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Inappropriate Prescriptions of Direct Oral Anticoagulants among Patients with Atrial Fibrillation in General Practice: a Cross-sectional Analysis of the French CACAO Cohort Study.

Running title: inappropriate prescription of DOACs

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CONFLICT OF INTEREST

None

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ABSTRACT

Background

Direct oral anticoagulants (DOACs) account for an increasing proportion of prescriptions in patients with nonvalvular atrial fibrillation (NVAF) in primary care. Inappropriate dosing of DOACs (especially under-dosing) is the most common problem. However, conflicting results have been reported with regard to the factors independently associated with inappropriate dosing.

Aim

The present study's objectives were to describe inappropriate prescriptions of DOACs in the "Comparison of Accidents and Circumstances with Oral Anticoagulants" (CACAO) French nationwide general practice cohort, and to identify factors independently associated with inappropriate DOAC doses.

Design and setting

We performed an ancillary cross-sectional baseline analysis of the CACAO French national multicentre prospective cohort of adult patients in primary care receiving an oral anticoagulant and recruited from April to October 2014. We selected the set of CACAO patients having taken a DOAC for NVAF on inclusion (n=1111).

Method

We described inappropriate prescriptions of DOACs (inappropriate dosage, contraindications, non-indications, interactions, and precautions for use) and then used multivariate logistic models to investigate factors associated with inappropriate DOAC dosing (under-dosing and over-dosing).

Results

Overall, 438 patients (39.4%) received at least one inappropriate DOAC prescription – mainly an inappropriate dosage (33.7%), and especially under-dosing (31.3%). In a multivariate

analysis, the factors independently associated with under-dosing were older age (odds ratio [95% confidence interval] =1.03[1.02-1.05]), prescription of apixaban (3.93[2.29-6.74]) or dabigatran (1.55[1.17-2.06]), and a CHA_2DS_2-VASc score ≥2 (2.39[0.92-6.18]) vs. a score=1 (0.73[0.23-2.34]). Factors independently associated with over-dosing were kidney failure (3.28[1.34-8.08]), a HAS-BLED score ≥3 (2.47[1.06-5.73]) and older age (1.05[0.99-1.10]).

Conclusion

The appropriateness of DOAC prescribing for NVAF can be improved, especially in older patients, those with kidney failure, a higher risk for ischemic stroke and/or a higher risk for bleeding. General practitioners have a key role in increasing the proportion of appropriate DOAC prescriptions via informational, educational and/or management strategies.

WORD COUNT: 297

Keyword: primary care, direct oral anticoagulant, prescription, public health

How this fits in

- Almost 40% of patients with non-valvular atrial fibrillation received at least one inappropriate prescription of a direct oral anticoagulant in primary care (inappropriate dosages, contraindications, non-indications, interactions, or precautions for use).
- The main inappropriate situation was inappropriate dosage (33.7%), and especially under-dosing (31.3%). Factors independently associated with under-dosing were older age, prescription of dabigatran or apixaban, and a higher thromboembolism (CHA_2DS_2-VASc) score.
- Factors independently associated with over-dosing were older age, kidney failure, and a higher haemorrhagic (HAS-BLED) score.
- Primary care physicians have a key role in increasing the proportion of appropriate prescriptions of direct oral anticoagulants.

INTRODUCTION

Nonvalvular atrial fibrillation (NVAF) is a common cardiac rhythm disorder and constitutes a significant risk factor for ischemic stroke. One in four middle-aged adults in Europe and the US will develop AF.[1] By 2030, 14 to 17 million people in the European Union will have AF, with 120,000 to 215,000 new cases per year.[1]

Oral anticoagulants are widely prescribed for an indication of AF in ambulatory care. However, these drugs constitute the leading cause of emergency department admissions for bleeding (.[2] In a recent French cohort study, 6% of the participants taking anticoagulants experienced one or more bleeding events.[3] Anticoagulant prescription patterns are now changing because direct oral anticoagulants (DOACs, e.g. rivaroxaban, apixaban, dabigatran, and edoxaban) are direct factor Xa-inhibitors that can replace vitamin K antagonists (VKAs) to prevent stroke in patients with AF.[1] Other indications for DOACs cover the treatment of thrombosis, the prevention of recurrent deep vein thrombosis/pulmonary embolism and (for rivaroxaban) the prophylaxis of atherothrombotic events in acute coronary syndrome (together with aspirin or both aspirin and clopidogrel).

