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Appropriateness evaluation of DOAC dosing, after implementation of algorithms designed to detect inappropriate dosing

Master Thesis - spring semester 2020

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ABSTRACT

BACKGROUND AND OBJECTIVES: In March 2019 at the tertiary care hospital in Aarau, several algorithms were implemented to detect inappropriate dosing of direct oral anticoagulants (DOACs). The dosage of the DOACs rivaroxaban, apixaban, edoxaban and dabigatran in terms of congruence of patient's age, weight, renal function and also indication with the prescribed DOAC dosage in a restricted form are checked by the algorithms. The main objective of this master thesis was to analyze the impact of the algorithm's implementation. Therefore, prevalence and risk for inappropriate dosing were determined. Risk factors for inappropriate dosing and the influence of possible reasons for underdosing (PRFU) on dosage appropriateness were explored. Further sensitivity, specificity and acceptance rates for interventions of the algorithms were calculated.

METHODS A retrospective cohort study was conducted on all inpatients with at least one DOAC intake between 01.03.-31.12.2018 (pre-implementation) and 01.03.-31.12.2019 (postimplementation). Exclusion criteria were no informed consent, age < 18, DOAC intake > 24 h before discharge, missing data for determination of correct dosage (e.g. indication). Congruence of age, weight, renal function (CKD-EPI) and indication of patient's last DOAC prescription before discharge were examined. Appropriateness was judged by summary of product characteristics (SmPC). Risk factors for inappropriate dosing (and its subgroups contraindications, overdosing and underdosing) were determined to adjust the logistic regression for any confounders, in order to analyze the impact of the algorithms on dosage appropriateness at discharge overall and per DOAC. PRFU were: Antiplatelet drug therapy, reduced eGFR calculated with Cockcroft Gault Formula, and only one instead of two fulfilled criteria for dosage reduction in case of apixaban in atrial fibrillation (AF). The influence of PRFU on dosage appropriateness was explored by a second logistic regression additionally fitted for PRFU.

RESULTS: A total of 4635 cases were evaluated, 2701 were included (2018: 1287, 2019: 1414). Most patients received an anticoagulation for AF. Rivaroxaban was the most prescribed DOAC in both years but prescriptions decreased significantly in 2019, whereas apixaban use increased in 2019. While the prevalence and risk for any inappropriate dosing in 2019 were significantly reduced for edoxaban/dabigatran prescriptions (21.8% to 8.6%, p: 0.002 // OR 0.31, p: 0.002), significant reduction was not achieved over all DOACs, (19.3% to 17.0%, p: 0.12 // OR 0.86, p: 0.141). There was a significant reduction of prevalence and risk for the subgroup contraindications (2.7% to 0.4 %, p < 0.001 // OR: 0.15, p < 0.001) in 2019. Contrary, the prevalence and risk for underdosed apixaban prescriptions increased in 2019 (13.6% to 19.5%, p: 0.023 // OR: 1.54, p: 0.025). It is to say that PRFU significantly increased overall prescriptions in 2019 and apixaban cases showed a very high prevalence (> 76%) of PRFU. Prevalence and risk for overdosing were insignificantly reduced overall DOAC prescriptions in 2019 compared to 2018 (3.2% to 2.5%, p: 0.32 // OR: 0.77, p: 0.275). The prevalence and risk of overdosed Rivaroxaban prescriptions were significantly reduced. A sensitivity of 62% and a specificity of 92% overall algorithms were calculated. The overall acceptance rate of interventions was 88% for contraindication, 85% for overdosing and 47% for underdosing.

CONCLUSION: The algorithms had a positive impact on dosage appropriateness even if significance could not be shown for every DOAC and every kind of inappropriateness. It was assumed that the prevalence and risk of underdosed prescriptions increased from 2018 to 2019, due to significantly more apixaban prescriptions in 2019 with dual or triple anticoagulation as supported by the adjusting for PRFU. The algorithms showed a good specificity, but a lower sensitivity because diagnoses are not coded in our clinical information system (CIS). Therefore, especially underdosed cases are less identified. Another limitation was that algorithms alerts were not sent directly to the physician in order to avoid clinically not relevant alerts. The overall high acceptance rate shows that this is a good strategy to get the intervention accepted and the therapy optimized. So far, the algorithms run on an external software. By implementing them directly into the clinical physician order entry (CPOE), a further reduction of inappropriate dosing of DOAC by shortening the timespan between inappropriate prescription and detection is estimated.

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1 INTRODUCTION

1.1 DOAC

Directly acting oral anticoagulants (DOACs) are factor-Xa-Inhibitors indicated for thrombosis prophylaxis after orthopedic surgery on the lower extremities (rivaroxaban and apixaban), non-valvular atrial fibrillation (nvAF) (exc. mechanical valve prostheses or moderate to severe mitral stenoses) and treatment as well as prophylaxis of deep venous thrombosis (DVT) and pulmonary embolism (PE).

DOACs are often used as they show a simple handling compared to vitamin K antagonists (VKAs). There is no need of a dosage adaption to the international normalized ratio (INR) value in opposition to VKAs. Therefore, routine monitoring of their anticoagulant activity is not required. Further advantages are: DOACs have no food interactions and a fast onset anticoagulant activity is given, due to their direct mode of action.

Nevertheless, factor Xa-inhibitors are, according to the institute for safe medication practices (ISMP), high-alert medications. These drugs bear a heightened risk of causing significant patient harm, when they are used in error. Bleeding associated with DOAC treatment is itself associated with major patient harm next to substantial healthcare costs that are amplified by an increased risk of thromboembolic events and mortality following major bleeding events, especially for patients with intracranial hemorrhages (ICHs) [1]. Not only overdosing of DOACs is potentially harmful, but also underdosing. A retrospective study showed that potential underdosing (using reduced dose DOACs in patients without severe renal impairment) was associated with a nearly 5-fold increased risk of stroke for patients treated with apixaban [2]. This outcome suggested that reduced apixaban dose prescriptions lead to reduced effectiveness of stroke prevention. That is why appropriate dosing of DOACs is highly important.

To maintain a correct dosage and therefore avoid under- as well as overdosing, several patient specific factors have to be considered. Those are age and weight (only apixaban and edoxaban) of a patient, as well as renal function (eGFR) as all DOACs show some degree of renal clearance (80% for dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 27% for apixaban) [2-6]. Co-medication has to be analyzed to detect drug-drug interactions, especially between DOACs and CYP 450 or p-glycoprotein (p-gp) both inhibitors and inductors as all DOACs show metabolism by CYP 450 respectively chemical affinity to p-gp in a certain extend. In addition, the patient's diagnosis becomes important in the appropriateness of the DOAC dosing and therefore has to be checked. This way, complications can be prevented and an ideal therapy for the patient can be assured.

Two retrospective cohort studies showed that inappropriate dosing of DOACs occurred in 25.0 % of hospitalizations. Underdosing is the most frequent inappropriate dosing using the summary of product characteristics (SmPC) as reference [7, 8]. According to another retrospective, observational cohort

study conducted at a large no university teaching hospital, up to 1/3 of all DOAC prescriptions were inappropriate [9].

A previous study compared the rate of inappropriate prescribing, from hospitalized patients with renal failure, where control and intervention periods where a clinical decision support system (CDSS) was implemented. They showed a significant decrease in inappropriate prescriptions from 70% (n = 6298/8950) in the control group to 49% (n = 2714/5490) in the intervention group [10]. Desment *et al.* reviewed prescriptions of patients with renal failure before and after the implementation of a CDSS. A significant reduction of inappropriate prescriptions could not be proven. It was reported that one in four alerts was overridden by prescribers [11]. Other studies reported even percentages as high as 90% of overridden alerts [12, 13]. Alert fatigue occurs when a high number of irrelevant alerts leads users to habitually override them. Alert fatigue limits the effectiveness of medication safety alerts. It can be assumed that CDSS can be an effective support for clinical pharmacists or doctors. Nevertheless, to achieve compliance with the CDSS recommendations, the alert-fatigue must be as minimal as possible. This means, the alerts must have a clinical relevance in a high proportion. That is why a high specificity of alerts is wanted.

1.2 Development of algorithm-based electronic agents to detect medication errors

At the tertiary care hospital in Aarau, algorithm-based electronic agents to detect medication errors have been developed and implemented in the main clinical information system (CIS) since 2017. This CIS (“KISIM”) includes a clinical physician order entry (CPOE), an electronic medication administration record (eMAR), as well as the patient's medical record and history. Since 2019, four such agents for dosage surveillance, of rivaroxaban, apixaban, edoxaban and dabigatran are used in clinical routine in all units, with the exceptions of the emergency unit, intermediate care unit and the intensive care units, as they were working with a different CPOE / eMAR. This means patients discharged directly from those units are never detected by the agent.

Since the implementation, the clinical pharmacy team checks the alerts made by the agents once a day from Monday to Friday and processes them. The agents check the congruence of the currently prescribed DOAC dose with age, current renal function and weight of the patients as well as interactions caused by CYP 450 or p-gp inhibitors or inductors.

Absolute overdoses (e.g. 2 x 20 mg Rivaroxaban) by a single prescription were not proven, as the prescribing doctor gets an alert directly from the dosing control which is deposited in the database of a DOAC itself.

Diagnoses of the patients are not automatically taken account of through the algorithms because they are not coded in the CIS, but when a clinical pharmacist processes an alert for inappropriate dosing, the patient record is looked at in more detail and the alert will be reevaluated before action is taken.

If an alert is judged relevant by the clinical pharmacist, the physician is informed through a message displayed in the CPOE/eMAR-part of the CIS or a phone call, reporting the potentially inappropriate dosage and a suggested action to take. The patient's case – ID together with the clinical pharmacist's recommendation (if done) were then stored, so that an analysis of specificity and sensitivity could be performed.

2 OBJECTIVES

The main objective of this master thesis was to analyze the impact of the implementation of the algorithms, designed to detect inappropriate dosing of the DOACs rivaroxaban, apixaban, edoxaban and dabigatran as well as contraindications. This was conducted by measuring the number of patients with a DOAC along with the correct dosage at discharge, according to summary of product characteristics (SmPC). The numbers were measured before and after the implementation of the algorithms at a tertiary care hospital during a time period of ten months before and after.

Further, the characteristics of patients with inappropriate DOAC dosage were analyzed in order to explore risk factors for inappropriate dosing and the risk of inappropriate dosing itself. An explorative analysis of possible reasons for underdosing was performed.

As a secondary objective, the sensitivity and specificity of the algorithms were calculated as well as the acceptance rates of the interventions due to algorithm-alerts. Further, the impact of these interventions on drug therapy was explored. Therefore, the acceptance rate of interventions, made for cases with appropriate dosage at discharge was compared to the one of cases with inappropriate dosage at discharge.

3 METHODS

3.1 Setting and study population

A retrospective cohort study was conducted on all stationary hospitalized patients with at least one intake of rivaroxaban, apixaban, edoxaban or dabigatran between 1 March 2018 and 31 December 2018 (pre-implementation) respectively 1 March 2019 and 31 December 2019 (post-implementation) at a tertiary care hospital and which left the hospital within the same time frame. The time slot of ten months was chosen because the algorithms were only fully operational since March 2019. As the algorithms were partly in operation during January to February 2019 this time period could not be used for the study.

Only data of patients age ≥ 18 , with DOAC intake > 24 h before discharge, which did not reject general consent for their data being used for research purposes was used. Cases with no data collected for patient specific factors like weight or serum creatinine were excluded from the study as well as patients which deceased during the hospital stay. Further cases with no documented indication for a DOAC were excluded. As an exception, patients with prescribed rivaroxaban 10 mg a day staying at the orthopedic department, were assumed to be cases with prophylaxis of DVT as DOAC indication.

The study protocol was approved by the ethics committee of northwestern and central Switzerland (EKNZ). Project-ID: 2020-00468

3.2 Data collection

All data for the stationary hospitalized patients were exported from the clinical information system (KISIM), laboratory system and data warehouse. The following data of patients was collected: patient characteristics (age, weight, gender), all diagnoses in form of the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes, prescribed DOAC with posology, serum creatinine values, co-medication during DOAC-intake, in particular the CYP 450 and p-pg inhibitors respectively inductors, department where the patient was admitted as well as the patient's ingress and leaving day.

3.3 Renal function

The renal function was estimated using the CKD-EPI formula, since it is more accurate than the Cockcroft and Gault formula [14]. Furthermore, the hospital's laboratory uses the same formula to calculate the eGFR and displays it together with the creatinine value. So, the prescribing doctors relied on this eGFR value while prescribing. Still the eGFR was additionally calculated with the Cockcroft and Gault formula for further explorative analysis of the study's results, as the clinical studies used for registration of the DOACs rely on this formula (see chapter 3.7.5).

For weight and serum creatinine, the value measured closest to the leaving day of a patient was used. With this limit the value is most appropriate to what the physician relied on while prescribing.

3.4 Indications and ICD-10 codifications for diagnoses

In the hospital, the indication of a given drug is not mentioned in any structured form together with that drug. Also, the diagnoses are not written in a structured form in the patient's medical record. To identify the most probable indication of the given DOAC, the diagnoses coded by the medical coding department for billing purposes were used. The diagnoses are coded according to the ICD-10 codes, but only if the time and effort for a patient's treatment due to a specific diagnosis caused a nursing effort ≥ 0 . If a diagnosis justifying the use of a DOAC was coded, the indication was directly derived through the ICD-10 code from exported data and used for the dosage testing. In case no such diagnosis was recorded by the medical coding department, the DOAC indication was looked up manually in the patient records. If there were more than one diagnosis justifying the use of the DOAC, the diagnosis that demanded the higher dose was chosen as indication. Additionally, the patient records were considered to collect the exact date of either diagnosed thromboses or pulmonary embolisms as these dates were not coded by the medical coding team. All manually extracted information from patient records were looked up by the same person.

3.5 CHA₂DS₂-VASc Score

The Score was retrospectively calculated for all patients using the ICD-10 codes recorded by the medical department (see Table 1) [15]. The patient's gender and age at the time of leaving the hospital was also used for the calculations.

Table 1 variables and ICD-10 codes used for CHA₂DS₂-VASc Score calculation

Diagnosis	ICD-Codes	Acronym
Congestive heart failure	I50.00–I50.01, I50.9, I50.11–I50.14, and I50.19	C
Hypertension	I10–I15	H
Age ≥ 75 years	-	A₂
Diabetes	E10.0– E14.91	D
Previous transient ischemic attack (TIA), stroke or arterial thromboembolism	G45.9, I63.0– I63.9, and I74–I74.9	S₂
Vascular diseases myocardial infarction	I21.0–I21.9, I22.0–I22.9, and I25.20–I25.29	
Coronary artery disease	I25.0–I25.19	V
Peripheral arterial occlusive disease	I70.2– I70.25	
Atherosclerosis of the aorta	I70.0	
Age 65-74 years	-	A
Female sex	-	Sc

3.6 Appropriateness of prescribing

The appropriateness of the dosage received by the patients was analyzed following the SmPC for Xarelto[®] (rivaroxaban) [6], Eliquis[®] (apixaban) [3], Lixiana[®] (edoxaban) [4] and Pradaxa[®] (dabigatran) [5] by Swissmedic . The actual dosage was specified as correct or inappropriate. Inappropriate cases were further divided in subgroups of underdosed, overdosed or contraindication.

In July 2018 there was a change in the Swiss SmPC of Xarelto concerning the dosing of Xarelto in nvAF in patients taking a PY12-Inhibitor. According to Gibson CM et al. the dose may be reduced to 15 mg [16]. An adapted dose to a simultaneously prescribed PY12-Inhibitor, was rated as wrong dosage for the whole analysis period, as the SmPC was different in the beginning of the study period. Another reason was, that the corresponding alert of the algorithm, was only active since June 2019 and therefore not the same for the whole study period.

In the study hospital, an internal DOAC comparison chart [17] is used, which mostly relies on the SmPC with a relevant exception: a consultation by a hematologist should be asked for patients with an eGFR of 15 – 30 ml/min. Further the chart defines interaction stricter than SmPC, as interactions are more generalized. For the analysis of the dosage appropriateness, these consultations were not taken account of. This means that a dosage which according to the SmPC was wrong but prescribed based on a consultation with a hematologist was counted as wrong in the analysis.

Further a dosage was rated correct if an intervention through the algorithm respective a notification through the clinical pharmacy led to that exact dosage, although it would have been assessed as wrong according to the SmPC. E.g. if an interaction with apixaban and low dose carbamazepine was detected, but then the clinical pharmacy recommended a blood level measurement for therapeutic monitoring, the prescribed dosage was not rated as a wrong dosage.

For dialysis patients with prescribed apixaban, no dosage adaption to the renal function was considered as necessary in the analysis. The reason is that the hospital's nephrologists recommend it based on a performed study [18]. Therefore, it was assumed that the resident physicians are more likely to continue with the specialist's decision dosage than following the SmPC.

Overall inappropriate assessed dosages through the analysis were looked at in more detail, when the reason for inappropriate dosing was linked to the indication. As this was the most arguable variable in the analysis due to the medical coding system, the patient record was looked into to ensure all diagnosis were taken into consideration. E.g. a patient prescribed 2 x 5 mg apixaban per day with coded diagnose for thrombosis would be considered to have a dosage reduction to 2 x 2.5 mg apixaban if the thrombosis

occurred more than seven months ago. If the patient was also diagnosed with AF but this was not coded the dosage would still be correct.

3.7 Data analysis

The exported datasets were matched according to the patient's case ID using Microsoft Excel (2019) 17.0. Also, the basic data analysis (e.g. calculation of eGFR, age) as well as the definition of indication and proper dosage was done using MS Excel. All statistical analyses were made using STATA/MP[®] 15.1.

3.7.1 Demographic data and patient specific characteristics

To describe the two populations, descriptive statistics were used: discrete variables are expressed as frequency (percentage) and continuous variables as means with standard deviation [SD] or medians and interquartile ranges [IQR]. All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance. The exact tests for different variable types are displayed in Table 2.

Table 2 variable indicators for the used statistical tests

Type	Explanation
binary	Binary with p-value from Pearson's χ^2
continuous	Normally distributed, continuous variable, which will give mean and SD
	Other continuous variable, which will give median and IQR
categorical	Categorical with p-value from Pearsons's χ^2

3.7.2 Prevalence of inappropriate dosing

The prevalence of inappropriate dosing was determined by year, DOAC and indication. The analysis of appropriateness of dosage, impact of the algorithms and risk factors for inappropriate dosage was done for all DOACs together, but also for the subgroups of patients having rivaroxaban (Group 1), apixaban (Group 2) and edoxaban or dabigatran (Group 3). Edoxaban and dabigatran were analyzed together as the expected number of patients with these two substances was too low to allow separate analysis.

