-marked. The maximum between-run coefficient of variation of the assays at our laboratory was 6.4%.

The intervals used for interpretation were 35–400 μg/L (dabigatran) and 25–500 μg/L (rivaroxaban and apixaban) based on previous publications [22–24]. The lowest cut-offs for interpretation for each of the DOACs were used by the clinicians at our institution as the cut-offs to determine when to allow or to contraindicate thrombolysis, postpone operation, give antidote or make dose-adjustment. This approach is in concordance with later published guidelines [7]. For data analyses, plasma levels below 35 μg/L were given the value of 34 μg/L (dabigatran) and levels below 25 μg/L the value 24 μg/L (rivaroxaban and apixaban). High levels were given the value of 401 μg/L (dabigatran) and 501 μg/L (rivaroxaban and apixaban).

2.3. Statistical analysis

Medians and the first and third quartile were calculated for continuous variables without a normal distribution. The differences in eGFR and body mass index (BMI) between the different DOACs were calculated by use of the Kruskal Wallis-test. All tests were two-sided, and p-values < 0.05 were considered to be statistically significant. Statistics analyses were performed using SPSS statistics version 25.0 for windows (IBM SPSS Statistics, Chicago, IL, USA). Graphic artwork was performed using GraphPad Prism 7 for windows (GraphPad Software, CA, USA).

3. Results

3.1. Patients

A total of 243 measurements were identified. Yet, two measurements were excluded as the DOAC testing was performed as part of a project (N = 1) or the patient record was unavailable (N = 1). Therefore, a total of 241 measurements were included. These measurements originated from 234 patients as seven patients had the test performed twice at different time points. Patient characteristics are shown in Table 1. Seventy-eight dabigatran-treated patients had a total of 81 measurements performed, 91 rivaroxaban-treated patients had 93 measurements while 65 apixaban-treated patients had 67 measurements. The predominant indication for the DOAC treatment was atrial fibrillation (81%) while the second most common indication was venous thromboembolism (11%).

Table 1
Patient characteristics (N = 234). Data is provided as N (%) or median (1st–3rd quartile).

Patient characteristics	All patients
Gender	
Male	139 (59%)
Age at testing, years	75 (69–82)
Body weight, kg (N = 218)	78 (65–91)
BMI, kg/m^2 (N = 213)	25 (23 – 30)
DOAC	
Dabigatran	78 (33%)
Median level[a], μg/L	80 (36–199)
Rivaroxaban	91 (39%)
Median level[a], μg/L	68 (25–184)
Apixaban	65 (28%)
Median level[a], μg/L	101 (54–149)
Indication for DOAC treatment[b]	
Arterial fibrillation	190 (81%)
Treatment of venous thromboembolism	26 (11%)
Secondary prevention of venous thromboembolism	5 (2%)
Mechanic heart valve	2 (1%)
Overdose (suicidal)	1 (0.5%)
Mural thrombus	1 (0.5%)
No DOAC treatment	9 (4%)
Estimated glomerular filtration[c]	
> 60 mL/min/1.73 m^2	101 (42%)
30–60 mL/min/1.73 m^2	76 (31%)
< 30 mL/min/1.73 m^2	16 (7%)
Missing data	48 (20%)

Abbreviations: BMI, body mass index; DOAC, direct-acting oral anticoagulant.
[a] When calculating the median plasma level, only the plasma level of patients treated with DOAC was included. The intervals used for interpretation were 35–400 μg/L (dabigatran) and 25–500 μg/L (rivaroxaban and apixaban) based on previous publications [22–24].
[b] Only the main indication for each patient included.
[c] Data for all 241 DOAC tests performed.

3.2. DOAC plasma levels

The median plasma levels of the three DOACs are show in Table 1. No difference was found in eGFR or BMI between patients treated with the three different DOACs (p-values > 0.77). Only three patients had plasma levels above the level of interpretation. These patients all had renal failure with eGFR levels below 40 mL/min/1.73 m^2.

Time of the most recent DOAC intake could be confirmed in 133 (57%) patients. Among these, 108 patients had taken a DOAC dose within the previous 24 h before the DOAC level testing while the remaining 25 patients had stopped DOAC treatment for a median of 3 days (1st–3rd quartile, 2–4) before the plasma measurement. Nine of these patients had a continuously measurable DOAC level (range, 26–114 μg/L). Renal parameters were available in seven of these patients and six of them had renal insufficiency.

