Original Contribution

Emergency Coagulation Assessment During Treatment With Direct Oral Anticoagulants

Limitations and Solutions

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Background and Purpose—In patients receiving direct oral anticoagulants (DOACs), emergency treatment like thrombolysis for acute ischemic stroke is complicated by insufficient availability of DOAC-specific coagulation tests. Conflicting recommendations have been published concerning the use of global coagulation assays for ruling out relevant DOAC-induced anticoagulation.

Methods—Four hundred eighty-one samples from 96 DOAC-treated patients were tested using prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT), DOAC-specific assays (anti-Xa activity, diluted TT), and liquid chromatography–tandem mass spectrometry. Sensitivity and specificity of test results to identify DOAC concentrations <30 ng/mL were calculated. Receiver operating characteristic analyses were used to define reagent-specific cutoff values.

Results—Normal PT and aPTT provide insufficient specificity to safely identify DOAC concentrations <30 ng/mL (rivaroxaban/PT: specificity, 77%/sensitivity, 94%; apixaban/PT: specificity, 13%/sensitivity, 94%, dabigatran/aPTT: specificity, 49%/sensitivity, 91%). Normal TT was 100% specific for dabigatran, but sensitivity was 26%. In contrast, reagent-specific PT and aPTT cutoffs provided >95% specificity and a specific TT cutoff enhanced sensitivity for dabigatran to 84%. For apixaban, no cutoffs could be established.

Conclusions—Even if highly DOAC-reactive reagents are used, normal results of global coagulation tests are not suited to guide emergency treatment: whereas normal PT and aPTT lack specificity to rule out DOAC-induced anticoagulation, the low sensitivity of normal TT excludes the majority of eligible patients from treatment. However, reagent-specific cutoffs for global coagulation tests ensure high specificity and optimize sensitivity for safe emergency decision making in rivaroxaban- and dabigatran-treated patients.

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Key Words: anticoagulants ■ blood coagulation tests ■ dabigatran ■ emergency medicine ■ emergency treatment ■ rivaroxaban ■ stroke

Direct oral anticoagulants (DOACs) have gained widespread popularity for the treatment of conditions that require long-term anticoagulation.[1] DOAC treatment is based on a fixed dose scheme, and monitoring of coagulation is not routinely required. Currently, availability of DOAC-specific coagulation tests, that is, calibrated anti-Xa activity for factor Xa inhibitors and diluted thrombin time or ecarin-based assays for dabigatran, is limited.[2,3] This lack of monitoring capability complicates treatment decisions in medical emergencies like ischemic or hemorrhagic stroke that require thrombolysis, urgent surgical intervention, or anticoagulation reversal.

Several authors have argued that normal test results of routinely available global coagulation assays like prothrombin time (PT), activated partial thromboplastin time (aPTT), or thrombin time (TT) suffice to rule out DOAC-induced anticoagulation, but this view has been contested (Tables I through

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III in the online-only Data Supplement). A recent publication found normal results of global coagulation tests insufficient for this purpose but acknowledged that their conclusion was limited by the use of nonreactive reagents.[4] Current recommendations on the use of global coagulation tests during DOAC treatment, including the latest guideline of the European Stroke Organization,[5] are conflicting and do not adequately answer whether PT, aPTT, or TT can be used to safely identify suitable patients for thrombolysis or surgery.

To clarify this important question and provide clinicians with guidance for emergency decision making, we investigated the diagnostic accuracy of PT, aPTT, and TT to identify rivaroxaban, apixaban, and dabigatran concentrations below 30 ng/mL—a concentration threshold that is considered safe for thrombolysis and surgery.[5,6]

Methods

Study Design

We studied all samples obtained from the POCT-DOAC trials (Point-of-Care Testing of Coagulation in Patients Treated With Direct Oral Anticoagulants),[7,8] 2 single-center, prospective observational trials with blinded outcome assessment that investigated the use of point-of-care coagulation testing in DOAC-treated patients. The studies enrolled real-life patients either newly started or on continuous DOAC therapy. Serial blood samples were collected from each patient during the course of 12 (apixaban, dabigatran) or 24 hours (rivaroxaban) to cover different DOAC concentrations, including peak and trough levels. Institutional review board approval was obtained from the ethics committee of Tübingen University Hospital (protocol no. 259/2013BO1 and 270/2015B01). The studies were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients before enrollment.

