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Appropriateness of Prescribing Dabigatran Etexilate and Rivaroxaban in Patients With Nonvalvular Atrial Fibrillation: A Prospective Study

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Abstract

Background: Direct oral anticoagulants have been developed to address some of the drawbacks of vitamin-K antagonists. However, special attention should be given when using these drugs, especially in patients with renal insufficiency, questionable compliance, and those at high risk of bleeding. **Objective:** To evaluate the appropriateness of prescribing dabigatran etexilate (DE) and rivaroxaban in patients with nonvalvular atrial fibrillation (NVAF) in real-life clinical practice. **Methods:** This was a prospective study that included patients presenting to a teaching hospital from April to mid-October 2013, who were taking rivaroxaban or DE for NVAF. Appropriateness of prescribing was evaluated using 9 of the 10 criteria of the Medication Appropriateness Index. The primary outcome measure was the prevalence of inappropriate prescribing. Secondary outcome measures included (*a*) categories of inappropriateness, (*b*) prevalence of adverse drug events, and (*c*) interventions made by a clinical pharmacist to optimize prescribing. **Results:** A total of 69 patients were evaluated; 16 patients (23%) had 1 inappropriate criterion, and an additional 18 (26%) had more than 1 inappropriate criterion. The most frequent inappropriate criteria were inappropriate choice (28% of patients), wrong dosage (26%), and impractical modalities of administration (26%). An adverse event (AE) was found in 51% of patients (including 8 patients with transient ischemic attack/stroke). The clinical pharmacists performed 48 interventions, and 94% were accepted by the physician. **Conclusions**: Inappropriate use of DE and rivaroxaban in patients with NVAF is frequent and possibly leads to AEs. Reinforcing education of health care professionals and patients is needed. Collaboration with clinical pharmacists can contribute to better use.

Keywords

dabigatran etexilate, rivaroxaban; atrial fibrillation, medication errors, drug-related side effects and adverse reactions

Introduction

Until recently, vitamin K antagonists (VKAs) were the only anticoagulants available for oral use in the prevention and treatment of thromboembolism. These are highly effective but have numerous limitations, including unpredictable anticoagulant response, need for regular therapeutic monitoring and dose adjustments, and drug interactions. Direct oral anticoagulant drugs (DOACs) have been developed in order to address some of the drawbacks of VKAs.[1] The advantages of DOACs over VKAs are a predictable therapeutic effect allowing a fixed-dose regimen, no drug monitoring, and fewer drug interactions.

However, the optimal use of DOACs in real life remains challenging for different reasons. First, the fixed-dosing strategy is erroneous because there are multiple dose regimens for the different indications and for some specific populations, including older patients, patients with renal insufficiency, or those taking interacting drugs.[2,3] Moreover, there are international variations in approved indications, dosages, and dosage forms (Appendix A). Second, the

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initial belief that therapeutic drug monitoring was useless is now highly debated. Point measurement is currently proposed in some specific situations (such as urgent surgery, stroke recurrence, and cardioversion).[4-6] Third, patient adherence could be decreased by the lack of regular drug monitoring.[3,7,8]

Deviations from the recommended use have been reported, sometimes leading to serious adverse events (AEs). A few studies have suggested that inappropriate use of DOACs might be an important concern, but the evaluations were retrospective, limited to dabigatran etexilate (DE), and in most cases, they addressed a single dimension of inappropriateness (indication or dosage).[9-12] A comprehensive evaluation of the appropriateness of prescribing DOACs has not yet been performed. Our objective was to prospectively evaluate the appropriateness of prescribing DE and rivaroxaban in patients with nonvalvular atrial fibrillation (NVAF) in real-life clinical practice.

Materials and Methods

Design, Setting, and Participants

We performed a prospective study in a 450-bed university hospital (CHU Dinant-Godinne UCL Namur, Belgium) between April and mid-October 2013. In collaboration with the Namur Thrombosis and Hemostasis Center, the hospital has been involved in research projects dealing with the development and validation of biological tests to monitor the effect of DOACs.[13,14] These tests are available to clinicians on request, and the laboratory provides support for interpretation of results. This is not yet part of routine practice in Belgium.

