Determinants for under- and overdosing of direct oral anticoagulants and physicians' implementation of clinical pharmacists' recommendations

Souad Moudallel[1], Pieter Cornu[1], Alain Dupont[1], and Stephane Steurbaut[1]

[1]Vrije Universiteit Brussel

February 22, 2024

Abstract

Aim: To analyze the appropriateness of DOAC dosing and determinants for under-and overdosing as well as acceptance and implementation rates of interventions by clinical pharmacists. Methods: Cross-sectional study from January 2019-December 2019 in a tertiary hospital in hospitalized patients with atrial fibrillation on DOACs (n=1688). Primary outcome was the proportion of patients with inappropriate DOAC prescribing with identification of determinants for under-and overdosing. Secondary outcomes included acceptance and implementation rates of pharmacists' advices and determination of reasons for non-acceptance/non-implementation. Results: In 16.9% of patients, inappropriate prescribing was observed. For all DOACs considered together, body weight<60 kg(OR 0.46 [0.27-0.77]), edoxaban use(OR 0.42 [0.24-0.74]), undergoing surgery(OR 0.57 [0.37-0.87]) and being DOAC naïve(OR 0.45 [0.29-0.71]) were associated with a significantly lower odds of underdosing. Bleeding history(OR 1.86 [1.24-2.80]) and narcotic use(OR 1.67 [1.13-2.46]) were associated with a significantly higher odds for underdosing. Determinants with a significantly higher odds of overdosing were renal impairment(OR 11.29 [6.23-20.45]) and body weight<60 kg(OR 2.34 [1.42-3.85]), whereas the use of dabigatran(OR 0.24 [0.08-0.71]) and apixaban(OR 0.18 [0.10-0.32]) were associated with a significantly lower odds of overdosing compared to rivaroxaban. Physicians accepted the pharmacists' advice in 179 cases (79.2%) consisting of 92 (51.4%) advices for underdosing, 82 (45.8%) for overdosing and 5 (2.8%) for contraindications. The advices were effectively implemented for 75 (81.5%) underdosed, 69 (84.1%) overdosed and 4 (80.0%) contraindicated cases. Conclusion: Inappropriate DOAC prescribing remains common. Clinical services led by pharmacists helps physicians to reduce the number of inadequate prescriptions for high risk medications such as DOACs.

Determinants for under- and overdosing of direct oral anticoagulants and physicians' implementation of clinical pharmacists' recommendations

Souad Moudallel[1*], Pieter Cornu[1], Alain Dupont[1**], Stephane Steurbaut[1**]

[1]Research Group Clinical Pharmacology and Clinical Pharmacy; Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Jette, Belgium

*Corresponding author. Laarbeeklaan 103, 1090 Jette, Belgium. Tel: +3224763385. E-mail address: Souad.Moudallel@vub.be

**Stephane Steurbaut and Alain Dupont should be considered joint senior authors

Running title: DOAC dosing/implementation of advices

Word count abstract: 246

Word count article: 2850

Number of References: 42

Number of Tables: 2

Number of Figures: 2

Key words: DOACs, clinical pharmacist, inappropriate prescribing, interprofessional collaboration

What is already known about this subject:

* DOACs are increasingly used high risk medications for stroke prevention in atrial fibrillation and other indications.

* DOAC prescribing is error prone given different dosage regimes depending on drug, indication and other factors.

* Only determinants associated with inappropriate prescribing in general have been identified so far.

What this study adds:

* Distinct determinants associated with under- and overdosing were identified and studied per DOAC.

* Acceptance and implementation rates of interventions by clinical pharmacists were studied in detail and high.

* Clinical services led by pharmacists help physicians to reduce the number of inadequate DOAC prescriptions.

Aim : To analyze the appropriateness of DOAC dosing and determinants for under-and overdosing as well as acceptance and implementation rates of interventions by clinical pharmacists.

Methods : Cross-sectional study from January 2019-December 2019 in a tertiary hospital in hospitalized patients with atrial fibrillation on DOACs (n=1688). Primary outcome was the proportion of patients with inappropriate DOAC prescribing with identification of determinants for under-and overdosing. Secondary outcomes included acceptance and implementation rates of pharmacists' advices and determination of reasons for non-acceptance/non-implementation.

Results : In 16.9% of patients, inappropriate prescribing was observed. For all DOACs considered together, body weight<60 kg(OR 0.46 [0.27-0.77]), edoxaban use(OR 0.42 [0.24-0.74]), undergoing surgery(OR 0.57 [0.37-0.87]) and being DOAC naïve(OR 0.45 [0.29-0.71]) were associated with a significantly lower odds of underdosing. Bleeding history(OR 1.86 [1.24-2.80]) and narcotic use(OR 1.67 [1.13-2.46]) were associated with a significantly higher odds for underdosing. Determinants with a significantly higher odds of overdosing were renal impairment(OR 11.29 [6.23-20.45]) and body weight<60 kg(OR 2.34 [1.42-3.85]), whereas the use of dabigatran(OR 0.24 [0.08-0.71]) and apixaban(OR 0.18 [0.10-0.32]) were associated with a significantly lower odds of overdosing compared to rivaroxaban. Physicians accepted the pharmacists' advice in 179 cases (79.2%) consisting of 92 (51.4%) advices for underdosing, 82 (45.8%) for overdosing and 5 (2.8%) for contraindications. The advices were effectively implemented for 75 (81.5%) underdosed, 69 (84.1%) overdosed and 4 (80.0%) contraindicated cases.