Setting and Eligibility Criteria

The studies were conducted at the Department of Neurology and Stroke and the Department of Cardiology and Cardiovascular Medicine of Tübingen University Hospital—a tertiary care facility. We analyzed a total of 481 samples acquired from 96 patients (dabigatran: N=34, samples=178; rivaroxaban: N=32, samples=146; apixaban: N=30, samples=157). Samples that had been obtained from treatment-naive patients before first intake of DOAC were removed from analysis (samples=88). Samples were acquired between July 2013 and November 2015. Seven samples could not be collected because of technical difficulties or unexpected clinical events. Main exclusion criteria were known coagulopathy, abnormal coagulation at baseline, or recent intake of other anticoagulants. A detailed list of inclusion and exclusion criteria can be found in our prior publications.[7,8]

Sample Collection and Coagulation Testing

Six blood samples were collected from each subject via an indwelling venous catheter or venipuncture: before DOAC intake, 30 minutes, 1, 2, and 8 hours after intake, and at trough (12 hours for apixaban/dabigatran and 24 hours for rivaroxaban). Samples were collected in 3.2% sodium-citrate tubes (Sarstedt, Nümbrecht, Germany) and instantly centrifuged to acquire plasma. In all samples, laboratory-based PT and aPTT were measured using a single reagent (HemosIL RecombiPlasTin 2G and HemosIL APTT-SP, respectively) on an ACL TOP 700 (all by Instrumentation Laboratory, Kirchheim, Germany). The normal ranges were quick ≥70%, international normalized ratio ≤1.2, and aPTT ≤37 seconds. In all samples containing factor Xa inhibitors, anti-Xa activity (chromogenix COAMATIC heparin test; Instrumentation Laboratory, Kirchheim, Germany) was measured, and TECHNOVIEW calibrators (Technoclone, Vienna, Austria) were used to determine DOAC concentrations.

Remaining plasma aliquots were stored at −80°C. From the frozen material, TT (test-thrombin reagent; Siemens Healthcare Diagnostics, Erlangen, Germany; normal range, <21 seconds), and diluted TT (Hemoclot assay; Hyphen BioMed, Neuville-sur-Oise, France) were measured in all samples containing dabigatran.

DOAC plasma concentrations were determined in all samples using ultraperformance liquid chromatography–tandem mass spectrometry (UPLC-MS),[9] which is the gold standard to obtain exact measurement of DOAC plasma concentrations.

All coagulation testing was performed according to manufacturers' instructions by thoroughly trained investigators and technicians.

Blinding

All global coagulation tests (PT, aPTT, and TT) and DOAC-specific coagulation assays (anti-Xa activity and diluted TT) were conducted and interpreted by technicians blinded to UPLC-MS results. Technicians performing coagulation tests using frozen samples (ie, TT and diluted TT), were additionally blinded for the time-point samples were drawn and whether different samples belonged to the same patient. Fully automated measurements of PT, aPTT and anti-Xa activity were conducted during routine operation at our central laboratory without further blinding.

Definition of Safe-for-Treatment Concentration Thresholds

We based our analyses on a concentration threshold of 30 ng/mL, which has recently been proposed as safe for thrombolysis in acute ischemic stroke and surgical procedures for all 3 investigated DOACs.[5,6]

Statistics

For test performance analyses, test results of all samples in each DOAC group were pooled. SPSS v23 (IBM, Armonk, NY) was used for statistics. Diagnostic accuracy was expressed in terms of sensitivity, specificity, and likelihood ratio.

For each coagulation test, sensitivity was defined as the percentage of samples that were correctly identified as being eligible for treatment with serum drug level <30 ng/mL Correspondingly, specificity was defined as the percentage of samples that were correctly identified as not eligible for treatment with serum drug level >30 ng/mL. Sensitivity and specificity are given with 2-sided 95% confidence intervals. Confidence intervals were calculated according to the efficient-score method using the free online VassarStats Clinical Calculator 1.[10] A specificity >95% was predefined as sufficient for clinical application. For different coagulation tests, reagent-specific cutoff values that fulfill this specificity target were established via receiver operating characteristic analyses. All DOAC concentrations are reported as median and interquartile range. This study was performed in accordance with the STARD guidelines (Standards for Reporting Diagnostic Accuracy) for studies on diagnostic tests.

Results

Characteristics of Study Samples

Using UPLC-MS, we found a median concentration of 27.5 ng/mL dabigatran (interquartile range, 10.0–66.5), 54.0 ng/mL rivaroxaban (interquartile range, 35.2–95.4), and 100 ng/mL apixaban (interquartile range, 34.3–189.0). DOAC concentrations below the investigated safe-for-treatment threshold of 30 ng/mL were detected in 51.7% (samples=92) of dabigatran samples, 23.3% (samples=34) of rivaroxaban samples, and 19.7% (samples=31) of apixaban samples. Patient characteristics and baseline laboratory values are provided in Tables IV and V in the online-only Data Supplement.

