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Full Length Article

DTI/DXI interferences with global coagulation tests in emergency hospital admissions - Results of the prospective Dresden NOAC Registry (NCT01588119)

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ABSTRACT

Background: Depending on test assays and the time of last DOAC intake, direct thrombin inhibitors (DTI) and direct FXa inhibitors (DXI) may or may not affect prothrombin time (PT), international normalized ratio (INR) or activated thromboplastin time (aPTT) but the clinical impact is unknown.

Methods: Using data from the Dresden NOAC Registry, we evaluated the impact of DOAC on first PT, INR or aPTT tests during emergency hospitalizations of DTI/DXI patients and the assay performance across 50 coagulation laboratories.

Results: In 724 emergency admissions (77 DTI; 647 DXI), 490 cases (67.7%) had a reported last DOAC intake within 12 h before blood sampling. INR and PT were elevated above the upper limit of normal (ULN) in > 65% of all cases and aPTT was elevated in 45%. On the other hand, > 30% of all cases had normal values of INR, PR and aPTT despite a DOAC intake within the last 12 h. Assay performance for detecting or ruling out therapeutic DOAC levels was highly variable and, overall, insufficient to guide clinical decisions. DOAC specific testing was performed in < 10% of all cases.

Conclusion: Many DOAC recipients present with elevated PT, INR or aPTT during emergency admissions but false negative values within 12 h of last intake as well as elevated values beyond 24 h after last DOAC intake are common. Both scenarios may result in clinical misinterpretation and, potentially, in patient harm, also because DOAC specific testing is rarely performed in emergency settings.

1. Introduction

With a widespread use of oral anticoagulation for stroke prevention in atrial fibrillation (SPAF) and for prevention and treatment of venous thromboembolism (VTE) a large proportion of patients presenting for acute conditions in emergency departments will have been taking anticoagulant drugs in the hours or days before admission [1,2]. With vitamin K antagonists (VKA), presence and intensity of anticoagulation could be easily detected with standard coagulation tests prothrombin time (PT) and international normalized ratio (INR), with normal values safely ruling out a clinically relevant antithrombotic effect and with elevated values strongly correlating to the intensity of antithrombotic effects. In contrast, VKA do not affect activated thromboplastin time (aPTT). As a consequence, emergency physicians have been comfortable to draw direct conclusions about the presence and intensity of VKA therapy and to make treatment decisions based on the values of PT or INR for decades. Similarly, unfractionated heparin could be monitored by aPTT measurements and normal values safely ruled out relevant anticoagulant activity and, although presence or intensity of low molecular weight heparins (LMWH) activity could not be judged by use of global coagulation tests, at least the "presence" of an anticoagulant could often be guessed from the skin hematoma at injection site, warning attending emergency physicians of the presence of an anticoagulant in situations when little information is available.

Over the last 10 years, non-vitamin K dependent, directly acting oral anticoagulants (DOACs) have replaced VKA in SPAF and VTE treatment. These compounds do not need routine monitoring but specific test assays to evaluate the plasma concentrations of these compounds [3]. For the direct thrombin inhibitor (DTI) dabigatran, these tests include thrombin time, diluted thrombin time or ecarine clotting time

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(ECT) [3]. For the direct factor Xa inhibitors apixaban, edoxaban and rivaroxaban, chromogenic aXa-assays are available, although not widely established at a 24/7 level [2–4]. For several reasons, the management of DOAC recipients presenting at emergency departments is challenging. DTI and DXI are characterised by a rapid onset of action (peak plasma levels are usually reached within 4 h after intake) and a rapid metabolism and excretion with a plasma half-life of 8–17 h [5]. This is in contrast to the slow onset and long half-life of VKA, which poses the first challenge: in a VKA patient, little variation anticoagulant activity (or PT/INR) is expected over a course of 6–12 h but, with DOAC, the anticoagulant activity may rapidly change from trough plasma levels to peak plasma levels to declining effects within the same timeframe. As a consequence, the impact of DXI on DTI on PT, INR and/or aPTT may change within a few hours and exact knowledge of time, type and dosage of last DOAC intake and time between last intake and blood sample collection for coagulation testing is, therefore, essential when DOAC levels or coagulation test results are being interpreted [4].

The second challenge results in the fact that several commercial test assays are available to test PT, INR or aPTT in plasma samples, with each assay being affected to a highly variable degree by the presence of DTI or DXI [4]. For instance, measurement of aPTT with Actin FS assays has been found to demonstrate a considerably higher sensitivity towards dabigatran than SnythasIL and other reagents. For PT/INR, TriniCLOT PT EXEl S and STA neoplastin R are much more sensitive assays to detect DXI, whereas DADE Innovin is very insensitive. Furthermore, the sensitivity of these PT assays varied considerably between rivaroxaban, apixaban and edoxaban with apixaban demonstrating the smallest effect on all PT assays [4].

