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Pharmacokinetics of direct oral anticoagulants in emergency situations – Results of the prospective observational RADOA-registry

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Ingvild Birschmann has received speaker's honoraria from Bristol-Myers Squibb/Pfizer, Siemens Healthcare, LFB biomedicaments and CSL Behring and reimbursement for congress travelling and accommodation from Aspen and Bristol-Myers Squibb. She has performed contract research for Siemens Healthcare and is a member of the advisory board of LFB biomedicaments and of the expert groups of CSL Behring GmbH and Siemens Healthcare Diagnostics Products GmbH.
Joachim Kuhn: none declared.
Simone Lindau: none declared.
Stavros Konstantinides has received lecture honoraria and advisory fees from Bayer AG, Boehringer Ingelheim, MSD, Actelion, and Daiichi-Sankyo; and institutional research support from Bayer AG, Boehringer Ingelheim, MSD, Actelion, and Daiichi-Sankyo.
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Sebastian Schellong has received honoraria for lectures from Bayer, Boehringer, Daiichi Sankyo and Pfizer, grants, and honoraria from BMS
Patrick Meybohm has received grants from B. Braun Melsungen, CSL Behring, Fresenius Kabi, and Vifor Pharma for the implementation of Frankfurt's Patient Blood Management program and honoraria for scientific lectures from B. Braun Melsungen, Vifor Pharma, Fearing, CSL Behring, and Pharmacosmos.
Andreas Greinacher has received lecture honoraria and advisory fees from Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer and Daiichi-Sankyo, ASPEN.
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Trial registration: ClinicalTrials.gov Identifier: NCT01722786, Reversal Agent use in patients treated with Direct Oral Anticoagulants or vitamin K antagonists Registry (RADOA-registry) https://clinicaltrials.gov/ct2/show/NCT01722786?term=lindhoff-last&rank=9, Prospective investigator-initiated multicenter cohort study

Abstract:

Background

Direct oral anticoagulants (DOAC) are increasingly used worldwide. Little is known so far about their pharmacokinetics in emergency situations.

Methods

A prospective, observational registry was performed to determine the clinical course in consecutive patients with major bleeding or urgent surgery treated with DOACs. In back-up blood samples from routine care DOAC drug concentrations were measured using UPLC-MS/MS. Anticoagulant intensity at first presentation and drug half-life (t1/2), tested in repeat samples, were evaluated.

Results

140 patients were prospectively included. Pharmacokinetic data were available in 94% (132/140) of patients. 67% (89/132) experienced life-threatening bleeding and 33% (43/132) needed an urgent surgery. For pharmacokinetic analysis a total of 605 blood samples was available.

Median concentration on admission was 205 ng/mL for rivaroxaban and 108 ng/mL for apixaban. All treatment groups showed a high variation of drug concentrations at baseline. In rivaroxaban treated patients t½ was 17.3 hours (95% CI: 15.4 – 19.7) without significant difference in both groups (major bleeding: t½ 16.7 hours, 95% CI: 14.7 - 19.3; urgent surgery: t½ 19.7 hours, 95% CI 15.2 - 27.9; p=0.292). In apixaban treated patients t½ was 25.0 hours (95% CI: 22.9 – 27.6) with a longer t½ after urgent surgery (t1/2: 30.8 hours; 95% CI: 26.9 – 36.4) compared to severe bleeding (t1/2: 20.8 hours; 95% CI: 18.8 – 23.2; p<0.001).

Conclusions

Emergency patients under DOAC treatment show a high variation of anticoagulant concentrations at baseline. Compared with rivaroxaban, apixaban showed a lower median concentration on admission and a longer t½.