3.7.3 Determination of risk factors for inappropriate dosing

Risk factors for inappropriate dosing and for its subgroups (contraindication, overdosing and underdosing) were determined, in order to later adjust the logistic regression (for a progressive analysis by year) for possible confounders (see chapter 3.7.4). The determination was conducted performing a binary logistic regression. Therefore, for variables of patient characteristics and demographic which were significantly different in the two study populations, a univariable analysis was performed. Variables with a p-value < 0.1 in the univariable analysis were included in the multivariable model, as

well as age and gender [19]. For all categorical variables, the group within the variable that represented the majority was chosen as reference.

In order to analyze the medical specialty as risk factor, the units where the patients were discharged from were divided into groups, as the expected number of patients of certain units was too low to allow separate analysis. The group's definition is visible in the Table 3.

Table 3 groups definitions for the variable unit

UNIT	GROUP	UNIT	GROUP
general medicine	internal medicine	vascular surgery	surgery
angiology	internal medicine	ear, nose and throat (ENT)	surgery
dermatology	internal medicine	maxillofacial surgery	surgery
endocrinology	internal medicine	plastic surgery	surgery
gastroenterology	internal medicine	urology	surgery
oncology	internal medicine	thorax surgery	surgery
pneumology	internal medicine	visceral	surgery
infectiology	internal medicine	cardiology	cardiology
nephrology	internal medicine	neurology	neurology
ophthalmology	internal medicine	neurosurgery	neurology
breast cancer center	internal medicine	orthopedics	orthopedics
gynecology	internal medicine	traumatology	orthopedics
rheumatology	internal medicine		

3.7.4 Progressive analysis of inappropriate dosing

A progressive analysis of inappropriate dosing by year was performed. Thus, a binary logistic regression for inappropriateness and for the subgroups of inappropriate prescriptions was conducted overall DOAC prescriptions. Risk factors with a p-value < 0.1 in the univariable analysis were included in the overall multivariate model. Additionally, the overall logistic regression was adjusted for the variables year, age and male sex ("Multivariate A").

Additionally, a progressive analysis of inappropriate dosing by year and DOAC was performed. For this a binary logistic regression was performed as well. Only the variables year, age, eGFR ≤ 50 ml/min/1.73m² and CHA₂DS₂VASc – Score were adjusted.

3.7.5 Explorative analysis for probable underdosing

As underdosing is one of the most common dosing errors [7] in inappropriate dosing, several reasons for possible underdosing PRFU were defined for the different DOACs:

Rivaroxaban, edoxaban and dabigatran:

- I. *Dosage adaption to low eGFR would have been correct, if the eGFR would have been calculated by the Cockcroft Gault formula*
- II. *Dual - or triple anticoagulation prescribed at the moment of analysis, which leads to a dosage reduction of the DOAC.*

Apixaban:

- I. *Only one out of three instead of two necessary criteria for dosage reduction in AF was fulfilled*
- II. *The patients calculated eGFR was ≤ 30 m/min (CG) or $\leq 30\text{ml/min}/1.73\text{m}^2$ (CKD-Epi).*
- III. *Dual - or triple anticoagulation prescribed at the moment of analysis, which leads to a dosage reduction of the DOAC*

The consideration of reason I. leading to underdosing, is that although the eGFR calculated by the CKD-EPI formula is more accurate than the calculated by Cockcroft Gault formula [14], the studies used for the SmPC are made using the Cockcroft Gault formula [20] [21] [22].

For further analysis the variable PRFU was treated as one variable. This meant, a patient case with PRFU fulfilled at least one of the defined possible reasons for underdosing.

Statistical analysis

The prevalence of the defined variable was examined in the two study populations, overall and for the defined DOAC groups. To explore the impact of the variable PRFU, a second determination for risk factors, as well as a second progressive analysis of inappropriate dosing and its subgroups were performed. The multivariate regression was adjusted for the same variables as defined in chapter 3.7.4. Further the results of this performed multivariate logistic regression (Multivariate “B”) were compared to the multivariate logistic regression (Multivariate “A”, see 3.7.4) without the variable PRFU.

3.8 Sensitivity and specificity of the algorithms

3.8.1 Definitions of alerts

In order to evaluate the interventions made based on alerts by the individual agents, the alert's statuses were first classified into two groups: "relevant" and "not relevant" alerts. An alert was considered "relevant", when it was classified with one of the following labels:

Table 4 Classification of relevant alerts

ALERT STATUS	DEFINITION
"NOTIFICATION"	A written, short message was sent to the prescribing physician.
"PHONE CALL"	The prescribing physician was called by phone
"CONSULTATION"	A written consultation was sent to the prescribing physician.
"PAUSED"	Paused alerts, which were observed from the clinical pharmacists for 1 to 4 days
"REMARK"	A reason for the inappropriateness / the alert is apparent (e.g. hematuria, increasing or decreasing renal function or in the patient record was already mentioned by another health care person or in the procedures that the dose should / will be corrected.)
"DONE"	If the reason was "patient is already discharged"

All other status entries resulted in a "not relevant" alert. There were different reasons for an alert not being relevant. E. g. as the alerts were only edited once a day (time bias), it was possible for an inappropriate dosage to be detected and in the meantime being already corrected by the prescribing physician. Another reason would have been that an alert for overdosing was rated not relevant, as the indication (looked for while checking the patients record) made an intervention unnecessary. E.g. potentially dosage adaption of rivaroxaban to low renal function, but the indication was DVT/PE and therefore no adaption was needed.

3.8.2 Classification of DOAC patient cases for sensitivity and specificity calculations

To calculate the sensitivity and specificity the outputs of the dosage analysis combined with the results of algorithm, alerts had to be classified into true/false as well as positive/negative. For the classification it was assumed that the pharmacist's assessment of the alerts was correct, and decisions made following gold standard of prescribing. Figure 1 shows the classification which was performed the same for every algorithm analysis. The total of cases is higher than in the retrospective analysis alone, as the total summarizes all patients with DOAC at discharge and the patients only detected by the algorithm the DOAC concerned by the alert is no longer prescribed, which means the therapy was changed between the creation of the alert and discharge.

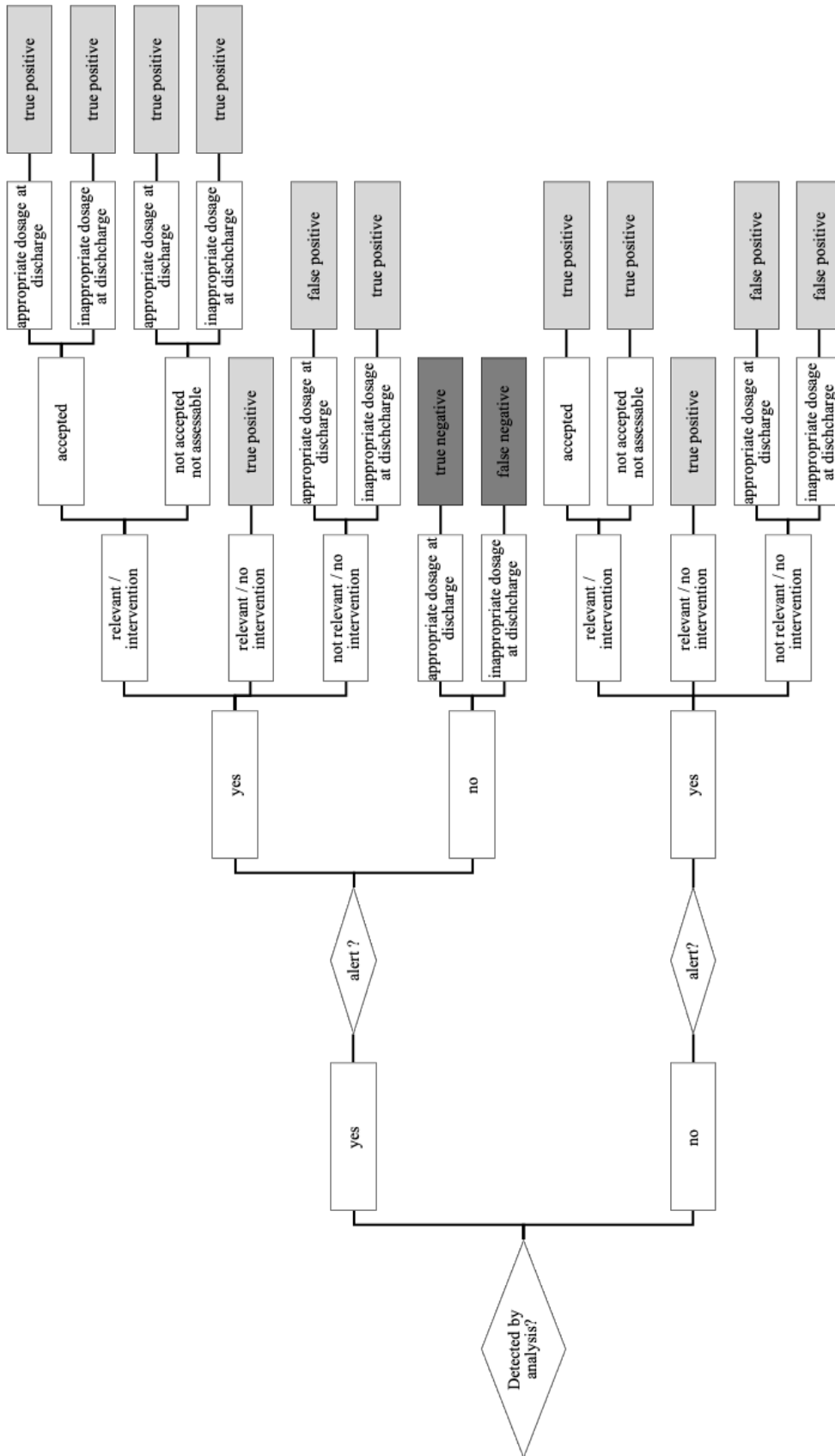


Figure 1 Classification of DOAC patient cases for sensitivity and specificity calculations

3.8.3 Sensitivity and specificity calculation

The sensitivity and specificity were calculated using the following formulas [23]:

$$\text{sensitivity} = \frac{n(\text{true positive})}{(n(\text{true positive}) + n(\text{false negative}))} \quad \text{Eq. (1)}$$

$$\text{specificity} = \frac{n(\text{true negative})}{(n(\text{false positive}) + n(\text{true negative}))} \quad \text{Eq. (2)}$$

3.8.4 Acceptance rates

An acceptance rate over all agents and for the each DOAC agent itself was calculated. Further acceptance rates by different variables were determined. Firstly, the acceptance rate by alert type (contraindication, overdosed or underdosed) and secondly by dosage appropriateness at discharge (appropriate/inappropriate and inappropriateness subgroups).

The acceptance rates were calculated according to the following equation:

$$\text{acceptance rate} = \frac{n(\text{accepted interventions})}{(n(\text{accepted interventions}) + n(\text{not accepted interventions}))} \quad \text{Eq. (3)}$$

4 RESULTS

4.1.1 Excluded cases

The following figures show the excluded cases in 2018 and 2019, as well as the determining criteria. Most cases were excluded because of a general consent not given.

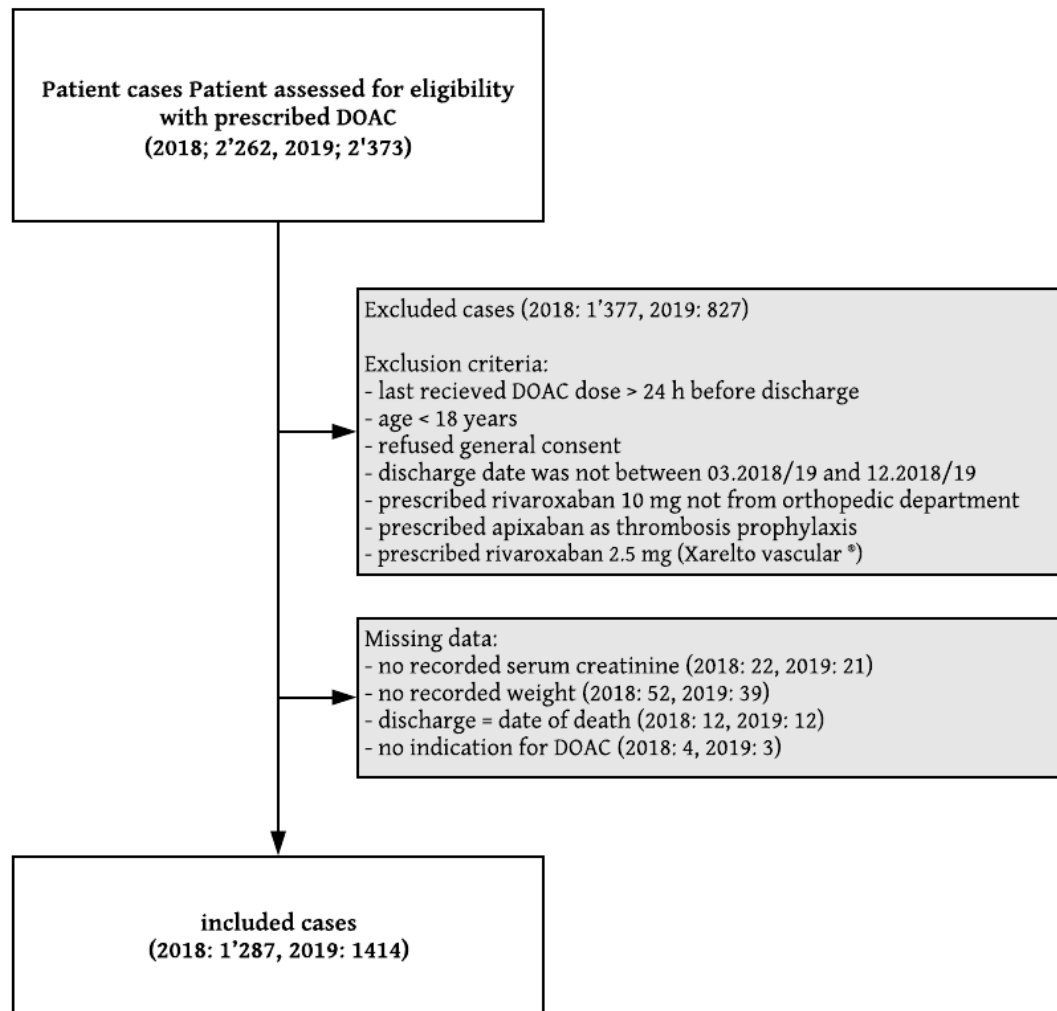


Figure 2 excluded cases

4.2 Demographic data and specific characteristics of included patients

A total of 2701 patient cases were included in this study (2018: 1287, 2019: 1414). Table 5 shows the demographic data and specific characteristics of included patient cases. Rivaroxaban and apixaban were the most frequently prescribed DOACs in both years, followed by edoxaban and dabigatran (Figure 3). The most prevalent indication for prescribing a DOAC was prevention of stroke and systemic embolism in atrial fibrillation (Figure 4). There was no significant difference between the two years except for the decreased rivaroxaban and increased apixaban prescriptions in 2019. The CHA₂DS₂VASc-Score 2-3 was significantly more prevalent in 2019, while the Score ≥ 4 was significantly less prevalent. The exact numbers and further population characteristics are summarized in Table 5. Table 6 to Table 8 show the baseline characteristics for the specific DOACs.