Therefore, even with therapeutic (or supratherapeutic!) DOAC levels, PT, INR and aPTT may be normal or abnormal, depending on the specific assay used to measure these global coagulation tests. As a consequence, even if the time, type and dosage of last DOAC intake is known, clinical interpretation of an individual coagulation test results would require a detailed knowledge on the assay's sensitivity to this specific DOAC. The third challenge represents from the fact that, even if sensitivity of the assay would be known to the emergency physician, the *in-vitro* effect of DOAC on PT, INR or aPTT does not correlate to the intensity of the antithrombotic effect *in-vivo*. Therefore, the probability of false-normal coagulation test results despite peak anticoagulant activity (if an insensitive assay is being used) may be as common as the probability of a false-abnormal test result at DOAC trough levels (if a highly sensitive assay is being used). These challenges carry a high potential for harming patients by inadequate clinical decision making. In emergency situations, information on last DOAC intake, time to blood sampling, test assay and its sensitivity is usually not available and, sometimes, even type and dosage of DOAC are unknown. In this setting, emergency physicians may proceed with invasive procedures (because false-normal coagulation tests do not indicate presence of DOAC anticoagulation) or may withhold urgently indicated interventions or thrombolytic therapies because false-abnormal test results indicate presence of antithrombotic effects [3,4].

Although these challenges are well recognized and guidance statements caution against the use of global coagulation tests to evaluate DOAC treatment effects, the magnitude of the problem in daily care in emergency departments has not been sufficiently evaluated. Using data from the large prospective *Dresden NOAC Registry*, we identified emergency admissions of DOAC patients and evaluated the impact of DOAC type and DOAC timing on PT, INR or aPTT measured with different test assays in routine care.

2. Methods

2.1. Data collection and outcome measures

The *Dresden NOAC Registry* (NCT01588119) is an ongoing large, prospective registry in the administrative district of Dresden (Saxony), Germany. Patients receiving NOACs are enrolled by physicians across 240 private practices and hospitals and undergo quarterly follow-up phone visits by the central registry office. The design and methodology of the *Dresden NOAC Registry* has been published previously [6–8].

For the present analysis, we aimed to evaluate global coagulation test results in relation to the type and timing of last DOAC intake in patients with unscheduled emergency hospital admissions. Since the registry does not routinely collect information on hospitalizations, potential cases were identified by extracting data on patients who had documented study endpoint in the registry database, namely patients with bleeding, cardiovascular events and/or surgical or interventional procedures between September 2011 and January 2017. For these endpoints, the database contains all relevant information on DOAC management, including information on hospitalization, type, dosage and last intake of NOAC before admission. All identified cases underwent manual chart review to establish unscheduled emergency admission. During this manual chart review, DOAC intake details were double-checked and cases were excluded from analysis if patients had stopped DOAC intake for > 72 h before emergency admission, were treated as outpatients, had a scheduled hospital admission or if patients experienced the qualifying outcome event only after hospital admission. Patients who had their first blood sample taken later than 48 h after emergency admission or had no coagulation tests ordered were also excluded. Results of coagulation tests were extracted from the charts, including the reference range provided by the specific laboratory. In case of missing database entries, the treating hospital was contacted and asked to provide laboratory test results and reference ranges for this specific case. Cases with missing values or where reference ranges were not available were excluded from distribution statistics (Fig. 1).

For the presented analysis, the first available PT, INR or aPTT tests after emergency admission were used and compared against the reference range provided by each specific laboratory. Of note, results of prothrombin time (PT) measurements are typically not provided as absolute PT values in seconds in Germany but reported as PT % activity (so called “Quick” value) and calculated as % from normal pooled plasma. Results of activated partial thromboplastin time (aPTT) measurements are presented in seconds.

2.2. Statistics

Because of the nature of the data, only descriptive comparisons were performed. Data are presented as absolute and relative frequencies, mean and standard deviation, or median with interquartile range as difference between 25th and 75th percentile, where appropriate. All statistical analyses were carried out using the IBM® SPSS® Statistics version 24, MedCalc® version 14.8.1.

2.3. Ethics

The study protocol of the *Dresden NOAC Registry* has been approved by the local ethics committee at the Technical University Dresden (AZ EK 349092011) and the study was registered at ClinicalTrials.gov (NCT01588119). The study complies with the principles and requirements of the Declaration of Helsinki. All patients provided written informed consent, including a data protection waiver, before enrolment.

3. Results

Between November 1st 2011 and January 31st 2017, 724 emergency admissions in 558 patients were identified (77 admissions with DTI intake; 647 admissions with DXI intake). Patients were admitted into 56 different hospitals which used 50 different laboratories for their routine blood analyses. Laboratory-specific reference values defining the upper-limit-of-normal (ULN) were available for 708 admissions with PT/INR tests (97.8%) and 692 admissions with aPTT tests