Conclusion: Inappropriate DOAC prescribing remains common. Clinical services led by pharmacists helps physicians to reduce the number of inadequate prescriptions for high risk medications such as DOACs.

Introduction

The direct oral anticoagulants (DOACs) are increasingly used as the treatment of choice for stroke prevention in atrial fibrillation (AF) and as treatment and prophylaxis of venous thromboembolisms (VTE)[1, 2]. DOACs are at least as effective as vitamin K antagonists (VKAs) and do not need routine monitoring, but also come with specific requirements and risks. DOACs require dosage adjustments for renal function, weight, age, and concomitant medications[2-4]. Several studies have shown that DOACs are frequently prescribed incorrectly with inappropriate dosing varying from 12.8% to 42.8% of AF patients as well as other patients[3, 5-19]. Inappropriate prescribing has been shown to be an independent risk factor for adverse

drug events (ADE) leading to potential clinical consequences including thromboembolism, bleeding, hospitalization and death [1, 20]. Older patients are especially susceptible to ADEs associated with inappropriate prescribing due to decreased drug metabolism, increased prevalence of hepatic/renal dysfunction, and the higher likelihood of drug-drug interactions as a result of polypharmacy [1]. Although prescribers may have valid reasons for using dosages that deviate from the Summary of Product Characteristics (SmPC), no studies have demonstrated improved anticoagulation therapy outcomes associated with this practice. It is therefore important to consistently monitor DOAC prescriptions and identify any related patient safety issues [2]. According to the literature, pharmacists can help patients and providers in preventing and managing DOAC related problems[21-23]. The purpose of this study was to assess the rate of inappropriate DOAC dosing and identify determinants associated with under- and overdosing. To the best of our knowledge, this hasn't been investigated before since previous literature commonly has focused only on determinants for inappropriate prescribing in general[1, 3, 11]. Given the increasing prescription rates of DOACs (including edoxaban) over the last years, this study intended to yield additional information about possible determinants for under- and overdosing compared to the study of 2018 [3]. Moreover and also innovative in aim, we assessed the physicians' acceptance and implementation rate of the pharmacists' DOAC dosing advice with listing of the reasons for non-acceptance and non-implementation for the cases where the pharmacists' advice was not followed.

Methods

Study design and study population

This was a cross-sectional study conducted at the UZ Brussel, a 721-bed university hospital in Brussels, Belgium. Via the prescription order validation tool, a tool that is used by clinical pharmacists to assess the appropriateness of drug prescriptions with a main focus on high risk medications (HRM), we identified all hospitalized patients who were initiated on or continued with dabigatran, rivaroxaban, apixaban or edoxaban between 1 January 2019 and 31 December 2019.

Patient demographic data (age, gender, weight, body mass index (BMI)), co-medication, co-morbidities (hypertension, heart failure, diabetes mellitus, cerebrovascular disease), most recent laboratory data at the time of the DOAC prescription in the hospital (renal function, liver parameters, anemia, thrombocytopenia), CHA_2DS_2-VASc and HAS-BLED scores, DOAC type and dosage, bleeding history, surgical procedures during hospital stay, whether or not the DOAC was already initiated before hospital admission, concomitant use of antiplatelet agents, P-glycoprotein and cytochrome P450 3A4 inhibitors and inducers were collected via manual chart review. Creatinine clearance (CrCl) was calculated via the Cockcroft-Gault equation. Drug interactions were assessed according to the 2018 European Heart Rhythm Association (EHRA) guidelines. In case a patient was hospitalized more than once in 2019, only the first prescription of the first admission was taken into account. Data collection was performed by one investigator (M.S.) for consistency.

Outcomes

The primary outcome was the percentage of patients with an inappropriate DOAC initiated at or continued during hospital admission together with the identification of determinants associated with DOAC under- and overdosing. Similar to our previous study [3], rivaroxaban was used as the reference category. Secondary outcomes included the quantification of the physicians' acceptance and implementation rate of the clinical pharmacists' interventions as well as the documentation of their non-acceptance and/or non-implementation. An inappropriate DOAC dose was defined as a deviation from the recommended dose in the SmPC. Underdosing was defined as the prescribing of a reduced DOAC dose despite the patient not meeting the dose reduction criteria. Overdosing was defined as the prescribing of the standard DOAC dose despite the patient meeting the dose reduction criteria. A contraindication was defined as a situation for which the prescription of the DOAC was inadvisable.

If an intervention by a clinical pharmacist was deemed necessary, the prescribing hospital physician was contacted by telephone after which the pharmacists' recommendations were documented in the patient's electronic medical record. General practitioners (GP) and/or community pharmacists involved in the patient's care were contacted if the prescribing hospital physician was unreachable, when more information

was needed, or in case the patient was already discharged.

Statistical analysis

Descriptive and statistical analyses were carried out with IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to test the normality of the continuous variables. Histograms were evaluated to assess normality. Categorical variables were expressed as percentages and continuous variables as medians with interquartile ranges (IQRs). Differences in the continuous variables among the four DOACs were evaluated using the Kruskal-Wallis test. The Chi-square test was used to compare categorical variables. A two-sided significance level of 0.05 was used. Binary logistic regression analysis was conducted to determine factors associated with the under- and overdosing of the DOACs. Factors that were significantly associated in the univariable analysis ($p<0.1$) were included in the multivariable logistic regression analysis. For the logistic regression models a corrected p-value <0.05 (Benjamini-Hochberg correction for multiple comparisons) was used, goodness of fit was assessed (R^2, receiver operator characteristics curve) and residuals were reviewed. The odds ratios (OR) were reported with their 95% confidence intervals (CI).