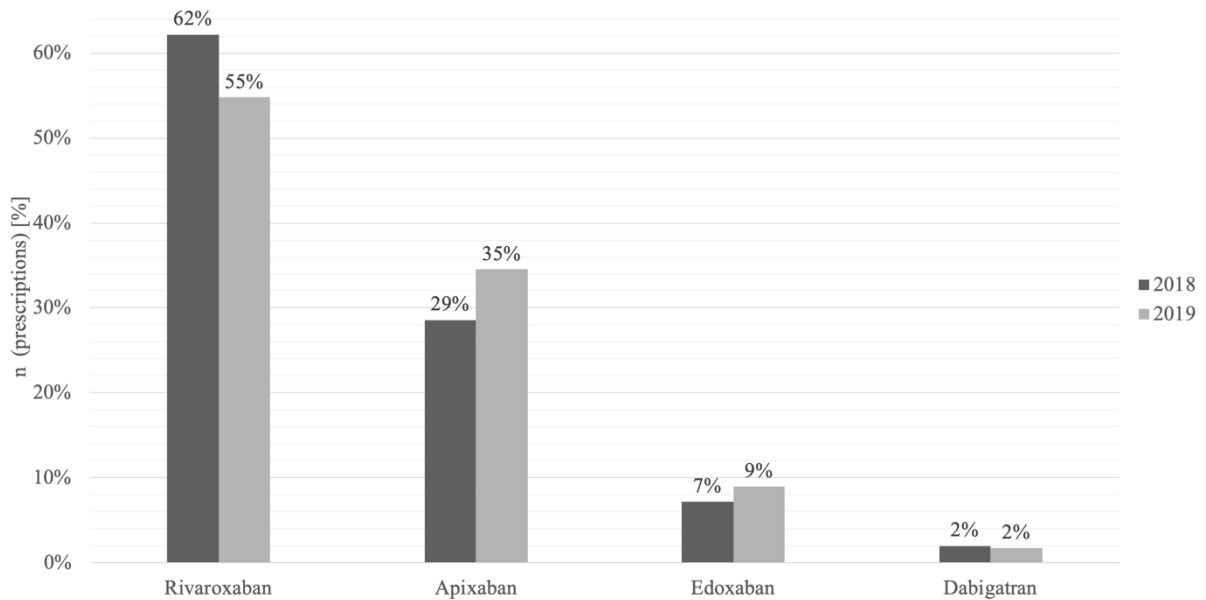


Figure 3 DOAC prescriptions [%] by DOAC and year

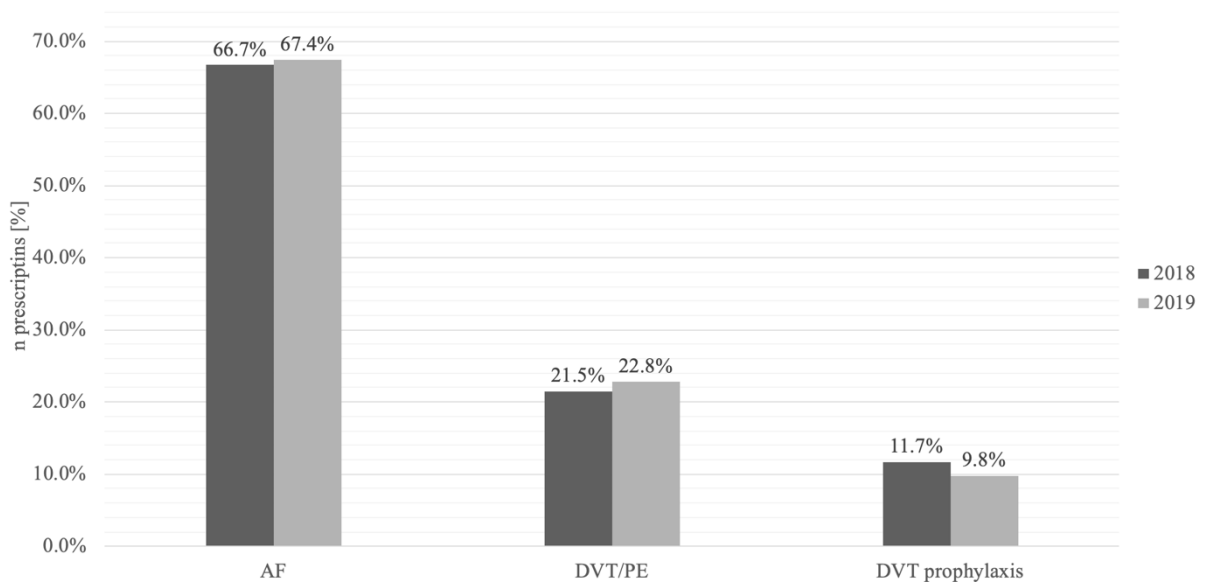


Figure 4 DOAC prescriptions [%] by indication and year

Table 5 Baseline characteristics of included patients by year

	2018 (n = 1287)	2019 (n = 1414)	<i>p-value</i>
Male gender	697 (54.2%)	790 (55.9%)	0.37
Age, mean (SD)	74.5 (11.7)	74.7 (12.1)	0.60
18-30 years	1 (0.1%)	4 (0.3%)	0.22
30-60 years	160 (12.4%)	178 (12.6%)	0.90
60-80 years	658 (51.1%)	677 (47.9%)	0.092
≥ 80 years	467 (36.3%)	555 (39.3%)	0.11
Weight, mean (SD)	78.6 (19.5)	78.4 (19.3)	0.85
eGFR (CKD-Epi), (IQR)	76.6 (55.0, 94.4)	74.8 (54.4, 93.4)	0.33
0-15 ml/min/1.73m ²	18 (1.4%)	12 (0.8%)	0.17
15-30 ml/min/1.73m ²	48 (3.7%)	72 (5.1%)	0.086
30-40 ml/min/1.73m ²	82 (6.4%)	89 (6.3%)	0.93
40-50 ml/min/1.73m ²	97 (7.5%)	110 (7.8%)	0.81
≥ 50 ml/min/1.73m ²	1042 (81.0%)	1131 (80.0%)	0.52
CHA₂DS₂-VASc			
0-1	218 (16.9%)	203 (14.4%)	0.065
2-3	472 (36.7%)	642 (45.4%)	<0.001
≥ 4	597 (46.4%)	569 (40.2%)	0.001
Units			
Internal medicine	401 (31.2%)	472 (33.4%)	0.22
Neurology	225 (17.5%)	264 (18.7%)	0.42
Cardiology	169 (13.1%)	217 (15.3%)	0.10
Surgery	265 (20.6%)	250 (17.7%)	0.054
Orthopedics	227 (17.6%)	211 (14.9%)	0.056
Indication			
AF	859 (66.7%)	953 (67.4%)	0.72
DVT/PE	277 (21.5%)	322 (22.8%)	0.44
DVT prophylaxis	151 (11.7%)	139 (9.8%)	0.11
DOAC			
Rivaroxaban	800 (62.2%)	774 (54.7%)	<0.001
Apixaban	368 (28.6%)	488 (34.5%)	<0.001
Edoxaban/Dabigatran	119 (9.2%)	152 (10.7%)	0.19

Table 6 Rivaroxaban: Baseline characteristics of included patients by year

RIVAROXABAN	2018 (n = 800)	2019 (n = 774)	p-value
Male gender	431 (53.9%)	426 (55.0%)	0.64
Age, mean (SD)	72.5 (11.7)	71.9 (12.6)	0.31
18-30 years	1 (0.1%)	4 (0.5%)	0.17
30-60 years	123 (15.4%)	136 (17.6%)	0.24
60-80 years	449 (56.1%)	407 (52.6%)	0.16
≥ 80 years	227 (28.4%)	227 (29.3%)	0.68
Weight, mean (SD)	79.7 (± 20.0)	80.1 (± 19.5)	0.70
eGFR (CKD-Epi), (IQR)	84.9 (64.5, 98.3)	84.4 (66.5, 98.1)	0.75
0-15 ml/min/1.73m ²	8 (1.0%)	2 (0.3%)	0.064
15-30 ml/min/1.73m ²	13 (1.6%)	10 (1.3%)	0.58
30-40 ml/min/1.73m ²	21 (2.6%)	16 (2.1%)	0.47
40-50 ml/min/1.73m ²	43 (5.4%)	38 (4.9%)	0.68
≥ 50 ml/min/1.73m ²	715 (89.4%)	708 (91.5%)	0.16
CHA₂DS₂-VASc			
0-1	169 (21.1%)	153 (19.8%)	0.50
2-3	341 (42.6%)	401 (51.8%)	<0.001
≥ 4	290 (36.2%)	220 (28.4%)	<0.001
Units			
Internal medicine	207 (25.9%)	238 (30.7%)	0.032
Neurology	59 (7.4%)	83 (10.7%)	0.51
Cardiology	171 (21.4%)	137 (17.7%)	0.020
Surgery	155 (19.4%)	140 (18.1%)	0.066
Orthopedics	208 (26.0%)	176 (22.7%)	0.13
Indication			
AF	457 (57.1%)	433 (55.9%)	0.64
DVT/PE	192 (24.0%)	202 (26.1%)	0.34
DVT prophylaxis	151 (18.9%)	139 (18.0%)	0.64

Table 7 Apixaban: Baseline characteristics of included patients by year

APIXABAN	2018 (n = 368)	2019 (n = 488)	p-value
Male gender	205 (55.7%)	277 (56.8%)	0.76
Age, mean (SD)	78.9 (10.0)	78.5 (10.6)	0.65
18-60 years	20 (5.4%)	29 (5.9%)	0.75
60-80 years	153 (41.6%)	201 (41.2%)	0.91
≥ 80 years	195 (53.0%)	258 (52.9%)	0.97
Weight, mean (SD)	76.9 (± 19.1)	76.1 (± 19.4)	0.55
eGFR (CKD-Epi), (IQR)	57.2 (41.1, 77.6)	58.6 (39.6, 78.8)	0.90
0-15 ml/min/1.73m ²	10 (2.7%)	10 (2.0%)	0.52
15-30 ml/min/1.73m ²	32 (8.7%)	58 (11.9%)	0.13
30-40 ml/min/1.73m ²	49 (13.3%)	58 (11.9%)	0.53
40-50 ml/min/1.73m ²	46 (12.5%)	57 (11.7%)	0.72
≥ 50 ml/min/1.73m ²	231 (62.8%)	305 (62.5%)	0.94
CHA₂DS₂-VASc			
0-1	27 (7.3%)	30 (6.1%)	0.49
2-3	96 (26.1%)	188 (38.5%)	<0.001
≥ 4	245 (66.6%)	270 (55.3%)	<0.001
Units			
Internal medicine	148 (40.2%)	180 (36.9%)	0.32
Neurology	79 (21.5%)	97 (19.9%)	0.15
Cardiology	72 (19.6%)	90 (18.4%)	0.57
Surgery	57 (15.5%)	94 (19.3%)	0.68
Orthopedics	12 (3.3%)	27 (5.5%)	0.11
Indication			
AF	310 (84.2%)	403 (82.6%)	0.52
DVT/PE	58 (15.8%)	85 (17.4%)	0.52

Table 8 *Edoxaban/dabigatran* Baseline characteristics of included patients by year

Edoxaban/Dabigatran	2018 (n = 119)	2019 (n = 152)	p-value
Male gender	61 (51.3%)	87 (57.2%)	0.33
Age, mean (SD)	74.4 (13.2)	77.0 (10.6)	0.065
18-60 years	17 (14.3%)	13 (8.6%)	0.14
60-80 years	56 (47.1%)	69 (45.4%)	0.79
≥ 80 years	45 (37.8%)	70 (46.1%)	0.17
Weight, mean (SD)	76.1 (± 17.0)	77.4 (± 16.9)	0.52
eGFR (CKD-Epi), (IQR)	71.3 (55.7, 93.1)	72.2 (52.4, 92.9)	0.73
15-30 ml/min/1.73m ²	3 (2.5%)	4 (2.6%)	0.95
30-40 ml/min/1.73m ²	12 (10.1%)	15 (9.9%)	0.95
40-50 ml/min/1.73m ²	8 (6.7%)	15 (9.9%)	0.36
≥ 50 ml/min/1.73m ²	96 (80.7%)	118 (77.6%)	0.54
CHA₂DS₂-VAsc			
0-1	22 (18.5%)	20 (13.2%)	0.23
2-3	35 (29.4%)	53 (34.9%)	0.34
≥ 4	62 (52.1%)	79 (52.0%)	0.98
Units			
Internal medicine	46 (38.7%)	54 (35.5%)	0.60
Neurology	13 (10.9%)	30 (19.7%)	0.049
Cardiology	31 (26.1%)	37 (24.3%)	0.75
Surgery	22 (18.5%)	23 (15.1%)	0.46
Orthopedics	7 (5.9%)	8 (5.3%)	0.82
Indication			
AF	92 (77.3%)	117 (77.0%)	0.95
DVT/PE	27 (22.7%)	35 (23.0%)	0.95

4.3 Prevalence of inappropriate dosing

The following two tables show the inappropriate cases detected by the performed analysis by year, DOAC and indication. Table 11 to Table 12 show the prevalence of inappropriate prescribing by subgroup and year. As visible in Table 9 inappropriate prescribing significantly decreased for edoxaban/dabigatran in 2019 compared to 2018. Significantly less inappropriate prescriptions were found for the indications DVT/PE and DVT prophylaxis in 2019 compared to 2018 (Table 10). In Table 11 to Table 12 it is visible, that contraindications significantly decreased in 2019 overall DOACs and in particular for rivaroxaban and apixaban as well as for the indications DVT/PE and DVT prophylaxis. Further, for apixaban significantly more underdosed cases were found in 2019 compared to 2018, whereas there were significantly less underdosed edoxaban/dabigatran cases in 2019. Also, significantly less underdosed cases for the indications DVT/PE were found in 2019 than in 2018. No under- or overdosed cases for the indication DVT prophylaxis were found.

Table 9 Dosage appropriateness by DOAC expressed as absolute number and percentage of patients with the corresponding DOAC

DOAC	Appropriate			Inappropriate		
	2018	2019	P	2018	2019	P
Rivaroxaban	655 (81.9%)	664 (85.8%)	0.035	145 (18.1%)	110 (14.2%)	0.035
Apixaban	290 (78.8%)	370 (75.8%)	0.30	78 (21.2%)	118 (24.2%)	0.30
Edoxaban / Dabigatran	93 (78.2%)	139 (91.4%)	0.002	26 (21.8%)	13 (8.6%)	0.002
Total	1'038 (80.7%)	1'173 (83.0%)	0.12	249 (19.3%)	241 (17.0%)	0.12

Table 10 Dosage appropriateness by indication expressed as absolute number and percentage of patients with the corresponding indication

Indikation	Appropriate			Inappropriate		
	2018	2019	P	2018	2019	p
AF	681 (79.3%)	757 (79.4%)	0.94	178 (20.7%)	196 (20.6%)	0.94
DVT / PE	216 (78.0%)	278 (86.3%)	0.007	61 (22.0%)	44 (13.7%)	0.53
DVT prophylaxis	141 (93.4%)	138 (99.3%)	0.009	10 (6.6%)	1 (0.7%)	0.009
Total	1'038 (80.7%)	1'173 (83.0%)	0.12	249 (19.3%)	241 (17.0%)	0.12

Table 11 *subgroups of inappropriate cases by DOAC expressed as absolute number and percentage of patients with the corresponding DOAC*

DOAC	contraindication			overdosed			underdosed		
	2018	2019	P	2018	2019	P	2018	2019	p
Rivaroxaban	18 (2.2%)	2 (0.3%)	<0.001	24 (3.0%)	11 (1.4%)	0.034	103 (12.9%)	97 (12.5%)	0.84
Apixaban	16 (4.3%)	4 (0.8%)	<0.001	12 (3.3%)	19 (3.9%)	0.62	50 (13.6%)	95 (19.5%)	0.023
Edoxaban / Dabigatran	1 (0.8%)	0 (0%)	0.26	5 (4.2%)	6 (3.9%)	0.92	20 (16.8%)	7 (4.6%)	<0.001
Total	35 (2.7%)	6 (0.4%)	0.94	41 (3.2%)	36 (2.5%)	0.32	173 (13.4%)	199 (14.1%)	0.63

< 0.001

Table 12 *subgroups of inappropriate cases by DOAC expressed as absolute number and percentage of patients with the corresponding indication*

Indikation	contraindication			overdosed			underdosed		
	2018	2019	p	2018	2019	p	2018	2019	p
AF	18 (2.1%)	4 (0.4%)	0.94	31 (3.6%)	24 (2.5%)	0.18	129 (15.0%)	168 (17.6%)	0.13
DVT/PE	7 (2.5%)	1 (0.3%)	0.018	10 (3.6%)	12 (3.7%)	0.94	44 (15.9%)	31 (9.6%)	0.021
DVT prophylaxis	10 (6.6%)	1 (0.7%)	0.009	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Total	35 (2.7%)	6 (0.4%)	<0.001	41 (3.2%)	36 (2.5%)	0.32	173 (13.4%)	199 (14.1%)	0.63

4.4 Risk factors

Table 13 to Table 16 show the results of the univariate and multivariate logistic regression for inappropriate DOAC prescriptions, as well as logistic regressions for contraindicated, overdosed and underdosed prescriptions.

Inappropriateness

Significant independent predictors were identified in the multivariable regression for the outcome of inappropriate prescription: CHA₂DS₂VASc – Score, as well as the units cardiology, surgery and orthopedics compared to internal medicine. There were also found negative predictors for inappropriate prescriptions: Edoxaban/Dabigatran as prescribed DOAC compared to rivaroxaban and the indication DVT prophylaxis as indication compared to AF.

Table 13 *Inappropriate prescriptions (2018: 249/1287, 2019: 241/1414): logistic regression*

RISK FACTORS	univariable		multivariable	
	Odds Ratio (95%CI)	<i>p</i>	Odds Ratio (95%CI)	<i>p</i>
Male sex	1.05 (0.87, 1.28)	0.599	1.11 (0.89, 1.39)	0.343
Age	1.02 (1.02, 1.03)	< 0.001	1 (0.99, 1.02)	0.529
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.54 (1.25, 1.89)	0	1.08 (0.85, 1.36)	0.538
Edoxaban / Dabigatran	0.87 (0.6, 1.25)	0.452	0.68 (0.46, 0.99)	0.042
Indication				
AF	ref		ref	
DVT/PE	0.82 (0.64, 1.04)	0.098	1.07 (0.82, 1.38)	0.63
DVT prophylaxis	0.15 (0.08, 0.28)	<0.001	0.15 (0.07, 0.32)	<0.001
eGFR ≤ 50 ml/min/1.73m²	1.76 (1.4, 2.21)	< 0.001	1.28 (0.99, 1.65)	0.058
CHA₂DS₂VASc	1.25 (1.18, 1.33)	< 0.001	1.21 (1.11, 1.31)	<0.001
Unit				
Internal medicine	ref		ref	
Neurology	0.93 (0.67, 1.3)	0.684	0.89 (0.63, 1.24)	0.491
Cardiology	1.55 (1.18, 2.02)	0.002	1.47 (1.11, 1.96)	0.007
Surgery	1.5 (1.14, 1.97)	0.004	1.59 (1.2, 2.1)	0.001
Orthopedics	0.61 (0.43, 0.87)	0.006	1.67 (1.09, 2.54)	0.017

Contraindication

Table 14 shows, that significant independent predictors were identified in the multivariable regression for contraindicated prescription: DVT prophylaxis as indication compared to AF, eGFR \leq 50 ml/min/1.73m² and CHA₂DS₂VASc – Score. There were no negative predictors for contraindicated prescriptions.

Overdosing

As shown in Table 15, significant independent predictors were identified in the multivariable regression for overdosed prescription: eGFR \leq 50 ml/min/1.73m² and the unit surgery compared to internal medicine. There was no negative predictor for overdosed prescriptions. No OR was calculated for DVT prophylaxis, as no overdosed cases were detected.

Underdosing

As visible in Table 16, significant independent predictors were identified in the multivariable regression for underdosed prescription: CHA₂DS₂VASc – Score and the units cardiology and orthopedics. There were also negative predictors for underdosed prescriptions: The DOAC group dabigatran / edoxaban as well as eGFR \leq 50 ml/min/1.73m². No OR was calculated for DVT prophylaxis, as no overdosed cases were detected.