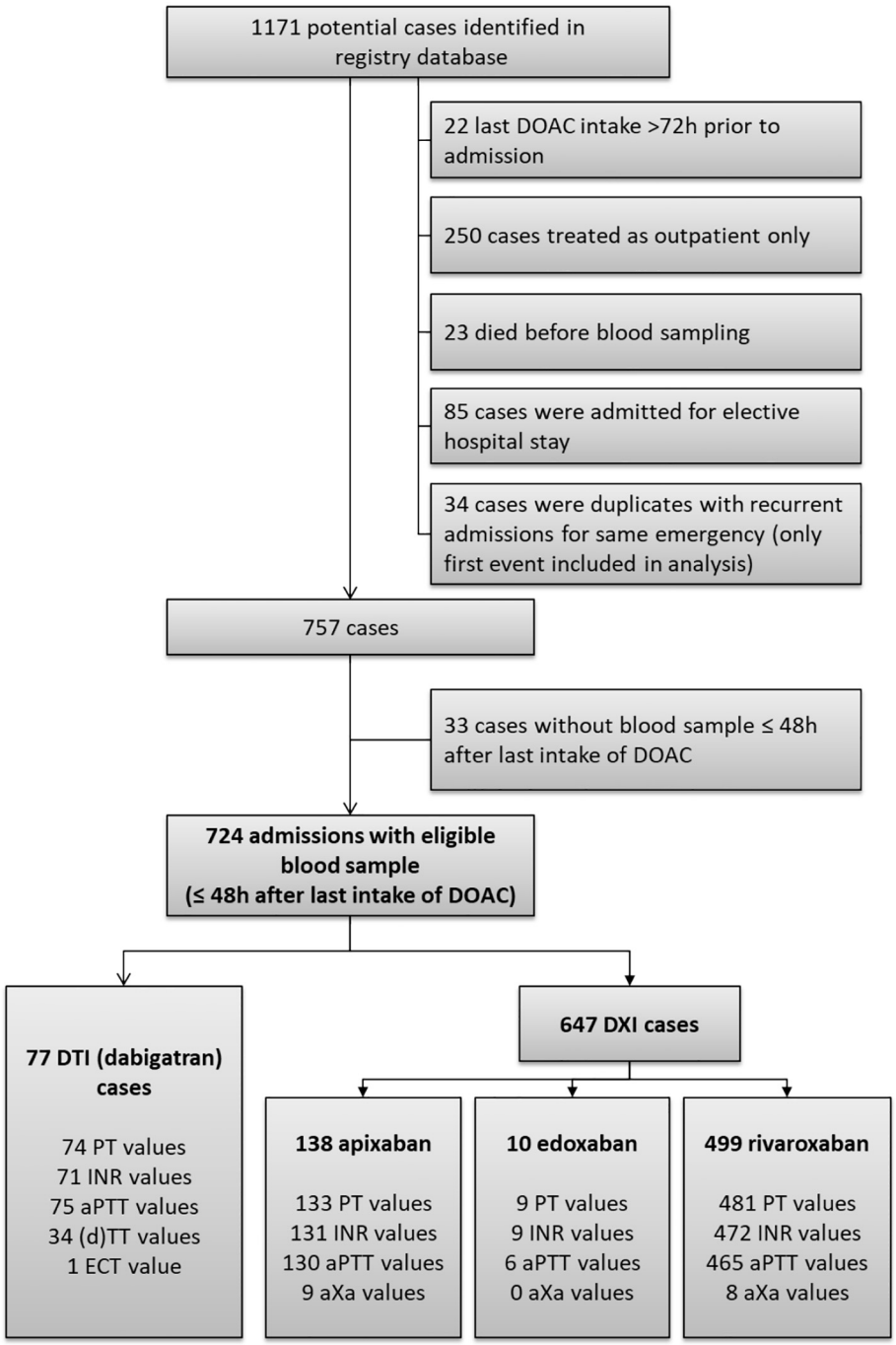

Fig. 1. Flowchart of data acquisition.
DOAC, direct oral anticoagulants; DTI, direct thrombin inhibitor; DXI, direct factor Xa inhibitor, PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time, (d)TT, (diluted) thrombin time; ECT, ecarin clotting time; aXa, chromogenic anti-Xa activity.

(95.6%).

Mean age of the DOAC patients was 75.9 ± 11.1 years and 294 patients (52.7%) were male (Table 1). Indication for anticoagulation was SPAF in 463 patients (83.0%), VTE treatment in 87 patients (15.6%) or other indications in 8 patients (1.4%).

Within the pre-specified selection criteria for this analysis, reasons for hospital admission included bleeding events in 380 (52.5%) cases, cardiovascular events in 208 (28.7%) cases and an unscheduled surgery in 136 (18.8%) cases (Fig. 1).

The distribution of DOAC exposure is demonstrated in Table 2. Patients reported a last DOAC intake within 6 h before blood sampling in 264/724 admissions (36.5%), followed by an interval of 6–12 h (226/724; 31.2%), 12–24 h (157/724; 21.7%) and 24–48 h (77/724; 10.6%).

Most laboratories reported use of STAGO®, SIEMENS® or WERFEN® assays for PT and aPTT measurements (Table 3).

3.1. Distribution of coagulation values for all DOAC patients

When the overall pattern of coagulation test abnormalities was assessed (reference ranges were not available for PT in 16 admissions, INR in 56 admissions and aPTT in 32 admissions) irrespective of the type of DOAC, we found that 461/708 admissions (65.1%) presented with a PT ratio > ULN (Table 2). On the other hand, 247/708

Table 1
Patient characteristics.

	All patients n = 558
Male, n (%)	294 (52.7)
Age, years (mean ± SD)	75.9 ± 11.1
Mean BMI ± SD, kg/m^2	28.5 ± 5.3
Heart failure, n (%)	214 (38.4)
Arterial hypertension, n (%)	461 (82.6)
Diabetes, n (%)	223 (40.0)
Prior TIA, stroke, or systemic embolism, n (%)	118 (21.1)
PAOD/CAD, n (%)	150 (26.9)
Impaired renal function, n (%)	88 (15.8)

admissions (34.9%) had normal PT ratios. Proportions of PT prolongation slowly decreased with longer intervals between last DOAC exposure and blood sampling, with 66.9 and 69.6% of all admissions having elevated PT values within 6 and 6–12 h after last DOAC intake, respectively. However, 57.5% of admissions with a last DOAC exposure beyond 24 h still had PT prolongation. Similar patterns were observed for INR measurements. The positive and negative predictive values (PPV; NPV) of PT were only moderate: for DOAC intake < 12 h before, the PPV was 71.6% and dropped to 28.4% in the setting of last DOAC intake > 12 h before blood sampling. In contrast, the NPV increased from 37.6% to 62.3%.