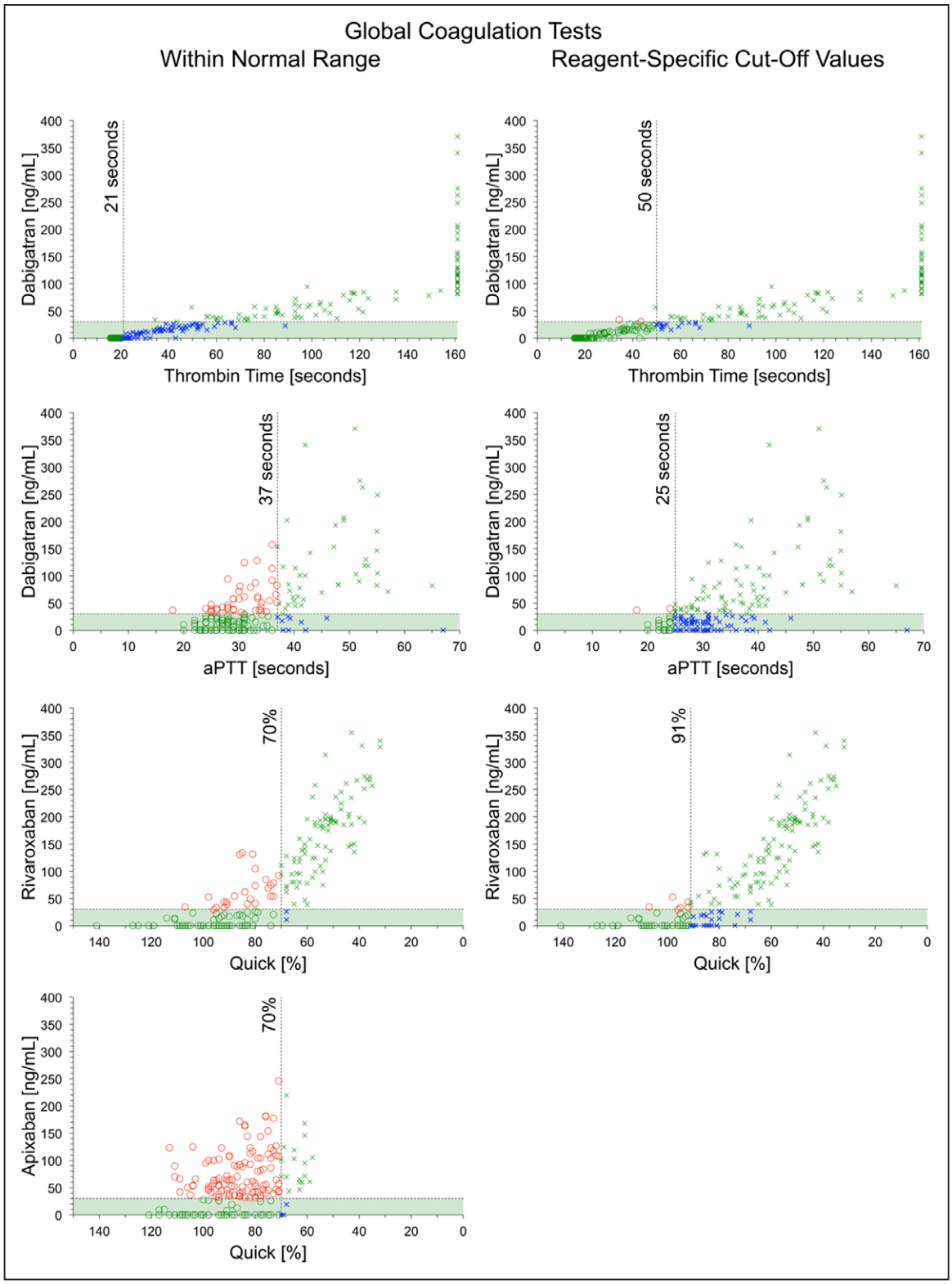

Figure. Scatter plots of direct oral anticoagulant (DOAC) concentrations and global coagulation test results. Scatter plots of DOAC concentrations and global coagulation test results to illustrate the diagnostic accuracy of global coagulation test results within normal range (**left** column) and reagent-specific cutoffs (**right** column) for the identification of patients with DOAC concentrations below the safe-for-treatment threshold of 30 ng/mL. Green circles represent samples below the safe-for-treatment threshold that are correctly identified as eligible for emergency treatment (true positive). Red circles represent samples incorrectly identified as eligible for treatment, despite DOAC concentrations above the safe-for-treatment threshold (false positive). Green crosses represent samples correctly identified as not eligible for treatment (true negative). Blue crosses represent samples below the safe-for-treatment threshold that are not detected (false negative). Row 1: Dabigatran/thrombin time (TT, test-thrombin reagent). Compared with TT within normal range (≤21 seconds; **left** column), a reagent-specific TT cutoff (<50 seconds; **right** column) significantly increases sensitivity (more true positives, ie, (*Continued*)

Diagnostic Accuracy of Global Coagulation Tests Within Normal Range

Results of test accuracy calculations for global coagulation tests are presented in the Figure and Table.

aPTT results within normal range were 49% specific to dabigatran concentrations <30 ng/mL. A combination of PT and aPTT did not result in a relevant increase in specificity.