We recruited all patients who were taking rivaroxaban or DE at home and/or during their hospital stay for NVAF. The prescriber could be a general practitioner or a specialist physician. Patients receiving rivaroxaban or DE during their hospital stay were identified through the computerized prescribing order entry system. Outpatients presenting to the laboratory for specific monitoring of DOACs were also included. Outpatients without specific monitoring could not be easily identified and were, therefore, not included. Apixaban was not considered because this drug was not reimbursed in NVAF at the time of the study. The local ethics committee gave approval for this study. Each participant provided informed consent before inclusion.

Baseline Data Collection

All the data were collected at one point in time. Data were first retrieved from the electronic medical record. Then, a clinical pharmacist (ASL or ALS) interviewed each patient to collect detailed information about their current and past drug history and about medical data relevant for the purpose of the study using a piloted data collection form. The general practitioner, the community pharmacist, or the family was contacted in case of missing data.

Clinical data that were relevant for the evaluation of appropriateness were recorded: (*a*) medical history (atrial fibrillation, myocardial infarction, diabetes, ischemic stroke, haemorrhagic stroke, dementia, hypertension, cancer); (*b*) HAS-BLED bleeding risk score (involving hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol); and (*c*) CHA_2DS_2-VASc score (thrombotic risk score involving congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65-74 years, and sex).

AEs were detected by asking the patient and/or general practitioner/specialist physician questions about the occurrence of any side effect as well as specific questions on the occurrence of bleeding or thrombotic events and on the occurrence of dyspepsia. For inpatients, we recorded AEs occurring during hospital stay as well as before hospital admission. Evaluation of probability took into account different elements: previous reports on the AE, time course, plasma concentration of the drug, result of dechallenge, and alternative causes.

Outcome Measures

The primary outcome measure was the prevalence of inappropriate prescribing—namely, the proportion of patients with ≥1 inappropriate criterion. Secondary outcome measures included (*a*) description of the main categories of inappropriate prescribing, (*b*) the prevalence of AEs and their relationship to inappropriate prescribing, and (*c*) a description of interventions made by the clinical pharmacist to optimize prescribing. Finally, we performed descriptive subgroup analysis according to age, drug, and VKA status.

Appropriateness of Prescribing. Evaluation of the appropriateness of prescribing was performed using the Medication Appropriateness Index (MAI). The MAI is a tool designed to measure appropriateness of prescribing for people 65 years and older using 10 criteria: indication, choice, dosage, modalities and practicability of administration, drug-drug interactions, drug-disease interactions, duplication, duration, and cost-effectiveness. For each criterion, the evaluator has to rate if the medication is (A) appropriate, (B) inappropriate but with limited clinical importance, (C) inappropriate, or (Z) insufficient information to evaluate appropriateness.[15] Only the inappropriate ratings (C) were considered for the primary outcome measure. The MAI has been used by different research teams worldwide and is

considered to be one of the most comprehensive tools to evaluate inappropriate prescribing of medications in older people.[16] The MAI was previously validated and used in our hospital.[17,18] For the present study, the MAI was adapted to DOAC prescribing: explicit instructions for the evaluation of each criterion were developed, based on information from the summary of product characteristics and international and local guidelines (Appendix B). Because of limited and sometimes controversial data on the cost-effectiveness of DE and rivaroxaban in Belgium and elsewhere, the tenth criterion related to cost-effectiveness was not considered for this analysis.[19,20]

In a pilot phase, the adapted MAI was applied separately by 2 clinical pharmacists (ASL and AS) on 7 patients. Discrepancies were discussed, and clarifications were added to the instructions to improve interrater reliability. For example, there were discrepancies on the criterion "indication" because of the term *nonvalvular* atrial fibrillation. After discussion with our cardiologists, we agreed that DOAC prescribing in patients with severe valvular insufficiency or in patients with a prosthetic valve would be considered as inappropriate for the "indication" criterion. This was done as an iterative process and no κ coefficient was calculated.

Clinical Pharmacy Interventions. As part of the work performed by clinical pharmacists in our hospital, 2 clinical pharmacists (ASL and ALS) were responsible for reviewing the use of DOACs in individual patients. Whenever the clinical pharmacists identified opportunities for improvement, they made specific proposals to the physician in charge. Interventions were transcribed in the electronic medical record and classified using a form validated and used routinely by clinical pharmacists in our hospital.