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Figure 1

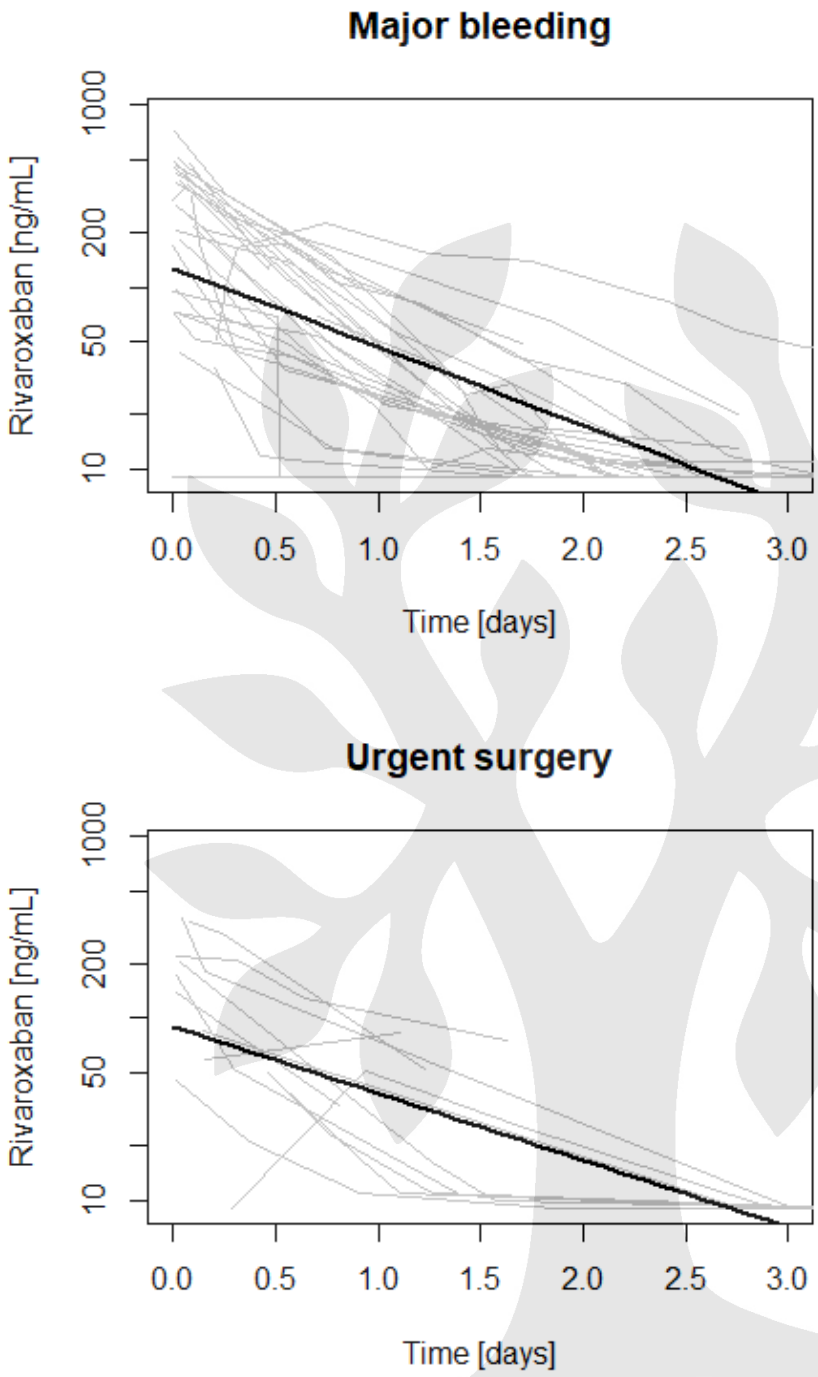
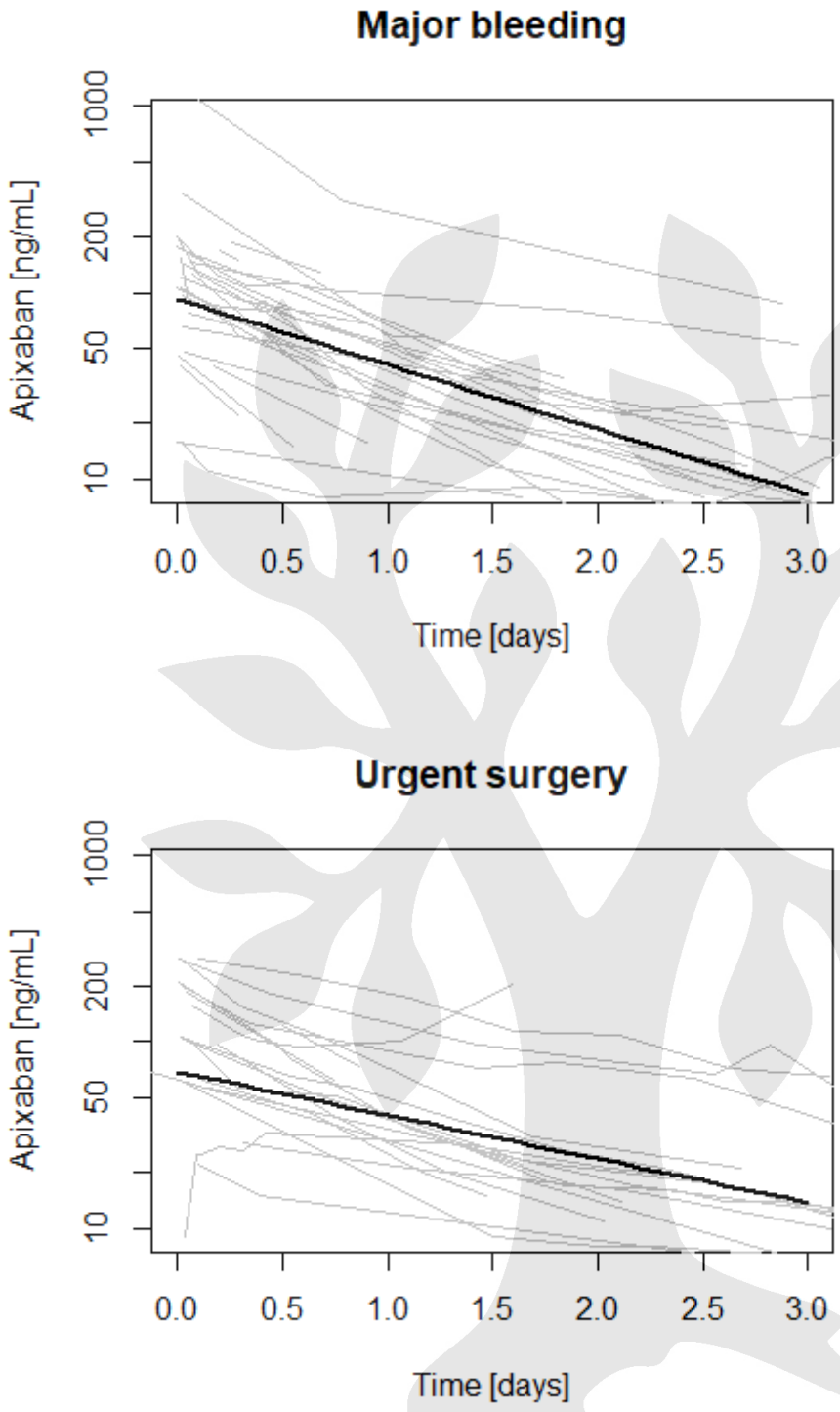