Since the introduction of this drug class in France in 2009, the proportion of anticoagulant-treated patients taking a DOAC has risen constantly, and was 38.0% in 2016.[4] A variety of DOACs are now available with prescription modalities that take account of several factors such as patient's adherence, age, and renal function.[1,5]

Several studies have investigated inappropriate DOAC prescriptions.[6-12] Inappropriate dosing of DOACs (especially under-dosing) is the most common issue, since it affects between 7.7% and 32% of patients. However, conflicting results have been reported with regard to factors independently associated with inappropriate dosing.[8, 10,11] Moreover, only one study was conducted in a primary care setting, and differences in prescribing patterns from one institution to another mean that its results cannot necessarily be generalized.[6]

The Comparison of Accidents and Circumstances with Oral Anticoagulants (CACAO) cohort is a French nationwide general practice cohort of patients taking an oral anticoagulant.[13] The study's primary objective was to determine whether mandatory data for the safe monitoring of oral anticoagulants are present in general practitioners' (GPs') records.[13]

In the present ancillary study, our objectives were to describe the distribution of inappropriate prescriptions of DOACs in CACAO patients with NVAF, and to investigate factors independently associated with inappropriate DOAC dosing.

MATERIALS AND METHODS

Setting design and participants

The CACAO study was a French nationwide multicentre prospective cohort of ambulatory consecutive patients having received an oral anticoagulant in general practice and recruited between April and October 2014. The duration of DOAC therapy is given in Table S1. The study's 463 GP investigators were located in 290 different rural and urban areas and in 47 different counties throughout France. The study had two phases: safety data from medical records at inclusion were examined in an initial cross-sectional phase, and the efficacy and safety of VKAs vs. DOACs were then monitored during a standard, 12-month longitudinal phase.[13] The CACAO study's main inclusion criteria were age 18 years or over, prescription of a VKA or a DOAC, and a consultation (for whatever reason) with a GP investigator during the study period. Patients taking injectable anticoagulants and those under 18 were not included. For the present ancillary study, we selected patients taking a DOAC for NVAF at inclusion (Figure S1).

Data collection

General assessment

For the purposes of the present study, we considered baseline data only. Using an electronic case report form, the GPs collected data anonymously on demographics, the personal medical history, current medications (from the French National Medicines Agency's list[16]), items from CHA_2DS_2-VASc and HAS-BLED (scores were calculated subsequently[14,15]), and laboratory tests (renal and hepatic function tests, coagulation assays). No biological samples were collected specifically for this study.

Outcomes

We assessed various inappropriate DOAC prescriptions that had been predefined by an expert group (a professor of therapeutics (LB), five GPs (EF, PG, JF, JLB, and PF), and an epidemiologist (SBG)) on the basis of the summaries of product characteristics from the European Medicines Agency (see Supplementary File 2, Table S2, and [17-19]). These situations involved inappropriate dose prescription (under-dosing or over-dosing); contraindication or prescriptions that were not recommended (due to a comorbidity or a concomitant medication); non-indication (a CHA_2DS_2-VASc <1); an at-risk interaction (antiaggregants or other reasons); and noncompliance with the precautions for use (concomitant treatments or comorbidities). The reference category was normal dosage.

Potential factors associated with inappropriate prescriptions

Potential GP-related associated factors were age, gender, and practice environment (urban vs. rural) (Table S1). Potential patient-related associated factors were age, gender, the DOAC molecule, the CHA_2DS_2-VASc score (which calculates the risk per year of stroke in patients with AF), the HAS-BLED score (calculates the risk per year of major bleeding in patients with AF), the duration of prescription (months), the specialty of the physician having first prescribed the DOAC, other oral anticoagulants used before the current prescription, independence for DOAC administration, BMI (kg/m^2), current pregnancy and/or breastfeeding,

concomitant antiaggregant treatment, current tobacco use, alcohol consumption, and associated comorbidities such as kidney failure (estimated creatinine clearance rate (Cockcroft-Gault equation), ml/min; no, moderate, severe), a personal history of hypertension, symptomatic heart failure, cancer treatment in the past 6 months, diabetes mellitus, coronary heart disease and/or myocardial infarction, stroke and/or transient ischemic attack, aortic and/or peripheral arterial disease, a personal history of haemorrhage requiring hospitalization, deep vein thrombosis and/or pulmonary embolism, chronic dialysis and/or kidney transplantation, and liver cirrhosis.

