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Complete List of Authors:	Silva Pinto, Susana; São Tomé Family Health Unit; University of Porto, CINTESIS@RISE Henriques, Teresa; University of Porto, CINTESIS@RISE ; Portuguese Oncology Institute of Porto Teixeira, Andreia; Faculty of Medicine, University of Porto, CINTESIS@RISE ; University of Porto, Department of Community Medicine, Information and Health Decision Sciences Monteiro, Hugo; Regional Health Administration of Northern, Min. of Health Martins, Carlos; University of Porto, CINTESIS@RISE ; H4A Primary Health Care Research Network
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Title Page

AF- React study: prescribing profile and the adherence with NOACs intake in patients with atrial fibrillation: a retrospective longitudinal study from real-world data in Northern Portugal

Authors

Pinto, Susana Silva;[1, 2,3] Email: susyapinto@gmail.com

[1] São Tomé Family Health Unit (ACeS Santo Tirso/Trofa), Portugal.

[2] Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal.

[3] CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

Henriques, Teresa S.;[3, 4] Email: teresasarhen@gmail.com

[3] CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[4] CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto, Porto, Portugal.

Teixeira, Andreia;[2, 3, 5] Email: andreiasofiat@hotmail.com

[2] MEDCIDS - Department of Community Medicine, Information and Decision in Health; Faculty of Medicine, University of Porto, Porto Portugal

[3]CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[5]ADiT-LAB, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial Nun'Álvares, 4900-347 Viana do Castelo, Portugal

Monteiro, Hugo;[6] Email: hfmonteiro@arsnorte.min-saude.pt

[6]Regional Health Administration of Northern, Min. of Health Portugal.

Martins, Carlos.[3, 7] Email: carlosmartins20@gmail.com

[3]CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[7]#H4A Primary Health Care Research Network, Porto, Portugal

Corresponding Author
Susana Silva Pinto
susyapinto@gmail.com

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atrial fibrillation, anticoagulants, prevention, stroke; primary health care.

ABSTRACT

Objectives: This retrospective longitudinal study aims to assess the appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients.

Design: Retrospective longitudinal study.

Setting: The study was conducted in the Regional Health Administration of Northern Portugal.

Participants: The authors selected a database of 21,854 patients with prescriptions from the same NOAC between January 2016 and December 2018 from all patients in the Regional Health Administration of Northern Portugal classified with the code K78 (Atrial fibrillation/flutter) of the International Classification of Primary Care until December 2018.

Results: Dabigatran had a lower percentage of suitable doses (50.1%) than other drugs, such as rivaroxaban (81.6%), apixaban (78.7%), and edoxaban (82.1%). Most patients with an unsuitable dose were prescribed a lower dose than recommended based on their glomerular filtration rate (GFR). Among patients under 75 years old with GFR > 60 ml/min, 59.8% had an adequate GFR range, while 27.8% of GFR measurements from patients over 75 years old and 29.4% of GFR measurements from patients under 75 years old with GFR < 60 ml/min were within an adequate time range. Adherence to NOACs varied across different drugs, with 59.1% adhering to edoxaban, 56.3% to rivaroxaban, 55.3% to dabigatran, and 53.3% to apixaban.

Conclusions: Dabigatran had the lowest percentage of suitable doses. Patients under 75 years old with GFR > 60ml/min had the highest percentage of an adequate GFR range,

while other groups that require closer GFR monitoring had a lower percentage of an adequate GFR range. Adherence to NOACs differed among different drugs, with greater adherence to treatment with edoxaban and less adherence to apixaban. In the future, it would be necessary to improve the appropriate prescribing of NOACs and understand the reasons for inadequate renal function monitoring in AF patients taking NOACs.

Strengths and limitations of this study

- The main limitation of this real-world study is possible registration and codification bias, as the data are obtained from electronic health records created by family doctors.
- This study is the first to examine the suitability of NOAC dosages, monitoring of renal function, prescribing NOACs, and adherence to NOACs in patients with AF in a real-world setting.
- Family doctors tend to follow an annual pattern for monitoring renal function in all patients taking NOACs, without individualized attention to the interval for monitoring renal function.
- Greater adherence to treatment with edoxaban than with apixaban seems to be related to the drugs' posology.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is frequently associated with chronic kidney disease (CKD) (1). The first part of the AF-React study revealed that 41.1% of 63,526 AF patients had a glomerular filtration rate (GFR) ≤ 60 ml/min (2). There is an intimate relationship between AF and CKD. On the one hand, kidney-specific mechanisms can alter the cardiac structure and predispose it to AF. On the other hand, the development of AF can accelerate the progression of CKD (1). As with the general population, AF in CKD patients is associated with an increased risk of thromboembolism and stroke (3). The synergistic effect of these two conditions raises serious issues concerning the balance between bleeding and thrombotic risk. Anticoagulant treatment can be challenging, especially in stage 5 CKD, where the clinical benefit is still unclear (1).