Figure 2



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Pharmacokinetics of Direct Oral Anticoagulants in Emergency Situations – Results of the Prospective Observational RADOA-registry

(**R**eversal **A**gent use in patients treated with **D**irect **O**ral **A**nticoagulants or vitamin K antagonists Registry)

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On behalf of the RADOA-Registry Investigators (Reversal Agent use in patients treated with Direct Oral Anticoagulants or vitamin K antagonists Registry)

Abstract

Background Direct oral anticoagulants (DOAC) are increasingly used worldwide. Little is known so far about their pharmacokinetics in emergency situations.

Methods A prospective, observational registry was performed to determine the clinical course in consecutive patients with major bleeding or urgent surgery treated with DOACs. In back-up blood samples from routine care DOAC drug concentrations were measured using

UPLC-MS/MS. Anticoagulant intensity at first presentation and drug half-life ($t_{1/2}$), tested in repeat samples, were evaluated.

Results 140 patients were prospectively included. Pharmacokinetic data were available in 94% (132/140) of patients. 67% (89/132) experienced life-threatening bleeding and 33% (43/132) needed an urgent surgery. For pharmacokinetic analysis a total of 605 blood samples was available. Median concentration on admission was 205 ng/mL for rivaroxaban and 108 ng/mL for apixaban. All treatment groups showed a high variation of drug concentrations at baseline. In rivaroxaban treated patients $t_{½}$ was 17.3 hours (95% CI: 15.4 – 19.7) without significant difference in both groups (major bleeding: $t_{½}$ 16.7 hours, 95% CI: 14.7 - 19.3; urgent surgery: $t_{½}$ 19.7 hours, 95% CI 15.2 - 27.9; p=0.292). In apixaban treated patients $t_{½}$ was 25.0 hours (95% CI: 22.9 – 27.6) with a longer $t_{½}$ after urgent surgery ($t_{1/2}$: 30.8 hours; 95% CI: 26.9 – 36.4) compared to severe bleeding ($t_{1/2}$: 20.8 hours; 95% CI: 18.8 – 23.2; p<0.001).

Conclusions Emergency patients under DOAC treatment show a high variation of anticoagulant concentrations at baseline. Compared with rivaroxaban, apixaban showed a lower median concentration on admission and a longer $t_{½}$.

Keywords

direct oral anticoagulants

pharmacokinetics

emergency

major bleeding

urgent surgery

Introduction

Patients with non-valvular atrial fibrillation or venous thromboembolism require therapeutic dose anticoagulation with either vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) [1-5]. With the increase in the aging population worldwide, there has been an increase in the prevalence of atrial fibrillation and venous thromboembolism and DOACs have replaced VKA in international guidelines as first choice of anticoagulant for these indications [6, 7]. The risk of intracranial hemorrhage is lower with DOACs compared to VKA, but major bleedings still occur in 1% to 3% of patients per year [8, 9]. The management of these bleeding complications and of urgent surgery in frail elderly patients under DOAC has become an unmet need in clinical practice and further improvement of care is warranted [9, 10]. However, data on drug levels and pharmacokinetic of DOAC in these urgent situations are sparse.

Due to the short half-life of DOACs, the timing of the last DOAC dose and the residual DOAC concentration at the time when the emergency event occurs is important to decide about the use of reversal agents [11-13]. Peak concentrations of DOACs are reached within 2–4 hours after oral intake. The half-lives of these drugs, depending on renal and hepatic function, are usually around 10–12 hours. Drug levels can be determined by anti-FXa assays, or the diluted thrombin time (in case of dabigatran), while for research purpose, LC-MS/MS is considered the gold standard method for the measurement of DOAC levels [14].