Results

A total of 1688 consecutive and unique AF patients were included for which the characteristics per DOAC are shown in table 1. Apixaban was the most prescribed DOAC (34.7%) followed by edoxaban (32.7%), rivaroxaban (23.8%) and dabigatran (8.8%). Apixaban users were significantly older (median 81.0 years), weighed significantly less (median 70.1 kg) and had a statistically lower renal function (median 52.0 mL/min) compared to users of another DOAC. Moreover, apixaban users were diagnosed more often with arterial hypertension (73.0%) and heart failure (HF) (35.5%). Combination with at least one antiplatelet drug was observed in 23.6% and 21.8% of rivaroxaban and apixaban users, respectively. Dual antiplatelet therapy was the highest in the apixaban group (3.2%).

The overall inappropriate prescribing rate in this study was 16.9% (n=286) with the highest underdosing and overdosing rates seen in the apixaban (14.2%) and rivaroxaban (9.7%) group, respectively (Figure 1). Overall, underdosing, overdosing and contraindications were seen in 9.7%, 6.9% and 0.4% of patients, respectively.

Considering the four DOACs together (see Table 2), a body weight <60 kg (adj. OR 0.46, 95% CI 0.27-0.77), the use of edoxaban compared to rivaroxaban (adj. OR 0.42, 95% CI 0.24-0.74), undergoing surgery (adj. OR 0.57, 95% CI 0.37-0.87), and being DOAC naive (adj. OR 0.45, 95% CI 0.29-0.71) were associated with a significantly lower odds of underdosing. On the other hand, having a bleeding history (adj. OR 1.86, 95% CI 1.24-2.80) and the use of narcotic analgesics (adj. OR 1.67, 95% CI 1.13-2.46) were associated with a significantly higher odds of underdosing. Determinants associated with a higher odds of overdosing were renal impairment (adj. OR 11.29, 95% CI 6.23-20.45) and a body weight <60 kg (adj. OR 2.34, 95% CI 1.42-3.85), whereas the use of dabigatran (adj. OR 0.24, 95% CI 0.08-0.71) and apixaban (adj. OR 0.18, 95% CI 0.10-0.32) were associated with a lower odds of overdosing compared to rivaroxaban.

For rivaroxaban (adj. OR 100.95, 95% CI 23.23-438.70) and edoxaban (adj. OR 3.25, 95% CI 1.49-7.12) users, a decreased renal function was associated with a higher odds of overdosing compared to patients with a normal renal function. For rivaroxaban, we observed a lower odds of underdosing in patients with a CrCl <50 mL/min (adj. 0.17, 95% CI 0.06-0.48).

A lower body weight was a risk factor for underdosing in apixaban users (adj. OR 0.26, 95% CI 0.12-0.55), whereas this factor was associated with a higher odds of overdosing in the edoxaban group (adj. OR 4.16, 95% CI 1.97-8.77). Having a history of bleeding (adj. OR 2.14, 95% CI 1.22-3.75) in apixaban users was associated with a higher odds of underdosing.

Of the 286 identified AF patients with an inappropriate DOAC dose, the physician was contacted by telephone in 226 (79.0%) cases of which 131 and 90 calls concerned underdosed and overdosed prescriptions, respectively. Five cases of dabigatran use and a CrCl <30 mL/min were classified as a contraindication. In addition, telephone calls were conducted for eight cases concerning drug interactions (not shown in figure 2) with rifampicin (n=5), carbamazepine (n=2) and cyclosporine (n=1). Physicians accepted the pharmacists' advice

in 179 cases (79.2%) which consisted of 92 (51.4%) advices for underdosing, 82 (45.8%) for overdosing and 5 (2.8%) for contraindicated dosages. Regarding the non-accepted interventions (n=47), it concerned 39 (83.0%) underdosed and 8 (17.0%) overdosed cases. The advices were effectively implemented, as evidenced by a correction of the prescription in the patient's electronic medical record, for 75 out of 92 (81.5%) underdosed, 69 out of 82 (84.1%) overdosed and 4 out of 5 (80.0%) contraindicated cases, a total of 148 cases (65.5%). Non-implemented advices, for which the reasons are listed in figure 2, were observed for 15 underdosed, 11 overdosed and 1 contraindicated case. For 2 underdosed as well as 2 overdosed cases we were unable to track whether the intervention was implemented or not

Discussion

Despite their increased use and substantial research focusing on their effectiveness and safety in clinical practice, appropriate DOAC prescribing remains a problem as also evidenced by our study[24, 25]. Inappropriate first DOAC prescriptions were found in 16.9% of the patients, with underdosing being more prevalent than overdosing. This is in line with a previous study conducted at our institution [3] as well as other studies[1, 2, 7-10]. The dosing recommendations differ depending on the DOAC, with some of them requiring dose reductions based solely on renal function and others taking additional criteria into consideration. The high underdosing rate found in apixaban users seems clinically relevant as underdosing with this DOAC was reported to be associated with a nearly 5-fold increased stroke risk in AF patients[26]. On the other hand, it has been reported in a prospective study that hydrophilic drugs like DOACs in frail older patients with low muscle mass can lead to supratherapeutic DOAC plasma levels, placing them at higher risk for major bleeding complications[27].