Analysis

Microsoft Office Excel for Windows was used to analyze descriptive statistics (median, mean, SD, range, and percentage).

Results

A total of 71 patients met the eligibility criteria. Two patients had to be excluded (one refused to consent, and another died before data collection—the death was unrelated to the DOAC), leaving 69 patients for data collection and analysis. Among the patients, 31% had normal weight (BMI = 20-25 kg/m²), 35% were overweight (25-30 kg/m²), and 31% were obese (>30 kg/m²). Five patients (7%) weighed ≥110 kg. One patient (1.5%) had severe renal failure (creatinine clearance [CrCl] < 30 mL/min), 18% had moderate renal impairment (CrCl = 30-49 mL/min), and 46% had mild renal impairment (CrCl = 50-80 mL/min). Also, 90% of patients were taking at least 5 drugs, and 41% were taking more than 10 drugs. Table 1 lists baseline patient characteristics.

It was found that 34 patients (49%) had at least 1 inappropriate rating; 16 patients (23%) had 1 inappropriate criterion, and 18 (26%) had more than 1 inappropriate criterion. Also, 8 patients had 6 inappropriate criteria. For these patients, the criterion "indication" was considered as inappropriate because of a valvular disease (n = 5), a bioprosthetic heart valve (n = 2), or an off-label indication (n = 1; secondary prevention of deep vein thrombosis in a patient with AF). Therefore, criteria 2, 3, 4, 5, and 9 were also rated as inappropriate according to the instructions of the MAI.

Table 2 lists the results on appropriateness per criterion and provides additional information on inappropriate ratings. The most frequent inappropriate criteria were choice (28% of cases), dosage (26%), practicability of administration (26%), and modalities of administration (23%). Concerning the criteria evaluated as "inappropriate but with limited clinical importance" (category B), a relatively high proportion were observed (Table 2) for criteria 2 (choice, 33%) and 6 (drug-drug interaction, 91%).

At least 1 inappropriate criterion was observed in 57% and 41% of patients taking rivaroxaban and DE, respectively; 56% (21/37) of patients younger than 75 years had at least 1 inappropriate criterion compared with 41% (13/32) of patients aged ≥75 years. Of 31 VKA-naïve patients 12 (39%) had at least 1 inappropriate criterion in comparison with 58% (22/38) of patients with previous VKA intake (Appendix C).

An AE was found in 32 (51%) patients, among whom 5 (8%) had more than 1 AE (6 patients have been excluded from AE evaluation because of treatment inclusion). It was found that 8 patients (12%) had a stroke or transient ischemic attack (TIA) while they were taking rivaroxaban (n = 4) or DE (n = 4); 5 of these patients presented with inappropriate modalities of administration (ie, 2 capsules of DE once daily, rivaroxaban taken on an empty stomach, and poor compliance), leading to a nonoptimal anticoagulant coverage. Table 3 lists all types of AEs reported. There was a trend toward a higher risk of adverse drug event (ADE; any ADE, thrombotic ADE, and hemorrhagic ADE) in the group of patients with ≥1 inappropriate rating as compared with patients without inappropriate rating. For example, 21% (7/33) of patients with ≥1 inappropriate rating had a thrombotic event as compared with 10% (3/30) of patients without an inappropriate rating.

The clinical pharmacist performed 48 interventions during the study period, for 36 (52%) patients (Table 4); 24 patients had 1 intervention, and 12 patients benefited from 2 interventions. In the majority of the cases (94%), the intervention was accepted by the physician.

Table 1. Baseline Characteristics (n = 69).