We have initiated the RADOA-registry (Reversal Agent use in patients treated with Direct Oral Anticoagulants or vitamin K antagonists), to prospectively assess outcomes in consecutive patients treated with either DOAC or VKA and admitted with major bleeding or with an indication for urgent surgery as recently described [10, 15]. We now report on anticoagulant intensity at first presentation and drug half-life ($t_{1/2}$) in the DOAC-treated patients of the RADOA registry [10].

Material and Methods

Study design and oversight

The RADOA-registry is a prospective, observational, non-interventional, open-label, investigator-initiated, multicenter clinical registry in Germany documenting the management of severe bleeding and/or urgent interventions in patients under treatment with VKA or DOAC. The rationale and design of the registry have been described previously [10].

Patients were recruited until the predefined sample size was reached in each group. Patients were then followed prospectively until day 30 after hospital admission.

Participating centers were hospitals with 24-hour interdisciplinary teams to manage anticoagulant-related bleeding in specialized units (i.e., emergency departments and intensive care units). The study protocol was approved by all relevant institutional review boards. An external independent monitor performed 100% of the on-site source data verification.

This work was supported by Bayer, Bristol-Myers Squibb/Pfizer, DAIICHI Sankyo and CSL Behring. The pharmaceutical companies which funded this project had no role in the design of the study, the collection and analysis of the data or the preparation of the manuscript.

Patients

The inclusion criteria were

- Age ≥ 18 years
- Patients anticoagulated with DOACs or VKA with clinically overt major bleeding according to a modified definition according to the International Society of Thrombosis and Hemostasis for non-surgical patients [16] that presented with at least one of the following criteria: Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or

intramuscular with compartment syndrome or acute life-threatening blood loss leading to hemodynamic instability and/or acute transfusion of two or more units of whole blood or red cells.

- Patients anticoagulated with DOACs or VKA needing an urgent surgical intervention within 24 hours after admission

The registry started including patients in 2014. The majority of patients was recruited between January 2016 and March 2018.

Ethics

Due to the emergency nature of the conditions under investigation, patient information and informed consent should not interfere with or delay acute treatment. With the approval of all ethics committees and institutional review boards, written informed consent was obtained from patients after the acute management phase. In the event of a patient's inability to provide written informed consent, this was obtained from his/her legal representative. Data of patients who remained unconscious or died before a legal representative had been appointed were also included. This was explicitly approved by the ethical boards to prevent major bias caused by exclusion of the most severely affected patients [15]. The study complies with the Declaration of Helsinki.

Substudy of the RADOA-registry to analyze pharmacokinetics of DOAC

In a subgroup of patients included in the RADOA-registry left-over from routine blood samples ("retention blood samples") which were taken during the management of the acute events were collected to analyze drug concentrations and pharmacokinetics of DOAC during these emergency situations [10].

No additional blood sampling for pharmacokinetics was allowed due to the observational

character of the registry. Therefore, time points at which these samples were taken were not pre-specified and, thus, non-systematic. Residual citrated plasma samples as well as serum samples were immediately frozen and stored at the participating centers and later shipped on dry ice to the Institute for Laboratory and Transfusion Medicine, Heart and Diabetes Centre, Ruhr University Bochum, Bad Oeynhausen, Germany, where the UPLC-MS/MS analysis of DOAC concentrations was centrally performed.

Sample preparation and UPLC-MS/MS analysis of DOACs

Sample preparation and measurement of dabigatran, rivaroxaban, apixaban and edoxaban was performed as described before [17].

In brief, analysis by UPLC-MS/MS was done on a 2D UPLC system (Waters Acquity UPLC H-class with 2D Technology System, Waters GmbH, Eschborn, Germany) directly coupled to a Xevo TQ-S tandem mass spectrometer (Waters GmbH, Eschborn, Germany) which was operated in electrospray positive ionization mode. The system control and data acquisition were performed using MassLynx NT 4.1 software with automated data processing by the MassLynx QuanLynx program provided with the instrument. The lower limit of detection for all DOACs of the UPLC-MS/MS method was <0.2 ng/mL. Since DOAC values <9 ng/mL were not clinically relevant, all time points below this value were considered zero.

Statistical analysis

The statistical analysis focuses on descriptive statistics (median and range or frequencies where appropiate) and two-sided 95 % confidence intervals.

Exponential decay of pharmacokinetics is assessed with linear mixed effect regression models to analyze $t_{1/2}$ together with 95% confidence intervals and to assess associations

between the exponential decay and baseline levels. All statistical tests are two-sided and use a significance level of alpha=5% without significance correction for multiple tests.

Results

140 patients treated with DOAC were prospectively included in the RADOA registry. Residual plasma samples and/or serum samples for measurements of DOAC concentrations were available in 132 patients (94%) which were further analyzed. The following results only refer to this subgroup of patients.