For rivaroxaban, normal PT had 77% specificity to concentrations <30 ng/mL. As for dabigatran, a combination of PT and aPTT within normal range did not increase test accuracy.

Normal TT was 100% specific to dabigatran concentrations <30 ng/mL and provided 26% sensitivity. Use of TT results <3 to 4× the upper normal range (UNR)[6,11] increased sensitivity to 95% (<3×UNR) and 99% (<4×UNR). However, the higher TT cutoffs decreased specificity to 90% (<3×UNR) and 78% (<4×UNR).

All used global coagulation assays were fairly unreactive to apixaban, and normal test results had <20% specificity for concentrations <30 ng/mL.

Diagnostic Accuracy of Reagent-Specific Cutoff Values

Using receiver operating characteristic analyses, we calculated optimized cutoff values for PT, aPTT, and TT assays that provide >95% specificity for the investigated safe-for-treatment threshold of 30 ng/mL. For apixaban, no such cutoff could be established because of the low reactivity of all 3 assays. Results are presented in the Figure and Table.

Discussion

Based on real-life patient samples and highly DOAC-reactive reagents, we found that normal test results of global coagulation assays are not suited for emergency coagulation assessment in DOAC-treated patients. PT and aPTT within normal range did not accurately identify samples with DOAC concentrations <30 ng/mL, which would allow thrombolysis or surgery (low specificity). TT results within normal range were accurate but failed to detect the majority of samples <30 ng/mL (low sensitivity).

Reagent-specific cutoff values can be used to overcome these limitations (Figure and Table). Use of these cutoffs increased specificity of PT and aPTT assays above the predefined safety goal of >95% and increased sensitivity of TT from 26% to 84%.

Concentration Thresholds

Data on what constitutes a relevant DOAC concentration, that is, a concentration that leads to clinically significant coagulation impairment, has not been established in prospective clinical trials. Previously, different thresholds have been proposed for each DOAC. Moreover, the recommended thresholds differed between thrombolysis for acute stroke and emergency surgery.[11–15] Recently, a uniform safe-for-treatment threshold of 30 ng/mL has been established that covers all substances and both thrombolysis situations and surgery.[5,6] This threshold is lower than most previous recommendations and in our opinion, has been chosen conservatively to emphasize safety. An alternative, less-conservative threshold of 50 ng/mL has been proposed for surgery with moderate bleeding risk.[12] Test accuracy calculations for this higher threshold can be found in Table VI in the online-only Data Supplement. Importantly, use of this higher cutoff did not lead to a relevant improvement in diagnostic accuracy of global coagulation tests within normal range. It certainly seems possible that these arbitrary definitions of the relevant DOAC concentrations will change at some point as clinical experience with DOAC increases, similar to the finding that thrombolysis in ischemic stroke can be performed safely, despite an elevated international normalized ratio (≤1.7) during warfarin treatment.[16]

Global Coagulation Test Results Within Normal Range

Results of PT and aPTT assays within normal range have been proposed as sufficient for the exclusion of relevant rivaroxaban[17,18] and dabigatran[11,15,19] concentrations if sensitive reagents are used (Tables I and II in the online-only Data Supplement). Based on the results of our study, we oppose this approach. Despite the use of highly DOAC-reactive PT and aPTT reagents (HemosIL RecombiPlasTin 2G and HemosIL APTT-SP),[20,21] we found that test results within normal range provided inadequate specificity (77% and 43%) for rivaroxaban and dabigatran concentrations below 30 ng/mL. This means, that a substantial fraction of patients (23% for rivaroxaban and 57% for dabigatran) with DOAC concentrations above the safe-for-treatment threshold would be incorrectly identified as eligible for treatment. Test results within normal range should, therefore, not be used to guide emergency treatment decisions.

Although little data is available for apixaban, less-pronounced effects on global coagulation assays have been described.[22] Nevertheless, some authors suggested that thrombolysis might still be performed in acute ischemic stroke, if both PT and aPTT are within normal range.[11,23] Our findings do not support this approach. Normal results of all global coagulation assays had <20% specificity for apixaban levels below 30 ng/mL.

TT has repeatedly been shown to be highly reactive to even minimal dabigatran concentrations.[22] In accordance to these reports, we found that TT results within normal range were 100% specific for dabigatran concentrations below 30 ng/mL.