Table 14 **Contraindicated** prescriptions (2018: 35/1287, 2019: 6/1414): logistic regression

RISK FACTORS	univariate		multivariate	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	1.42 (0.75, 2.7)	0.281	1.5 (0.73, 3.09)	0.268
Age	1 (0.98, 1.03)	0.8	0.97 (0.94, 1.01)	0.119
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.86 (0.99, 3.47)	0.052	1.74 (0.73, 4.14)	0.212
Edoxaban / Dabigatran	0.29 (0.04, 2.15)	0.225	0.38 (0.05, 3.09)	0.367
Indication				
AF	ref		ref	
DVT/PE	1.1 (0.49, 2.49)	0.816	1.9 (0.79, 4.57)	0.152
DVT prophylaxe	3.21 (1.54, 6.69)	0.002	13.84 (1.61, 119.14)	0.017
eGFR \leq 50 ml/min/1.73m²	5.45 (2.92, 10.18)	< 0.001	5.83 (2.66, 12.79)	<0.001
CHA₂DS₂VASc	1.19 (0.98, 1.44)	0.081	1.36 (1.03, 1.79)	0.028
Unit				
Internal medicine	ref		ref	
Neurology	0.52 (0.15, 1.83)	0.307	0.6 (0.16, 2.18)	0.434
Cardiology	0.91 (0.36, 2.3)	0.845	0.85 (0.32, 2.22)	0.739
Surgery	0.82 (0.31, 2.18)	0.693	0.92 (0.34, 2.49)	0.866
Orthopedics	1.86 (0.84, 4.12)	0.124	0.59 (0.07, 4.67)	0.616

Table 15 *Overdosed prescriptions (2018: 41/1287, 2019: 36/1414): logistic regression*

RISK FACTORS	univariate		multivariate	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	0.98 (0.62, 1.54)	0.928	0.61 (0.37, 1.03)	0.063
Age	1.01 (0.99, 1.03)	0.401	0.98 (0.96, 1.01)	0.178
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.65 (1.01, 2.7)	0.045	0.88 (0.51, 1.52)	0.637
Edoxaban / Dabigatran	1.86 (0.93, 3.71)	0.078	1.25 (0.61, 2.6)	0.541
Indication				
AF	ref		ref	
DVT/PE	1.22 (0.74, 2.01)	0.442	1.51 (0.86, 2.64)	0.152
eGFR ≤ 50 ml/min/1.73m²	5.28 (3.34, 8.36)	< 0.001	6.98 (4, 12.19)	< 0.001
CHA₂DS₂VASc	1.09 (0.95, 1.26)	0.23	0.98 (0.8, 1.19)	0.823
Unit				
Internal medicine	ref		ref	
Neurology	1.52 (0.73, 3.2)	0.265	1.93 (0.9, 4.14)	0.09
Cardiology	1.33 (0.65, 2.69)	0.432	1.44 (0.69, 3.01)	0.332
Surgery	2.78 (1.51, 5.09)	0.001	2.96 (1.58, 5.55)	0.001
Orthopedics	0.66 (0.26, 1.67)	0.381	1.81 (0.68, 4.81)	0.231

Table 16 *Underdosed prescriptions (2018: 173/1287, 2019: 199/1414): logistic regression*

RISK FACTORS	univariate		multivariate	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	1.03 (0.82, 1.28)	0.805	1.2 (0.94, 1.54)	0.146
Age	1.03 (1.02, 1.04)	< 0.001	1.01 (1, 1.02)	0.079
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.4 (1.11, 1.77)	0.004	1.08 (0.84, 1.4)	0.555
Edoxaban / Dabigatran	0.76 (0.5, 1.16)	0.205	0.6 (0.39, 0.93)	0.022
Indication				
AF	ref		ref	
DVT/PE	0.73 (0.56, 0.96)	0.023	0.92 (0.69, 1.24)	0.6
eGFR ≤ 50 ml/min/1.73m²	0.95 (0.72, 1.25)	0.702	0.6 (0.44, 0.82)	0.001
CHA₂DS₂VASc	1.27 (1.18, 1.36)	< 0.001	1.22 (1.11, 1.34)	< 0.001
Unit				
Internal medicine	ref		ref	
Neurology	0.89 (0.62, 1.28)	0.539	0.79 (0.54, 1.15)	0.21
Cardiology	1.61 (1.2, 2.16)	0.001	1.51 (1.11, 2.05)	0.009
Surgery	1.29 (0.95, 1.76)	0.108	1.37 (1, 1.88)	0.051
Orthopedics	0.48 (0.32, 0.74)	0.001	1.72 (1.09, 2.71)	0.02

4.5 Risk for inappropriate prescriptions

4.5.1 Inappropriate dosing overall

The following table shows the prevalence of inappropriate prescriptions in the two study populations, as well as the risk for inappropriate dosing in 2019 compared to 2018, expressed as odds ratios. As visible, inappropriate dosages slightly decreased overall DOAC prescriptions from 2018 to 2019, although the risk reduction was not significant. The same result is reported for overdosed cases. Underdosed prescriptions insignificantly increased in 2019, as well as the risk for underdosing insignificantly increased for the year 2019. A significant reduction of contraindicated prescriptions, as well as a significant risk decrease for contraindicated prescriptions were assessed in 2019, as visible in the results of the multivariate logistic regression.

Table 17 Overall prevalence of inappropriate DOAC dosing with logistic regression by year (expressed as absolute numbers and percentage of all included patients)

subgroups	2018 (n = 1287)		2019 (n = 1414)		Univariate		Multivariate	
	n (%)	n (%)	p	OR (95%CI)	p	OR (95%CI)	p	
Inappropriateness	249 (19.3%)	241 (17.0%)	0.12	0.86 (0.7, 1.04)	0.121	0.86 (0.7, 1.05)	0.141	
- contraindication	35 (2.7%)	6 (0.4%)	<0.001	0.15 (0.06, 0.36)	<0.001	0.15 (0.06, 0.36)	<0.001	
- overdosed	41 (3.2%)	36 (2.5%)	0.32	0.79 (0.5, 1.25)	0.319	0.77 (0.48, 1.23)	0.275	
- underdosed	173 (13.4%)	199 (14.1%)	0.63	1.05 (0.85, 1.31)	0.634	1.08 (0.86, 1.36)	0.49	

4.5.2 Inappropriate dosing for the individual DOACs

Table 18 to Table 20 show the prevalence of inappropriate dosing of the individual DOACs in the two study populations, as well as the risk for the three subgroups of inappropriate dosing in 2019 compared to 2018, expressed as odds ratios. Although inappropriate prescriptions significantly decreased in 2019 for the DOACs rivaroxaban and edoxaban/dabigatran, the risk for inappropriateness was only significantly reduced for edoxaban/dabigatran, as visible from the results of the multivariate logistic regression. The risk for contraindicated prescriptions in 2019 was significantly reduced for rivaroxaban and apixaban. No logistic regression was made for contraindicated edoxaban/dabigatran prescriptions as the number of such cases was too small. Although overdosing was reduced in 2019 for all DOACs, no significance was assessed for any DOAC. Underdosing was significantly reduced in edoxaban/dabigatran prescriptions and significantly increased in apixaban prescriptions in 2019. The multivariate logistic regression showed a significant decreased respectively increased risk for underdosing in 2019.

Table 18 Rivaroxaban: inappropriate dosing with logistic regression by year

(expressed as absolute numbers and percentage of all patients receiving rivaroxaban)

subgroups	2018 (n = 800)	2019 (n = 774)	univariate		multivariate		
	n (%)	n (%)	p	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	145 (18.1%)	110 (14.2%)	0.035	0.75 (0.57, 0.98)	0.036	0.79 (0.6, 1.04)	0.09
- contraindication	18 (2.2%)	2 (0.3%)	<0.001	0.11 (0.03, 0.49)	0.003	0.12 (0.03, 0.52)	0.005
- overdosed	24 (3.0%)	11 (1.4%)	0.034	0.47 (0.23, 0.96)	0.038	0.54 (0.25, 1.19)	0.127
- underdosed	103 (12.9%)	97 (12.5%)	0.84	0.97 (0.72, 1.3)	0.838	1.01 (0.75, 1.38)	0.926

Table 19 Apixaban: prevalence of inappropriate dosing with logistic regression by year

(expressed as absolute numbers and percentage of all patients receiving apixaban)

subgroups	2018 (n = 368)	2019 (n = 488)	univariate		multivariate		
	n (%)	n (%)	p	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	78 (21.2%)	118 (24.2%)	0.3	1.19 (0.86, 1.64)	0.304	1.21 (0.87, 1.68)	0.253
- contraindication	16 (4.3%)	4 (0.8%)	<0.001	0.18 (0.06, 0.55)	0.002	0.23 (0.08, 0.64)	0.005
- overdosed	12 (3.3%)	19 (3.9%)	0.62	1.2 (0.58, 2.51)	0.624	1.2 (0.57, 2.52)	0.627
- underdosed	50 (13.6%)	95 (19.5%)	0.023	1.54 (1.06, 2.23)	0.024	1.54 (1.06, 2.24)	0.025

Table 20 Edoxaban/dabigatran: inappropriate dosing with logistic regression by year

(expressed as absolute numbers and percentage of all patients receiving edoxaban/dabigatran)

subgroups	2018 (n = 119)	2019 (n = 152)	univariate		multivariate		
	n (%)	n (%)	p	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	26 (21.8%)	13 (8.6%)	0.002	0.33 (0.16, 0.68)	0.003	0.31 (0.15, 0.64)	0.002
- contraindication	1 (0.8%)	0 (0.0%)	0.26	-	-	-	-
- overdosed	5 (4.2%)	6 (3.9%)	0.92	0.94 (0.28, 3.15)	0.916	0.8 (0.23, 2.75)	0.726
- underdosed	20 (16.8%)	7 (4.6%)	<0.001	0.24 (0.1, 0.59)	0.002	0.22 (0.09, 0.56)	0.001

4.6 Possible reasons for underdosing

For an explorative analysis possible reasons for underdosing (PRFU) were defined (chapter 3.7.5) and the prevalence was determined over all DOAC cases (Table 21). The determined prevalence for inappropriate prescriptions, as well as for the subgroups contraindications, underdosed and overdosed are displayed in (Table 23 to Table 25).

Apixaban is the DOAC and AF the indication with the highest prevalence of PRFU (Figure 5 and Figure 6). As visible in Table 21, the prevalence of PRFU did significantly increase overall DOAC prescriptions. While rivaroxaban prescriptions significantly decreased in 2019, the prevalence of “PRFU” did significantly increase in rivaroxaban cases from 2018 to 2019.

As visible in Table 22, the prevalence of PRFU in inappropriate cases did significantly increase in 2019, due to the significant increase of PRFU in underdosed cases (Table 24). It is visible that the prevalence of PRFU is overall the highest in underdosed prescriptions and apixaban shows the highest prevalence of PRFU, especially underdosed apixaban cases (Table 23 -Table 25). For contraindicated edoxaban/dabigatran cases no p-value PRFU difference is shown, as no cases with PRFU were detected.

Table 21 All included cases: DOAC prescriptions and prevalence of PRFU by year (expressed as absolute numbers and percentage of all patients respectively of the corresponding DOAC)

All included cases	all			cases with PRFU		
	2018	2019	<i>p</i>	2018	2019	<i>p</i>
total	1287	1414		529 (41.1%)	689 (48.7%)	<0.001
- Rivaroxaban	800 (62.2%)	774 (54.7%)	<0.001	203 (25.4%)	251 (32.4%)	0.002
- Apixaban	368 (28.6%)	488 (34.5%)	<0.001	282 (76.6%)	383 (78.5%)	0.52
- Edoxaban/Dabigatran	119 (9.2%)	152 (10.7%)	0.19	44 (37.0%)	55 (36.2%)	0.89

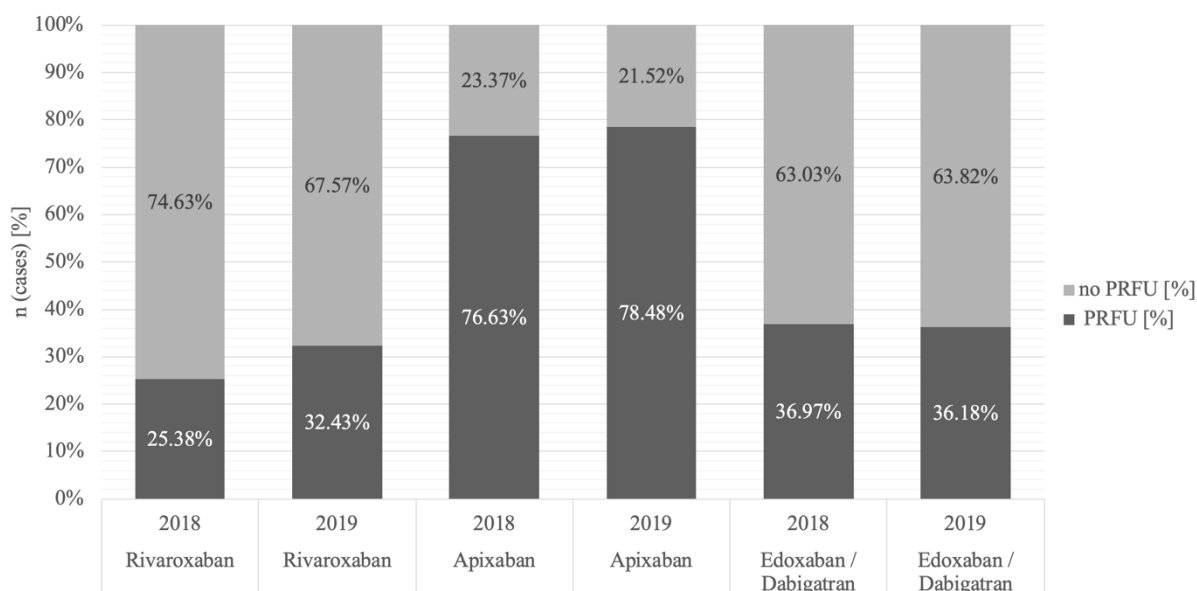


Figure 5 prevalence of PRFU in all included cases by DOAC and year (expressed as percentage of all patients getting a specific DOAC)

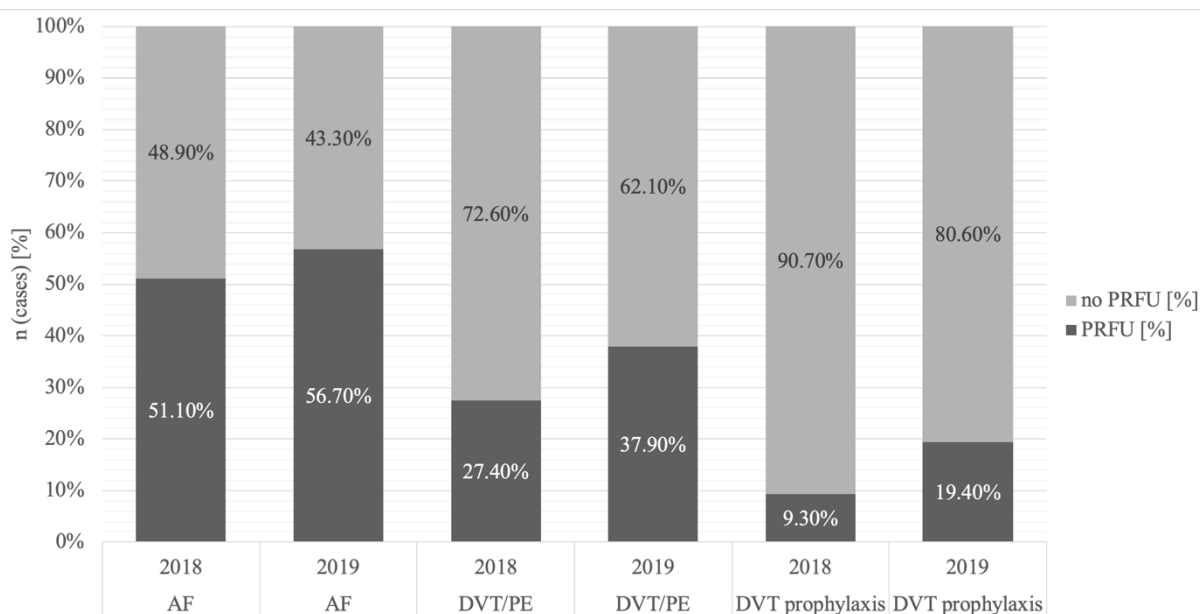


Figure 6 prevalence of PRFU in all included cases by DOAC and year (expressed as percentage of all patients getting a specific DOAC)

Table 22 *Inappropriate dosed cases: Prevalence of PRFU by year (expressed as absolute numbers and percentage of all inappropriate cases respectively all inappropriate cases having a PRFU)*

INAPPROPRIATENESS	all cases			PRFU		
	2018	2019	<i>p</i>	2018	2019	<i>p</i>
total	249	241		161 (64.7%)	187 (77.6%)	0.002
- Rivaroxaban	145 (58.2%)	110 (45.6%)	0.005	90 (62.1%)	78 (70.9%)	0.14
- Apixaban	78 (31.3%)	118 (49.0%)	<0.001	63 (80.8%)	104 (88.1%)	0.16
- Edoxaban/Dabigatran	26 (10.4%)	13 (5.4%)	0.039	8 (31.0%)	5 (38.0%)	0.63

Table 23 *Overdosed cases: Prevalence of PRFU by year (expressed as absolute numbers and percentage of all overdosed cases respectively all overdosed cases having a PRFU)*

OVERDOSED	all cases			PRFU		
	2018	2019	<i>p</i>	2018	2019	<i>p</i>
total	41	36		21 (51.0%)	24 (67.0%)	0.17
- Rivaroxaban	24 (59%)	11 (31%)	0.014	15 (62.0%)	9 (82.0%)	0.25
- Apixaban	12 (29%)	19 (53%)	0.036	5 (42.0%)	13 (68.0%)	0.14
- Edoxaban/Dabigatran	5 (12%)	6 (17%)	0.58	1 (20.0%)	2 (33.0%)	0.62

Table 24 *Underdosed cases: Prevalence of PRFU by year (expressed as absolute numbers and percentage of all underdosed cases respectively all underdosed cases with a PRFU)*

UNDERDOSED	all cases			PRFU		
	2018	2019	<i>p</i>	2018	2019	<i>p</i>
total	173	199		115 (66.5%)	157 (78.9%)	0.007
- Rivaroxaban	103 (59.5%)	97 (48.7%)	0.037	65 (63.1%)	67 (69.1%)	0.37
- Apixaban	50 (28.9%)	95 (47.7%)	<0.001	43 (86.0%)	87 (92.0%)	0.29
- Edoxaban/Dabigatran	20 (11.6%)	7 (3.5%)	0.003	7 (35.0%)	3 (43.0%)	0.71

Table 25 *contraindicated cases: Prevalence of PRFU by year (expressed as absolute numbers and percentage of all contraindicated cases respectively all contraindicated cases with a PRFU)*

CONTRAINDICATED	all cases			PRFU		
	2018	2019	<i>p</i>	2018	2019	<i>p</i>
total	35	6		25 (71%)	6 (100%)	0.13
- Rivaroxaban	18 (2.2%)	2 (0.3%)	<0.001	10 (56%)	2 (100%)	0.22
- Apixaban	16 (4.3%)	4 (0.8%)	<0.001	15 (94%)	4 (100%)	0.61
- Edoxaban/Dabigatran	1 (0.8%)	0 (0%)	0.26	-	-	-

4.6.1 Risk factors for inappropriate prescribing

The following passage shows the comparison of the two performed multivariate logistic regressions. “Multivariate A” is the regression without adjustment for the variable PRFU and “Multivariate B” with the adjustment for the said variable.