Characteristics	All Patients (n = 69)	Rivaroxaban (n = 35)	Dabigatran (n = 34)
Age			
Median, range (years)	74, 45-89	73, 46-89	75, 45-89
≥75 years, n (%)	33 (48)	16 (46)	17 (50)
Female:Male, n (%)	26:43 (38:62)	12:23 (34:66)	14:20 (41:59)
Weight, median, range (kg)	78, 52-151	83, 56-151	77, 52-140
BMI, mean ±SD (kg/m²)	29 ± 6	30 ± 7	28 ± 6
CrCl (CG), mean ± SD (mL/min)	76 ± 31	75 ± 33	77 ± 30
CrCl (MDRD), mean ± SD (mL/min)	74 ± 26	70 ± 22.5	78 ± 28
Inpatient:Outpatient, n (%)	66:3 (96:4)	32:3 (91:9)	34:0 (100:0)
Clinical data, n (%)			
Ischemic stroke	21 (30)	11 (30)	10 (29)
Heart failure	12 (17)	8 (23)	4 (12)
Hypertension	49 (71)	25 (71)	24 (71)
Vascular disease[a]	31 (45)	19 (54)	12 (35)
Diabetes mellitus	14 (20)	7 (20)	7 (21)
Cancer	7 (10)	4 (11)	3 (9)
Hepatic failure (Child Pugh B/C)	2 (3)	0 (0)	2 (6)
Renal failure (CrCl < 30 mL/min)	1 (1.5)	1 (3)	0 (0)
Previous bleeding	16 (23)	9 (26)	7 (21)
CHA_2DS_2-VASc, mean ± SD	4.1± 1.5	4.0 ± 2	4.1 ± 1
HAS-BLED, mean± SD	2.3 ± 1.1	2.3 ± 1.2	2.4± 1.1
Drugs			
Number of drugs, median (range)	8 (2-17)	8 (2-14)	9 (3-17)
Previous anticoagulant, n (%)			
Previous VKA	38 (55)	16 (46)	22 (65)
Previous DOAC	6 (9)	3 (9)	3 (9)
Current treatment			
Aspirin	28 (41)	14 (40)	14 (41)
Clopidogrel	2 (3)	1 (3)	1 (3)
NSAID	5 (7)	3 (9)	2 (6)

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; CG, Cockroft-Gault; MDRD, Modification of Diet in Renal Disease; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug.
[a]Vascular disease: prior myocardial infarction, peripheral artery disease, and aortic plaque.

Discussion

This study shows that inappropriate prescribing of DOACs is frequent because almost half of patients met at least 1 criterion for inappropriateness. Choice of drug, dosage, and practicality of administration were each found to be inappropriate in more than one-fourth of patients.

With regard to indication, off-label use was frequent, similar to that in previous studies. A study evaluating trends in oral anticoagulation use in the United States demonstrated that DE had been rapidly adopted into ambulatory practice, but increasingly for off-label indications.[21] Retrospective audits in the United States and Australia reported off-label use in 8% to 20% of patients.[10,12] A Danish study reported that only 56% of patients treated with DE 150 mg twice daily were treated in a manner consistent with recommendations set by the European Medicines Agency (EMA).[11]

Both rivaroxaban and DE are not recommended in patients with extreme weight (<50 kg and >110-120 kg) because of missing data, and we considered the choice of drug to be inappropriate in these patients. A total of 5 patients (7%) weighing more than 110 kg were treated with DE (n = 4) and rivaroxaban (n = 1), and 2 of these presented with stroke/TIA (one on DE, one on rivaroxaban). A previous case of stroke in an obese patient has been reported.[22] In the absence of dose regimen recommendations in this population, dose adjustment and a personalized monitoring may be necessary.[4] Further study is necessary to assess the safety and efficacy of DOACs in these populations before wider adoption into practice.

Table 2. Detailed Ratings of Appropriateness Using the MAI (n=69).

Criterion	Rating[a] (n)				Percentage	Additional Information on Inappropriate (C) Ratings
	A	B	C	Z	C	
1. Indication	56	5	8	0	12	Valvular disease (n = 5); bioprosthetic heart valve (n = 2); secondary prevention of deep vein thrombosis (n = 1)
2. Choice	19	29	19	2	28	VKA first choice (n = 8), for example, as a result of suboptimal compliance, extreme weight; other DOAC first choice (n = 3), for example, as a result of renal insufficiency (with DE) or swallowing problems (DE); inappropriate indication (n = 8)[b]
3. Dosage	40	8	18	3	26	Too high (n = 3); too low (n = 7); inappropriate indication (n = 8)[b]
4. Modalities of administration, correct	34	14	16	5	23	Rivaroxaban not taken with food (n = 5); DE taken once daily (n = 3); inappropriate indication (n = 8)[b]
5. Modalities of administration, practical	46	0	18	5	26	DE twice daily in patient with poor compliance or swallowing difficulties; inappropriate indication (n = 8)[b]
6. Drug-drug interaction	5	63	1	0	1	Rivaroxaban + aspirin + simvastatin + amiodarone and evidence of bleeding
7. Drug-disease interaction	54	12	1	2	1	Rivaroxaban in a patient with esophageal varices
8. Duplication	67	2	0	0	0	—
9. Duration	61	0	8	0	12	Inappropriate indication (n = 8)[b]