Figure Continued. green circles). The low number of false-positive test results (red circles) fulfills the predefined specificity target of >95%. Rows 2 and 3: Dabigatran/activated partial thromboplastin time (activated partial thromboplastin time [aPTT], HemosIL APTT-SP) and rivaroxaban/prothrombin time (PT, HemosIL RecombiPlasTin 2G). Use of reagent-specific aPTT and PT cutoffs (<25 seconds and quick >91%, respectively) reduces the number of false-positive test results (red circles) and meets the predefined specificity target of >95%. Although this increase in specificity limits sensitivity, use of reagent-specific cutoffs still allowed to identify a considerable fraction of patients (22% and 47%, respectively) who can be treated safely without further delay (green circles). Patients eligible for treatment who are not detected (blue crosses) can potentially receive delayed treatment if slower DOAC-specific tests are available. Row 4: Apixaban/PT. For apixaban, no cutoffs could be established for the predefined specificity target of >95%.

Table. Test Accuracy of Global Coagulation Tests

Substance and Safe-for-Treatment Threshold	Coagulation Test	Result Within Normal Range			Result Below Reagent-Specific Cutoff			
		Specificity (%)	Sensitivity (%)	LR+	Cutoff	Specificity (%)	Sensitivity (%)	LR+
Dabigatran <30 ng/mL	aPTT	49 (38–60)	91 (83–96)	1.8	aPTT <25 s	98 (91–100)	22 (14–32)	9.3
	PT and aPTT	55 (44–65)	80 (71–88)	1.8				
	TT	100 (95–100)	26 (18–37)	∞	TT <50 s	98 (91–100)	84 (74–90)	35.9
	TT <3×UNR	90 (81–95)	95 (87–98)	9.0				
	TT <4×UNR	78 (67–86)	99 (93–100)	4.5				
Rivaroxaban <30 ng/mL	PT	77 (68–84)	94 (79–99)	4.1	Quick >91%	96 (89–98)	47 (30–65)	10.5
	PT and aPTT	77 (68–84)	94 (79–99)	4.1				
Apixaban <30 ng/mL	PT	13 (8–20)	94 (77–99)	1.1				
	PT and aPTT	17 (11–25)	90 (73–97)	1.1				

Samples: 178 (dabigatran), 146 (rivaroxaban), and 157 (apixaban). Sensitivity and specificity are provided with 95% confidence intervals. aPTT indicates activated partial thromboplastin time (HemosIL APTT-SP); LR+, positive likelihood ratio; PT, prothrombin time (HemosIL RecombiPlasTin 2G); TT, thrombin time (test-thrombin reagent); and UNR, upper normal range.

However, sensitivity was merely 26%, and hence, >2/3 of eligible patients would not have been recognized. This finding supports the previously voiced concern that reliance on TT might exclude patients from beneficial procedures.[15] For this reason, some authors recommended higher cutoff values that were arbitrarily chosen as 3 or 4× the UNR.[6,11] Although these higher cutoffs had excellent sensitivity for dabigatran concentrations <30 ng/mL, we found that specificity did not meet the predefined safety target of >95%.

Diagnostic Accuracy of Reagent-Specific Cutoff Values

Recently, Lippi et al[24] propagated the use of reagent-specific cutoffs to increase the diagnostic accuracy of PT and aPTT assays for DOAC. We applied this approach at our institution and used receiver operating characteristic analysis to establish optimized cutoff values for rivaroxaban and dabigatran (Figure and Table). No cutoffs were established for apixaban because of the low reactivity of all assays.

To ensure patient safety, we only considered cutoffs that were highly specific (>95%) for DOAC concentrations below the safe-for-treatment threshold. Following this approach, PT and aPTT cutoffs with a specificity of 96 and 98% could be established for rivaroxaban and dabigatran. We acknowledge that the resulting significant restriction in sensitivity (22% and 47%, respectively) might be regarded as a major drawback. However, reagent-specific cutoffs maximize the (still considerable) fraction of patients who can be identified for emergency thrombolysis or surgery without compromising patient safety. Importantly, the time period between last drug intake and coagulation testing should always be considered because DOAC plasma concentrations increase rapidly after intake until reaching a peak after 2 to 4 hours. Hence, results of coagulation tests should always be interpreted cautiously taking into aspect additional clinical information.

In cases of TT and dabigatran, the reagent-specific cutoff maintained a high specificity of 98% (compared with 100% for TT results within normal range). This minimal reduction in specificity led to a >3-fold increase in sensitivity (from 26% to 84%) and hence, significantly increased the number of patients that can be identified as eligible for treatment.