3.3. DOAC testing indication and clinical consequence

The majority of DOAC tests (88%) were performed in an acute clinical situation. The most frequent indication for acute testing was acute ischemic stroke where the patient could be a candidate for thrombolysis (53%). This was followed by bleedings (26%) and acute perioperative evaluation (20%) (Table 2). In the non-acute setting, 25 tests (11%) were performed during routine monitoring of patients with renal (32%) or liver failure (4%), after gastrointestinal surgery (8%) or for dose-adjustment (56%). Nine DOAC tests were performed in patients with no history of DOAC treatment; five patients with acute stroke and four patients with no clinical indication reported.

As shown in Table 2, DOAC testing was part of the clinical management in 185 of patients (77%). The most frequent decisions based on DOAC-measurements were omission of thrombolysis due to high DOAC levels (N = 53), ruled out the need for/for more reversal therapy (N = 30) and administration of prothrombin complex concentrate or reversal therapy with idarucizumab (N = 27). In the remaining 56 patients (23%), the test result had no reported clinical consequence either because it became clinical irrelevant (N = 52) or because the test was measured without any clinical indication (N = 4).

3.4. DOAC testing in Denmark

The number of DOAC tests performed in relation to the number of patients treated with DOACs in Denmark from 2012 to 2017 is illustrated in Fig. 1. The number of tests performed from 2012 to 2015 was very limited varying between 0.05% and 0.39%. However, the frequency of tests increased from 2016. In 2017, the number of tests performed for rivaroxaban activity in relation to the number of treated patients was significantly higher (2.10%) than for apixaban-treated (1.43%) and, especially, for dabigatran-treated patients (0.74%).

3.5. Association between DOAC levels and standard coagulation tests

Not all patients with measurable DOAC levels had elevated APTT and/or INR. An APTT level within the reference interval was found in 6% (3/47) of patients with measurable dabigatran activity, in 26% (10/39) of patients with measurable rivaroxaban activity and in 56% (24/43) with measurable apixaban activity. The DOAC level in patients misclassified with normal APTT had DOAC-levels well within the range for patients receiving DOAC treatment. In patients with normal APTT, the DOAC levels ranged from 48 to 86 μg/L for dabigatran treated, 26–190 μg/L for rivaroxaban and from 31 to 381 μg/L in apixaban treated. Likewise, INR was normal in 26% (11/43) of patients with measurable rivaroxaban activity, 30% (14/47) of patients with measurable dabigatran activity and 50% (23/46) of patients with measurable apixaban activity. The correlations between DOAC levels and APTT as well as INR are depicted in Supplementary Fig. 1.

4. Discussion

Here, we evaluated the impact of laboratory testing of DOACs on the clinical management in a real-life clinical setting. We demonstrate that the indications for DOAC testing were in concordance with the clinical scenarios recommended in international guidelines [7,9,13,14]. The majority of measurements were performed in an acute setting. Only 11% of tests were performed in a non-acute setting, and in most of these situations, an underlying condition justified the testing. Moreover, very few tests were requested without any clinically relevant indication. These findings are in concordance with a recent study by Denny et al. [25] where only 9.5% of DOAC tests were requested without any clear reason; however, in contrast to Rottenstreich et al. [19] who found that 17.5% of tests were performed during routine follow-up of patients without any other reason. Further, we found that the DOAC measuring had a reported impact on the clinical management in 77% of patients. This result demonstrates a high degree of knowledge about the clinical utilization of the testing among clinicians. However, the frequency of patients, where a clinical consequence of the DOAC testing was found, varied between the different indications; in the setting of acute stroke, patients with no recorded consequence of the testing were found to be higher than for other clinical indications. Our data indicate that the main reason for this was that the test was requested before the diagnosis of stroke was confirmed and the test result therefore became redundant if the diagnose was ruled out. However, in some cases the test result became redundant due to the narrow thrombolysis window and in such situations, reducing the turnaround time of the tests would be of great value to improve the diagnostic work-up. Promising strategies could be to implement a rapid centrifugation protocol [26] or to develop a point of care test with high enough accuracy for implementation in the clinic [27].