Of the 692 admissions with aPTT tests available, 313 (45.2%) had prolonged aPTT values (129 cases with prolongation > 20%), which declined from 51.0% (if last DOAC intake was < 6 h) to 39.4% (24–48 h). 54.8% of all and 49.0% of all exposures within the last 6 h had normal aPTT values.

Similar to the findings for PT, the PPV and NPV for aPTT were only moderate: for DOAC intake < or > 12 h, the PPV dropped from 72.2% to 27.8%, whereas the NPV increased from 34.6% to 65.4%.

3.2. Distribution of coagulation values for DTI patients

Reference ranges of PT ratio were available for 75 admissions (Table 4). Mean time between last DTI intake and blood sampling was 11.5 h (range 1.1–38.9 h) and mean ± SD of PT ratio was 66.7 ± 20.4%. 34/75 cases (45.3%) had normal PT ratios and 41/75 admissions (54.7%) had a PT ratio > ULN. Proportions of abnormal PT ratios slowly decreased with longer intervals between last DTI exposure and blood sampling but 66.7% of admissions with a last DTI exposure beyond 24 h still had abnormal PT ratios prolongation (Fig. 2).

Similar patterns were observed for INR measurements (Table 5).

Reference ranges of aPTT ratio were available for 75 admissions (Table 6). Mean time between last DTI intake and blood sampling was 11.5 h (range 1.1–38.9 h) and mean ± SD aPTT on admission was 55.1 ± 30.5 s (range 25.0–180.0 s). In total, 61/75 admissions (81.3%) showed prolonged aPTT values, which declined from 83.3% (if last DTI intake was < 6 h) to 88.9% (24-48 h). On the other hand, 18.7%% of all and 16.7% of all DTI exposures within the last 6 h had normal aPTT values (Fig. 2)

Table 3
Distribution of PT and aPTT assays across the 50 participating laboratories.

	n (%)
PT assays	
Roche® - PT Screen®	3 (5.7)
Siemens® - Dade® Innovin®	7 (13.2)
Siemens® - Thromborel® S	12 (22.6)
STAGO® - Neoplastine®	6 (11.3)
STAGO® - Neoplastine® CI	1 (1.9)
STAGO® - Neoplastine® CI plus	7 (13.2)
Werfen® - RecombiPlasTin 2G®	17 (32.1)
aPTT assays	
Roche® - MedS®	52 (7.2)
Siemens® - Pathromtin® SL	198 (27.4)
STAGO® - C.K. Prest®	173 (23.9)
STAGO® - Cephascreen®	31 (4.3)
STAGO® - PTT A®	21 (2.9)
Werfen® - aPTT-SP®	51 (7.1)
Werfen® - SynthASil	197 (27.2)

3.3. Distribution of coagulation values for DXI patients

Reference ranges of PT ratio were available for 633 admissions (Table 4). Mean time between last DXI intake and blood sampling was 10.4 h (range 0–47.9 h) and mean ± SD of PT ratio was 59.2 ± 23.4%. 213/633 admissions (33.6%) had normal PT ratios and 420/633 cases (66.4%) had a PT ratio > ULN. Proportions of abnormal PT ratios slowly decreased with longer intervals between last DXI exposure and blood sampling but 52.9% of admissions with a last DXI exposure beyond 24 h still demonstrated abnormal PT ratio prolongation (Fig. 2)

Similar patterns were observed for INR measurements (Table 5).

The performances of Siemens®, STAGO®; Werfen® and Roche® PT assays was highly variable in detecting DOAC intake < 6, < 12 or > 12 h before blood sampling. For last DXI intake < 6 or < 12 h, PT measured by STAGO® Neoplastin CI plus demonstrated the highest proportion of abnormal results, followed by Roche® PT Screen and Werfen® RecombiPlasTin 2G. Despite recent intake of DXI, Siemens® Thromborel S and Siemens® Dade Innovin assays resulted in 33–36% (intake < 6 h) or 46–50% (intale < 12h) of normal PT results. In contrast, for a DOAC intake > 12 h before blood sampling, Werfen® RecombiPlasTin 2G and Siemens® Dade Innovin demonstrated higher proportions of patients with normal PT (50 and 47%, respectively) compared to Siemens® Dade Innovin, Roche® PT Screen and STAGO® Neoplastin CI plus (35%, 33% and 32%, respectively).

Reference ranges of aPTT ratio were available for 617 admissions (Table 6). Mean time between last DXI intake and blood sampling was 10.4 h (range 0–47.9 h) and mean ± SD of aPTT ratio was 37.8 ± 14.4%. 252/617 admissions (40.8%) had prolonged aPTT values, which declined from 45.8% (if last DXI intake was < 6 h) to 29.4% (24–48 h). On the other hand, 59.2%% of all and 3.8% of all DXI exposures within the last 6 h had normal aPTT values (Fig. 2)

The proportion of normal or abnormal values for PT and aPTT in

Table 2
Distribution of normal or elevated global coagulation test results in relation to last DOAC exposure.