Among patients prescribed DOACs, those receiving apixaban had a lower renal function, were older and weighed significantly less compared to users of other DOACs. According to recent literature, including a systematic review in frail AF patients, apixaban was associated with a lower risk of major bleedings compared to rivaroxaban and dabigatran, although their effectiveness was comparable [28-31]. As shown in a registry of rivaroxaban users, renal impairment was a risk factor for experiencing major bleeding events [32]. The risk of major bleedings was comparable between apixaban and edoxaban[29]. Intra DOAC comparisons still need to be confirmed by findings from randomized controlled trials that are expected to be released in the upcoming years e.g., the DARING-AF trial and DANNOAC-AF trial [28, 29].

According to the literature, physicians may place more value on the avoidance of bleeding in high risk AF patients, especially in those with a high fall and bleeding risk [3, 33, 34]. Results of previous studies suggest an increased risk of falls and fractures among older adults using opioids [35, 36]. Walenga and colleagues describe that the relative rate of clinically relevant bleedings with the use of opioids was nearly twofold greater with low dose rivaroxaban compared with enoxaparin [37].

The higher OR for underdosing apixaban in patients with a lower weight may be related to the fact that weight is often used as a single criterion for dose reduction in apixaban, while this is only to be adapted in combination with an age [?]80 years and/or serum creatinine [?]1.5 mg/dL.

The association of weight with overdosing in edoxaban users is mainly due to younger patients with a weight <60 kg who were hospitalized to undergo an ablation.

The association between a reduced CrCl and the higher odds to receive a supratherapeutic dose as found for rivaroxaban and edoxaban users could be due to a fluctuating renal function or physicians being unaware of the CrCl threshold for dose adjustment [2].

A high percentage of the advices by the clinical pharmacists was immediately accepted (79.2%) and effectively implemented (65.5%) by the physicians. The accepted advices consisted for 79.9% of prescriptions for DOACs that were initiated prior to the hospital admission. Physicians acknowledged that they did not consistently check the DOAC dose upon admission due to a lack of time. A history of bleeding and a fluctuating renal function were the most important factors why advices to adjust the dose were not accepted. Some physicians, less familiar with anticoagulation, preferred to discuss the proposed dosage adjustment with the

GP/cardiologist. In some cases, as depicted in figure 2, renal function altered during hospitalization so no adjustment was needed anymore, even if the advice was already accepted. Other important reasons retrieved from the medical record for non-implementation of accepted advices were the patients' bleeding risk (n=2) and concomitant use of antiplatelet drugs (n=2). Despite the initial acceptance, physicians chose to keep the reduced DOAC dose in these cases after consultation with the head of department. After implementation of the recommended dose adjustments, the total inappropriate prescribing rate according to the SmPC was 8.2% vs. the initial 16.9%, keeping in mind most of these off-label doses were intentional due to the abovementioned reasons.

Some institutions have an integrated pharmacist-led DOAC service or antithrombotic stewardship programs with the aim of improving the safety and efficacy of DOAC use through identification and resolution of dosing errors, patient education, improved patient follow-up and laboratory monitoring [16, 20, 22, 38, 39]. Studies showed that such services increase appropriate DOAC dosing at baseline and follow-up, which is in line with the recommendations of organizations like EHRA and the American College of Cardiology (ACC)[38, 40, 41]. Clinical pharmacists are well positioned to provide recommendations regarding the DOAC choice and dose, presence of a contraindication as well as potential drug-drug and drug-disease interactions [20]. They are also able to inform physicians of patients who may not be the best candidates for DOACs (e.g., extremes of body weight, severe renal impairment)[16]. In addition, they also provide motivational interviewing to promote patient understanding of DOAC therapy and emphasize the importance of DOAC adherence [38].

Involvement of clinical pharmacists should be more mainstream in the hospitals, especially for HRM such as DOACs. Quintens et al. highlighted the greater impact of advices given by telephone since half of the advices were not accepted/read if only an electronic note was left[20]. In addition, a study of Dreijer et al. conducted in patients using anticoagulants showed that implementation of a multidisciplinary antithrombotic team over time significantly reduces adverse drug reactions (ADRs) like bleedings or thrombotic events from hospitalization until three months after hospitalization and resulted in a lower all-cause mortality [42].

A useful recommendation for physicians could be to clearly document the rationale for deviating from the approved dose in the patient's medical record to avoid unnecessary phone calls. Physicians should be aware of the most common mistakes concerning DOAC prescriptions[14].

To our knowledge, this is the first study to assess determinants for DOAC under- and overdosing in AF patients, nevertheless there are limitations to our study. First, this was a single center study, therefore the results may not be generalizable to other populations. Due to the cross-sectional nature of our study, only the initial DOAC prescription of a patient was taken into account. However, the conditions necessitating a DOAC change or dose adaptation during hospitalization were only present in a minority of patients. We also did not examine the effect of inappropriate dosing and the dose adaptations on the thromboembolic/bleeding event rate. In addition, our results may be biased by inaccurate or incomplete information in the electronic medical records. Further, this study was neither directed to identify high risk AF patients who did not receive oral anticoagulants, nor to assess DOAC adherence.

Additional research regarding the long term effects of the clinical pharmacists' interventions is needed. Lastly, it would be of interest for future research to focus on the interventions with the highest impact on patient outcomes and to investigate which patients would benefit most from the implementation of a multidisciplinary clinical DOAC service.

In conclusion, in this study where for the first time determinants for under- and overdosing of DOACs were assessed, inappropriate DOAC prescribing was found to be still common. Interventions by clinical pharmacists can reduce this burden. We recommend that clinical services led by pharmacists play a greater role in assisting physicians during the prescription process of high risk medications such as DOACs, in order to reduce the number of inadequate prescriptions.