Patient characteristics

47% (62/132) of patients were treated with Apixaban, 42% (55/132) with Rivaroxaban, 6% (8/132) with Dabigatran and 5% (7/132) with Edoxaban. One further patient received DOAC treatment (Apixaban) as well as VKA treatment (Phenprocoumon) because of a medication error and was excluded from the analysis.

Of the evaluable 132 patients, 89 (67%) experienced a life-threatening bleeding event and 43 patients (33%) needed urgent surgery (not driven by severe bleeding) within 24 hours after admission.

Baseline characteristics of patients are given in Table 1.

Patients were on average 79 years old. In patients suffering from life-threatening bleeding 43% (38/89) presented with intracranial or intraspinal hemorrhage and 35% (31/89) had gastrointestinal bleeding. In patients with urgent surgery, 54% (23/43) had a trauma, mainly fractures and 28% (12/43) needed the intervention because of an acute abdomen. Overall, 9% (12/132) of patients died during the first 30 days after hospital admission.

For pharmacokinetic analysis a total of 605 blood samples was available.

Rivaroxaban Pharmacokinetics (pk)

In 52 patients treated with rivaroxaban 266 concentration measurements were performed. Baseline samples (defined as blood sample taken within 3 hours after presentation) were not available in 13 patients. In the remaining patients rivaroxaban levels showed a high variation from undetectable levels below 9 ng/mL to 803 ng/mL.

A total of 206 rivaroxaban blood samples were available for pk-analyses. This analysis included all samples taken during the first 3.5 days after admission (see figure 1) but excluded patients who were re-exposed to rivaroxaban (n=3).

Fitting revealed a mean decay rate of 0.96 per day corresponding to a half-life time of 17.3 hours (95% CI: 15.4 – 19.7). There was no significant difference in the decay rate or the baseline levels between patients with severe bleedings and patients requiring urgent surgery (major bleeding: $t_{½}$ 16.7 hours; 95% CI: 14.7 - 19.3; urgent surgery: $t_{½}$ 19.7 hours; 95% CI 15.2 - 27.9, p=0.292; see figure 1).

Results of the rivaroxaban levels, creatinine levels, Cockcroft-Gault formula and coagulation assays during the time course of the registry are shown in table 2.

At baseline the median rivaroxaban level was 205 ng/mL, 59% (23/37) of patients had rivaroxaban levels > 200 ng/L and 19% (7/37) presented with rivaroxaban concentrations ≤ 75 ng/mL.

Apixaban Pharmacokinetics (pk)

In 61 patients treated with apixaban 267 concentration measurements were performed.

Baseline samples (defined as blood sample taken within 3 hours after presentation) were not

available in 15 patients. In the remaining patients apixaban concentrations showed a high variation from undetectable levels below 9 ng/mL to 1222 ng/mL.

A total of 221 apixaban blood samples were available for pk analyses. This analysis included all samples taken during the first 3.5 days after admission (see figure 2) but excluded patients who were re-exposed to apixaban (n=6).

Fitting revealed a mean decay rate of 0.66 per day corresponding to a half-life time of 25 hours (95% CI: 22.9 – 27.6). There was a significant difference in the decay rate in patients with severe bleedings ($t_{½}$: 20.8 hours; 95% CI: 18.8 – 23.2) compared to patients with urgent surgery ($t_{½}$: 30.8 hours, 95% CI: 26.9 – 36.4; $p<0.001$; see figure 2).

Results of the apixaban levels, creatinine levels, Cockcroft-Gault formula and coagulation assays during the time course of the registry are shown in table 3. On admission the median apixaban level was 108 ng/mL, 20% (9/46) of patients had apixaban levels > 200 ng/mL and 28% (13/46) presented with apixaban concentrations ≤ 75ng/mL.

Dabigatran and Edoxaban Pharmacokinetics

In 8 patients treated with Dabigatran 48 concentration measurements were performed. In 7 patients treated with Edoxaban 24 blood samples for concentration measurements were available. Due to the small sample size statistical analysis of

t ½ was not performed. Results are shown in Appendix B, Figure S1 and Figure S2.

Discussion

Baseline anticoagulant concentrations on admission

In our registry, baseline DOAC-concentrations on admission varied widely and ranged from 0 to more than 1000 ng/mL, which is in agreement with findings from an observational prospective cohort study in which baseline plasma DOAC-concentrations were measured in 62% of 732 DOAC-treated patients with severe bleeding [18].

In our study baseline median concentrations of rivaroxaban were higher compared to apixaban concentrations due to the once daily intake of a high dose of rivaroxaban compared to apixaban which is applied at lower dosages twice daily.

Median baseline PT and aPTT were only slightly prolonged in the DOAC-treated patients. These routine coagulation assays are not sensitive enough to detect clinically relevant residual DOAC-concentrations on admission [10].