In some institutions, DOAC-specific tests can be conducted, but compared with global coagulation tests, results are commonly slower to obtain. In this case, global and DOAC-specific coagulation tests can be used sequentially to optimize speed and sensitivity. Such an approach has been recently published by Kepplinger et al[25]: if global coagulation tests yield results below prespecified cutoff values, thrombolysis in ischemic stroke patients may be initiated without the need of further coagulation testing. Calibrated DOAC-specific tests are only required if the results of global coagulation tests are elevated. We would like to point out that this approach critically relies on the use of reagent-specific cutoffs for global coagulation tests that ensure high specificity. As an example, Kepplinger et al proposed an international normalized ratio <1.4 (measured using the neoplastin reagent) as the cutoff for ruling out relevant rivaroxaban concentrations. In our analysis (Table VII in the online-only Data Supplement) an international normalized ratio <1.4 (measured using the HemosIL RecombiPlasTin 2G reagent) was fairly unspecific (≤80%) to rivaroxaban and would be unsuitable for clinical decision making.

Strengths and Limitations

We are the first to report a comprehensive evaluation and comparison of all current recommendations for the use of global coagulation assays to guide emergency treatment in DOAC-treated patients. To provide clinicians with a tool for decision making, we included a detailed report of the diagnostic accuracy of the different tests. Our analyses are based on a large number of real-life patient samples. This represents an advantage compared with previous reports that were either solely based on expert opinions,[11,15,19,23] relied on the use of DOAC-spiked plasma samples rather than samples obtained from real-life patients,[22] or comprised of only few samples with low DOAC concentrations.[26–28] In addition, rather than relying on indirect measurements of DOAC concentrations using calibrated coagulation tests[4,22] we chose UPLC-MS, which is the gold standard to obtain exact measurement of DOAC plasma concentrations.

Edoxaban was not included in the study because this DOAC was not authorized for clinical use when the study was initiated. Sequential samples were acquired from individual patients. Hence, a bias because of repeated measurements in individual patients cannot be excluded. Furthermore, the precision of our results might be limited by the moderate number of patients included in the study. Generalizability of our results is limited by the single-center nature of the trial. Although we only used a single reagent for PT and aPTT testing, the used reagents have been previously shown to provide high reactivity to DOAC.[20,21]

Conclusions

In summary, this study demonstrates that results of global coagulation tests within normal range are not suited to safely identify DOAC concentrations below the suggested safe-for-treatment threshold of 30 ng/mL, even when using highly DOAC-reactive reagents. Normal results of PT and aPTT provide insufficient specificity to safely select patients with DOAC concentrations below the safe-for-treatment threshold. Normal TT has low sensitivity and, thus, excludes the majority of eligible patients from potentially beneficial procedures. Hence, the use of test results within normal range should become obsolete for the identification of patients suitable for thrombolysis in acute ischemic stroke or emergency surgery.

However, reagent-specific cutoffs provide excellent specificity and optimized sensitivity to allow safe emergency decision making in rivaroxaban and dabigatran-treated patients. This finding does not apply to apixaban.

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Emergency Coagulation Assessment During Treatment With Direct Oral Anticoagulants: Limitations and Solutions

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SUPPLEMENTAL MATERIAL

Supplemental Table I: Recommendations for the use of global coagulation to tests for the identification of relevant anticoagulant effect of dabigatran

Dabigatran			
	Sufficient	Sufficient in most cases	Insufficient
PT within normal range			Cuker 2014[1] Diener 2013[2] Hayes et al. 2013[3] Heidbuchel 2013[4] Lippi 2014[5] Siegal et al. 2013[6] Tripodi 2013[7]
aPTT within normal range	Lippi 2014*[5] Steiner 2013[8]	Diener 2013[2] Eickelboom 2013[9] Kitchen 2014[10] Konkle 2013[11] Levy 2013[12] Siegal 2013[6] Tran 2014[13] Tripodi 2013[7]	Cuker 2014[1] Douxfils 2014[14] Hankey 2014[15] Hayes et al. 2013[3] Hapgood 2013[16] Heidbuchel 2013[4]
TT within normal range	Cuker 2014[1] Diener 2013[2] Douxfils 2014[14] Hankey 2014[15] Hayes 2013[3] Heidbuchel 2013[4] Kepplinger 2014*[17] Kitchen 2014[10] Konkle 2013[11] Siegal 2013[6] Steiner 2013[8] Tran 2014[13] Tripodi 2013[7]	Hapgood 2013[16] Levy 2013[12]	
aPTT and TT within normal range	Eickelboom 2013[9] Hapgood 2013[16] Tran 2014[13]		

* using reagent-specific cut offs

Supplemental Table II: Recommendations for the use of global coagulation to tests for the identification of relevant anticoagulant effect of rivaroxaban