Conflict of Interest

The authors declare that they do not have a conflict of interest.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Sanghai S, Wong C, Wang Z, et al. Rates of Potentially Inappropriate Dosing of Direct-Acting Oral Anticoagulants and Associations With Geriatric Conditions Among Older Patients With Atrial Fibrillation: The SAGE-AF Study. *J Am Heart Assoc* . Mar 2020;9(6):e014108. doi:10.1161/JAHA.119.014108

2. Gustafson WL, Saunders J, Vazquez SR, Jones AE, Witt DM. Real-world study of direct oral anticoagulant dosing patterns in patients with atrial fibrillation. *Pharm Pract (Granada)* . 2019 Oct-Dec 2019;17(4):1709.

3. Moudallel S, Steurbaut S, Cornu P, Dupont A. Appropriateness of DOAC Prescribing Before and During Hospital Admission and Analysis of Determinants for Inappropriate Prescribing. *Front Pharmacol* . 2018;9:1220. doi:10.3389/fphar.2018.01220

4. Ezekowitz MD, Spahr J, Ghosh P, Corelli K. Stroke prevention in atrial fibrillation: established oral anticoagulants versus novel anticoagulants-translating clinical trial data into practice. *J Interv Card Electrophysiol* . Sep 2014;40(3):261-8. doi:10.1007/s10840-014-9893-z

5. Armbruster AL, Buehler KS, Min SH, Riley M, Daly MW. Evaluation of dabigatran for appropriateness of use and bleeding events in a community hospital setting. *Am Health Drug Benefits* . Oct 2014;7(7):376-84.

6. Larock AS, Mullier F, Sennesael AL, et al. Appropriateness of prescribing dabigatran etexilate and rivaroxaban in patients with nonvalvular atrial fibrillation: a prospective study. *Ann Pharmacother* . Oct 2014;48(10):1258-68. doi:10.1177/1060028014540868

7. Kucey M, Bolt J, Albers L, Bell A, Iroh N, Toppings J. Prescribing of Direct Oral Anticoagulants in Atrial Fibrillation Based on Estimation of Renal Function Using Standard and Modified Cockcroft-Gault Equations: A Retrospective Analysis. *Can J Hosp Pharm* . 2016 Sep-Oct 2016;69(5):409-414.

8. Pattullo CS, Barras M, Tai B, McKean M, Donovan P. New oral anticoagulants: appropriateness of prescribing in real-world setting.*Intern Med J* . Jul 2016;46(7):812-8. doi:10.1111/imj.13118

9. Steinberg BA, Shrader P, Thomas L, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. *J Am Coll Cardiol* . Dec 2016;68(24):2597-2604. doi:10.1016/j.jacc.2016.09.966

10. Basaran O, Filiz Basaran N, Cekic EG, et al. PRescriptiOn PattERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation (PROPER study). *Clin Appl Thromb Hemost* . May 2017;23(4):384-391. doi:10.1177/1076029615614395

11. Howard M, Lipshutz A, Roess B, et al. Identification of risk factors for inappropriate and suboptimal initiation of direct oral anticoagulants. *J Thromb Thrombolysis* . Feb 2017;43(2):149-156. doi:10.1007/s11239-016-1435-3

12. Shrestha S, Baser O, Kwong WJ. Effect of Renal Function on Dosing of Non-Vitamin K Antagonist Direct Oral Anticoagulants Among Patients With Nonvalvular Atrial Fibrillation. *Ann Pharmacother* . Aug 2017:1060028017728295. doi:10.1177/1060028017728295

13. Whitworth MM, Haase KK, Fike DS, Bharadwaj RM, Young RB, MacLaughlin EJ. Utilization and prescribing patterns of direct oral anticoagulants.*Int J Gen Med* . 2017;10:87-94. doi:10.2147/IJGM.S129235

14. Jacobs MS, van Hulst M, Campmans Z, Tieleman RG. Inappropriate non-vitamin K antagonist oral anticoagulants prescriptions: be cautious with dose reductions. *Neth Heart J* . Jul 2019;27(7-8):371-377. doi:10.1007/s12471-019-1267-9

15. Yu HT, Yang PS, Kim TH, et al. Impact of Renal Function on Outcomes With Edoxaban in Real-World Patients With Atrial Fibrillation. *Stroke* . 10 2018;49(10):2421-2429. doi:10.1161/STROKEAHA.118.021387

16. Shum P, Klammer G, Toews D, Barry A. Anticoagulant Utilization and Direct Oral Anticoagulant Prescribing in Patients with Nonvalvular Atrial Fibrillation. *Can J Hosp Pharm* . 2019 Nov-Dec 2019;72(6):428-434.

17. Jang BM, Lee OS, Shin EJ, et al. Factors related to inappropriate edoxaban use. *J Clin Pharm Ther* . Oct 2019;44(5):760-767. doi:10.1111/jcpt.12999

18. Angel Y, Zeltser D, Berliner S, et al. Hospitalization as an opportunity to correct errors in anticoagulant treatment in patients with atrial fibrillation. *Br J Clin Pharmacol* . 12 2019;85(12):2838-2847. doi:10.1111/bcp.14116

19. Antoniazzi S, Ardoino I, Proietti M, et al. Appropriateness of prescription of oral anticoagulant therapy in acutely hospitalized older people with atrial fibrillation. Secondary analysis of the SIM-AF cluster randomized clinical trial. *Br J Clin Pharmacol* . 09 2019;85(9):2134-2142. doi:10.1111/bcp.14029