Risk factors for overall inappropriate prescriptions

Compared to multivariate “A”, the unit cardiology was no longer a significant risk factor for inappropriate prescriptions. Further, edoxaban/dabigatran were no longer a significant negative predictor for inappropriateness, whereas apixaban appeared to be a negative predictor in multivariate ”B”. The additionally adjusted variable PRFU in multivariate “B” was a highly significant risk factor for inappropriate dosing. In both regressions CHA₂DS₂VASc – Score and the units surgery and orthopedics were significant predictors for inappropriate dosing, as well as DVT prophylaxis was a negative predictor.

Table 26 *Inappropriate prescriptions (2018: 249/1287, 2019: 241/1414): logistic regression additionally fitted for PRFU*

RISK FACTORS	Multivariate «A»		Multivariate «B»	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	1.11 (0.89, 1.39)	0.343	1.14 (0.91, 1.43)	0.253
Age	1 (0.99, 1.02)	0.529	0.99 (0.98, 1)	0.034
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.08 (0.85, 1.36)	0.538	0.77 (0.61, 0.99)	0.039
Edoxaban / Dabigatran	0.68 (0.46, 0.99)	0.042	0.71 (0.49, 1.05)	0.087
Indication				
AF	ref		ref	
DVT/PE	1.07 (0.82, 1.38)	0.63	1.05 (0.8, 1.37)	0.732
DVT prophylaxis	0.15 (0.07, 0.32)	<0.001	0.16 (0.08, 0.34)	<0.001
eGFR ≤ 50 ml/min/1.73m²	1.28 (0.99, 1.65)	0.058	0.81 (0.62, 1.06)	0.128
CHA₂DS₂VASc	1.21 (1.11, 1.31)	<0.001	1.14 (1.05, 1.25)	0.003
Unit				
Internal medicine	ref		ref	
Neurology	0.89 (0.63, 1.24)	0.491	0.9 (0.64, 1.26)	0.54
Cardiology	1.47 (1.11, 1.96)	0.007	1.33 (0.99, 1.77)	0.057
Surgery	1.59 (1.2, 2.1)	0.001	1.53 (1.15, 2.04)	0.004
Orthopedics	1.68 (1.1, 2.56)	0.015	1.72 (1.12, 2.64)	0.014
POSSIBLE REASON FOR UNDERDOSING	-	-	3.92 (2.97, 5.17)	<0.001

Contraindicated prescriptions

As shown in Table 27, the same significant independent predictors were identified in the multivariable regressions “A” and “B” (DVT prophylaxis as indication, eGFR \leq 50 ml/min/1.73m² and CHA₂DS₂VASc – Score). The additionally adjusted variable “PRFU” in multivariate “B” was a highly significant risk factor for contraindicated dosing.

Overdosed prescriptions

As shown in Table 28, the same significant independent predictors were identified in the multivariable regressions “A” and “B” (eGFR \leq 50 ml/min/1.73m² and the unit surgery). The additionally adjusted variable “PRFU” in multivariate “B” was a significant negative predictor for overdosed prescriptions.

Underdosed prescriptions

As visible in Table 29, CHA₂DS₂VASc – Score and the unit orthopedics were significant risk factors and eGFR \leq 50 ml/min/1.73m² a significant negative predictor for underdosed cases in both multivariate regressions. Compared to multivariate “A”, the unit cardiology was no longer a risk factor for underdosing in multivariate “B”. While edoxaban/dabigatran was a negative predictor for underdosing in multivariate “A”, it was apixaban in multivariate “B”. The additionally adjusted variable PRFU in multivariate “B” was a significant risk factor for underdosed prescriptions.

Table 27 **Contraindicated prescriptions** (2018: 35/1287, 2019: 6/1414): logistic regression additionally fitted for PRFU

RISK FACTORS	Multivariate «A»		Multivariate «B»	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	1.5 (0.73, 3.09)	0.268	1.48 (0.72, 3.05)	0.286
Age	0.97 (0.94, 1.01)	0.119	0.97 (0.93, 1)	0.057
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.74 (0.73, 4.14)	0.212	1.49 (0.63, 3.52)	0.365
Edoxaban / Dabigatran	0.38 (0.05, 3.09)	0.367	0.39 (0.05, 3.21)	0.385
Indication				
AF	ref		ref	
DVT/PE	1.9 (0.79, 4.57)	0.152	1.91 (0.8, 4.57)	0.147
DVT prophylaxis	13.84 (1.61, 119.14)	0.017	15.69 (1.8, 136.51)	0.013
eGFR \leq 50 ml/min/1.73m²	5.83 (2.66, 12.79)	<0.001	3.66 (1.59, 8.42)	0.002
CHA₂DS₂VASc	1.36 (1.03, 1.79)	0.028	1.32 (1, 1.73)	0.05
Unit				
Internal medicine	ref		ref	
Neurology	0.6 (0.16, 2.18)	0.434	0.61 (0.17, 2.23)	0.458
Cardiology	0.85 (0.32, 2.22)	0.739	0.83 (0.32, 2.16)	0.696
Surgery	0.92 (0.34, 2.49)	0.866	0.88 (0.32, 2.39)	0.803
Orthopedics	0.59 (0.07, 4.67)	0.616	0.58 (0.07, 4.61)	0.607
POSSIBLE REASON FOR UNDERDOSING			2.95 (1.08, 8.11)	0.036

Table 28 **Overdosed** prescriptions (2018: 41/1287, 2019: 36/1414): logistic regression additionally fitted for PRFU

RISK FACTORS	Multivariate «A»		Multivariate «B»	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	0.61 (0.37, 1.03)	0.063	0.61 (0.36, 1.03)	0.062
Age	0.98 (0.96, 1.01)	0.178	0.99 (0.96, 1.02)	0.443
DOAC				
Rivaroxaban	ref		ref	
Apixaban	0.88 (0.51, 1.52)	0.637	0.99 (0.56, 1.76)	0.983
Edoxaban / Dabigatran	1.25 (0.61, 2.6)	0.541	1.24 (0.6, 2.56)	0.567
Indication				
AF	ref		ref	
DVT/PE	1.51 (0.86, 2.64)	0.152	1.5 (0.85, 2.62)	0.16
eGFR ≤ 50 ml/min/1.73m²	6.98 (4, 12.19)	<0.001	10.59 (5.15, 21.77)	<0.001
CHA₂DS₂VASc	0.98 (0.8, 1.19)	0.823	1 (0.81, 1.22)	0.975
Unit				
Internal medicine	ref		ref	
Neurology	1.93 (0.9, 4.14)	0.09	1.88 (0.87, 4.03)	0.106
Cardiology	1.44 (0.69, 3.01)	0.332	1.43 (0.68, 3)	0.34
Surgery	2.96 (1.58, 5.55)	0.001	3.04 (1.62, 5.69)	0.001
Orthopedics	1.81 (0.68, 4.81)	0.231	1.82 (0.69, 4.81)	0.23
POSSIBLE REASON FOR UNDERDOSING			0.45 (0.21, 0.98)	0.045

Table 29 **Underdosed** prescriptions (2018: 173/1287, 2019: 199/1414): logistic regression additionally fitted for PRFU

RISK FACTORS	Multivariate «A»		Multivariate «B»	
	OR (95%CI)	p	OR (95%CI)	p
Male sex	1.2 (0.94, 1.54)	0.146	1.25 (0.97, 1.62)	0.084
Age	1.01 (1, 1.02)	0.079	0.99 (0.98, 1)	0.191
DOAC				
Rivaroxaban	ref		ref	
Apixaban	1.08 (0.84, 1.4)	0.555	0.72 (0.55, 0.94)	0.016
Edoxaban / Dabigatran	0.6 (0.39, 0.93)	0.022	0.65 (0.42, 1.01)	0.058
Indication				
AF	ref		ref	
DVT/PE	0.92 (0.69, 1.24)	0.6	0.89 (0.65, 1.2)	0.435
eGFR ≤ 50 ml/min/1.73m²	0.6 (0.44, 0.82)	0.001	0.38 (0.28, 0.52)	<0.001
CHA₂DS₂VASc	1.22 (1.11, 1.34)	<0.001	1.14 (1.03, 1.26)	0.008
Unit				
Internal medicine	ref		ref	
Neurology	0.79 (0.54, 1.15)	0.21	0.79 (0.54, 1.16)	0.229
Cardiology	1.51 (1.11, 2.05)	0.009	1.3 (0.95, 1.79)	0.103
Surgery	1.37 (1, 1.88)	0.051	1.3 (0.94, 1.8)	0.112
Orthopedics	1.72 (1.09, 2.71)	0.02	1.77 (1.11, 2.84)	0.017
POSSIBLE REASON FOR UNDERDOSING			4.95 (3.64, 6.73)	<0.001

4.6.2 Inappropriate prescribing

The following tables (Table 30 to Table 33) show the prevalence of inappropriate prescriptions in the two study populations as well as the calculated risk for inappropriate dosing in the year 2019. The results of the two performed multivariate logistic regressions overall and for the individual DOACs are shown. In comparison to multivariate “A”, a significant risk reduction was found for overall inappropriateness for the year 2019 in multivariate “B”. No difference in risk is noticeable between the two logistic regressions for any subgroup or DOAC. The significance of the increase in underdosed apixaban prescriptions is less, but still significant. For contraindicated edoxaban/dabigatran no logistic regression was made, as the number of cases was too small.

Table 30 Overall: prevalence and risk of inappropriate DOAC dosage with logistic regressions A and B by year

subgroup	2018		2019		Multivariate «A		Multivariate B	
	(n = 1287)	(n = 1414)	n (%)	n (%)	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	249 (19.3%)	241 (17.0%)			0.86 (0.7, 1.05)	0.141	0.79 (0.64, 0.97)	0.023
- contraindication	35 (2.7%)	6 (0.4%)			0.15 (0.06, 0.36)	<0.001	0.13 (0.05, 0.32)	<0.001
- overdosed	41 (3.2%)	36 (2.5%)			0.77 (0.48, 1.23)	0.275	0.8 (0.5, 1.28)	0.348
- underdosed	173 (13.4%)	199 (14.1%)			1.08 (0.86, 1.36)	0.49	1 (0.79, 1.26)	0.974

Table 31 Rivaroxaban: prevalence and risk of inappropriate dosage with logistic regressions A and B by year

subgroup	2018		2019		Multivariate A		Multivariate B	
	(n = 1287)	(n = 1287)	n (%)	n (%)	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	145 (18.1%)	110 (14.2%)			0.79 (0.6, 1.04)	0.09	0.6 (0.44, 0.81)	0.001
- contraindication	18 (2.2%)	2 (0.3%)			0.12 (0.03, 0.52)	0.005	0.1 (0.02, 0.46)	0.003
- overdosed	24 (3.0%)	11 (1.4%)			0.54 (0.25, 1.19)	0.127	0.56 (0.25, 1.24)	0.15
- underdosed	103 (12.9%)	97 (12.5%)			1.01 (0.75, 1.38)	0.926	0.75 (0.54, 1.05)	0.096

Table 32 Apixaban: prevalence and risk of inappropriate dosage with logistic regressions A and B by year

subgroup	2018		2019		Multivariate A		Multivariate B	
	(n = 1287)	(n = 1287)	n (%)	n (%)	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	78 (21.2%)	118 (24.2%)			1.21 (0.87, 1.68)	0.253	1.18 (0.84, 1.64)	0.337
contraindication	16 (4.3%)	4 (0.8%)			0.23 (0.08, 0.64)	0.005	0.22 (0.08, 0.62)	0.004
overdosed	12 (3.3%)	19 (3.9%)			1.2 (0.57, 2.52)	0.627	1.26 (0.6, 2.64)	0.544
underdosed	50 (13.6%)	95 (19.5%)			1.54 (1.06, 2.24)	0.025	1.47 (1.01, 2.15)	0.046

Table 33 Edoxaban/dabigatran: prevalence and risk of inappropriate dosage with logistic regressions A and B by year

subgroup	2018		2019		Multivariate A		Multivariate B	
	(n = 1287)	(n = 1287)	n (%)	n (%)	OR (95%CI)	p	OR (95%CI)	p
inappropriateness	26 (21.8%)	13 (8.6%)			0.31 (0.15, 0.64)	0.002	0.31 (0.15, 0.65)	0.002
contraindication	1 (0.8%)	0 (0.0%)			-		-	
overdosed	5 (4.2%)	6 (3.9%)			0.8 (0.23, 2.75)	0.726	0.8 (0.23, 2.76)	0.721
underdosed	20 (16.8%)	7 (4.6%)			0.22 (0.09, 0.56)	0.001	0.24 (0.09, 0.6)	0.002

4.7 Sensitivity and specificity of the algorithms

4.7.1 Detected alerts

Table 34 shows the classification and amount of the different alerts by relevance and DOAC. As visible, overall, most alerts were classified as not relevant, in particular for apixaban and edoxaban.

Table 34 Alert classification by relevance and DOAC

ALERT TYPE	Overall (n = 1457)	Rivaroxaban (n = 808)	Apixaban (n = 493)	Edoxaban (n = 127)	Dabigatran (n = 29)
relevant	136	66	52	12	6
not relevant	153	59	77	16	1
no alert	1168	683	364	99	22

The table below shows that for most relevant alerts an intervention was made.

Table 35 specific classification of relevant alerts by intervention and DOAC

RELEVANT ALERT	Overall (n = 136)	Rivaroxaban (n = 66)	Apixaban (n = 52)	Edoxaban (n = 12)	Dabigatran (n = 6)
intervention	66	65	35	8	5
no intervention	24	1	17	4	1

Table 36 shows the appropriateness at discharge of cases where an intervention was made.

Table 36 specific classification of not relevant alerts by appropriateness at discharge and DOAC

APPROPRIATENES AT DISCHARGE	Overall (n = 153)	Rivaroxaban (n = 59)	Apixaban (n = 77)	Edoxaban (n = 16)	Dabigatran (n = 1)
appropriate*	88	34	39	14	1
inappropriate	65	25	38	2	0

*.... or changed anticoagulation

4.7.2 Not detected cases

The following table shows the inappropriateness subgroups of not detected cases by the agents.

Table 37 Not detected, but inappropriate cases by DOAC

ALERT	Rivaroxaban		Apixaban	
	no (n = 683)	yes (n = 91)	no (n = 364)	yes (n = 124)
inappropriate	62 (9.1%)	48 (52.7%)	55 (15.1%)	63 (50.8%)
contraindication	2 (4%)	0 (0%)	0 (0%)	4 (6%)
overdosed	2 (4%)	4 (13%)	14 (25%)	5 (8%)
underdosed	46 (92%)	26 (87%)	41 (75%)	54 (86%)

ALERT	Edoxaban		Dabigatran	
	no (n = 99)	yes (n = 28)	no (n = 22)	yes (n = 3)
inappropriate	3 (3%)	7 (25%)	2 (9%)	1 (33%)
contraindication	-	-	-	-
overdosed	1 (33%)	4 (57%)	1 (50)	0 (0%)
underdosed	2 (67%)	3 (43%)	1 (50%)	1 (100%)

4.7.3 Sensitivity and specificity

Table 42 show the contingency tables for the separate DOACs, used to calculate the sensitivity and specificity of the corresponding agents.

Table 38 Contingency table for **overall** agent sensitivity and specificity calculations

ALERT	TRUE	FALSE
Yes (positive)	201	88
No (negative)	1046	122
Total	1247	210

Table 41 Contingency table for **edoxaban** agent sensitivity and specificity calculations

ALERT	TRUE	FALSE
Yes (positive)	14	14
No (negative)	96	3
Total	110	17

Table 39 Contingency table for **rivaroxaban** agent sensitivity and specificity calculations

ALERT	TRUE	FALSE
Yes (positive)	91	34
No (negative)	621	62
Total	712	96

Table 42 Contingency table for **dabigatran** agent sensitivity and specificity calculations

ALERT	TRUE	FALSE
Yes (positive)	6	1
No (negative)	20	2
Total	26	3

Table 40 Contingency table for **apixaban** agent sensitivity and specificity calculations

ALERT	TRUE	FALSE
Yes (positive)	90	39
No (negative)	309	55
Total	399	94

In the following table the results of sensitivity and specificity calculations are visible. An overall specificity of 92% and a sensitivity of 62 % were calculated. Looked at the individual agents, rivaroxaban and dabigatran agent had the highest specificity, while edoxaban and dabigatran agents had the highest sensitivities.

Table 43 Sensitivity and Specificity of DOAC Agents

AGENT	Sensitivity [%]	Specificity [%]
Overall	62%	92%
Rivaroxaban	59%	95%
Apixaban	62%	89%
Edoxaban	82%	87%
Dabigatran	80%	95%

4.8 Acceptance rates

In Table 44 the results of interventions are presented. The most interventions were made for the rivaroxaban agent, followed by the apixaban agent. The least interventions were made for the dabigatran agent. In general, most interventions were accepted. The result of second most interventions was not assessable and the fewest interventions were not accepted.

Table 44 Results of relevant alerts by DOAC agent

RESULT	Overall (n = 136)	Rivaroxaban (n = 66)	Apixaban (n = 52)	Edoxaban (n = 12)	Dabigatran (n = 6)
intervention: accepted	60	34	18	5	3
intervention: not accepted	30	13	7	1	0
intervention: not assessable	22	8	10	2	2
no intervention	24	1	17	4	1

An overall acceptance rate of 67 % was determined. The highest acceptance rates were calculated for edoxaban and dabigatran. The lowest for apixaban.

Table 45 Acceptance rates for the interventions suggested to prescribers

Overall	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
67%	72%	72%	83%	100%

4.8.1 Acceptance rate by alert type

Overall, the acceptance rate for interventions due to contraindicated prescriptions is the highest, followed by interventions suggested for overdosed prescriptions. The least accepted interventions are those for underdosed prescriptions.

Table 46 Acceptance rates by alert type

Alert type	Overall	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
overdosed	85%	78%	100%	100%	100%
underdosed	59%	60%	59%	50%	-
contraindication	88%	80%	100%	100%	-

4.8.2 Acceptance rates by dosage appropriateness at discharge

Table 47 shows the acceptance rate for cases with appropriate dosing at discharge is higher than for cases with inappropriate dosing at discharge. As for dabigatran all interventions were accepted it resulted to be the agent with the highest acceptance rate

Table 48 shows the acceptance rates for overdosed cases at discharge was higher than for underdosed cases at discharge. As visible, no acceptance rates for the subgroup contraindication were calculated, as no cases with an intervention had a contraindicated prescription at discharge.