Oral anticoagulation (OAC) is the most effective form of thromboprophylaxis in AF patients with an increased risk of stroke. However, reducing stroke risk is directly related to the appropriateness of OAC prescription and adherence to OAC intake in these patients (4).

Previous studies have shown that non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban are superior to warfarin in preventing thromboembolic events in patients with non-valvular AF, providing increased safety and a reduction in the number of bleeding events overall (5–8). Therefore, they are currently recommended for AF patients at risk for stroke after calculating the CHA_2DS_2-VASc score (9).

However, the metabolism of NOACs largely depends on the kidneys for elimination, and patients with creatinine clearance <25 ml/min, who were excluded from all phase 3 NOAC trials, are not well studied (3).

The 2020 ESC Guidelines (9) and 2021 EHRA practical guide (10) recommend dose adjustment for apixaban, rivaroxaban, and edoxaban in stage 4 CKD and do not recommend the use of dabigatran. For GFR ≤ 50ml/min, dose adjustment is recommended for all NOACs.

This is particularly relevant since the kidneys are responsible for partially eliminating all four available NOACs. Dabigatran has the greatest extent of renal elimination (80%),

while 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared via the kidneys (11).

Other conditions also influence the appropriate prescription of NOACs in AF patients. For dabigatran, a reduced dose should be prescribed if the patient is over 80 years old, has concomitant administration with verapamil, or has an increased risk of bleeding. For apixaban, a reduced dose is recommended for patients over 80 years old or with a body weight < 60 kg. For edoxaban, a reduced dose is recommended for patients with a body weight < 60 kg or with concomitant administration of dronedarone, cyclosporine, erythromycin, or ketoconazole (10).

Lowres et al. identified various factors associated with poor adherence to OAC intake. Medical factors include no prior history of stroke/TIA or low stroke risk, fewer comorbidities, high bleeding risk, paroxysmal AF, lack of AF symptoms, electrical cardioversion after commencing OAC and taking ≥2 dosages per day. Patient factors include younger age, lower health literacy, low AF knowledge, unawareness of associated stroke risk, poor OAC knowledge, concerns about bleeding and lifestyle changes, information overload, anger, depression, or anxiety from the AF diagnosis, low treatment satisfaction, busy work schedule, lack of health insurance coverage, and low ability to pay for medications (4).

This study aims to assess the appropriateness of the prescribing profile and adherence to the intake of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF.

METHODS

Data collection

This study was performed with the AF-React project database. The Department of Studies and Planning within the Regional Health Administration of Northern Portugal developed the AF-React project database, which includes data from 2016, 2017, and 2018. To identify patients with AF, the ICPC-2 code K78 for AF was utilized.

The AF-React study encompasses all adults (18 years or older) whose clinical records in Primary Health Care, under the purview of the Regional Health Administration of Northern Portugal, included the K78 code prior to December 2018. For the purpose of

this study, we focused on individuals who were prescribed the same NOAC (novel oral anticoagulant) within the study period of 2016 to 2018. So, a retrospective longitudinal study was conducted.

NOAC dosage suitability

In order to investigate the appropriate dosages of NOAC for patients with AF, we classified patients into one of three dosage suitability categories: contraindicated, unsuitable, and suitable. The patient's most recent GFR value was considered when making these classifications.

Regarding dabigatran (10), a GFR < 30 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if 1) the patient was not prescribed a 110mg dose when the GFR was between 50 and 30 ml/min, or a 150 mg dose when the GFR was above 50 ml/min, or 2) the patient was over 80 years old and not prescribed a 110 mg dose. Suitable dosage status was assigned if 1) the patient was prescribed a 110 mg dose when the GFR was between 50 and 30 ml/min, or a 150 mg dose when the GFR was above 50ml/min, and 2) the patient was over 80 years old and prescribed a 110 mg dose with a GFR above 30 ml/min.