	All emergency admissions (n = 724)[a]	Last intake < 6 h (n = 264)[a]	Last intake 6–12 h (n = 226)[a]	Last intake 12–24 h (n = 157)[a]	Last intake 24–48 h (n = 77)[a]
PT > ULN	461/708 (65.1)	174/260 (66.9)	156/224 (69.6)	89/151 (58.9)	42/73 (57.5)
PT normal	247/708 (34.9)	86/260 (33.1)	68/224 (30.4)	62/151 (51.1)	31/73 (42.5)
INR > ULN	459/668 (68.7)	169/243 (69.5)	157/211 (74.4)	91/141 (64.5)	42/73 (57.5)
INR normal	209/668 (31.3)	74/243 (30.5)	54/211 (25.6)	50/141 (35.5)	31/73 (42.5)
aPTT > ULN	313/692 (45.2)	130/255 (51.0)	96/219 (43.8)	59/147 (40.1)	28/71 (39.4)
aPTT normal	379/692 (54.8)	125/255 (49.0)	123/219 (56.2)	88/147 (59.9)	43/71 (60.6)

[a] Reference ranges were not available for PT in 16 emergency admissions, INR in 56 emergency admissions and aPTT in 32 emergency admissions.

Table 4
Impact of DTI or DXI on PT.

	Total (n = 724)[a]	DTI (n = 77)	DXI (n = 647)	Rivaroxaban (n = 499)	Apixaban (n = 138)	Edoxaban (n = 10)
Reference range available, n (%)	708/724 (97.8)	75/77 (97.4)	633/647 (97.8)	488/499 (97.8)	136/138 (98.6)	9/10 (90.0)
Mean time between last DOAC and blood sample, h (range)	10.6 (0–47.9)	11.5 (1.1–38.9)	10.4 (0–47.9)	11.0 (0–47.9)	8.2 (0–37.8)	12.8 (1.8–30.3)
Mean ± SD	60.0 ± 23.2	66.7 ± 20.4	59.2 ± 23.4	55.1 ± 22.7	73.8 ± 20.3	60 ± 12.3
Median (IQR)	59.0 (36)	67.2 (25.8)	58.0 (35.0)	52.0 (33.5)	73.7 (27)	55.0 (15.0)
Minimum/maximum	7.0/126.0	7.0/105.9	10.0/126.0	10.0/126.0	20.0/118.0	39.0/81.0
Normal values, n (%)	247/708 (34.9)	34/75 (45.3)	213/633 (33.6)	132/488 (27.0)	79/136 (58.1)	2/9 (22.2)
Abnormal values, n (%)	461/708 (65.1)	41/75 (54.7)	420/633 (66.4)	356/488 (73.0)	57/136 (41.9)	7/9 (77.8)

[a] Values were not available for PT in 16 emergency admissions.

patients treated with either of the three DXI within the last 12 h or beyond is depicted in Fig. 3.

DOAC specific testing was performed in a total of 53/724 (7.3%) admissions only and more often applied in DTI cases (n = 35/77; thrombin time or diluted thrombin time in 34 and ecarin clotting time in 1 case) compared to DXI cases (n = 18/647; all chromogenic aXa assays). Most of these DOAC specific tests were ordered in one of the five tertiary hospitals in the region, which offer 24/7 availability of DOAC specific tests.