20. Quintens C, De Rijdt T, Van Nieuwenhuyse T, et al. Development and implementation of "Check of Medication Appropriateness" (CMA): advanced pharmacotherapy-related clinical rules to support medication surveillance. *BMC Med Inform Decis Mak* . 02 2019;19(1):29. doi:10.1186/s12911-019-0748-5

21. Barnes GD, Nallamothu BK, Sales AE, Froehlich JB. Reimagining Anticoagulation Clinics in the Era of Direct Oral Anticoagulants. *Circ Cardiovasc Qual Outcomes* . Mar 2016;9(2):182-5. doi:10.1161/CIRCOUTCOMES.115.002366

22. Uppuluri EM, McComb MN, Shapiro NL. Implementation of a Direct Oral Anticoagulation Screening Service at a Large Academic Medical Center Provided by a Pharmacist-managed Antithrombosis Clinic as a Method to Expand Antithrombotic Stewardship Efforts. *J Pharm Pract* . Jun 2020;33(3):271-275. doi:10.1177/0897190018799200

23. Boswell R, Bungard TJ. More than Just Chasing INRs: Patient-Centred Care in an Anticoagulation Clinic. *Can J Hosp Pharm* . 2015 May-Jun 2015;68(3):254-7. doi:10.4212/cjhp.v68i3.1460

24. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* . Mar 2014;383(9921):955-62. doi:10.1016/S0140-6736(13)62343-0

25. Cools F, Wollaert B, Vervoort G, et al. Treatment patterns in anticoagulant therapy in patients with newly diagnosed atrial fibrillation in Belgium: results from the GARFIELD-AF registry. *Acta Cardiol* . Aug 2019;74(4):309-318. doi:10.1080/00015385.2018.1494089

26. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol* . Jun 2017;69(23):2779-2790. doi:10.1016/j.jacc.2017.03.600

27. Bendayan M, Mardigyan V, Williamson D, et al. Muscle Mass and Direct Oral Anticoagulant Activity in Older Adults With Atrial Fibrillation. *J Am Geriatr Soc* . Jan 2021;doi:10.1111/jgs.16992

28. Lip GYH, Keshishian A, Li X, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. *Stroke* . 12 2018;49(12):2933-2944. doi:10.1161/STROKEAHA.118.020232

29. Chan YH, Lee HF, See LC, et al. Effectiveness and Safety of Four Direct Oral Anticoagulants in Asian Patients With Nonvalvular Atrial Fibrillation. *Chest* . 09 2019;156(3):529-543. doi:10.1016/j.chest.2019.04.108

30. Van Ganse E, Danchin N, Mahe I, et al. Comparative Safety and Effectiveness of Oral Anticoagulants in Nonvalvular Atrial Fibrillation: The NAXOS Study. *Stroke* . Jul 2020;51(7):2066-2075. doi:10.1161/STROKEAHA.120.028825

31. Grymonprez M, Steurbaut S, De Backer TL, Petrovic M, Lahousse L. Effectiveness and Safety of Oral Anticoagulants in Older Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Front Pharmacol* . 2020;11:583311. doi:10.3389/fphar.2020.583311

32. Beyer-Westendorf J, Forster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* . Aug 2014;124(6):955-62. doi:10.1182/blood-2014-03-563577

33. Turpie AGG, Purdham D, Ciaccia A. Nonvitamin K antagonist oral anticoagulant use in patients with renal impairment. *Ther Adv Cardiovasc Dis* . Sep 2017;11(9):243-256. doi:10.1177/1753944717714921

34. Miyazaki M, Matsuo K, Uchiyama M, et al. Inappropriate direct oral anticoagulant dosing in atrial fibrillation patients is associated with prescriptions for outpatients rather than inpatients: a single-center retrospective cohort study. *J Pharm Health Care Sci* . 2020;6:2. doi:10.1186/s40780-020-0157-z

35. Yoshikawa A, Ramirez G, Smith ML, et al. Opioid Use and the Risk of Falls, Fall Injuries and Fractures among Older Adults: A Systematic Review and Meta-Analysis. *J Gerontol A Biol Sci Med Sci* . Feb 2020;doi:10.1093/gerona/glaa038

36. Seppala LJ, van de Glind EMM, Daams JG, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *J Am Med Dir Assoc* . 04 2018;19(4):372.e1-372.e8. doi:10.1016/j.jamda.2017.12.099

37. Walenga JM, Adiguzel C. Drug and dietary interactions of the new and emerging oral anticoagulants. *Int J Clin Pract* . Jun 2010;64(7):956-67. doi:10.1111/j.1742-1241.2009.02286.x

38. Ashjian E, Kurtz B, Renner E, Yeshe R, Barnes GD. Evaluation of a pharmacist-led outpatient direct oral anticoagulant service. *Am J Health Syst Pharm* . Apr 2017;74(7):483-489. doi:10.2146/ajhp151026

39. Hendriks JM, de Wit R, Crijns HJ, et al. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J* . Nov 2012;33(21):2692-9. doi:10.1093/eurheartj/ehs071

40. Kovacs RJ, Flaker GC, Saxonhouse SJ, et al. Practical management of anticoagulation in patients with atrial fibrillation. *J Am Coll Cardiol* . Apr 2015;65(13):1340-1360. doi:10.1016/j.jacc.2015.01.049

41. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace* . 08 2018;20(8):1231-1242. doi:10.1093/europace/euy054

42. Dreijer AR, Kruip MJHA, Diepstraten J, et al. Effect of antithrombotic stewardship on the efficacy and safety of antithrombotic therapy during and after hospitalization. *PLoS One* . 2020;15(6):e0235048. doi:10.1371/journal.pone.0235048

Table 1 Baseline characteristics of the hospitalized AF patients per DOAC. IQR= interquartile range; BMI= body mass index; SSRIs= selective serotonine reuptake inhibitors.