Table 47 Acceptance rates by dosage appropriateness at discharge

APPROPRIATENESS	Overall	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
appropriate	87%	85%	86%	100%	100%
inappropriate	48%	40%	56%	50%	100%

Table 48 Acceptance rates by inappropriateness subgroup at discharge

INAPPROPRIATENESS SUBGROUP	Overall	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
contraindication	-	-	-	-	-
overdosed	50%	40%	100%	-	-
underdosed	48%	40%	50%	50%	100%

5 DISCUSSION

5.1 Demographic data and specific characteristics of included patients

The characteristics of the included patients did not differ significantly, except for the CHA₂DS₂-VASc Score which decreased from 2018 to 2019. A possible explanation could be the significant increase of patients with PE as diagnosis, even if together with DVT as diagnosis, this difference was no longer statistically significant.

5.2 Risk factors for inappropriate dosing

The logistic regression (multivariate “A”) for inappropriate dosing showed that multiple risk factors were found (chapter 4.4). In the following passage the risk factors found performing the two different logistic regressions multivariate “A” and multivariate “B” are discussed by variable. The variables unit and indication were discussed in combination, as they are related.

Unit / Indication

Compared to the unit internal medicine, the following units showed a significant risk for inappropriate dosing: cardiology (OR: 1.47, p: 0.007), surgery (OR: 1.59, p: 0.001), orthopedics (OR: 1.67, p: 0.017). In particular cardiology (OR: 1.51, p: 0.009) and orthopedics (OR: 1.72, p: 0.02) were significant risk factors for underdosing, while surgery (OR: 2.96, p: 0.001) was a significant risk factor for overdosing compared to internal medicine. None of the units emerged to be a risk factor for contraindications.

In surgical and orthopedic wards, DOACs were often paused at admission, due to the upcoming surgery. Often the prescriptions were reactivated just before discharge. As the agents did ignore suspended prescription, the time period between a possible alert (including its evaluation by the pharmacist) and discharge was relatively short. That is why it would be understandable that a possible intervention has been received too late by the prescribing physicians. As cases with prophylactic rivaroxaban dosing in orthopedic units were assumed to be treated for DVT prophylaxis in case of no coded diagnosis, patients with DVT prophylaxis were always orthopedic patients (see limitations). DVT prophylaxis can be assumed a risk factor for receiving a contraindicated DOAC, mainly because of comedication. Patients suffering a prosthetic joint infection often receive the CYP344/p-gP-Inducer rifampicin. In the hospital, there is usually consultation done by the infectologist in case of prosthetic joint infection, and the hospitals infectiologist mention in all their consil messages that rifampicin is a strong CYP-3A4 inducer and that in particular a simultaneous DOAC prescription is contraindicated. So, the risk of a contraindicated prescription may be minimized as consequence respectively that DOACs are paused even more often. But this could also promote more inappropriate dosage undetected by the agents. On the other hand, the clinical pharmacy receives an automatically generated message when rifampicin is prescribed and a clinical pharmacist will look into a patients record and check its medication. If the

clinical pharmacy therefore notices a paused but inappropriate DOAC prescription, still a message is left in the patients record as a precaution in the event of the DOAC prescription being reactivated. This action should decrease inappropriate prescriptions at discharge. Unfortunately, the clinical pharmacy's experience is that those messages were easily overlooked by the physicians. So, even in the logistic regression orthopedics was not a risk factor for contraindication, it can be assumed that these cases contributed for the overall higher risk of inappropriateness in orthopedic units. As patients with DVT prophylaxis were all discharged from orthopedics (see limitations), and as DVT prophylaxis has the simplest dosage scheme [3, 6], over- and underdosing are naturally uncommon for this indication. Therefore, and because it is possible that there were cases with another indication and that these were probably underdosed (see limitations), it is not surprising that no over- or underdosed cases were analyzed but contraindications for the said indication. Consequently, the risk for contraindicated prescriptions was significantly increased with DVT prophylaxis as indication (OR: 13.84, p: 0.017) compared to AF.

Surgical patients are at higher risk of overdosing. Renal function is usually monitored less frequent in surgical patients, and the physicians may be less sensitive to the importance of adapting drug dosing to changes in renal function, especially for drugs which the patients had already before admission. This is also true for necessary adaptations to weight, which can also change especially during a long stay.

The unit cardiology was a significant risk factor for underdosing. Dual or triple anticoagulation is a possible reason for underdosing as defined by the SmPC. As probably the most patients with dual or triple anticoagulation stay at the cardiology, this is a possible reason for this unit being a risk factor. In the logistic regression additionally fitted for PRFU (multivariate "B"), the unit cardiology was no longer a risk factor for inappropriate dosing. This underlines this possible explanation.

There was no significant risk for inappropriate dosing for DVT/PE compared to AF. The indications DVT/PE showed a tendency for being a risk factor for overdosing (OR: 151, p: 0.152) and a tendency for being a negative predictor for underdosing (OR: 0.92, p: 0.6). This seems plausible, as it is more likely to uncertainly underdose a DOAC for the indication AF than for DVT/PE as for this indication no dosage adaption to renal function, age or weight is required for most DOACs. Further, it is more likely to forget to reduce the initially higher therapeutic dosage after the first days (rivaroxaban: after 21, apixaban: after 7), than to prescribe a underdosed dosage directly from the beginning of the therapy.

No change in risk for inappropriate dosing and it's subgroups by indication was noticeable, between the multivariate logistic regressions "A" and "B". It can be assumed that the dosage appropriateness by indications were not significantly affected by PRFU.

DOAC

None of the DOACs were a risk factor for inappropriate dosing. The group edoxaban/dabigatran was a significant negative predictor for inappropriate dosing (OR 0.68, p: 0.042) compared to rivaroxaban. Further that group was a negative predictor for underdosed prescriptions (OR: 0.6, p: 0.022). Edoxaban is the last introduced DOAC on the market. As a result, it is the least established DOAC. This led to less patients with an already (potentially inappropriate) prescribed edoxaban at admission. Further edoxaban was often prescribed on recommendation of a specialist (hematology or the clinical pharmacy) done in a consultation. Therefore, an appropriate dosage can be assumed to be more likely. Additionally, edoxaban and dabigatran have the easiest dosage schemes of all DOACs as it is the same for every indication plus these DOACs are not approved for the indication DVT prophylaxis.

In multivariate “B” apixaban was the negative predictor for inappropriate dosing (OR: 0.77, p: 0.039) and underdosing (OR: 0.72, p: 0.016). This result made sense as apixaban is the DOAC with most possible reasons for underdosing and it shows that apixaban is the DOAC most prone for underdosing.

eGFR < 50 ml/min

An eGFR ≤ 50 ml/min/1.73m² showed a tendency but no significance in risk increase for inappropriate dosing (OR 1.28, p: 0.058). It did show a significant risk increase for contraindicated (OR: 5.83, p < 0.001) and overdosed prescriptions (OR: 6.98, p < 0.001). It was a negative predictor for underdosing (OR: 0.6, p: 0.001). In multivariate “B”, eGFR ≤ 50 ml/min/1.73m² showed even a stronger significance for being a negative predictor (OR 0.38, p < 0.001). These results explain why there was no significance for all inappropriate prescriptions, as one of the specifications was a significant negative predictor. The results made sense, as far as eGFR ≤ 15 ml/min is a contraindication and a normal dosage with eGFR ≤ 50 ml/min/1.73m² would be overdosed and therefore the higher risk for those two cases is naturally given. Reverse, a lower dose than an adapted dose for eGFR ≤ 50 ml/min/1.73m² is not found in the possible dosing schemes according to SmPC [3-6] except for rivaroxaban. That is why it is plausible that this risk factor is a negative predictor for underdosing. Additionally, renal function can change during the hospital stay. That’s why a correctly prescribed DOAC dosage at admission was likely to change to an overdosed dosage, during the hospital stay.

CHA₂DS₂VASc-Score

A higher CHA₂DS₂VASc-Score was a significant risk factor for inappropriate dosing overall in both performed logistic regressions (“A”: OR 1.21 / p < 0.001, “B”: OR 1.14 / p: 0.003). For the subgroups contraindication (OR: 1.36, p: 0.028) and underdosing (OR: 1.22, p < 0.001) the score appeared to be a risk factor as well. Interestingly in the performed multivariate “B”, the risk decreased in those subgroups. For contraindications the score is no longer a significant risk factor. The CHA₂DS₂VASc-Score was a not significant, but a tendentious negative predictor for overdosing (OR: 0.98, p:0.823). As a high

CHA₂DS₂VASc-Score often correlates with a high HAS-BLED-Score, a tendency for underdosing is understandable, as doctors want to prevent a bleeding event. A plausible explanation for the score being a risk factor for contraindications was not found. It is to say that this risk factor is potentially biased, as the score was looked at over the whole population, not only for the indication AF. It was assumed, that the CHA₂DS₂VASc-Score would have been a more significant risk factor for underdosing, if it would have been calculated for patients with AF only (see limitations).

PRFU

The prevalence of PRFU was the highest for apixaban, that was understandable, as it was the DOAC with the most defined reasons for possible underdosing. It was not surprising that the prevalence for PRFU in underdosed cases was similar to the prevalence in overall inappropriateness, as most inappropriate cases are underdosed. Nevertheless, the prevalence of PRFU was surprisingly high in overdosed prescriptions as well.

Overall the explorative logistic regression additionally fitted for PRFU showed a high significance as risk factor for inappropriate dosing (OR: 3.92, $p < 0.001$). While PRFU was a significant risk factor for contraindications (OR: 2.95, $p: 0.036$) and underdosing (OR: 4.95, $p < 0.001$), it was a significant negative predictor for overdosing (OR 0.45, $p: 0.45$). It makes sense that patients with PRFU are more likely to be prescribed a underdosed dosage and less likely to receive an overdosed dosage. A possible explanation for PRFU being a risk factor for contraindicated prescriptions could be that an eGFR under a certain value is considered a contraindication. As one PRFU was related to a low eGFR this result is explainable.

5.3 Sensitivity and specificity of the algorithms

Detected alerts

As shown in chapter 4.7.1. the number of alerts per DOAC correlates with the prescription prevalence of each DOAC. Most alerts were classified as not relevant, especially for apixaban and edoxaban. A possible explanation is that edoxaban is often suggested from specialists or after a consil from the clinical pharmacy or the hematology. Therefore, the clinical pharmacy saw a reason for the inappropriate dosing (according to SmPC) more often for this DOAC compared the others and alerts were rated “not relevant” more often. A possible explanation for the not relevant apixaban prescriptions is, that the indication often was the reason (E.g. an alert for underdosed apixaban but the indication, looked up by the pharmacist, was PE and therefore no dosage adaption is needed) and that probably not only prescribers are likely to underdose apixaban but also the clinical pharmacy for the same reasons (see chapter 5.2).

Not for all relevant alerts an intervention was made. This was mainly due to patients which were already discharged by the time an alert was rated as relevant. Most cases with an intervention had an appropriate dosage or a changed anticoagulation therapy at discharge. This result indicates that the algorithm works.

Not detected cases

The cases which were inappropriate dosed at discharge but were not detected by the algorithm (chapter 4.7.2) were mostly underdosed cases. It was expected that those were going to be the cases which were not detected. E.g. cases with a dosage for DVT prophylaxis (rivaroxaban 1 x 10 mg, apixaban 2 x 2.5 mg) are never detected as underdosed from the agents, as indications are not checked by the agents (see limitations). That is probably also why there were more undetected overdosed cases for apixaban, as a dosage reduction for DVT/PE after seven months is required and that is the same dosage as for DVT prophylaxis. An overall explanation for cases not being detected is the limitation of the agents, as they did not run on weekends and holidays. E.g. patients who entered the hospital on Friday afternoon and left after the weekend on Monday morning were never detected by the algorithms.

Sensitivity and specificity

The results for the agent’s specificities were all between 87-95% and was overall agents 92%. The sensitivity results were between 59 - 82% and overall 62% (chapter 4.7.3). It is logic that a high specificity decreases the sensitivity. I. e. there were pitfalls, which affected mainly the sensitivity. Namely, that no indications were checked by the algorithms, further that the data report which was only made once a day and that the agents did only run on workdays (see limitations). Other than that, a high specificity is what the clinical pharmacy wanted to achieve, as alert fatigue should be minimized. Overall the results for sensitivity and specificity calculations were expected and wanted.

Acceptance rates

As visible from the tables in chapter 4.8, most interventions were accepted. An overall acceptance rate of 67 % was determined. As rivaroxaban and apixaban had the highest part on alerts because of underdosing and this is the least well accepted alert type (chapter 4.8.1), it is understandable why the overall acceptance rate is lower than the ones of the agents for the other DOACs. Interventions for contraindications were the best accepted interventions, followed by interventions for overdosing. These results suggest that doctors are more likely to prescribe an underdose than the overdose. A hypothesis could be made, that doctors are more afraid of bleeding than of stroke, DVT or PE. As contraindications were very well accepted it can be assumed, that they were rarely intended and an intervention by the clinical pharmacy were wanted.

The acceptance rates by dosage appropriateness at discharge (chapter 4.8.2) show, the cases which were appropriate at discharge also had a higher acceptance rate for its interventions than cases which were inappropriate at discharge. This result indicates that the agents worked. Also, no case with a made intervention had a contraindicated dosage at discharge. This underlines the assumption that interventions by the clinical pharmacy were wanted for contraindications. There were not clearly more underdosed than overdosed cases at discharge with not accepted interventions. In comparison there were clearly more alerts for underdosed than for overdosed cases and also interventions for the alert type underdosed cases were less accepted than for the alert type overdosed. This indicates, that time bias lead to more inappropriate cases at discharge.

5.4 Inappropriate prescriptions and impact of the algorithm

The retrospective cohort study showed a prevalence of inappropriate dosing of 19.3% in 2018 and 17.0% in 2019 (chapter 4.3). Compared to other retrospective cohort studies there was less inappropriate prescribing of DOACs [7-9] at the tertiary care hospital in Aarau. Although prevalence for overall inappropriate prescriptions of all DOACs decreased in 2019, no significance in risk decrease for inappropriate dosing was noticeable (chapter 4.5) for the named year. Only for rivaroxaban and edoxaban/dabigatran a significant decrease in prevalence and risk for inappropriate prescriptions in 2019 was detected. It was assumed that inappropriate dosing decreased due to the algorithm for those DOACs.

Similar to other studies, underdosing was the most prevalent subgroup of inappropriate dosing (2018: 13.4%, 2019: 14.1%) [7, 9]. In particular the prevalence of underdosed apixaban cases was the highest after implementation of the algorithms (2019), whereas in 2018 edoxaban/dabigatran showed the highest percentage of underdosed cases. In both years the percentage of underdosed rivaroxaban prescriptions was smaller than the one of apixaban. Comparable results for apixaban underdosing were found in the studies of Zhang *et al.* and Moudallel *et al.* . As the algorithms implemented were less likely to detect underdosed cases, most notably as indications could not be taken account of, the increase of prevalence and risk for underdosed apixaban prescriptions in 2019 is explainable.

It is to say that an adaption to dual or triple anticoagulation was counted as a wrong dosage, according to SmPC. Although for rivaroxaban the SmPC said an adaption to dual anticoagulation may be considered this adaption of the SmPC occurred during the study period, that may be the reason why it was counted as wrong for the whole period. In contrast the algorithms did detect a triple anticoagulation (if: DOAK + acetylsalicylic acid (ASA) + clopidogrel) and suggested to consider a dosage adaption for triple anticoagulation in case of nvAF, according to the hospital's cardiology and the ESC (European Society of Cardiology) guidelines since June 2019. Also, considering other risk factors for bleeding, renal function in time, comedication etc. also the clinical pharmacist may have suggested to consider a dosage reduction after assessment of ischemic and bleeding risk, even if not necessary according to SmPC. On the other hand, this may actually also be a reason why – according to SmPC – there were more underdosed cases in 2019. Zhang *et al.* analyzed the prevalence of inappropriate dosing for AF according to SmPC and according to European guidelines. The prevalence of underdosing was lower when the appropriateness was analyzed according to ESC or European Heart Rhythm Association (ERHA) guidelines [9]. Therefore, a lower prevalence of underdosing and a higher impact of the algorithms could be assumed if dosage appropriateness was checked according to those guidelines. Looking at the logistic regression additionally fitted for “PRFU” (multivariate “B”, chapter 4.6), the risk for inappropriate dosing was significantly decreased in 2019 compared to multivariate “A”. A possible explanation is visible in the decreased risk for underdosed apixaban prescriptions in multivariate “B”. This underlines the assumption of less underdosed prescriptions, if the dosage appropriateness would

have been analyzed according to ESC or ERHE guidelines. This means in particular, when dosage adaption for dual or triple anticoagulation of rivaroxaban and apixaban would have been considered appropriate. Further, the study Zhang *et al.* showed that the prevalence of only one criterion for dose reduction of apixaban was one of the main reasons for underdosing in patients with AF [9]. The results of the performed logistic regression (multivariate “B”) are in line with the study of Zhang *et al.*, as the most prevalent indication for all DOACs was AF and apixaban was the DOAC with the highest prevalence of PRFU (chapter 4.6), as there were significant more apixaban prescription in 2019 than in 2018. It is to say that by experience the most prevalent reason in PRFU was dual or triple anticoagulation.

It could be assumed that if apixaban prescriptions would not have increased and rivaroxaban prescriptions would have been more prevalent in 2019, a significant decrease of overall risk for inappropriate dosing would have been achieved thanks to the algorithms.

The overall reduction for overdosed cases in 2019 compared to 2018 was not significant. Overdosed cases were significantly reduced for rivaroxaban, but overdosed apixaban cases did increase in 2019. This increase was explainable, as there were more cases of apixaban with relapse prophylaxis of DVT/PE without a reduced dose to 2 x 2.5 mg / d. These cases were overdosed but not detected by the algorithm, as the indication could not be checked for.

The prevalence and risk for contraindications were significantly minimized for all the DOACs where a logistic regression was made. This showed that contraindications are the best detected inappropriate dosages by the algorithms. Further the high acceptance rate for interventions for contraindications underlines this assumption.