We found that all patients with very high DOAC plasma levels had renal failure. Further, six out of the seven patients, who had a measurable DOAC level after more than two days without DOAC intake, had renal failure. These data support previous data on highly inter-individual variability in plasma concentrations in real-life patients [28,29] and a close relationship between renal function and DOAC plasma levels [30]. It highlights the importance of measuring DOAC plasma levels on a regular basis in patients evolving renal insufficiency to prevent thrombotic complications as well as bleedings [28,29].

The study showed that the frequency of DOAC tests performed related to the consumption of DOACs in Denmark was very low in the first four years after implementation of the tests. This indicates that even though the clinicians prior had a strong request for the tests to be available and a clear guideline for its use was published by international societies, the awareness of the tests was low. This is in line with data from Wright et al. [20] who found that only 0.33% of all DOAC-treated patients had a DOAC test performed during the two and a half year after implementation of the tests at their institution. These data illustrate that implementation of a new test can be challenging and highlights the importance for laboratories to educate and guide clinicians not only in awareness of the test but also that knowledge regarding the timing between drug administration and testing is essential for interpretation of the test result.

Since 2016, the number of tests performed has increased for all DOACs in Denmark; though not equally for all DOACs. Interestingly, the frequency of tests was lower for dabigatran than for the two other DOACs. One possible explanation for this could be that dabigatran is more affected by renal function than the other two DOACs, and therefore not the drugs of choice in patients with high comorbidity. Moreover, dabigatran and apixaban have shown lower risk of major bleedings than rivaroxaban in several studies performed in nonvalvular atrial fibrillation patients [31–33]. This also could explain the relative high number of rivaroxaban activity tests performed.

Even though specific DOAC tests are recommended for DOAC measurements, the tests are still not widely available in all hospitals.

Table 2
Clinical management according to indication for DOAC plasma measuring.
The total number of DOAC test was 241. These were performed in 234 patients as seven patients had two measurements performed at different time points.

Indication for plasma measuring	Number of DOAC tests	Median DOAC level, μg/L (1st–3rd quartile)[a]	Clinical management	Number of DOAC tests (%)
Acute, N = 212 tests (88%)				
Acute ischemic stroke				
Dabigatran	35	78 (38–143)[b]	Thrombolytic therapy omitted due to DOAC treatment	53 (47%)
Rivaroxaban	41	74 (24–186)[c]	No recorded consequence (actilyse omitted of other reason)	44 (39%)
Apixaban	37	103 (47–188)[d]	Confirmation of no DOAC therapy	8 (7%)
			Actilyse administrated	5 (4%)
			Dose adjustment (increase) of DOAC	2 (2%)
			Antidote: idarucizumab	1 (1%)
Cerebral bleeding				
Dabigatran	14	119 (34–217)	Ruled out need for reversal therapy	15 (38%)
Rivaroxaban	16	69 (28–167)	Prothrombin complex concentrate	9 (23%)
Apixaban	10	98 (71–149)	Antidote: idarucizumab	5 (13%)
			No recorded consequence	5 (13%)
			Discontinuation of DOAC therapy	2 (5%)
			Postponed operation	2 (5%)
			Delayed re-administration of DOAC	1 (3%)
			Confirmation of no DOAC therapy	1 (3%)
Preoperative evaluation				
Dabigatran	12	65 (35–124)	Ruled out need for reversal therapy	11 (26%)
Rivaroxaban	15	50 (24–75)	Postponed operation	10 (24%)
Apixaban	15	83 (47–141)	Enabling operation	8 (19%)
			Prothrombin complex concentrate	6 (15%)
			Antidote: idarucizumab	4 (10%)
			Confirmation of no DOAC therapy	1 (2%)
			Discontinuation of DOAC therapy	1 (2%)
			Operation cancelled of other reason	1 (2%)
Bleeding				
Dabigatran	10	48 (34–216)	Ruled out DOAC as the reason for bleeding	6 (38%)
Rivaroxaban	5	218 (25–405)	Ruled out need for reversal therapy	4 (25%)
Apixaban	1	35	No recorded consequence	2 (13%)
			Dose adjustment (increase) of DOAC	2 (13%)
			Antidote: idarucizumab	1 (6%)
			Discontinuation of DOAC	1 (6%)
Sepsis				
Dabigatran	1	501	Antidote: idarucizumab	1 (100%)
Non-acute, N = 25 tests (11%)				
Dose adjustment				
Dabigatran	3	177	No dose adjustment	13 (93%)
Rivaroxaban	10	111 (44–224)	Dose adjustment (decrease) of DOAC	1 (7%)
Apixaban	1	105		
Renal failure				
Dabigatran	4	308 (96–474)	No dose adjustment	4 (50%)
Rivaroxaban	2	217	Dose adjustment (decrease) of DOAC	2 (25%)
Apixaban	2	116	Discontinuation of DOAC	2 (25%)
Post-gastrointestinal surgery				
Rivaroxaban	2	177	Dose adjustment (increase) of DOAC	1 (50%)
			Discontinuation of low-molecular-weight heparin	1 (50%)
Liver failure				
Apixaban	1	81	No recorded consequence	1 (100%)
No clinical indication reported, N = 4 tests (1%)				
Dabigatran	2	0[e]	None	4 (100%)
Rivaroxaban	2	0[e]		