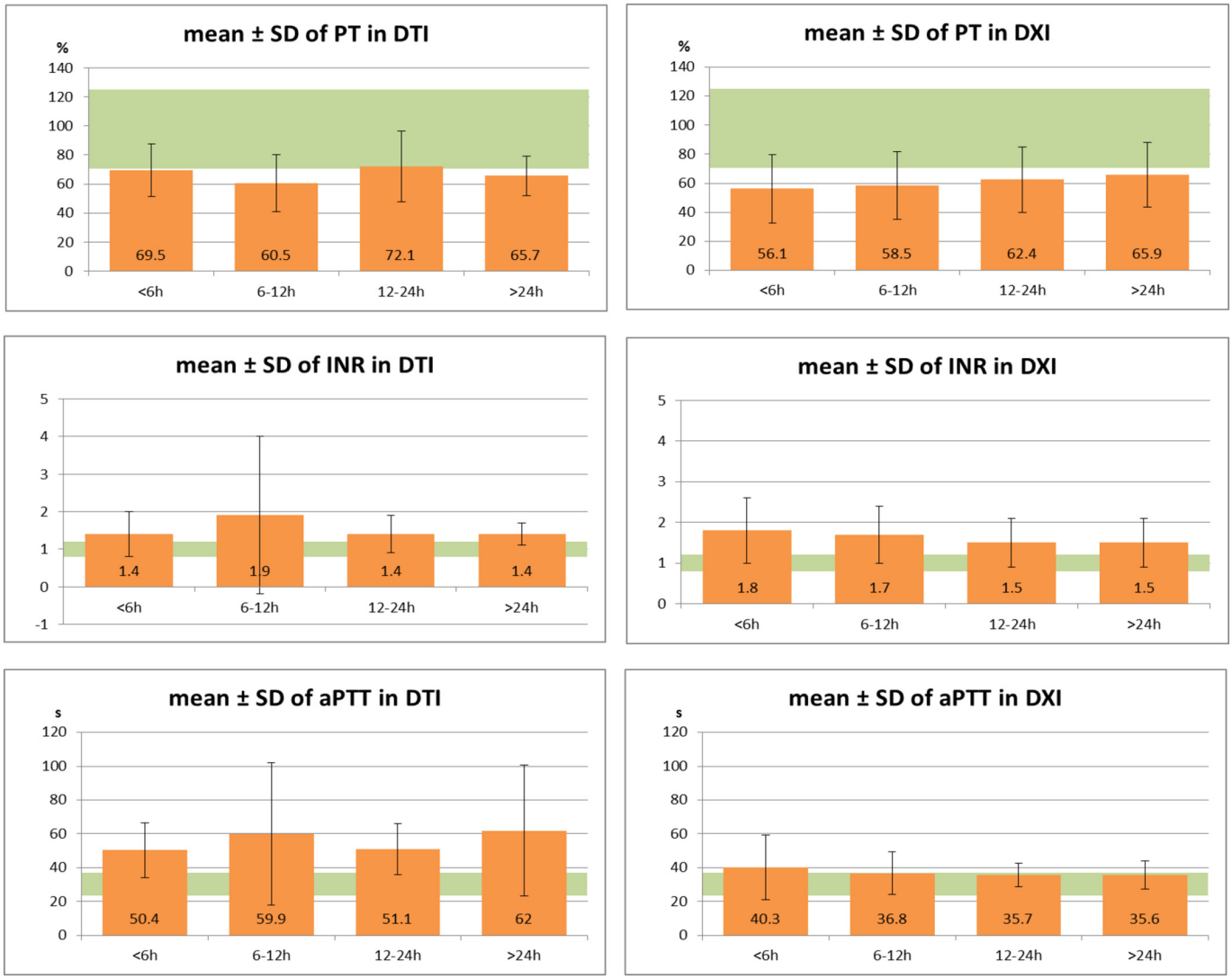

Fig. 2. Distribution (mean ± SD) of PT% activity, INR and aPTT in DXI and DTI patients according to timing of last DOAC intake. Green areas present mean upper and lower limits of normal across participating laboratories. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Impact of DTI or DXI on INR.

	Total (n = 724)[a]	DTI (n = 77)	DXI (n = 647)	Rivaroxaban (n = 499)	Apixaban (n = 138)	Edoxaban (n = 10)
Reference range available, n (%)	668/724 (92.3)	70/77 (90.9)	598/647 (92.4)	461/499 (92.4)	130/138 (94.2)	7/10 (70.0)
Mean time between last DOAC and blood sample, h (range)	10.7 (0–47.9)	11.7 (1.1–38.9)	10.6 (0–47.9)	11.1 (0–47.9)	8.1 (0–37.8)	11.6 (1.8–30.3)
Mean ± SD	1.6 ± 0.8	1.6 ± 1.3	1.6 ± 0.7	1.7 ± 0.7	1.3 ± 0.4	1.5 ± 0.2
Median (IQR)	1.4 (0.6)	1.3 (0.3)	1.4 (0.7)	1.5 (0.8)	1.2 (0.3)	1.4 (0.1)
Minimum/maximum	0.8/11.2	0.9/11.2	0.8/5.7	0.8/5.7	1.0/3.9	1.2/2.1
Normal values, n (%)	209/668 (31.3)	27/70 (38.6)	182/598 (30.4)	120/461 (26.0)	62/130 (47.7)	0
Abnormal values, n (%)	459/668 (68.7)	43/70 (61.4)	416/598 (69.6)	341/461 (74.0)	68/130 (52.3)	7/7 (100)

[a] Values were not available for INR in 56 emergency admissions.

4. Discussion

Global coagulation tests such as PT/INR or aPTT belong to the laboratory routine tests obtained in most emergency admissions. Correct interpretation of these test results is vital since emergency patients may require urgent surgical or interventional procedures, antithrombotic or thrombolytic therapies or transfusion of coagulation factors. For decades, emergency physicians have learned to rely on PT, INR or aPTT when the effects of VKA or UFH on the coagulation capacity had to be evaluated. Due to the high sensitivity of these tests towards VKA or UFH, false-negative coagulation test results despite therapeutic anticoagulant activity were uncommon. LMWH, on the other hand, usually did not affect PT, INR or aPTT and, therefore, the presence of these drugs was not indicated by elevated PT or aPTT values but, due to the subcutaneous application, bruising at injection site often was a warning sign for emergency physicians.

With DOAC, all of this has changed and our data clearly indicate that the interpretation of global coagulation tests in DOAC recipients represents a major challenge for emergency physicians. In our study, deviations of PT ratio and aPTT were seen in many patients with a recent intake of DTI or DXI. At the same time, approximately one out of three patients with a DOAC intake within the last 12 h (and, therefore, relevant antithrombotic activity) had normal coagulation tests, which demonstrates the high risk of “false negative” tests. This may leave the physician unaware of the anticoagulant status of the patient and may contribute to false management decisions and significant bleeding complications. On the other hand, approximately 50% of DXI and > 80% of DTI patients with a last DOAC intake > 24 h (trough status) had at least one of the three coagulation tests still elevated. In this situation, false-abnormal global coagulation tests may lead to over-concern, an over-treatment with coagulation factors or an unnecessary delay of urgently indicated invasive procedures or thrombolytic therapies.

All of this is further complicated by relevant inter-individual differences in bioavailability and clearance of DOAC and by the variable impact of different DOACs on different test assays for PT/INR or aPTT measurements [9–12].