Abbreviations: MAI, Medication Appropriateness Index; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; DE, dabigatran etexilate.
[a](A) appropriate, (B) inappropriate but with little clinical importance, (C) inappropriate, (Z) insufficient information to evaluate appropriateness.
[b]According to the instructions of the MAI, when indication is rated as inappropriate, criteria 2, 3, 4, 5, and 9 were also rated as inappropriate.

Table 3. Prevalence of Adverse Events.

Adverse Events	Patients, n (%) (N = 69)	Patients With ≥1 Inappropriate Criterion, n (N = 34)	Patients Taking Rivaroxaban, n (N = 35)	Patients Taking Dabigatran, n (N = 34)
Thromboembolic events				
Stroke/TIA	8 (12)	6	4	4
DVT/PE	1 (1)	1	0	1
Recurrent atrial thrombus	1 (1)	0	0	1
Bleedings				
Epistaxis	3 (4)	0	1	2
Melena, hematemesis	1 (1)	1	1	0
Anemia	1 (1)	1	1	0
Gynecological bleeding	1 (1)	1	1	0
Gingival bleeding	2 (3)	1	1	1
Hemoptysis	1 (1)	1	1	0
Hemorrhagic shock[a]	1 (1)	0	0	1
Death[b]	1 (1)	1	1	0
Other (hematomes, noncharacteristic bleedings)	7 (10)	5	6	1
Miscellaneous				
Dyspepsia	7 (10)	6	2	5
Vomiting	1 (1)	0	0	1
Diarrhea	1(1)	1	1	0

Abbreviations: TIA, transient ischemic attack; DVT, deep venous thrombosis; PE, pulmonary embolism.
[a]Hemorrhagic and cardiogenic shock during an atrial fibrillation ablation procedure.
[b]Evaluation by the Belgian pharmacovigilance center pending.

Table 4. Types of Interventions Made by the Clinical Pharmacists (n = 48).

Clinical Pharmacy Interventions	n
Therapeutic education of the patient	15
Request for specific coagulation assay	13
Switch to another OAC	11
Dose adjustment	4
Discontinuation of DOAC	2
Discontinuation/Modification of a concomitant drug because of a PK/PD interaction	2
Modification of modalities of administration	1

Abbreviations: OAC, oral anticoagulant; DOAC, direct oral anticoagulant; PK, pharmacokinetic; PD, pharmacodynamic.

With regard to dosage, our results are similar to those of a drug use evaluation of DE in a hospital in the United Arab Emirates, where the dosage was inappropriate in 25% of patients with NVAF.[9] Surprisingly, we had more events of too low dosages as compared with too high dosages. This suggests that prescribers might be too cautious and decide to prescribe lower doses when they fear bleeding, but drug efficacy might then be impaired. Further research is needed to address this issue. Dose adjustment should be carefully considered in older patients, in renal insufficiency, and in case of drug interactions. Several cases of severe bleeding (sometimes leading to death) have been reported in older patients taking DE.[23,24] DOACs should be used with great caution in patients with CrCl between 15 and 30 mL/min. Such patients were excluded from the phase 3 clinical trials, and recommendations on dosage adjustments were approved based on pharmacokinetic studies in small populations.

In addition to dosage problems, dose regimen was frequently inappropriate. This can be explained partly by multiple dose regimens for the different indications and for some specific populations. Some patients reported taking 2 capsules of DE once a day, others did not observe the interval of 12 hours between 2 doses of DE, and one of these patients was admitted with TIA.