Characteristics	**RIVAROXABAN (n=402)**	**DABIGATRAN (n=148)**	**EDOXABAN (n=552)**	**APIXABAN (n=586)**	**p-value**
Age (years), median (IQR)	77.0 (70.0-84.3)	76.0 (68.0-84.0)	72.0 (60.0-82.0)	81.0 (72.0-87.0)	<0.01
Male gender, n (%)	240 (59.7)	85 (57.4)	316 (57.2)	285 (48.6)	<0.01
Weight (kg), median (IQR)	78.9 (67.0-90.0) 48	79.0 (67.0-90.0) 18	77.0 (65.0-89.3) 78	70.1 (59.5-85.0) 147	<0.01 <0.01
<60 kg, n (%)	(11.9)	(12.2)	(14.1)	(25.1)	

BMI (kg/m^2), median (IQR)	27.3 (24.0-31.0) 8	27.0 (24.2-30.9) 1	26.6 (23.0-30.1) 17	25.4 (22.0-29.7) 28	<0.01 0.02 0.04
BMI <18 kg/m^2, n (%)	(2.0) 116 (28.9)	(0.7) 43 (29.1)	(3.1) 135 (24.5)	(4.8) 127 (21.7)	
BMI >30 kg/m^2, n (%)					
Residential care center, n (%)	40 (10.0)	20 (13.5)	42 (7.6)	91 (15.5)	<0.01
Preadmission medication, n (%)	328 (81.6)	127 (85.8)	295 (53.4)	410 (70.0)	
Surgery during hospital stay, n (%)	159 (39.6)	54 (36.5)	255 (46.2)	156 (26.6)	<0.01
Bioprosthetic heart valve n, (%)	31 (7.7)	4 (2.7)	23 (4.2)	31 (5.3)	0.04
Renal function (mL/min), median (IQR)	67.0 (48.0-88.0) 25 (6.2) 82 (20.4)	69.0 (51.5-91.5) 6 (4.1) 26 (17.6)	76.0 (53.0-104.0) 22 (4.0) 83 (15.0)	52.0 (36.0-74.0) 86 (14.7) 189 (32.3) 307 (52.4) 4 (0.7)	<0.01 <0.01 <0.01 <0.01
<30 mL/min, n (%) 30-49 mL/min, n (%) [?]50 mL/min, n (%) Missing, n (%)	291 (72.4) 4 (1.0)	113 (76.4) 3 (2.0)	442 (80.1) 5 (0.9)		
Co-morbidities n, (%)	280 (69.7) 112 (27.9) 112 (27.9) 45 (11.2)	105 (70.9) 36 (24.3) 42 (28.4) 8 (5.4)	352 (63.8) 113 (20.5) 122 (22.1) 42 (7.6)	428 (73.0) 153 (26.1) 208 (35.5) 68 (11.6)	<0.01 0.04 <0.01 0.03
Hypertension Diabetes Heart failure Cancer					
Co-medication n, (%)	172 (42.8) 60 (14.9) 195 (48.5) 103 (25.6) 104 (25.9) 31 (7.7)	83 (56.1) 18 (12.2) 71 (48.0) 43 (29.1) 37 (25.0) 20 (13.5)	225 (40.8) 53 (9.6) 212 (38.4) 91 (16.5) 119 (21.6) 40 (7.2)	244 (41.6) 97 (16.6) 294 (50.2) 104 (17.7) 148 (25.3) 60 (10.2)	<0.01 <0.01 <0.01 <0.01 0.42 0.06
Lipid lowering Levothyroxine Gastrointestinal Narcotic analgesics Benzodiazepines SSRIs					

Concomitant use of antiplatelets n, (%) Aspirin Clopidogrel Ticagrelor Aspirin + clopidogrel Aspirin + ticagrelor	95 (23.6) 72 (17.9) 15 (3.7) / 6 (1.5) 2 (0.5)	18 (12.2) 12 (8.1) 4 (2.7) 1 (0.7) 1 (0.7) /	86 (15.6) 66 (12.0) 14 (2.5) / 6 (1.1) /	128 (21.8) 78 (13.3) 30 (5.1) 1 (0.2) 19 (3.2) /	<0.01
Thrombocytopenia n, (%)	57 (14.2)	25 (16.9)	60 (10.9)	97 (16.6)	0.04
Anaemia n, (%)	198 (49.3)	61 (41.2)	172 (31.2)	277 (47.3)	<0.01
History of bleeding n, (%)	56 (13.9)	14 (9.5)	58 (10.5)	100 (17.1)	<0.01
CHA_2DS_2-VASc, median (IQR)	4 (3-5)	4 (3-5)	3 (2-5)	4 (3-5)	<0.01
HASBLED, median (IQR)	2 (1-3)	2 (2-3)	2 (1-3)	2 (2-3)	<0.01

Table 2 Significant (white) and non-significant (grey) determinants for under- and overdosing for all DOACs and per DOAC. DOAC= direct oral anticoagulant; REF= reference category; adj. OR= adjusted odds ratio; CI= confidence interval; CrCl= creatinine clearance. The p-value was corrected with Benjamini-Hochberg correction for multiple testing.