Pharmacokinetics of DOACs in emergency situations

To best of our knowledge this sub-study of the RADOA-registry is the first to systematically analyze pks and half-life times of in emergency situations under DOAC therapy. The observed $t_{½}$ of rivaroxaban (17.3 hours) and apixaban (25 hours) in this elderly patient population clearly exceeds the reported $t_{½}$ of these DOACs in clinical routine (apixaban: 12h, rivaroxaban: 11h - 13h [19]) and are in agreement with data of Viktil et al [20]. In this study evaluating 8 patients with acute hip fractures treated with DOACs, the average elimination half-live was prolonged to 21.6 hours [20].

Reasons for these significantly prolonged half-lives could be altered pks due to the fragile old patient population and the emergency situation itself. As observed in patients with bleeding events in phase III trials, the median age of patients in our registry was 79 years.

At baseline the median Cockroft-Gault-formula was lower in apixaban treated patients (50 mL/min) compared to rivaroxaban treated patients (66 mL/min), which might explain the longer $t_{½}$ of apixaban in our patient population.

Apixaban is cleared via a variety of pathways, including metabolism, biliary excretion, and direct intestinal excretion, with approximately 27% of total apixaban clearance occurring via renal excretion. Rivaroxaban is eliminated either renally (66% in total; 36% unchanged mainly through active renal secretion) or hepatobiliary [21]. Both drugs have a high degree of plasma protein binding of around 87% for apixaban and 95 % for rivaroxaban. The volume of distribution is 21 l for apixaban and 50 l for rivaroxaban [22, 23]. Redistribution from extravascular compartments may therefore be an additional reason for the prolonged DOAC half-lives in our patient-population.

Limitations

We acknowledge that the RADOA registry has a nonrandomized observational design. To obtain the highest possible data quality and to minimize any bias, however, patients were included prospectively and consecutively, and all enrolled patients were on-site monitored by an independent external monitor. Since we analyzed all residual blood samples available and were allowed to include patients who were unable to provide informed consent, there is minimal selection bias.

Conclusions

In conclusion, this subgroup analysis of the RADOA registry shows that baseline concentrations of DOACs differ widely in patients admitted to hospital because of major bleeding or urgent surgery. Quantitative DOAC point of care testing on admission would improve the management of this patient group because only 70 – 80% of these patients might need specific antidotes on admission due to increased DOAC-concentrations. Without rapid DOAC-measurements many patients will either receive reversal agents unnecessarily which

might increase thrombotic complications in this fragile patient population or may proceed to urgent treatments with high DOAC plasma levels and prolonged anticoagulant activity resulting in prolonged blood loss.

Taken together these observations suggest the urgent need for more research with a focus on rapid DOAC concentration measurements in these life-threatening situations. Further prospective multicenter studies are necessary to investigate the concentrations of DOACs in the perioperative urgent setting and in major bleeding in higher numbers of patients to be able to correlate these drug concentrations to clinical outcomes and to improve patient care.

What is known on this topic

DOACs have replaced VKA in international guidelines as first choice of anticoagulant for non-valvular atrial fibrillation and venous thromboembolism.

The management of bleeding complications and of urgent surgery in patients under DOAC is a challenge.

So far data on drug levels and pharmacokinetics of DOAC in these urgent situations are sparse.

What does this paper add?

Baseline concentrations of DOACs differ widely in patients admitted to hospital because of major bleeding or urgent surgery.

Compared with rivaroxaban, apixaban showed a lower median concentration on admission and a longer $t_{½}$.

Author contributions

Edelgard Lindhoff-Last was responsible for the conceptualization and the methodology of the RADOA-registry, organized funding acquisition, and wrote the original draft preparation; Ingvild Birschmann performed the masspectrometry analysis of the DOAC-levels and reviewed major parts of the manuscript, Joachim Kuhn performed the masspectrometry analysis of the DOAC-levels, Simone Lindau, Stavros Konstantinides, Oliver Grottke, Ulrike Nowak-Goettl, Barbara Zydek, Christian von Heymann, Ingvild Birschmann, Ariane Sümnig, Jan Beyer-Westendorf, Sebastian Schellong, Patrick Meybohm and Andreas Greinacher recruited patients and supported the writing of the manuscript; Jessica Lucks and Barbara Zydek were responsible for the project administration; Eva Herrmann performed the statistical analysis and was responsible for the validation and visualization of the results. All the authors have read and agreed to the published version of the manuscript.

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Statement of equal authors' contribution

EL and IB contributed equally to this work

Clinical Trial Registration

ClinicalTrials.gov Identifier: NCT01722786

URL: https://clinicaltrials.gov/ct2/show/NCT01722786?term=lindhoff-last&rank=9

Institutional Review Board Statements

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Boards of all participating hospitals.
Informed Consent Statements see Ethics as part of the Material and Methods Section of the Manuscript.

Conflicts of Interest

Edelgard Lindhoff-Last has received lecture honoraria and advisory fees from Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Portola, CSL Behring and Aspen and institutional research support from Bayer AG, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo and CSL-Behring.