5.5 Study Limitation

This study has several limitations. First, due to the retrospective study design, only data recorded in the medical record could be used. That's why cases with missing values were excluded from the study. Further cases with no coded or no manually found diagnosis (by looking into the patient records) were excluded if it was other than rivaroxaban 1 x 10 mg/d for cases staying at the orthopedics unit. Those cases were assumed to be treated for DVT prophylaxis. This leads to the limitation that among these cases there were some, which were potentially underdosed because they were treated for a different indication. This could lead the performed appropriateness analysis resulted better than analyses performed in other studies [2, 7-9]. As DVT prophylaxis was the indication with the fewest cases (2018: 11.7%, 2019: 9,8%) compared to the other indications, the risk may remained small.

When at least one coded diagnosis was found as DOAC indication for a case, it was not further investigated if there were more possible diagnosis which may have affected the dosage appropriateness. Then, the dosage closest to discharge was assumed to also be the prescription patients were discharged with.

Although the HAS-BLED-Score would have been interesting to analyze as a risk factor for inappropriate dosing, it was not calculated. Certain data used for its calculation could not be extracted from the medical records. E.g. the variable labile international normalized ratio [INR].

The CHA₂DS₂VASc- Score was calculated for the whole population, not only for patients diagnosed with nvAF. This possibly led to an underestimated significance for the score being a risk factor for underdosing. Further, for the statistical analysis dual or triple anticoagulation was not analyzed as risk factor itself. An analysis would have most probably shown that it was a risk factor for underdosing and a fitted logistic regression would have probably showed more significance in risk decrease for inappropriate dosing in 2019, as the increased underdosed apixaban cases would have probably been balanced out by this variable.

5.6 Limitations of the algorithms

The algorithms cannot check congruence of the dosage with diagnosis or indication, which is the main pitfall for the high percentage of not detected underdosed cases, and overall for the lower sensitivity of the rivaroxaban and apixaban agents. Although in case of an alert the patient's dossier is looked at in detail and the diagnosis list is taken account of, patients with correct dosage in relation to age, eGFR and weight is correct but wrong indication are not detected by the algorithms. E.g. a patient receiving 1 x 10 mg rivaroxaban with nvAF will not be detected.

The results of alerts were probably biased by time. It happened that the time from the evaluation process to the moment when the prescribers received the intervention suggestion took too long and patients were already discharged at the receiving time of the intervention. This made an intervention void. Another time bias resulted in prescriptions paused during the whole stay (not evaluated by agents), which were reactivated shortly before discharge. Consequently, the intervention may be received too late by the treating physician. Further the agents did only run on workdays. This means that patients which entered the hospital on a Friday afternoon and left on the following Monday morning, were never detected by the agents.

Another limitation was that algorithms alerts were not sent directly to the physician in order to avoid clinically not relevant alerts. The overall high acceptance rate shows that this is a good strategy to get the intervention accepted and the therapy optimized.

Then, for some interventions no appropriateness at discharge was determinable, as for the specific patient case the DOAC corresponding to the alert was no longer prescribed. Most likely because a switch to heparin or to another DOAC was suggested through the intervention.

Further an alert for dosage adaption to triple anticoagulation of rivaroxaban and apixaban (DOAK + ASA + Clopidogrel) was implemented to the algorithms in June 2019. As dosage adaption for triple anticoagulation was counted as wrong in the analysis, but from June on a few interventions for dosage adaption to triple anticoagulation were suggested by the clinical pharmacy team. That is why, some cases were probably counted as underdosed in the performed analysis, although the dosage was recommended by the clinical pharmacy.

The calculation of the agent's sensitivity and specificity was limited, as far as the excluded cases from the study were consequently not included in the made calculations. That means, more interventions were actually made. Then, as the indication is not checked by the agents the sensitivity for the edoxaban and dabigatran agents is consequently higher as all indications show the same or similar dosage scheme.

6 CONCLUSION AND PERSPECTIVE

Although inappropriate prescriptions of DOACs decreased overall in 2019 compared to 2018, the results showed no statistical significance. However, a significant reduction in prevalence and risk for contraindications was achieved in 2019 (mainly contraindicated combination with the given DOAC or due to severe kidney disease).

As to rivaroxaban and edoxaban/dabigatran prescriptions, the prevalence and risk for inappropriate dosing significantly decreased in 2019. Furthermore, a significant reduction of overdosed prescriptions was achieved for rivaroxaban, whereas the results obtained from the adjusted logistic regression showed no significant risk reduction.

In contrast, underdosed apixaban prescriptions did significantly increase in 2019. This contrary effect may be due to various reasons, the two most important of which are to be recapitulated/pointed out here:

- A lower dosing in case of dual or triple anticoagulation was always considered as wrong, whereas the local clinical pharmacists and cardiologists may actually suggest to use a reduced dosage in accordance with the pertinent ESC guidelines.
- The algorithm cannot use the diagnoses (obtained) since/because they are not embedded/included in the CIS in a structured manner/form; as a consequence, especially underdosed cases are not well detected/cannot be detected properly.

The explorative analysis of PRFU showed, that the variable was a significant predictor for underdosing. The adjusted logistic regression that was conducted indeed showed a significant risk reduction for inappropriate dosing in 2019. The results obtained for sensitivity and specificity calculations of the algorithms confirmed the expectations. The major pitfall for sensitivity were the indications that could not be verified by the agents.

For the future, it is envisaged to implement the algorithms in the CIS. This would lead to qualified standard notifications of high specificity. This in turn may result in a reduction of alerts being received too late, especially after weekends. This may apply for instance to patients that had already been discharged when processing of the alerts was completed. In this context, it could be useful if the pharmacist that is on call would process the incoming alerts immediately. Moreover, the algorithm will differentiate between simultaneously prescribed PY12-inhibitors, which in turn will lead to a more differentiated dual and triple anticoagulation management. The implementation of an indication check to the algorithms would entail an extensive, i.e., costly and resource-intensive process change at the Cantonal Hospital of Aarau (KSA) or the implementation of a text recognition software. Therefore, given the current resource limitations, the implementation of such an improvement project is unfortunately considered unlikely at this time.

7 LITERATURE

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9 APPENDIX

DOAC comparison chart

Kantonsspital Aarau		Vergleichstabelle DOAKs - Direkte orale Antikoagulantien			KD 023.035, Version 01 Gültig ab 08.11.2017						
Zielmolekül		Rivaroxaban (Xarelto®)		Apixaban (Eliquis®)		Edoxaban (Lixiana®)		Dabigatran (Pradaxa®)			
Darreichungsform & Dosis / KSA-Artikel		Tbl. 10mg, 15mg, 20mg / Ja		Tbl. 2.5mg, 5mg / Ja		Tbl. 15mg, 30mg, 60mg / Nein		Kps. 110mg, 150mg / Ja			
Zugelassene Indikationen bei Erwachsenen, Dosierung und Dosisanpassungen											
vor Beginn jeder Antikoagulation: Blutungsanamnese; Kontrolle Blutbild und Gerinnungsstatus; Bestimmung Kreatinin (eGFR) und Leberwerte											
Thromboseprophylaxe nach orthopädischen Eingriffen an den unteren Extremitäten		1 x tgl. 10mg (Beginn frühestens 6-10h postop)		2x tgl. 2.5mg (Beginn frühestens 12-24h postop)		nicht zugelassen		nicht zugelassen			
Nicht-valvuläres Vorhofflimmern KI bei valvul. VHF (mech. Klappenprothesen, mittel- bis schwere Mitralklappenstenosen)		1x tgl. 20mg GFR 30-49ml/min → 1x tgl. 15mg		2x tgl. 5mg 2x tgl. 2.5mg → wenn 2 der Kriterien: ≥ 80 J., ≤ 60kg, Krea ≥ 133µmol/l		1x tgl. 60mg 1x tgl. 30mg wenn: GFR 15-50ml/min oder ≤ 60kg oder Komb. mit P-gp Inhibitoren		2x tgl. 150mg 2x tgl. 110mg → wenn: > 80 J. oder GFR 30-50ml/min, erhöhtes Blutungsrisiko			
Therapie der TVT und LE		Tag 1-21: 2x tgl. 15mg ab Tag 22: 1x tgl. 20mg		Tag 1-7: 2x tgl. 10mg ab Tag 8: 2x tgl. 5mg		Tag 1-5: Heparin oder NMH ab Tag 6: 1x tgl. 60mg Dosisanpassung analog VHF		Tag 1-5: Heparin oder NMH ab Tag 6: 2x tgl. 150mg Dosisanpassung analog VHF			
Rezidivprophylaxe der TVT und der LE		1x tgl. 20mg		2x tgl. 2.5mg (ab 7. Monat der Antikoagulation)		1x tgl. 60mg Dosisanpassung analog VHF		2x tgl. 150mg Dosisanpassung analog VHF			
Anwendung bei Niereninsuffizienz		GFR < 15ml/min: kontraindiziert (alle DOAK's); GFR 15-30ml/min: nur in Rücksprache mit Hämatologie									
Einnahmehinweise möglichst immer zur gleichen Tageszeit		Tbl 15 und 20mg mit Mahlzeit einnehmen. Zermörserbar; Gabe über Sonde möglich		Einnahme unabhängig von der Mahlzeit. Zermörserbar; Gabe über Sonde möglich		Einnahme unabhängig von der Mahlzeit. Zermörserbar; Gabe über Sonde möglich		Einnahme unabhängig von der Mahlzeit. Kapseln nicht öffnen; keine Gabe über Sonde!			
Kontraindikationen											
Kontraindikationen (Details s. Fachinformation)		Klinisch relevante aktive Blutung; Niereninsuffizienz mit eGFR < 15ml/min; Leberfunktionsstörungen CHILC oder Lebererkrankungen, die mit einer Koagulopathie einhergehen; aktive gastrointest. Ulcerose; Schwangerschaft und Stillen; akute bakterielle Endokarditis									
Interaktionen											
Kontraindikationen Kombination nicht empfohlen		Starke P-gp Induktoren: Rifampicin, Carbamazepin, Phenobarbital, Phenytoin, Johanniskraut, HIV-Proteaseinhibitoren Starke CYP3A4 Inhibitoren: Azol-Antimykotika ausser Fluconazol (Ketoconazol, Itraconazol, Voriconazol, Posaconazol); Chinidin, Dronedaron, Ciclosporin, Clarithromycin, HIV-Proteaseinhibitoren									
Übrige Interaktionen Kombination möglich, Beeinflussung Plasmaspiegel mässig		Amiodaron, Chinidin, Dronedaron, Diltiazem, Verapamil, Erythromycin, Naproxen, Fluconazol, Ciclosporin, Tacrolimus → bei ≥ 2 Risikofaktoren (wie Alter ≥ 75), eGFR < 50ml/min, Gewicht ≤ 60kg, Behandlung mit Gerinnungshemmern od. Medis die Blutungsneigung erhöhen (Steroide, NSAR), HAS-BLED-Score ≥ 3) → Dosisreduktion Xarelto 1x tgl. 15mg und Eliquis 2x tgl. 2.5mg evaluieren.				Duale Thrombozytenaggregationshemmung oder Komb mit NSAR, SSRI oder SNRI		Starke P-gp-Inhibitoren: Ciclosporin, Dronedaron, Erythromycin, Azol-Antimykotika (ausser Fluconazol), Chinidin, Verapamil → Dosisreduktion, 1x tgl. 30mg.		Antazida, Amiodaron und Verapamil (moderate P-gp-Inhibitoren): Jeweils 2 Std. nach Pradaxa einnehmen	
Vorgehen bei Blutung											
Vorgehen bei Blutung Immer Zeitpunkt der Einnahme der letzten Tablette evaluieren		Kleine Blutungen: 1. zuwarten, ev. lokale Massnahmen, DOAK pausieren; 2. lokal Tranexamsäure (Cyklokapron) Grosse Bl.: Gerinnungsstatus, Blutbild, Plasmaspiegelbestimmung; Kompression/Chirurgie/Volumenersatz 1. Cyklokapron 1-2g iv (Beachte KI); 2. Minirin 0.3mg/kgKG i.v. (Beachte KI); 3. PCC 25-30E/kgKG; Lebensbedrohliche oder ZNS-Blutung: 4. ev. Rekomb. aFVII (Novoseven) 45-90mcg/kg i.v. 1x (ev. 2. Mal nach 2h)									
		Idarucizumab (Praxbind® 2.5g/50ml); Ind.: Notfalloperationen/dringende Eingriffe, nicht beherrschbare Blutungen 5g i.v.; RS Hämatologie empfohlen									

Name (INN/Brand)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)	Dabigatran (Pradaxa®)
Vorgehen bei Dosierungsfehlern/Intoxikation				
Vorgehen bei Dosierungsfehlern	Wurde eine Dosis vergessen, soll bei der nächsten regulären Einnahme keine doppelte Dosis genommen werden. Ein Nachholen der verpassten Dosis ist bis zur Hälfte des Dosierungsintervalls erlaubt (d.h. bis zu 6 Std. bei 2x bzw. 12 Std. bei 1x tgl. Verabreichung). Falls dies nicht mehr möglich ist, auf Dosis ganz verzichten. Bei versehentlicher Einnahme der doppelten Dosis, sollte die nächste Dosis ausgelassen werden. Weiss der Patient nicht mehr, ob er die letzte Dosis eingenommen hat: Bei 2x tgl. Einnahme: keine weitere Tablette nehmen, sondern nach 12 Std normal weiterfahren. 1x tgl. Einnahme: Eine Dosis einnehmen und dann normal weiterfahren.			
Intoxikation	Kontrolle Blutbild, Nieren- und Leberfunktion, Gerinnungsstatus und Plasmaspiegel bei Eintritt, nach 12h und ggf. nach 24h Ceiling-Effekt (v.a. bei Xarelto, ev. Eliquis, nicht bei Lixiana) ohne Blutung Patient ohne Massnahmen überwachen; bei Blutung: "Vorgehen wie bei Blutung" s.o.			Dabigatran ist dialysierbar; bei Blutung: Vorgehen s.o.
Pharmakokinetik				
Orale Bioverfügbarkeit	10mg: 80-100%; 15-20mg: 66%	ca. 50%	62%	3-7%
Plasmapbindung	92-95%	87%	ca. 55%	35%
Metabolismus und Elimination	M: 2/3 über CYP450 E: 1/3 unverändert renal	M: über CYP3A4 zu inaktiven Metaboliten E: über Fäzes, 27% aktive Substanz	M: minimal (<10% zu aktivem Metabolit), <4% über CYP3A4 E: 50% biliär, 50% renal	Prodrug, Hydrolyse zur aktiven Form M: <20% zu aktiven Metaboliten E: renal
HWZ bei normaler Nierenfunktion	5-9 Std. (jüngere Patienten) 11-13 Std. (ältere Patienten)	12 Std., bei schwerer NI ca. 17 Std.	10-14 Std., bei schwerer NI ca. 17 Std.	12-17 Std., bei schwerer NI bis zu 28 Stunden
Zeitpunkt nach Absetzen, wo Spiegel für Hämostasie nicht mehr relevant ist	16 - 24 Stunden bei normaler Nieren- und Leberfunktion	24 - 30 Stunden bei normaler Nieren- und Leberfunktion	k.A.	k.A.
Plasmaspiegel relevant für Hämostasie	> 50ng/ml	> 50ng/ml	k.A.	> ca. 60ng/ml
Zeitintervalle bei Eingriffen und periduralen Kathetern; Wechsel zwischen Antikoagulantien				
Zeitintervall Anästhesie Zeitintervall vor tiefen Nervenblockaden, Spinalanästhesien, Legen und Entfernen epiduraler Katheter	GFR > 30ml/min 10mg > 24h; 15 und 20mg > 48h GFR 15-30ml/min je 24h länger	2x tgl. 2.5mg: > 36h (GFR < 50ml/min: > 72h) 2x tgl. 5mg: > 72h	> 48h (bei Niereninsuffizienz bis 5 Tage)	> 36h (GFR < 80ml/min länger)
Bei älteren Patienten, eingeschränkter Nieren- oder Leberfunktion oder eine Komedikation, die die Elimination verlängert oder die Gerinnung zusätzlich beeinflussen, müssen Zeitintervalle verlängert und/oder Plasmaspiegel bestimmt werden				
Zeitintervalle nach tiefen Nervenblockaden, Spinalanästhesie, Legen und Entfernen epiduraler Katheter: mind. 6h; nach traumatischer Punktion: 24h				
Zeitintervall bei invasiven Verfahren und chirurgischen Eingriffen	niedriges Blutungsrisiko: > 24h hohes Blutungsrisiko: > 48h	niedriges Blutungsrisiko: > 24h hohes Blutungsrisiko: > 48h	niedriges Blutungsrisiko: > 24h hohes Blutungsrisiko: > 48h (bei Niereninsuffizienz bis 5 Tage)	GFR > 80ml/min: > 24h (* > 48h) GFR 50-79ml/min: > 48h (* > 72h) GFR 30-49ml/min: > 72h (* > 96h) * bei hohem Blutungsrisiko (s.u.)
Wechsel von/auf Heparin (Liquemim)	hohes Blutungsrisiko: wenn gleichzeitige Einnahme von Thrombozytenaggregationshemmer und/oder GFR < 30ml/min; gilt auch für alle Eingriffe an Hirn, Rückenmark und hintere Augenkammer; Ein Bridging mit LMWH bei Unterbruch bis 2 Tage entfällt; prüfe LMWH bei Unterbruch > 2 Tage Stopp Heparin (Liquemim) und Beginn DOAK 2-4 Stunden nach Absetzen der i.v. Infusion Stopp DOAK und Beginn Heparin (Liquemim) ohne Bolus bei der nächsten geplanten DOAK-Dosis			
Wechsel von/auf Marcoumar	Marcoumar stopp und Beginn DOAK sobald INR < 2.0 Beginn Marcoumar, Fortsetzung DOAK bis INR an 2 aufeinanderfolgenden Tagen im Zielbereich, mind. 5 Tage überlappend (gilt nicht für Pradaxa, immer zuerst Umstellung auf LMWH oder UFH); DOAK beeinflusst INR, INR unmittelbar vor Tabletteneinnahme bestimmen			

Begriffe: ASS (Acetylsalicylsäure), GFR (geschätzte) (glomeruläre Filtrationsrate), HWZ (Halbwertszeit), KG (Körpergewicht), LE (Lungenembolie), NIM (niedermolekulare Heparine), NI (Niereninsuffizienz), RS (Rücksprache) TVT (Tiefe Venenthrombose), UFH (unfraktioniertes Heparin, Liquemim), SNRI (Serotonin-Noradrenalin-Reuptake Inhibitor), SSRI (Serotonin-Reuptake-Inhibitor).