Poor compliance was identified in 16% of patients, and in these patients, "choice of medicine" and/or "modalities of administration, practical" were rated as inappropriate. Few studies have addressed the issue of compliance with DOAC.[3,7,8] The noncompliance rate with DOACs could reach 50% because it is the case with cardiovascular medications for chronic use.[7] The absence of symptoms, the absence of regular monitoring with DOAC, a twice-daily intake (DE, apixaban), and gastrointestinal AEs (dyspepsia with DE) could contribute to poor compliance. Our results

highlight that optimizing compliance in patients taking DOACs is essential.

Few prescriptions were inappropriate with regard to drug-drug interactions. However, there was a large proportion of "B ratings" (91% of patients)—namely, potential drug interactions without AEs at the time of evaluation. For example, 26 (38%) patients were taking amiodarone, a strong inhibitor of CYP3A4 (cytochrome P450 3A4) and P-gp (P-glycoprotein). Current data have shown clinically significant interactions for DOACs with some drugs but not with others.[25] In most cases, caution is recommended, but there is no formal contraindication.[26] Further data on the frequency and severity of drug interactions are needed.

Almost half of the patients experienced an AE, including 8 patients who had a stroke or TIA while on DOACs. This could raise concern about effective anticoagulant coverage. Two elements have to be considered when interpreting this result. First, there is a selection bias because we mainly included inpatients. Second, 6 of these 8 patients with TIA/stroke had at least 1 inappropriate criterion, and some of these might have contributed to the AE. Among these 6 patients, two patients weighed more than 110 kg, 5 had inappropriate modalities of administration, and 3 had poor compliance. Infratherapeutic trough levels of DOAC were documented in 3 patients in whom administration was not optimal. These cases emphasize the problems of compliance and off-label use with DOACs. It also highlights the potential added value of specific dosages.

Although we did not perform a qualitative study to identify the causes of inappropriate prescribing, our results suggest that education of health care professionals and of patients must be reinforced and that collaboration with clinical pharmacists is valuable. There is good evidence on the role that pharmacists can play in the safe and effective use of VKAs.[27] Similarly, there is emerging evidence that pharmacists can contribute to improving the use of DOACs.[28] In the present study, the clinical pharmacist made interventions for half of the patients, with a relatively large acceptance rate by physicians.

Another component for improving use in clinical practice consists of therapeutic monitoring in specific situations. The advantage of "no monitoring with DOACs" may only be correct for patients with a standard weight, with good compliance or taking no interacting drug, but it is prone to fail in outliers such as obese or frail individuals. The clinical community has already developed specific coagulation assays.[13,14] However, in the absence of international consensus on therapeutic target levels and because fixed-dose regimens have been registered instead of variable dose, implementation of routine laboratory testing is currently not considered.[3,29]

The present study has several limitations. First, the sample was small, and the study was monocentric. However, to the best of our knowledge, this is the first prospective study to provide data on several dimensions of appropriateness in patients on DE as well as rivaroxaban. Although applying the MAI or a similar tool to large administrative databases is unfeasible, it would be useful to complement our data with patients from a larger, multicentric cohort. Second, some of the explicit instructions relative to the evaluation of appropriateness that were validated by the expert panel might be subject to discussion, especially in cases where no international consensus exists (eg, choice of drug). Third, there was no control group. We, therefore, could not compare appropriateness of prescribing between DOAC and VKA. Data on VKA patients from a previous study where we applied the MAI show that dosage was inappropriate in 70% of patients but that the other criteria were (almost) never rated as inappropriate.[17] Data from the literature suggest that time to therapeutic range (and therefore dosage) is suboptimal in VKA patients.[30] However, heterogeneity between the studies precludes direct comparison. A larger prospective study comparing appropriateness between VKA and DOAC patients is needed. Finally, a selection bias cannot be excluded. We had a large proportion of hospitalized patients, and this could have affected the prevalence of severe AEs reported because several patients in our study were admitted to hospital secondary to a problem with their DOAC. In fact, the prevalence of stroke in the present study was much higher than the prevalence reported in clinical trials or epidemiological studies. Furthermore, the only outpatients that could be included were those presenting to the laboratory for DOAC monitoring. Such patients are at greater risk for adverse drug reactions or treatment failure than other outpatients taking a DOAC, and this increased risk is precisely the reason for having monitoring performed.

Conclusion

DOACs are indisputably an important step in the field of anticoagulation. However, inappropriate use is frequent and can possibly lead to bleeding or thrombotic events. This pilot study has highlighted the main problems associated with prescribing DOACs and identified the priorities for strengthening the education of health care professionals and patients with regard to the choice of anticoagulant, dose adjustment, modalities of administration, and compliance.