Ingvild Birschmann has received speaker's honoraria from Bristol-Myers Squibb/Pfizer, Siemens Healthcare, LFB biomedicaments and CSL Behring and reimbursement for congress travelling and accommodation from Aspen and Bristol-Myers Squibb. She has performed contract research for Siemens Healthcare and is a member of the advisory board of LFB biomedicaments and of the expert groups of CSL Behring GmbH and Siemens Healthcare Diagnostics Products GmbH.

Joachim Kuhn: none declared.

Simone Lindau: none declared.

Stavros Konstantinides has received lecture honoraria and advisory fees from Bayer AG, Boehringer Ingelheim, MSD, Actelion, and Daiichi-Sankyo; and institutional research support from Bayer AG, Boehringer Ingelheim, MSD, Actelion, and Daiichi-Sankyo.

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Ulrike Nowak-Goettl has received lecture honoraria and advisory fees from Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Octapharma and LFB.

Jessica Lucks: none declared.

Barbara Zydek: none declared.

Christian von Heymann has received honoraria for lectures and consultancy work potentially related to this topic, as well as travel reimbursements from Bayer GmbH, Biotest GmbH, Pfizer GmbH, Daiichi Sankyo, CSL Behring, NovoNordisk GmbH, and HICC GbR.

Ariane Sümnig: none declared.

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Eva Herrmann: none declared

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Figure 1: Results of rivaroxaban concentrations within the first 3.5 days after admission in patients without early re-exposure to rivaroxaban.

Major bleeding: n=36, 161 rivaroxaban concentration measurements

Urgent surgery (OP): n=13, 45 rivaroxaban concentration measurements

Figure 2: Results of apixaban concentrations within the first 3.5 days after admission in patients without early re-exposure to apixaban.

Major bleeding: n=38, 113 apixaban concentration measurements

Urgent surgery (OP): n=22, 108 apixaban concentration measurements

Table 1: Baseline characteristics and mortality in patients by treatment and event.

Variable	Total (n=132)	Major Bleeding (n=89)	Urgent Surgery (n=43)
Male sex n (%)	67 (51%)	47 (53%)	20 (47%)
Age median (1st to 3rd quartile)	79 (72-84)	80 (74-84)	77 (69-83)
BMI (kg/m²) median (1st to 3rd quartile)	26.4 (23.8-30.1)	26.4 (23-30)	26.6 (24-30)
Type of bleeding[1]			
Intracranial/intraspinal n (%)	38 (28.8%)	38 (43%)	
GI-bleeding n (%)	31 (23.5%)	31 (35%)	
Other locations n (%)	19 (14.4%)	19 (21%)	
Type of Surgery[1]			
Trauma n (%)	23 (17.4%)		23 (54%)
Acute abdomen n (%)	12 (9.1%)		12 (28%)
Other surgery n (%)	12 (9.1%)		8 (19%)
Primary Endpoint:			
30-day in hospital mortality n (%)	12 (9%)	7 (7%)	5 (12%)

[1]Multiple types of bleeding location and surgery are possible.

Table 2: **Rivaroxaban levels and laboratory results (number and rates, median and 1st to 3rd quartile) in 47 patients without reexposure to rivaroxaban within the first week after admission.**

Rivaroxaban-treated patients (n=47)	**baseline**	**after 24 hours**	**after 2-3 days**	**after 4-6 days**
Rivaroxaban level ≤ 9 ng/mL[1]	2/37 (5%)	0/29 (0%)	47/79 (59%)	31/40 (78%)
Rivaroxaban level >9 ng/mL and ≤ 30 ng/mL	0/37 (0%)	16/29 (55%)	20/79 (25%)	5/40 (13%)
Rivaroxaban level >30 ng/mL and ≤ 75 ng/mL	5/37 (14%)	8/29 (28%)	8/79 (10%)	2/40 (5%)
Rivaroxaban level > 75 ng/mL and ≤ 200 ng/mL	9/37 (23%)	5/29 (17%)	4/79 (5%)	2/40 (5%)
Rivaroxaban level > 200 ng/mL	23/37 (59%)	0/29 (0%)	0/79 (0%)	0/40 (0%)
Rivaroxaban level (ng/ml)	205 (102-365)	23 (16-51)	≤9 (≤9-13)	≤9 (≤9-≤9)
creatinine (mg/dl)	0.9 (0.7-1.3)	1.0 (0.8-1.6)	0.9 (0.7-1.4)	0.8 (0.6-1.2)
Cockcroft-Gault formula (mL/min)	66 (41-98)	65 (44-101)	75 (49-133)	63 (51-127)
INR	1.4 (1.3-2.0)	1.2 (1.1-1.5)	1.1 (1.1-1.2)	1.1 (1.1-1.2)
aPTT (sec)	32 (28-36)	31 (28-34)	31 (28-35)	32 (28-42)

[1]relative to all measurements. In some patients, multiple quantifications were available in the time period analyzed.