Rivaroxaban			
	Sufficient	Sufficient in most cases	Insufficient
PT within normal range	Kepplinger 2014*[17] Lippi 2014*[5] Shahoun 2015[18] Siegal 2013[6] Tripodi 2013[7]	Crowther 2015[19] Douxfils 2014[14] Kitchen 2014[10] Tran 2014[13]	Cuker 2014[1] Francard 2014[20] Hankey 2014[15] Heidbuchel 2013[4] Levy 2013[12]
aPTT within normal range			Cuker 2014[1] Francard 2014[20] Hankey 2014[15] Heidbuchel 2013[4] Kitchen 2014[10] Levy 2013[12] Tran 2014[13]
PT and aPTT within normal range		Diener 2013[2] Steiner 2013[8]	

* using reagent-specific cut offs

Supplemental Table III: Recommendations for the use of global coagulation to tests for the identification of relevant anticoagulant effect of apixaban

Apixaban			
	Sufficient	Sufficient in most cases	Insufficient
PT within normal range		Shahoun 2015[18]	Cuker 2014[1] Douxfils 2014[14] Hankey 2014[15] Kepplinger 2014[17] Kitchen 2014[10] Siegal 2013[21] Tran 2014[13] Tripodi 2013[7] Ward 2013[22]
aPTT within normal range			Cuker 2014[1] Hankey 2014[15] Kitchen 2014[10] Tran 2014[13] Ward 2013[22]
PT and aPTT within normal range		Diener 2013[2] Steiner 2013[8]	

Supplemental Table IV: Patient characteristics in the three DOAC groups

	Rivaroxaban	**Apixaban**	**Dabigatran**
Dose[1]	15 mg: 2 (7%) 20 mg: 28 (93%)	2.5 mg: 13 (41%) 5 mg: 19 (59%)	110 mg: 10 (39%) 150 mg: 16 (62%)
Sex, female[1]	13 (43%)	15 (47%)	13 (50%)
Age, years[2]	69 ± 15	75 ± 13	74 ± 14
Body weight, kg[2]	80 ± 19	72 ±15	80 ± 23
Body mass index[2]	27 ± 6	25 ± 4	27 ± 6
Risk Factors			
Arterial hypertension[1]	19 (63%)	27 (84%)	20 (77%)
Diabetes mellitus[1]	5 (17%)	8 (25%)	6 (23%)
Hyperlipidemia[1]	7 (23%)	17 (53%)	15 (58%)
Smoking[1]	4 (13%)	3 (9%)	2 (8%)
Concomitant antiplatelet agents (last dose <7 days)			
Acetylsalicylic acid[1]	15 (50%)	15 (47%)	7 (27%)
Others[1]	1 (3%)	1 (3%)	0 (0%)
Prophylactic dose of heparins at any time during admission			
Heparin[1]	20 (67%)	23 (72%)	19 (73%)
Enoxaparin[1]	14 (47%)	12 (38%)	6 (23%)
Indication for oral anticoagulation			
Atrial fibrillation[1]	21 (70%)	15 (47%)	24 (92%)
Patent foramen ovale[1]	9 (30%)	0 (0%)	2 (8%)
ESUS[1]	0 (0%)	17 (53%)	0 (0%)

[1]number (%), [2]mean ± standard deviation; ESUS = Embolic Stroke of Undetermined Source

Supplemental Table V: Baseline lab results of patients in the three DOAC groups

	Rivaroxaban	**Apixaban**	**Dabigatran**	**Reference Range**
WBC, /µl[1]	7147 ± 2013	6969 ± 1581	8297 ± 2889	3800-10300
RBC, 10^6/µl	4.4 ± 0.6	4.2 ± 0.7	4.5 ± 0.5	4.2-6.2
Hematocrit	0.4 ± 0.05	0.38 ± 0.05	0.4 ± 0.04	0.42-0.52
Hemoglobin, mmol/L	8.4 ± 1.1	7.88 ± 1.3	8.4 ± 1	8.7-11.2
Platelet Count, 10^3/µl	236 ± 57	239 ± 70	226 ± 79	150-450
Quick, %	99 ± 11	96 ± 13	92 ± 12	70-120
INR	1.0 ± 0.	1.0 ± 0.1	1.1 ± 0.1	0.9-1.2
aPTT, seconds	26 ± 6	27 ± 5	27 ± 4	<40
Anti-Xa, IE-aXa/mL	<0.09	<0.09	<0.09	<0.09
Fibrinogen, µmol/L	10.1 ± 2.4	9.8 ± 2.1	9.8 ± 2.3	5-12.1
D-dimer, nmol/L	4.9 ± 7.7	2.7 ± 3.3	3.8 ± 4.3	<2.7
Creatinine, µmol/L	68.6 ± 15.3	76.3 ± 38.1	68.6 ± 15.3	45.8-83.9
GFR, mL/min/kg	81 ± 19	78 ± 31	75 ± 17	>60
Protein total, g/L	70 ± 7	68 ± 7	68 ± 7	65-85
Albumin, g/L	41 ± 4	39 ± 5	40 ± 4	34-48
CRP, nmol/L	285.7 ± 438.1	219.1 ± 342.9	142.9 ± 123.8	<47.6
Procalcitonin, µg/L	0.10 ± 0.08	0.11 ± 0.09	0.09 ± 0.04	≤0.10
AST, µkat/L	0.55 ± 0.2	0.65 ± 0.42	0.58 ± 0.3	≤0.83
ALT, µkat/L	0.53 ± 0.3	0.6 ± 0.53	0.52 ± 0.33	≤0.83
GGT, U/L	0.78 ± 0.6	1.15 ± 1.49	1.05 ± 1.15	≤1.00