For rivaroxaban (10), a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if the patient was not prescribed a 15 mg dose when the GFR was between 50 and 15 ml/min or a 20 mg dose when the GFR was above 50 ml/min. Suitable dosage status was assigned if the patient was prescribed a 15 mg dose when the GFR was between 50 and 15 ml/min or a 20 mg dose when the GFR was above 50 ml/min.

For apixaban, a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if 1) the patient was not prescribed a 2.5 mg dose when the GFR was between 30 and 15 ml/min, or a 5mg dose when the GFR was above 30 ml/min, or 2) the patient was over 80 years old or weighed less than 60 kg and not prescribed a 2.5 mg dose of apixaban. Suitable dosage status was assigned if 1) the patient was prescribed a 2.5mg dose when the GFR was between 30 and 15ml/min, or a 5 mg dose when the GFR was above 30 ml/min, or 2) the patient was over 80 years old

or weighed less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 2.5 mg dose of apixaban.

For edoxaban, a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if 1) the patient was not prescribed a 30 mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50 ml/min, or 2) the patient weighed less than 60 kg and was not prescribed a 30mg dose of edoxaban. Suitable dosage status was assigned if 1) the patient was prescribed a 30 mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50 ml/min, or 2) the patient weighed less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 30 mg dose of edoxaban.

Monitoring renal function and prescribing NOAC

Regarding the monitoring of renal function and prescribing NOAC, the analysis was divided into three groups: patients over 75 years old (monitored every 6 months), patients 75 years old or younger with a GFR over 60 ml/min (monitored annually), and patients 75 years old or younger with a GFR under 60 ml/min (monitored according to the most recent GFR measurement). For each group, the number of patients with a GFR within the appropriate range (within 0 months or earlier), a GFR up to 6 months after the appropriate range, and a GFR after 6, 12, or 24 months after the appropriate range is provided.

Adherence to NOAC

To examine adherence to NOAC intake among AF patients who received the same NOAC during the study period, all NOAC dispensations were evaluated, regardless of whether the prescription was issued by a family doctor, hospital doctor from the National Health Service, or doctor from a private institution. Patients were considered adherent if they received at least 90% of the prescribed pills from the time of the AF diagnosis or the beginning of the study until the end (12).

Data analysis

The categorical variables were described using absolute and relative frequencies, n (%).

The statistical analysis was performed using software R (13).

Ethic issues

The Department of Studies and Planning of the Regional Health Administration of Northern Portugal (Ministry of Health, Portugal) processed the data. Anonymized data processing and editing were conducted on a secure platform, and the data were extracted from the server in compliance with legal regulations and with the approval of the Health Ethics Committee of the Regional Health Administration of Northern Portugal.

Patient and public involvement

Patients and the public were not involved in developing the research question.

RESULTS

Data description

Out of a total of 63,526 patients diagnosed with atrial fibrillation/flutter (ICPC-2, K78 code) in the northern region of Portugal until December 2018, we identified 21,854 patients who were prescribed the same non-vitamin K antagonist oral anticoagulant (NOAC) during the study period. These NOACs included dabigatran (5,219 prescriptions), rivaroxaban (8,801 prescriptions), apixaban (7,052 prescriptions), and edoxaban (782 prescriptions). Understanding the temporal relationship between NOAC prescription and K78 coding is crucial to determine whether NOACs were prescribed after AF diagnosis. Of the 21,455 (98%) patients, 188,780 prescriptions were issued after the K78 code.

In the first part of the AF-React study, a primary limitation was identified: the assessment of AF was based on data coded in the clinical process in primary healthcare. Therefore, in this analysis, we examined how codification has evolved over the years (see Figure 1). Our findings indicate that the frequency of ICPC-2 K78 encoding has

increased over time. Additionally, since 2015, the number of AF diagnoses coded has decreased, suggesting that from this date, the ICPC-2 K78 coding is more closely related to new and accurate diagnoses rather than the detection of previous diagnostic coding errors.

NOAC dosage suitability

The appropriate dosage of NOAC is critical for anticoagulation to effectively prevent stroke. To evaluate the suitability of the prescribed dose, we analyzed 128,603 prescriptions from 16,282 patients with at least one GFR value (Table 1). Approximately 89.1% (14,507) of patients maintained the same suitability dose status: 19 were contraindicated, 10,660 were suitable, and 3,828 were unsuitable. Notably, dabigatran had fewer suitable doses than other drugs: dabigatran - 50.1%; rivaroxaban - 81.6%; apixaban - 78.7%; and edoxaban - 82.1%. Most patients with an unsuitable dose were on a lower dose than recommended based on their GFR: dabigatran - 46.5%; rivaroxaban - 11.7%; apixaban - 20.0%; and edoxaban - 9.4%. For patients in an unsuitable dose condition due to weight and age: those on dabigatran who were over 80 years of age were prescribed a dose of 150mg (27 patients) or 75mg (61 patients); those on apixaban who were over 80 years of age or weighed less than 60 kilograms were prescribed a dose of 5mg (47 patients); and those on edoxaban who weighed less than 60 kilograms were prescribed a dose of 60mg (18 patients).