Appendix A

International Variations in Approved Indications and Approved Dosages for Direct Oral Anticoagulants

	Dabigatran etexilate	Rivaroxaban	Apixaban
Atrial fibrillation			
Mild RI	150 mg bid: EMA/FDA	20 mg od: EMA/FDA	5 mg bid; 2.5 mg bid If serum creatinine >1.5 mg/dL + age >80 years or weight <60 kg: EMA/FDA
Moderate RI	110 mg bid if risk bleeding > risk recurrent DVT: EMA	15 mg od: EMA/FDA	5 mg bid; 2.5 mg bid If serum creatinine >1.5 mg/dL + age >80 years or weight <60 kg: EMA/FDA
	150 mg bid: FDA		
Severe RI	Contraindicated: EMA	15 mg od: EMA/FDA	2.5 mg bid: EMA
	75 mg bid[a]: FDA		5 mg bid; 2.5 mg bid If serum creatinine >1.5 mg/dL + age >80 years or weight <60 kg: FDA
ESKD	Contraindicated: EMA	Not recommended: EMA	Not recommended: EMA
	Dosing recommendation cannot be provided: FDA	Avoid the use[b]: FDA	Not recommended: FDA
VTE prophylaxis after joint replacement			
Mild RI	220 mg od: EMA	10 mg od: EMA/FDA	2.5 mg bid: EMA/FDA
Moderate RI	150 mg od: EMA	10 mg od: EMA/FDA	2.5 mg bid: EMA/FDA
Severe RI	Contraindicated: EMA	Use with caution: EMA	Use with caution: EMA
		Avoid the use[b]: FDA	Use with caution: FDA
ESKD	Contraindicated: EMA	Not recommended: EMA	Not recommended: EMA
		Avoid the use[b]: FDA	Not recommended: FDA
VTE treatment			
Mild RI	150 mg bid: FDA	15 mg bid For 21 days followed by 20 mg od: EMA/FDA	Not approved by both the EMA and FDA
Moderate RI	150 mg bid: FDA	15 mg bid For 21 days followed by 15 mg od if risk bleeding >risk recurrent VTE[a]: EMA	
		15 mg bid For 21 days followed by 20 mg od: FDA	
Severe RI	dosing recommendations cannot be provided: FDA	15 mg bid For 21 days followed by 15 mg od if risk bleeding >risk recurrent VTE[a]: EMA	
		Avoid the use: FDA	
ESKD	dosing recommendations cannot be provided: FDA	Not recommended: EMA	
		Avoid the use: FDA	

Abbreviations: RI, renal insufficiency; EMA, European Medicines Agency; FDA, Food and Drug Administration; DVT, deep venous thrombosis; ESKD, end-stage kidney disease; VTE, venous thromboembolism.

[a]Recommendation is based on pharmacokinetic modeling and has not been studied in this clinical setting.

[b]Discontinue Xarelto in patients who develop acute renal failure.