Abbreviations: DOAC, direct-acting oral anticoagulant.
[a] The drug levels for patients receiving DOACs were 35–400 μg/L (dabigatran) and 25–500 μg/L (rivaroxaban and apixaban) based on previous publications [22–24].
[b] One patient was excluded as he/she did not receive dabigatran.
[c] Two patients were excluded as they did not receive rivaroxaban.
[d] Two patients were excluded as they did not receive apixaban.
[e] Patients did not receive a DOAC.

Therefore, more widely available coagulation test as APTT, thrombin time and INR are still used for evaluating DOAC levels. Although the majority of patients with a measurable dabigatran activity had a prolonged APTT, a few patients were misclassified by a normal APTT in spite of measurable dabigatran. For the two other DOACs, the relationship between plasma concentration and APTT as well as INR was poor, especially for apixaban. These observations are in line with previous studies showing that APTT and, especially, INR are not sensitive enough to rule out the presence of therapeutic DOAC levels, even though there are differences between the different APTT and INR reagents [7]. However, some degree of correlation exists between dabigatran and APTT and between rivaroxaban and INR [34–36].

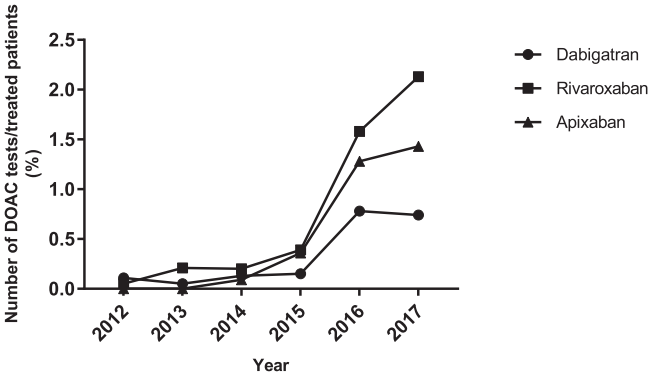

Fig. 1. Number of dabigatran, rivaroxaban and apixaban tests performed in relation to the number of Danish patients treated with DOACs from 2012 to 2017. The DOAC tests are performed at seven different laboratories in Denmark.

Our study has some limitations to consider. Although the study is the largest real-life study performed in this field, it was performed as a single-center study and may not reflect practice at other institutions. Collection of clinical data from medical records may be affected by bias; only data registered in the patient record was accessible and a clinical consequence of the DOAC testing may have existed, although not registered. Moreover, it was not possible to obtain reliable data on last DOAC intake in all patients, and thus not possible to correlated plasma level with time since last intake. Further, in this study we evaluated patients where a DOAC testing was performed but did not evaluate situations where a DOAC test would have been valuable for clinical management but omitted. Thus, we are not able to conclude whether an even more frequent use of DOAC testing would be relevant. Also, we are aware that the assay used for dabigatran measurements might overestimate the level at low concentrations around 30 μg/L [37]. However, this potential problem did not influence the data collected on indication and clinical decision making. Finally, we used a different centrifugation protocol than recommended [38]. Though, we have no reason to believe that this has influenced our data.

5. Conclusion

We demonstrate that DOAC testing is performed in line with international recommendations and, most important, that drug testing has an impact on clinical management in a significant number of patients. The study highlights the importance of availability to specific DOAC tests, especially in institutions handling emergent settings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.01.016.

Declarations of interest

None.

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