Monitoring renal function and prescribing NOAC

Another crucial aspect of NOAC therapy to effectively prevent stroke is adequate renal monitoring by physicians. Analyzing renal function monitoring, we found that 19,877 patients had at least one GFR measurement during the 3-year study, resulting in 45,679 recordings. Of these, 25,819 (56.5%) measurements were from 10,792 (54.3%) patients over 75 years old, while 16,757 (36.7%) GFR recordings were from 8,469 (45.4%) patients younger than 75 years old with GFR levels above 60 ml/min. Only 1,737 (8.7%) patients 75 years or younger had 3,103 (6.8%) GFR values at most 60 ml/min.

Regarding the appropriate GFR ranges for monitoring renal function and prescribing NOAC, we found that 1) 7,166 (27.8%) GFR measurements from patients over 75 years old, 2) 10,028 (59.8%) GFR measurements from patients under 75 years old with GFR

levels above 60 ml/min, and 3) 913 (29.4%) measurements from patients under 75 years old with GFR levels below 60 ml/min fell within the recommended time range. However, many GFR measurements did not have an adequate range. For those with an inadequate range of GFR, we documented the number of months beyond the recommended range, which is described in Table 2.

Adherence to NOAC

To analyze adherence to NOAC intake in AF patients, we considered the NOAC dispensed due to adherence to therapy, regardless of whether the patient had a medical prescription for the medication.

Regarding dispensation analysis, 24,426 patients dispensed the same NOAC at the pharmacy during the study period. When we examined the relationship between dispensation and the K78 coding date, we found that 5,837 patients dispensed 25,890 NOA before the K78 coding date, while 24,164 patients dispensed 295,551 NOA after the K78 coding date. Additionally, 5,576 patients dispensed the same NOAC before and after the atrial fibrillation/flutter coding. Of the 24,164 patients who dispensed NOAC after the K78 coding date, 5,683 (23.5%) dispensed dabigatran, 9,667 (40.0%)dispensed rivaroxaban, 7,901 (32.7%) dispensed apixaban, and 913 (3.8%) dispensed edoxaban.

Figure 2 shows the difference between the number of pills required to complete the therapy and the number of pills actually dispensed.

Based on this analysis, there was greater adherence to treatment with edoxaban and less adherence with apixaban. Patients who were considered adherent had received at least 90% of the pills intended to be taken from the time of diagnosis of AF or the start of the study until the end (12). Approximately 59.1% of patients adhered to edoxaban, 56.3% to rivaroxaban, 55.3% to dabigatran, and 53.3% to apixaban.

We also analyzed which patients had received all the pills necessary to complete the entire treatment during the study period: edoxaban - 29.4%; rivaroxaban - 24.3%; apixaban - 22.6%; and dabigatran - 18.5%.

DISCUSSION

Summary

Dabigatran has the lowest percentage of suitable doses, with 46.5% of patients being medicated with an unsuitable lower dose. Patients who are 75 years old or younger and have a GFR greater than 60 ml/min, whose renal function should be monitored annually, have the highest percentage of an adequate range of GFR. Other groups that require closer GFR monitoring have a lower percentage of an adequate range of GFR. Adherence to NOACs varies with different drugs: There was greater adherence to treatment with edoxaban and less adherence to apixaban.

Comparison with existing literature

Antunes et al. evaluated the prescription of oral anticoagulation in four family health units in northern Portugal from January 2010 to December 2015. They found that 76.7% of patients diagnosed with atrial fibrillation based on ICPC-2 coding were medicated with OAC (14). However, in the period from 2016 to 2018, there was an increase in prescriptions to 98%. This suggests an improvement in the anticoagulation of patients with atrial fibrillation in the northern region of Portugal over the years. These results contradict some European studies that showed resistance from family physicians to introduce anticoagulation after the diagnosis of atrial fibrillation (15–18) and contradict the findings of the study by Turakhia et al., which showed that the medical speciality that diagnoses AF influences the decision to anticoagulate or not (19).