Figure 7 Rivaroxaban agent

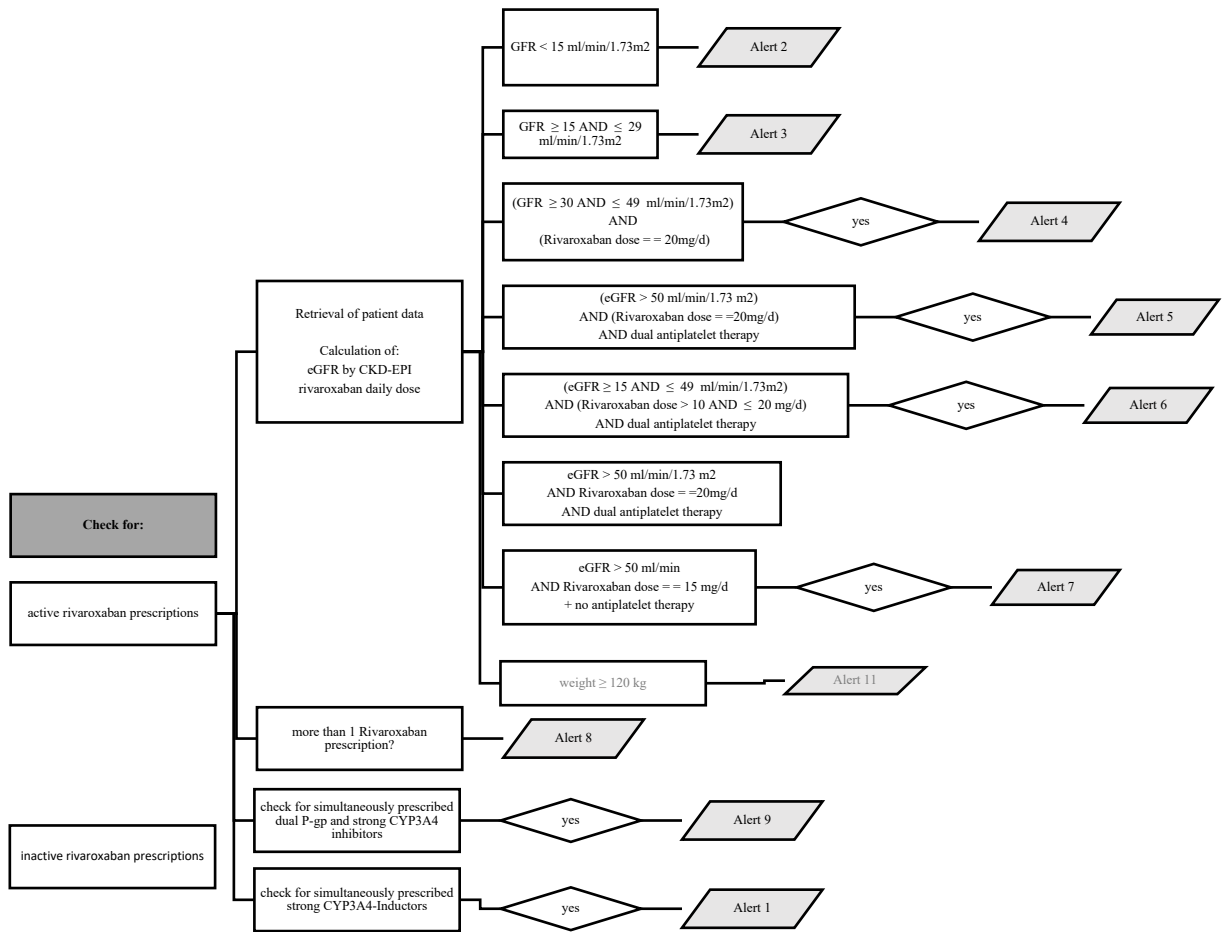


Figure 8 Apixaban agent

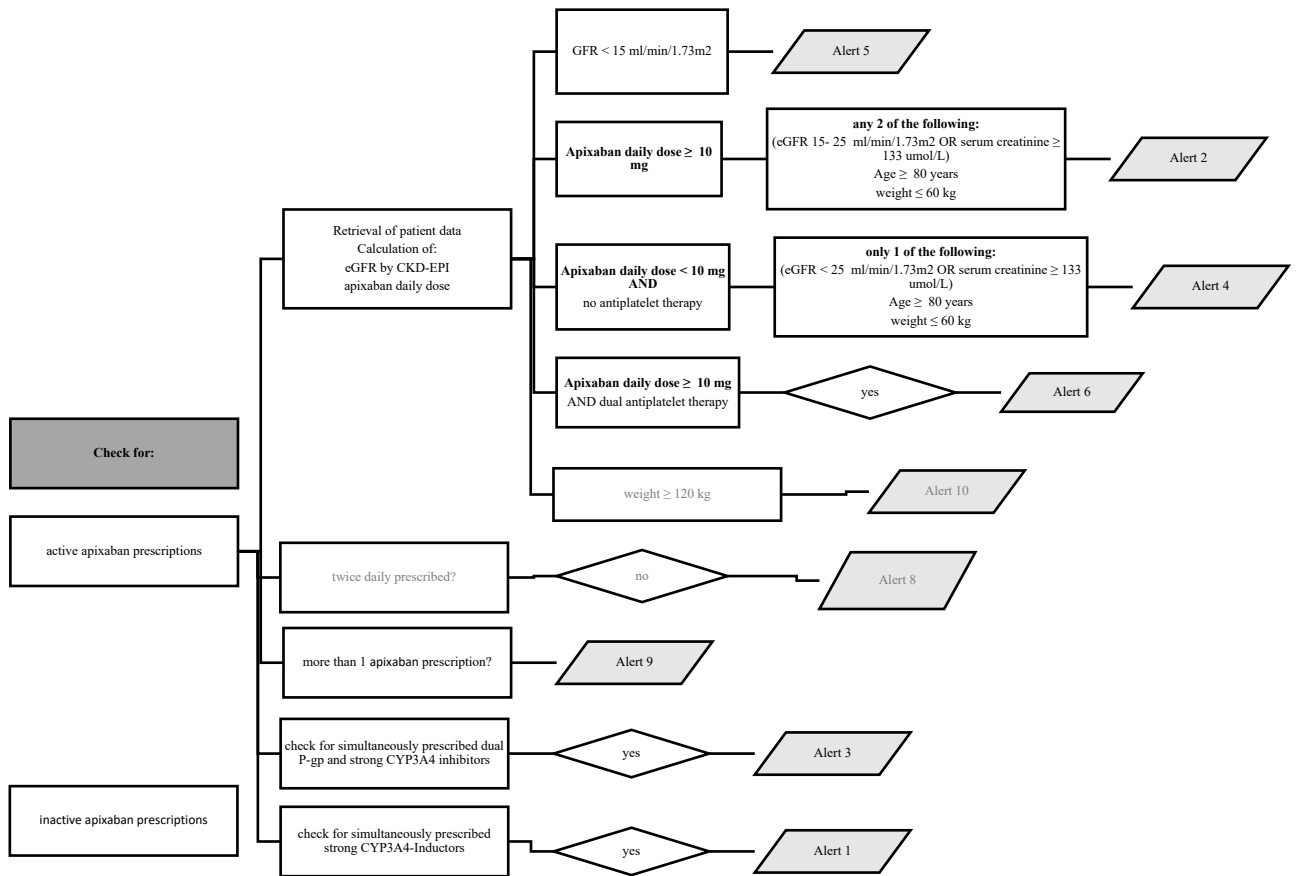


Figure 9 Edoxaban agent

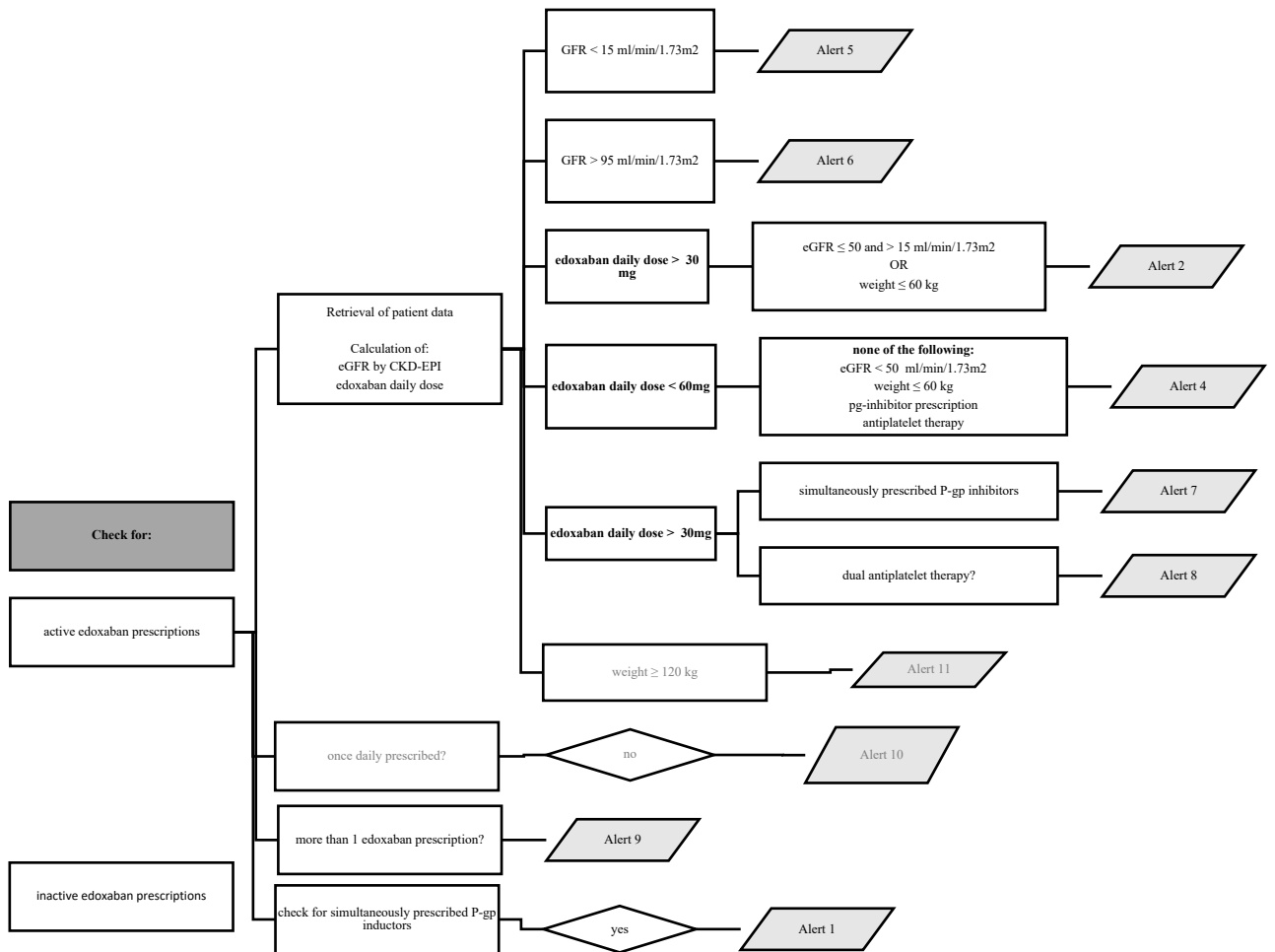
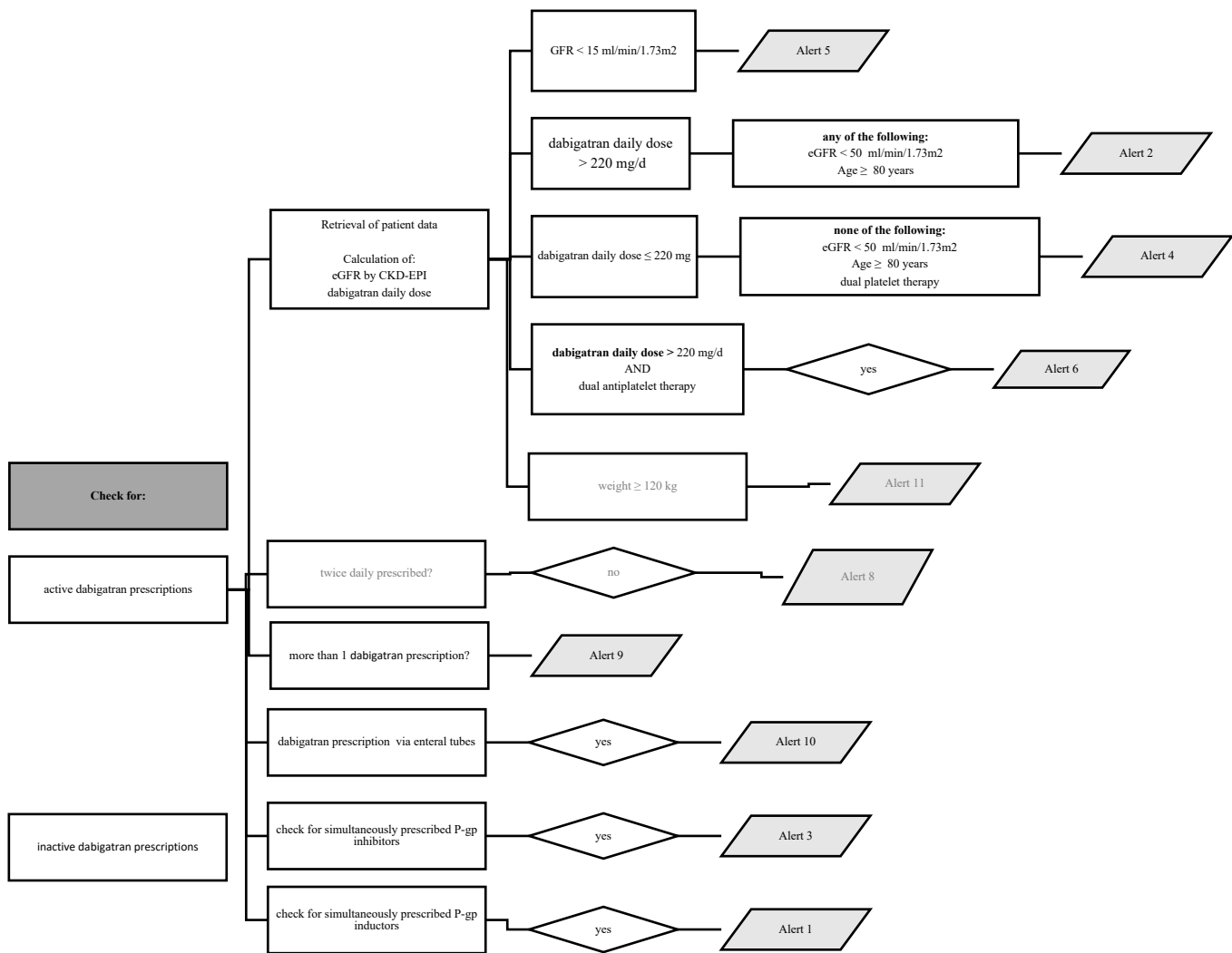


Figure 10 Dabigatran agent



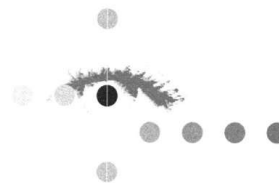
Research Project Application Form

Project title							
Masterarbeit EKNZ: Evaluation of appropriateness of DOAC dosing in patients after implementation of an algorithm designed to detect under- and overdosing.	<table border="1"> <tr> <td>BASEC-ID</td> <td>2020-00468</td> </tr> <tr> <td>Acronym</td> <td>--</td> </tr> <tr> <td>Internal ID</td> <td>--</td> </tr> </table>	BASEC-ID	2020-00468	Acronym	--	Internal ID	--
BASEC-ID	2020-00468						
Acronym	--						
Internal ID	--						
Project overview							
Ethics Committee	Ethikkommission Nordwest- und Zentralschweiz EKNZ						
Project Leader	Prof. Dr. med Philipp Schütz, Medizinische Universitätsklinik, Kantonsspital Aarau						
Application type	Further use of health-related personal data and/or biological material						
Initiator	investigator						
Used for degree of	Carmen Reist, Master (e.g. Master of Medicine, other Masters)						
Brief description of the research plan	<p>At the Kantonsspital in Aarau (KSA) algorithms for real time dosage surveillance of rivaroxaban, apixaban, edoxaban and dabigatran are used since March 2019.</p> <p>The main objective of this master thesis is to analyze the impact of these algorithms on the appropriateness of DOAC dosage on discharge, by comparing the number of patients with a dosage not corresponding to label information during a ten month period before and after the implementation of the algorithm (before-after study). The secondary objectives are:</p> <ul style="list-style-type: none"> - to evaluate the specificity and sensitivity of the algorithms - to explore the possible reasons for inappropriate dosing by analyzing the characteristics of patients. 						
Start date	01.03.2018						
End date	31.12.2019						
Submission details and comments (last update)							
Date last update	05.03.2020 <i>Please note: this date always shows the date of the latest edit. It either corresponds to the last update done by the applicant or to administrative changes done by the (Lead-) ethics committee to the submission.</i>						
Submission concerning	first submission of this project						
Comments	--						

EKNZ

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Basel, 10.03.2020/ vj

Verfügung der Ethikkommission Nordwest- und Zentralschweiz (EKNZ)

Project-ID	2020-00468
Projekttitel	Masterarbeit EKNZ: Evaluation of appropriateness of DOAC dosing in patients after implementation of an algorithm designed to detect under- and overdosing.
Master-/Doktorarbeit von	Reist, Carmen
Projektleitung	Prof. Dr. med Philipp Schütz
Sponsor	Prof. Dr. med Philipp Schütz
Zentren	<ul style="list-style-type: none">Prof. Dr. med Philipp Schütz, Medizinische Universitätsklinik, Kantonsspital Aarau, Aarau

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- Forschung mit Personen
- Weiterverwendung des biologischen Materials oder der gesundheitsbezogenen Personendaten
- mit Verstorbenen
- mit Embryonen / Föten
- mit ionisierender Strahlung

Kategorie: --



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Bachelor's / Master's Thesis *(Please cross out what does not apply)*

Title of Thesis *(Please print in capital letters):*

APPROPRIATENESS EVALUATION OF DOAC DOSING, AFTER IMPLEMENTATION
OF ALGORITHMS DESIGNED TO DETECT INAPPROPRIATE DOSING

First Name, Surname *(Please print in capital letters):* CARMEN REIST

Matriculation No.: 2015-117-062

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I have mentioned all source materials used and have cited these in accordance with recognised scientific rules.

In addition to this declaration, I am submitting a separate agreement regarding the publication of or public access to this work.

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January 2017