Recently, attempts have been made to provide guidance for the interpretation of such test results [2–4,13] it has been universally acknowledged that relevant limitations remain which may affect patient safety in case of misinterpretation of aPTT and PT in DTI and DXI patients in the absence of specific tests that provide accurate NOAC plasma levels. Furthermore, variation of PT and aPTT may also result from underlying diseases in emergency patients such as consumption coagulopathy and other coagulation disorders related to acute changes of coagulation proteins. This makes the interpretation of PT and aPTT results in emergency patients on DOACs even more challenging, since all these factors may overlap.

The fact that DOAC affect global coagulation tests has been confirmed early after these drugs entered the clinical development phase [14]. However, the true magnitude of this problem on clinical care and, especially, on care in emergency settings has not been systematically studied before. Therefore, it is difficult to place our findings into a broader context, also because the intra- and inter-individual variability of PT and aPTT can also be significant in non-anticoagulated patients. In our population, we have further influencing factors from DOAC liver metabolism, renal clearance, P-gp clearance (all of which affect half-life of DOACs), body weight (affecting volume of DOAC distribution), underlying emergency conditions and time variations between last DOAC intake and blood sampling to consider. All of this likely contributed to the observed large variability but it is impossible to speculate on the impact of either of these factors. However, in the end, a physician is faced with a PT and aPTT value from a specific patient and clinical interpretation needs to consider the impact of all these factors, indicating the magnitude of the challenge. The use of DOAC Stop, a

Table 6
Impact of DTI or DXI on aPTT.

	Total (n = 724)[a]	DTI (n = 77)	DXI (n = 647)	Rivaroxaban (n = 499)	Apixaban (n = 138)	Edoxaban (n = 10)
Reference range available, n (%)	692/724 (95.6)	75/77 (97.4)	617/647 (95.4)	477/499 (95.6)	133/138 (96.4)	7/10 (70.0)
Mean time between last DOAC and blood sample, h (range)	10.5 (0–47.9)	11.5 (1.1–38.9)	10.4 (0–47.9)	10.9 (0–47.9)	8.2 (0–37.8)	11.6 (1.8–30.3)
Mean ± SD	39.7 ± 17.8	55.1 ± 30.5	37.8 ± 14.4	39.0 ± 14.6	32.3 ± 6.3	56.8 ± 46.4
Median (IQR)	36.0 (10.9)	47.0 (19.8)	35.2 (9.9)	36.5 (9.7)	31.1 (6.4)	37.3 (8.7)
Minimum/maximum	18.0/180.0	25.0/180.0	18.0/180.0	18.0/180.0	19.2/74.7	29.7/160.0
Normal values, n (%)	379/692 (54.8)	14/75 (18.7)	365/617 (59.2)	253/477 (53.0)	108/133 (81.2)	4/7 (57.1)
Abnormal values, n (%)	313/692 (45.2)	61/75 (81.3)	252/617 (40.8)	224/477 (47.0)	25/133 (18.8)	3/7 (42.9)

[a] Values were not available for aPTT in 32 emergency admissions.