The electronic clinical files of primary health care contain a list of health problems for which there is a follow-up plan, relevant diseases, and those that require continuous medical treatment. Accurate records ensure the adequacy of care and enable monitoring and evaluation of the care provided to the population (20). The use of the International Classification of Primary Care, 2nd edition (ICPC-2) is essential for this purpose. Data published in 2015 by the Central Administration of the Health System (CAHS) showed a growing codification of health problems at a national level, reflecting the increase in computerized clinical records and demand from users and healthcare providers (21). This study found that the ICPC-2 K78 encoding has become more frequent over the years, which is consistent with the CAHS data at the national level. In 2011, 20.6

million health problems were identified, and by 2013, this figure had increased to 30.2 million. The percentage of consultations with ICPC-2 coding in primary health care is high in Portugal (69.2% in 2011, 83.9% in 2012, and 84% in 2013) (21).

Sugrue et al. found that NOAC dosing was unsuitable in 14.8% of patients at the Mayo Clinic: 12.4% received an inappropriate lower dose, and 2.4% received an unsuitable high dose (22). Even the ORBIT-AF II Registry, a nationwide AF registry conducted in a community practice in the US, showed that an unsuitable dose of a NOAC was prescribed in only 12.5% of cases: underdosing in 9.3% of patients and overdosing in 3.3% of patients, respectively (23). However, a real-world registry in Spain reported higher rates of underdosing and overdosing on NOAC therapy: 17.5% and 14.9%, respectively (24). This study's results agree with those of the Mayo Clinic and ORBIT-AF II Registry studies, with underdosing in 15.1% of patients and overdosing in 1.8%. These findings are consistent with studies conducted in other countries. Nevertheless, due to the risks associated with unsuitable prescribing, greater attention is needed from Portuguese family doctors.

Stamellou and Floege highlighted the importance of regular checks of renal function in patients receiving NOACs to avoid overdosing, especially in situations that may cause acute-on-chronic kidney injury. In such patients, apixaban may be the safest licensed NOAC because of its relatively low renal elimination. In more advanced CKD, i.e., stage 4 and particularly in stage 5, NOACs are not recommended due to the lack of RCT data and concerns of overdosing with the risk of bleeding and anticoagulant-related nephropathy (25). A prudent approach is to check renal function at the initiation of treatment with NOACs, after three months, and then every year, except for high-risk patients (elderly >75 years, patients with low body mass) who require monitoring at least every six months (26). In patients with declining renal function, the current position of EHRA is to estimate the recheck intervals individually using a simple calculation: if creatinine clearance (CrCl) is ≤60 mL/min, the recheck interval in months is CrCl/10 (11).

Cayuelas et al. assessed compliance with kidney function monitoring recommendations in NVAF patients starting NOAC therapy (27). Compliance with kidney function monitoring recommendations was 61%, similar to the group of patients younger than 75 years with a GFR > 60ml/min in this study. Patients younger than 75 years with a GFR > 60ml/min had the highest rate of adequate GFR range, at about 60%, followed by

patients ≤75 years old with a GFR <60ml/min at 29.4%, and patients >75 years old at 27.8%. Another noteworthy finding is the low percentage of patients with a GFR range assessed beyond the appropriate 12-month interval in patients >75 years old and in patients ≤75 years old with a GFR <60ml/min (10.4% and 10.2%, respectively). Family doctors appear to follow an annual pattern for monitoring renal function in all patients receiving NOACs, without individualizing the interval for monitoring renal function according to the criteria mentioned here. Therefore, patients who receive annual GFR evaluations have the highest rate of adequate renal monitoring. More training for individualized tracking of patients with other conditions may help Portuguese family doctors improve these results.

There was greater adherence to treatment with edoxaban and less adherence to apixaban, likely due to differences in drug posology, with edoxaban taken once daily and apixaban taken twice daily. Brízido et al. evaluated adherence to NOACs and its determinants in a population of AF patients from the outpatient general cardiology list at a tertiary centre in Portugal. The median adherence was 91% (IQR 74-100%) for rivaroxaban, 87% (IQR 74-100%) for apixaban, 82% (IQR 48-100%) for dabigatran, and 96% (IQR 83-100%) for edoxaban. There were no statistically significant differences between the NOACs (p = 0.102). Half of the patients (51%) were classified as non-compliant, which is consistent with the findings of this study. Therapy duration, NOACs taken twice daily, and higher out-of-pocket costs were independent predictors of non-compliance (12).