Table 3. Apixaban levels and laboratory results (number and rates, median and 1st to 3rd quartile) in 56 patients without reexposure to apixaban within the first week after admission.

Apixaban-treated patients (n=56)	**baseline**	**after 24 hours**	**after 2-3 days**	**after 4-6 days**
Apixaban level ≤ 9 ng/mL[1]	3/46 (7%)	1/23 (4 %)	18/75 (15.0 %)	24/40 (60 %)
Apixaban level >9 ng/mL and ≤ 30 ng/mL	3/46 (7%)	10/23 (43%)	38/75 (25%)	10/40 (25%)
Apixaban level >30 ng/mL and ≤ 75 ng/mL	7/46 (15%)	9/23 (39%)	11/75 (10%)	6/40 (15%)
Apixaban level > 75 ng/mL and ≤ 200 ng/mL	24/46 (52%)	3/23 (13%)	7/75 (9%)	0/40 (0%)
Apixaban level > 200 ng/mL	9/46 (20%)	0/23 (0%)	1/75 (1%)	0/40 (0%)
Apixaban level (ng/mL)	108 (67-181)	32 (21-58)	17 (10-30)	≤9 (≤9-15)
creatinine (mg/dl)	1.1 (0.8-1.5)	1.0 (0.8-1.5)	1.0 (0.7-1.6)	0.9 (0.7-1.7)
Cockcroft-Gault formula (mL/min)	50 (32-79)	60 (40-91)	57 (32-85)	54 (32-76)
INR	1.3 (1.1-1.4)	1.2 (1.1-1.5)	1.2 (1.1-1.4)	1.1 (1.0-1.2)
aPTT (sec)	29 (26-34)	30 (27-34)	31 (28-36)	30 (27-40)

[1]relative to all measurements. In some patients, multiple quantifications were available in the time period analyzed.

Supplement

Figure S1: Results of Edoxaban concentrations within the first 3.5 days after admission in patients with major bleeding (n=5) or urgent surgery (n=2).

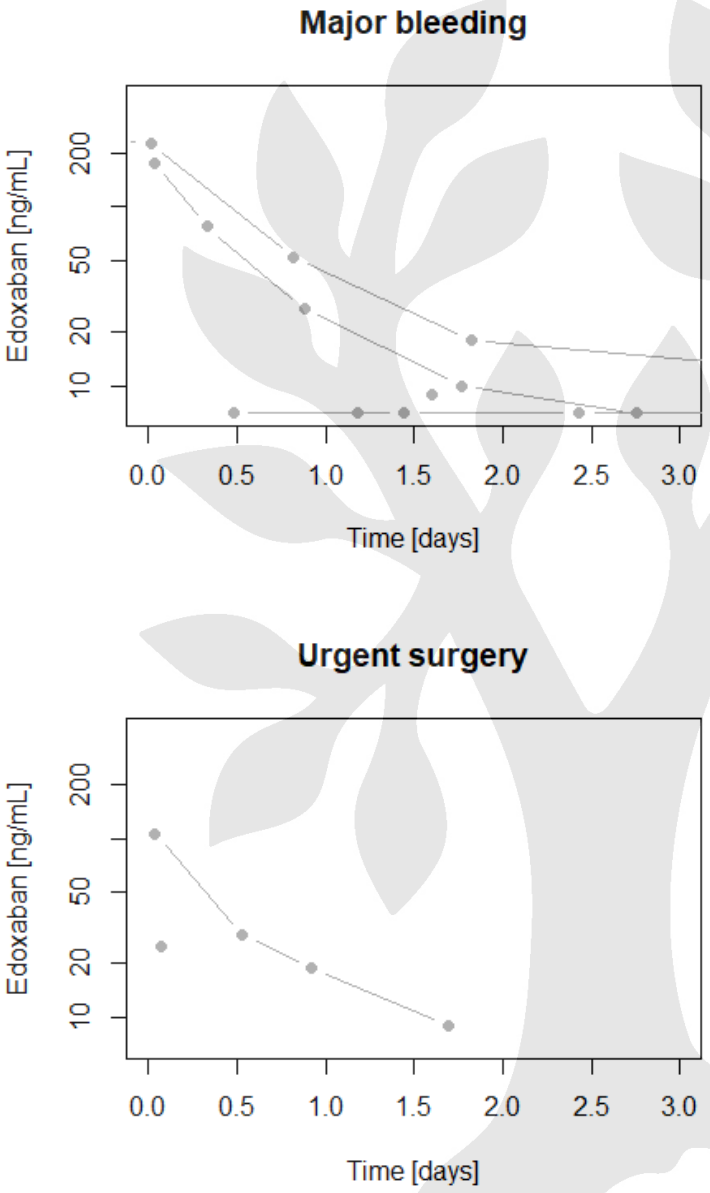

Figure S2: Results of Dabigatran concentrations within the first 3.5 days after admission in patients with major bleeding (n=4) or urgent surgery (n=4)