Statistical analysis

Qualitative variables were described as the number (%), and quantitative variables were described as the mean (standard deviation (SD)) or the median [interquartile range (IQR)] depending on their distribution. We first described the characteristics of the GPs, the patients and the inappropriate DOAC prescription and then searched for factors associated with the most prevalent type of inappropriate prescription. Univariable analyses involved the chi-squared or Fisher's test for categorical variables and Student's test or Kruskal-Wallis tests for continuous variables, as appropriate. Variables with p <0.2 were selected for multivariable analysis and the estimation of unadjusted odds ratios (ORs). Confounders and interactions were tested in bivariate models. To avoid the introduction of highly correlated variables (e.g. CHA_2DS_2-VASc with HAS-BLED and age; HAS-BLED with renal function), we built several different logistic regression models. A logistic model was used, since no effect of GPs was observed in an empty multilevel model. Adjusted ORs [95% confidence interval (CIs)] were estimated using multinomial logistic or exact logistic regression models. The reference category was the appropriate DOAC dose. We chose rivaroxaban as the reference category for the "DOAC molecule" factor because it was the most prescribed drug and thus facilitated the interpretation of ORs. Goodness of fit was assessed using the Akaïke and Bayesian information criteria

(lowest value = best fit). All tests were two-sided, and the threshold for statistical significance was set to $p \leq .05$. Analyses were performed with Stata software (version 15, StataCorp, College Station, TX, USA).

Ethics

The CACAO study was approved by the independent ethics committee at Saint-Etienne University Hospital (Saint-Etienne, France; reference: IRBN112014/CHUSTE) and was registered at ClinicalTrials.gov (NCT02376777). All patients received written information about the study. In line with French legislation on observational studies, written informed consent was not required.

RESULTS

Study population and inappropriate DOAC prescriptions

The main characteristics of the 1111 patients analysed and the 112 investigating GPs are summarized in Table S1. The median [IQR] patient age was 76 [68-82], 47% of the patients were female, 90% had a CHA_2DS_2-VASc score ≥2, 39% had a HAS-BLED score ≥3, and 54% had received a DOAC for over a year. Rivaroxaban was the most commonly prescribed DOAC (received by 51% of patients). We observed that 39.4% of the patients had at least one inappropriate prescription (inappropriate dosage, contraindication, non-indication, interaction, or precaution for use) (Table S1) – mainly inappropriate dosage (33.7%), and especially under-dosing (31.3%).

Factors associated with inappropriate DOAC dosage

In an univariable analysis (Table S3), the factors associated with inappropriate dosage were older patient age (for under- and over-dosing), prescription of apixaban or dabigatran (for

under-dosing), a higher CHA_2DS_2-VASc score (under-dosing), a higher HAS-BLED score (for over-dosing), and kidney failure (for over-dosing). The proportion of appropriate prescriptions was higher for rivaroxaban (74%) than for dabigatran (61%) or apixaban (45%) ($p<0.001$ for both; Figure S2).

In a multivariable model including age, the factors independently associated with under-dosing (relative to appropriate dosing) were older age, prescription of apixaban or dabigatran, and CHA_2DS_2-VASc score ≥2 (Table 1 and Table S4).

Factors independently associated with over-dosing, were kidney failure, a HAS-BLED score ≥3 and older age (Table 1 and Table S5).

DISCUSSION

Summary

In this large, prospective nationwide cohort study conducted in general practice, 39% of the patients received at least one inappropriate DOAC prescription. The main type of inappropriate prescription was inappropriate dosing (33.7% of the patients), and especially under-dosing (31.3%). In a multinomial multivariable analysis, factors independently associated with DOAC under-dosing (vs. appropriate dosing) were older age, the prescribed molecule (dabigatran and apixaban), and a higher CHA2DS2-Vasc score. Factors independently with over-dosing were kidney failure, a HAS-BLED score ≥3, and older age.

Strengths and limitations

The study's multicentre design and the large sample size may mean that the results can be generalized more reliably. Moreover, only one other study has exclusively focused on primary care – despite the fact that GPs are intensely involved in the management of patients with chronic conditions taking oral anticoagulants.[6] Given that the investigator was the patient's family physician in 95% of cases, our study data were easy to access via a questionnaire.

However, the data were declarative and were not checked objectively - representing a potential source of measurement bias. It is also possible that GPs who agreed to participate in the study were more motivated by issues such as continuing medical education, patient education, and/or anticoagulants than the average GP.

Lastly, the GPs' records may not have included all the factors that influence decisions about DOAC dosing (including patient preferences and values,and plans for imminent cardioversions). The HAS-BLED and CHA_2DS_2-VASc scores were assessed *a posteriori.* Therefore, it was not possible to tell whether the prescribers knew of these scores and took them into account when prescribing DOACs. We also included other confounders, such as a personal history of haemorrhage requiring hospitalization (Table 1).