[1]mean ± standard deviation, WBC = white blood count, RBC = red blood count, INR = international normalized ratio, aPTT = activated partial thromboplastin time, GFR = glomerular filtration rate, CRP = C-reactive protein, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma-glutamyl transferase.

Supplemental Table VI: Test accuracy of a 50 ng/ml concentration threshold

Substance and safe-for-treatment threshold	Coagulation test	Result within normal range			Result below reagent-specific cut-off			
		Specificity (%)	Sensitivity (%)	LR+	Cut-off	Specificity (%)	Sensitivity (%)	LR+
Dabigatran <50 ng/mL	aPTT	62 (48-74)	88 (81-93)	2.3	aPTT <29 sec	98 (90-100)	57 (47-66)	32.9
	PT and aPTT	66 (52-77)	78 (69-84)	2.2				
	TT	100 (92-100)	20 (14-29)	∞	TT <75 sec	98 (90-100)	87 (79-92)	50.2
	TT <3xUNR	98 (90-100)	79 (70-86)	45.8				
	TT <4xUNR	95 (85-99)	99 (93-100)	4.5				
Rivaroxaban <50 ng/mL	PT	83 (74-90)	89 (76-96)	5.2	Quick >84%	96 (89-99)	61 (45-75)	15.2
	PT and aPTT	83 (74-90)	89 (76-96)	5.2				
Apixaban <50 ng/mL	PT	16 (9-25)	94 (85-98)	1.1				
	PT and aPTT	20 (13-30)	91 (81-96)	1.1				

Samples=178 (dabigatran); 146 (rivaroxaban); 157 (apixaban). Sensitivity and specificity are provided with 95% confidence intervals. aPTT, activated partial thromboplastin time (HemosIL APTT-SP); LR+, positive likelihood ratio; PT, prothrombin time (HemosIL RecombiPlasTin 2G); TT, thrombin time (Test-Thrombin Reagent).

Supplemental Table VII: Test accuracy of a sequential algorithm [17]

Substance	Test result	Specificity (%)	Sensitivity (%)	LR+
Dabigatran <31 ng/mL	TT <21 seconds	100 (95-100)	26 (18-36)	∞
	TT <21 sec or TT ≥21 sec and dTT <31 ng/mL	93 (85-97)	78 (68-86)	11.1
Dabigatran <62 ng/mL	TT <21 seconds	100 (90-100)	18 (12-26)	∞
	TT <21 sec or TT ≥21 sec and dTT <62 ng/mL	91 (78-97)	78 (70-84)	9.0
Rivaroxaban <20 ng/mL	INR <1.4	57 (47-65)	100 (83-100)	2.3
	INR <1.4 or INR ≥1.4 and anti-Xa <20 ng/mL	57 (47-65)	100 (83-100)	2.3
Rivaroxaban <91 ng/mL	INR <1.4	80 (69-88)	92 (83-97)	4.6
	INR <1.4 or INR ≥1.4 and anti-Xa <91 ng/mL	80 (69-88)	92 (83-97)	4.6
Apixaban <21 ng/mL	INR <1.4	5 (2-11)	100 (83-100)	1.1
	INR <1.4 or INR ≥1.4 and anti-Xa <21 ng/mL	5 (2-11)	100 (83-100)	1.1
Apixaban <40 ng/mL	INR <1.4	6 (3-13)	100 (91-100)	1.1
	INR <1.4 or INR ≥1.4 and anti-Xa <21 ng/mL	6 (3-13)	100 (91-100)	1.1

Samples=178 (dabigatran); 146 (rivaroxaban); 157 (apixaban). Sensitivity and specificity are provided with 95% confidence intervals. INR, international normalized ratio time (HemosIL RecombiPlasTin 2G); LR+, positive likelihood ratio; TT, thrombin time (Test-Thrombin Reagent).

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