Determinants UNDER-DOSING	*Corrected p-value*	*Adj. OR*	*95% CI*	*Determinants OVER-DOSING*	*Corrected p-value*	*Adj. OR*	*95% CI*
All DOACs	All DOACs	All DOACs	All DOACs	All DOACs	All DOACs	All DOACs	All DOACs
Age [?]80 years	0.43	0.83	0.56-1.21	Age [?]80 years	0.16	0.60	0.36-1.02
Benzodiazepines	0.34	1.22	0.84-1.78	Male sex	0.90	1.19	0.72-1.97
Diabetes	0.64	1.09	0.73-1.63	Surgery	0.16	0.61	0.35-1.06
CHA_2DS_2-VASc	0.08	1.17	1.05-1.30	CHA_2DS_2-VASc	0.43	0.92	0.76-1.10
Heart failure	0.55	1.12	0.77-1.64	Weight <60 kg [?]60 kg (REF)	<0.01	2.34	1.42-3.85
Weight <60 kg [?]60 kg (REF)	0.02	0.46	0.27-0.77	DOAC Dabigatran Apixaban Rivaroxaban (REF)	0.04 <0.01	0.24 0.18	0.08-0.71 0.10-0.32

Determinants UNDER-DOSING	*Corrected p-value*	*Adj. OR*	*95% CI*	*Determinants OVER-DOSING*	*Corrected p-value*	*Adj. OR*	*95% CI*
DOAC Edoxaban Rivaroxaban (REF)	<0.01	0.42	0.24-0.74	Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	<0.01	11.29	6.23-20.45
Surgery	0.05	0.57	0.37-0.87				
Narcotic analgesics	0.04	1.67	1.13-2.46				
Bleeding history	0.02	1.86	1.24-2.80				
Initiation at hospital	<0.01	0.45	0.29-0.71				
DABIGATRAN	DABIGATRAN	DABIGATRAN	DABIGATRAN	DABIGATRAN	DABIGATRAN	DABIGATRAN	DABIGATRA
Diabetes	0.14	2.79	0.94-8.29	Weight <60 kg [?]60 kg (REF)	0.27	4.14	0.48-35.49
Narcotic analgesics	0.06	3.52	1.23-10.12	Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	0.16	8.08	0.73-88.84
RIVAROXABAN	RIVAROXABAN	RIVAROXABAN	RIVAROXABAN	RIVAROXABAN	RIVAROXABAN	RIVAROXABAN	RIVAROXABA
Surgery	0.30	0.63	0.30-1.32	Age [?]80 years	0.16	0.43	0.16-1.14
Bleeding history	0.29	1.68	0.74-3.77	Weight <60 kg [?]60 kg (REF)	0.48	1.47	0.60-3.62
Initiation at hospital	0.08	0.21	0.05-0.91	CHA_2DS_2-VASc	0.26	0.82	0.62-1.09
Age [?]80 years	0.06	2.34	1.15-4.74	Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	<0.01	100.95	23.23-438.70
Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	<0.01	0.17	0.06-0.48				
APIXABAN	APIXABAN	APIXABAN	APIXABAN	APIXABAN	APIXABAN	APIXABAN	APIXABAN

Determinants UNDER-DOSING	*Corrected p-value*	*Adj. OR*	*95% CI*	*Determinants OVER-DOSING*	*Corrected p-value*	*Adj. OR*	*95% CI*
Hypertension	0.46	1.32	0.72-2.43	Age [?]80 years	0.51	0.62	0.19-2.07
Diabetes	0.21	1.50	0.89-2.52	Weight <60 kg [?]60 kg (REF)	0.56	1.34	0.57-3.19
Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	0.08	1.80	1.06-3.04	Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	0.08	4.37	1.13-16.91
Heart failure	0.08	1.78	1.07-2.96	Surgery	0.26	0.25	0.03-1.92
Weight <60 kg [?] 60 kg (REF)	<0.01	0.26	0.12-0.55	Heart failure	0.64	1.27	0.52-3.10
Bleeding history	0.03	2.14	1.22-3.75	CHA_2DS_2-VASc	0.90	0.98	0.68-1.41
				HAS-BLED	0.26	1.42	0.85-2.35
EDOXABAN	EDOXABAN	EDOXABAN	EDOXABAN	EDOXABAN	EDOXABAN	EDOXABAN	EDOXABAN
Surgery	0.20	0.36	0.10-1.33	Surgery	0.13	0.48	0.20-1.18
Initiation at hospital	0.12	0.36	0.12-1.03	CHA_2DS_2-VASc	0.23	0.79	0.58-1.08
HAS-BLED	0.90	0.96	0.52-1.77	HAS-BLED	0.56	1.02	0.64-1.63
CHA_2DS_2-VASc	0.08	1.48	1.02-2.14	Male sex	0.16	0.52	0.24-1.12
Narcotic analgesics	0.08	2.98	1.14-7.80	Weight <60 kg [?] 60 kg (REF)	<0.01	4.16	1.97-8.77
				Renal function (CrCl) <50 mL/min [?]50 mL/min (REF)	0.01	3.25	1.49-7.12

Figure 1 Appropriate vs. inappropriate (contraindication, under-and overdosing) prescribing rates per DOAC

Figure 2 Overview of the number of phone calls conducted for inappropriate DOAC prescriptions, accepted advices and implemented advices. Reasons for not contacting the physician in case of inappropriate prescriptions as well as reasons for non-acceptance and non-implementation of the pharmacists' interventions are listed in the orange boxes. SAPT= single antiplatelet therapy; DAPT= dual antiplatelet therapy; DOAC= direct oral anticoagulant; GP= general practitioner. *The appropriateness of 7 prescriptions could not be assessed due to lack of renal function data