Although the concomitant prescription of DOAC and aspirin is not recommended, rivaroxaban and low-dose aspirin can be given concurrently in acute coronary syndrome and AF. However, the dose of aspirin prescribed was not recorded in the study database. Lastly, the absence of longitudinal data on inappropriate prescriptions constitutes a limitation for the present analysis but this was not the CACAO cohort study's main objective.[3]

Comparison with existing literature

In line with our present findings, inappropriate dosing of DOAC (especially under-dosing) is usually the most prevalent issue (ranging from 7.7%[6] to 32%[8] in previous studies[6-12]). However, the incidence of under-dosing observed here (31.3%) was higher than in the literature. For example, the corresponding values were respectively 7.2%, 9.4%, and 18% in the Canadian primary care cohort, the ORBIT-AF II registry, and the FANTASIIA registry.[6,11,8] This difference might be explained by the characteristics of the study populations. In our study, patients were older (79 on average, vs. 71 to 75 in other studies) and more likely to have comorbidities and/or frailty factors (e.g. kidney failure and higher CHA_2DS_2-VASc scores).[6,8,11]

The most prescribed drug was rivaroxaban in our study, the Canadian cohort[6] and the ORBIT-AF registry[11] (51%, 57%, and 54%, respectively) and dabigatran in the FANTASIIA study (50%).[8]

The literature data on factors associated with inappropriate dosing are contradictory.[6-12] Older age[9, 10, 11] and a higher CHA_2DS_2-VASc score[10, 11] were also factors associated with under-dosing in other studies. The fact that a higher CHA_2DS_2-VASc score (i.e., higher risk of ischemic score) was associated with under-dosing might reflect a degree of frailty among patients and the fear of over-dosing among prescribers. Similarly, the FANTASIIA study found that dabigatran was associated with under-dosing,[8] and the ORBIT-AF study found the same association for apixaban.[11] In contrast to the literature data on comorbidity, heart failure was not a significant factor in our study[6].

Few studies have found that kidney failure is associated with over-dosing.[9,11] This finding conflicts with other previous reports[6,8,10] and might be due to the higher incidence of kidney failure in our population. However, our observation suggests that physicians either (i) do not adjust the dose level according to kidney function (e.g. due to lack of awareness or a lack of laboratory data), (ii) adapt the dose using the Modification of Diet in Renal Disease equation or another equation that gives better renal scores than the Cockcroft equation, or (iii) do not have an up-to-date record of the patient's body weight.

Other similar factors associated with over-dosing in the literature include a higher bleeding score and older age.[9,11] However, bleeding scores (ORBIT and/or HAS-BLED) may also reflect comorbidities and/or frailty (e.g. older age and kidney failure), suggesting that GPs do not follow the guidelines on DOAC prescriptions.

The only other study of primary care (performed in Canada) reported a lower incidence of inappropriate DOAC prescription.[6] Although this differences may be explained (at least in part) by the characteristics of the respective study populations (with more kidney failure and higher

CHA2DS2-VASc scores in our study), dabigatran was also less frequently prescribed in the Canadian study (34% of patients) than in the present study (43%). Moreover, Moreover, around 20% of the participating physicians in the Canadian cohort was in academic practice that may explain the lowest inappropriate prescription rate.

Here, most of the patients were first prescribed an oral anticoagulant by a cardiologist; it is likely that GPs were reluctant to modify another physician's prescription (i.e. therapeutic inertia).

Implications for research and/or practice

It is well established that (i) higher-than-recommended dose levels of DOACs are associated with elevated all-cause mortality, and (ii) under-dosing is associated with more frequent hospitalization for cardiovascular problems.[11] However, some studies of off-label prescriptions have reported that stroke severity and clinical outcomes are no worse in patients with under-dosed DOACs than in patients on the recommended dose.[10,20]

In the present cohort of patients managed in primary care, the great majority of DOAC prescriptions were for the recommended doses. However, the appropriateness of DOAC prescribing can be improved for a third of patients, especially in older individuals, those with kidney failure, a higher risk of ischemic stroke and/or higher risk for bleeding.

Conclusions

In this large, prospective, nationwide cohort study conducted in general practice, 33.7% of DOAC-treated patients received at least one inappropriate dose prescription of DOACs (mainly under-dosing, in a third of patients). Factors independently associated with DOAC under-dosing were older age, prescription of dabigatran or apixaban, and a higher CHA_2DS_2-VASc

score. Factors independently associated with over-dosing were older age, kidney failure, and a HAS-BLED score ≥3. Cardiologists and GPs have a key role in increasing the proportion of appropriate DOAC prescriptions via informational, educational and/or management strategies.