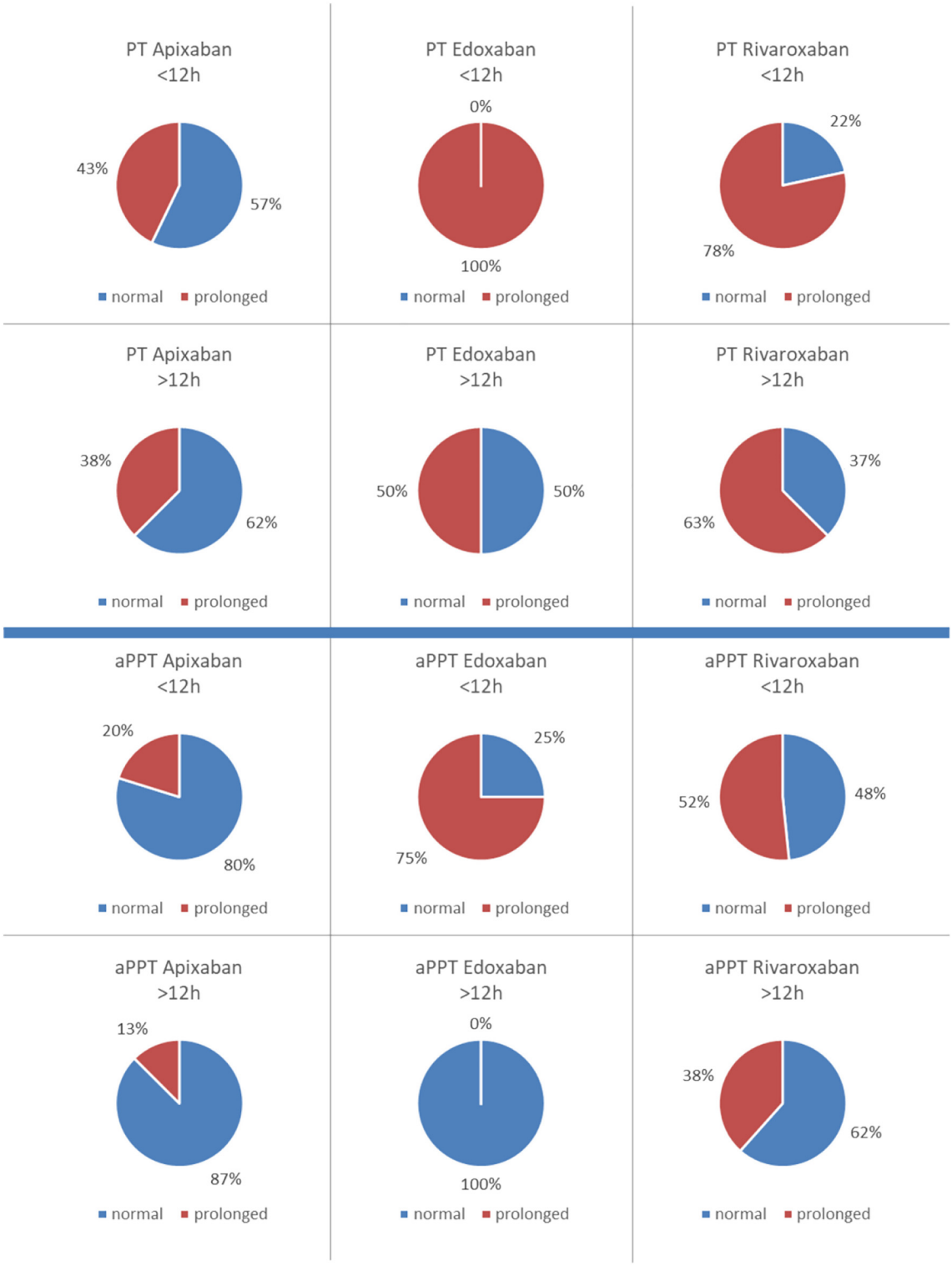

Fig. 3. Impact of timing (≤ or < 12h) of last dose of apixaban edoxaban or rivaroxaban on prothrombin time (PT; top panel) or activated partial thromboplastin time (aPTT, lower panel).

substance that can be added to blood samples from DOAC patients to eliminate the DOAC impact on coagulation may help to evaluate the degree to which DOAC related and –unrelated factors contribute to abnormal PT and aPTT values [15,16].

The main finding of our study, namely the lack of sensitivity and specificity of aPTT or PT to demonstrate or rule out presence of relevant anticoagulation activity, was demonstrated for all DOACs and for all test assays used in a spectrum of 50 routine care laboratories. Taken together, PPV and NPV values ranged between 28 and 73% for the dichotomized timeframe DOAC-intake < or > 12 h, which likely is the most important timeframe for clinical decision making, since all DOACs achieve maximum plasma levels around 4 h after intake and share elimination half-lives of approximately 12 h. The calculated PPV and NPV change over time but remain in a range that is not useful for assessment of anticoagulant activity.

Finally, the fact that specific tests such as diluted thrombin time (for

DTI) or anti-Xa activity (for DXI) were found to be rarely used in emergency settings (approximately 7% of cases only) needs further attention and research. The reason for this under-use of specific testing is unknown and not captured in our present analysis. Therefore, we can only speculate if this is due to a lack of availability of these tests on a 24/7 basis (only available in the five tertiary hospitals in the region but not in secondary hospitals, some of which offer in-house testing usually only during working hours or totally depend on large external reference laboratories, limiting the availability of specific DOAC tests in emergency situations). Further reasons for the under-use of DOAC specific testing could include a lack of knowledge about availability, about interpretation of these specific assays [17,18] or, maybe, cost considerations.

On the other hand, it may also be that the clinical picture of emergencies observed in DOAC recipients leads to a focus on clinical decisions that can be made without quantifying the anticoagulant activity in this patient exactly. For instance, several guidance statements recommend to focus DOAC-related treatment decisions on clinical parameters such as type, time and dosage of last DOC intake and renal function, since these information will allow for a clinical estimate of the anticoagulant activity in an emergency situation [19].

Furthermore, some common emergency scenarios such as gastrointestinal bleedings can often be handled without detailed information on coagulation status, since the focus on a fast and dedicated endoscopic treatment of the bleeding lesion may be more relevant than the type or intensity of DOAC treatment at the time of presentation and a wait for specific test results may unnecessarily delay some of these treatment decisions. Further studies are needed to improve our understanding of the reasons behind the under-use of DOAC specific lab testing. Furthermore, management of emergency admissions of DOAC patients may change in future because of the emergence of data for thrombelastography [10] or point-of-care (POC) test systems such as Hemachrome®Signature POCT cards [20] or the DOASENSE® urine dipstick [21].

As with all observational research, our study has limitations that need to be addressed. First, the Dresden NOAC Registry does not routinely collect information on hospitalization. As a consequence, we could only identify the study cohort for this analysis by identification of common clinical outcomes (bleeding, cardiovascular events, surgical or interventional procedures) that are routinely collected in our database. It may therefore be that our findings may not be generalizable to the management of other emergency admission. On the other hand, our findings were very consistent across different hospitals, different laboratories and different DOAC types and there is little reason to suspect that the indication for emergency admission would affect the impact of DOAC on coagulation tests to a different degree. Another limitation is that our work does not contain information on how the lab results were interpreted by attending clinicians and how the treatment of emergency patients was affected. This would be extremely difficult and highly subjective in a post-hoc approach. Therefore, we did not attempt to evaluate the cases for management issues but strongly believe that this needs to be the next step of research on this specific topic, ideally by performing a prospective management study.

5. Conclusion

Many DOAC recipients present with elevated PT, INR or aPTT during emergency admissions but false negative (normal) values within 6 h of last intake as well as elevated values beyond 24 h after last DOAC intake are common. DOAC specific testing is rarely performed in emergency settings, the reasons for which are not well enough understood. Future clinical initiatives as well as research should focus on the development and implementation of specific DOAC tests, including POC devices in routine care.

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Declaration of competing interest

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