Appendix B

Medication Appropriateness Index: Summary of Categories and Instructions

Criterion		Instructions (Summary)
Indication[a]	A	There is a valid indication, that is, the patient has NVAF
	B	The patient has NVAF but does not fit within the reimbursement criteria; or patients where the DOAC is used as a last resort
	C	Off-label use
Choice	A	DOAC is the preferred choice because labile INR with VKA, CI to VKA, patient preference for DOAC, recurrent stroke/VTE on VKA, resistance to VKA
	B	VKA could have been a first choice: no CI, not yet tested, no recurrent stroke or VTE on VKA
	C	DOAC is inappropriate and VKA is the first choice: severe renal insufficiency (CrCl <30 mL/min), poor compliance, extreme weight (<50 kg or >110 kg), need for drug monitoring LMWH is the first choice: severe hepatic impairment Another DOAC is the first choice: for example, recurrent VTE/stroke on actual DOAC and labile INR
Dosage	A	Patient receives the daily dose recommended in the SmPC
	B	Patient receives a label daily dose, but specific coagulation assays show that patient is subtherapeutic or supratherapeutic
	C	Patient receives an inappropriate daily dose (too low or too high); for example, no dose adjustment to renal function
Modalities of administration, correct	A	Modalities of DOAC intake are correct; for example, dabigatran taken twice a day with a 12-hour interval between 2 doses; rivaroxaban taken with meal in the morning, DOAC intake every day at the same hour
	B	Modalities of DOAC intake with limited clinical relevance are not respected; for example, rivaroxaban taken in the evening instead of morning, dabigatran taken without meals
	C	Modalities of DOAC intake that are clinically relevant are not correct; for example, once-daily administration of dabigatran instead of twice daily, time of DOAC intake is variable, rivaroxaban is not taken with meals
Modalities of administration, practical	A	Patient has no difficulty taking the drug
	C	Patient has difficulties taking the drug: dabigatran twice daily in a patient with poor compliance; dabigatran in a patient with swallowing difficulties (capsules cannot be opened)
Drug-Drug Interaction (DDI)	A	There is no DDI
	B	Potential PK or PD DDI but without any sign of adverse consequence; for example, amiodarone + dabigatran without any bleeding event (amiodarone is a substrate of CYP3A4 and an inhibitor of CYP3A4/P-gp: a potential drug-drug interaction exists). We used the drug interactions table of Hôpitaux Universitaires de Genève (HUG, 2012 #117) to identify potential pharmacokinetic drug interactions with DOAC. These have been listed as P-gp or CYP3A4 substrate, inhibitor or inducer
	C	DDI with a combination that is contraindicated (eg, dabigatran + cyclosporin or DDI with an adverse consequence (eg, dabigatran + amiodarone and the patient has serious bleeding)
Drug-disease interaction	A	There is no drug-disease interaction
	B	Databases mention an interaction (caution or warning), but the patient does not show signs of worsening of the disease; for example, patient with a known thrombocytopenia and no signs of platelet decreasing on DOAC
	C	DOAC is contraindicated (eg, DOAC in a patient with Child Pugh B cirrhosis) or presents a high risk in case of the disease. Patient has a disease/condition where the DOAC must be used with caution and has signs of worsening of the disease
Duplication	A	DOAC is the only anticoagulant of the treatment
	B	Concomitant anticoagulant prescription in case of a switch from, for example, DOAC to VKA
	C	Duplication of anticoagulants; for example, DOAC associated with LWMH

(continued)

Appendix B (continued)

Criterion		Instructions (Summary)
Duration	A	The intake duration is in accordance with manufacturer indications and reimbursement criteria
	C	The intake duration is not in accordance with manufacturer indications or reimbursement criteria

Abbreviations: NVAF, nonvalvular atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio; VKA, vitamin K antagonist; CI, contraindication; VTE, venous thromboembolism; CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; SmPC, summary of product characteristic; DDI, drug-drug interaction; PK, pharmacokinetic; PD, pharmacodynamic; CYP3A4, cytochrome P450 3A4.
[a]When the criterion "indication" is considered inappropriate, the criteria "choice," "dosage," "administration," "practicality," and "duration" are also automatically considered inappropriate.

Appendix C

Prevalence of Inappropriate Ratings, Subgroup Analysis

	Drug		Age		Previous VKA	
Criterion (n, %)	Rivaroxaban (n = 35)	Dabigatran (n = 34)	<75 Years (n = 37)	≥75 years (n = 33)	VKA Naïve (n = 31)	Previous VKA (n = 38)
Indication	4 (11)	4 (12)	4 (11)	4 (12.5)	4 (13)	4 (10.5)
Choice	11 (31)	8 (24)	13 (35)	6 (19)	8 (26)	11 (29)
Dosage	10 (29)	8 (23.5)	9 (24)	9 (20)	9 (29)	9 (24)
Modalities of administration, correct	9 (26)	7 (21)	10 (27)	6 (19)	5 (16)	11 (29)
Modalities of administration, practical	10 (29)	8 (23.5)	11 (30)	7 (22)	8 (26)	10 (25)
Drug-drug interaction	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	1 (2.5)
Drug-disease interaction	1 (3)	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)
Duplication	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Duration	4 (11)	4 (12)	4 (11)	4 (12.5)	4 (13)	4 (10.5)

Abbreviations: VKA, vitamin K antagonist.

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