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Table 1: Multivariate multinomial logistic regression of factors associated with inappropriate dosing of DOACs in patients with AF (n=1020)

Model including age	Adjusted OR [95% CI] for under-dosing	p*	Adjusted OR [95% CI] for over-dosing	p*
Patient age (years)	1.03 [1.02-1.05]	<0.001	1.05 [0.99-1.10]	0.084
DOAC molecule		<0.001		0.223
Apixaban	3.93 [2.29-6.74]		3.14 [0.82-12.06]	
Dabigatran	1.55 [1.17-2.06]		1.02 [0.43-2.42]	
Rivaroxaban	1 (ref)		1 (ref)	
Kidney function (Cockcroft) (ml/min)		0.002		0.010
Normal, ≥60	1 (ref)		1 (ref)	
Moderate/severe/terminal failure, <60	0.59 [0.42-0.83]		3.28 [1.34-8.08]	

Akaike information criterion = 1455.14; Bayesian information criterion =1504.42

* Adjusted P for all the reported variables, obtained from the Wald test using multinomial multivariate logistic regression

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Essential fields *			
Print article summary*	**min 10, max 25 words**	**How would you describe your research in one sentence?** Please avoid saying: "we undertook a randomised controlled trial…", more like "Primary care patients treated with oseltamivir recovered from influenza-like illness one day sooner than usual care."	33.7% of DOAC-treated patients with atrial fibrillation received at least one inappropriate dose prescription (mainly under-dosing, in a third of patients).
How this fits in* (research statement)	**min 50, max 100 words**	**How does your study fit into what is currently known in this field of research?** Summarise, in no more than four short sentences, what was previously known or believed on the topic and what your research adds, particularly focusing on relevance to clinicians.	• Almost 40% of patients with non-valvular atrial fibrillation received at least one inappropriate prescription of a direct oral anticoagulant in primary care • The main inappropriate situation was inappropriate dosage (33.7%), and especially under-dosing (31.3%). Factors independently associated with under-dosing were older age, prescription of dabigatran or apixaban, and a higher thromboembolism
Clinical impact* (clinical statement)	**min 3, max 15 words**	**What is the impact of your research in a clinical settings?** If your findings were implemented, what would be the clinical impact? e.g. 'More accurate diagnosis, fewer antibiotic prescriptions', 'Non-pharmacologic treatment with additional health benefits'. See https://youtu.be/xHmlJG59nZI	Targetting factors independently associated with inappropriate DOAC dosing to improve the appropriateness of prescription and maybe reduce iatrogeny and/or other complications

Press summary*	**min 200, max 300 words (1-2 sentences per question)**	**How would you tell the world about your work?** To help consider whether your research will be considered for a press release please answer the following 3 questions: **1) What is your main message/what have you found?** (e.g. obesity is linked to a sense of smell). **2) So what? Why is it important to a general audience?** (e.g. it contributes to explanations of why some struggle to stay slim). **3) Key background** (e.g. 1/4 of UK adults are obese...). Please structure this as a reversal of the usual research methodology which begins with background. See https://www.bbc.co.uk/news/health-11755995. Include location, number of patients, and method. *Note: Press summary text may be sent to media outlets and also appear as a homepage features on BJGP.org for selected articles.*	1)The appropriateness of DOAC prescribing for non valvular atrial fibrillation can be improved, especially in older patients, those with kidney failure, a higher risk for ischemic stroke and/or a higher risk for bleeding. 2) To limit iatrogeny and/or complications 3) the proportion of anticoagulant-treated patients taking a DOAC has risen constantly
Press release from institution	**n/a**	Please send any institutional/academic organisation press releases to Moira.Davies@rcgp.org.uk when available	

Please note that you must supply the above information before we can finally accept your paper.

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Twitter handles	**n/a**	**Do you have Twitter handles for promotion?** Please provide twitter handles of authors who have consented to sharing their twitter handle when BJGP posts their article. We can also use organisational Twitter handles. The text from Print article summary/How this fits in, and/or Clinical impact will be used in tweets.	
Multimedia (if applicable)	**max 200 + images/multimedia files**	**Would you like your article to be considered for a video animation or infographic?** Of so, please state: 1) What could be the single subject/focus of a visualisation of your article? 2) What are some highlights that would be relevant to visualise?, e.g. - findings that are surprising or unexpected - contrasts, e.g. between study groups or conditions, or proportions - visual motifs, symbols, diagrams, pictures, or videos (with subjects' consent) Sketches and sample images can be uploaded to the submission system, and links can be added here. *Articles with clear visual angles which are being considered for multimedia production will be contacted shortly after acceptance.*	1) 2)

If you have any queries please email journal@rcgp.org.uk