In another real-world analysis of adherence to NOACs, rivaroxaban and apixaban had favourable profiles compared to dabigatran, and rivaroxaban appeared to have higher overall adherence among the NOACs, although edoxaban was not included in this analysis. (28) A systematic review and meta-analysis of observational studies found that up to 30% of patients with AF are non-adherent to NOAC therapy (29).

Limitations

The primary limitation of the AF-React study is that it relies on AF assessment data coded during the clinical process in primary healthcare. While there are some defects in the coding, it appears that the ICPC-2 K78 encoding has become more common over the years, and since 2015, there has been a decrease in the number of AF diagnoses

coded. This suggests that the increase in K78 encoding is related to real new diagnoses rather than simply detecting coding errors in previous diagnoses.

When assessing the appropriateness of the prescribed NOAC dose, only the most recent GFR, weight, and age criteria were considered. Unfortunately, other relevant NOAC dosage criteria were not available in the database. It is also important to consider frailty when assessing the appropriate range of GFR to monitor renal function and prescribe NOACs. However, this data was not available for analysis.

Implications for research and practice

The AF-React study enabled an analysis of the appropriateness of NOAC dosage prescriptions, the appropriate range of GFR for monitoring renal function and prescribing NOACs, and adherence to NOAC intake in AF patients. As such, the study provides highly relevant conclusions for Portugal. In the future, it will be necessary to improve the appropriate prescribing of NOAC doses and understand the reasons for inadequate monitoring of renal function in AF patients receiving NOACs. Additionally, further studies are needed to identify reasons for non-adherence to NOAC treatment in AF patients.

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AUTHOR STATEMENT

SSP and CM contributed to the conception of the work. All authors contributed to the design of the study. HM contributed to the data acquisition process. SPP, ASCT, and TSH contributed to the analysis and interpretation of the data. SSP drafted the manuscript, and HM, ASCT, TSH, and CM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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COMPETING INTERESTS

None declared.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in this research's design, conduct, reporting, or dissemination plans.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

The Health Ethics Committee of the Regional Health Administration of Northern Portugal approved the study protocol.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

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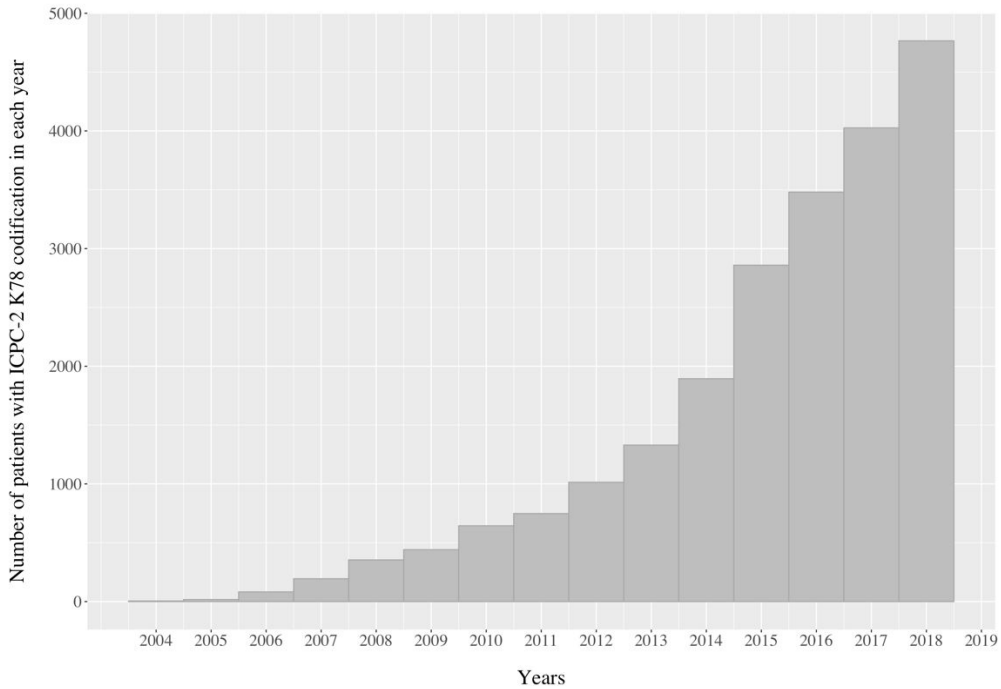

Figure 1. ICPC-2 K78 codification over the years.

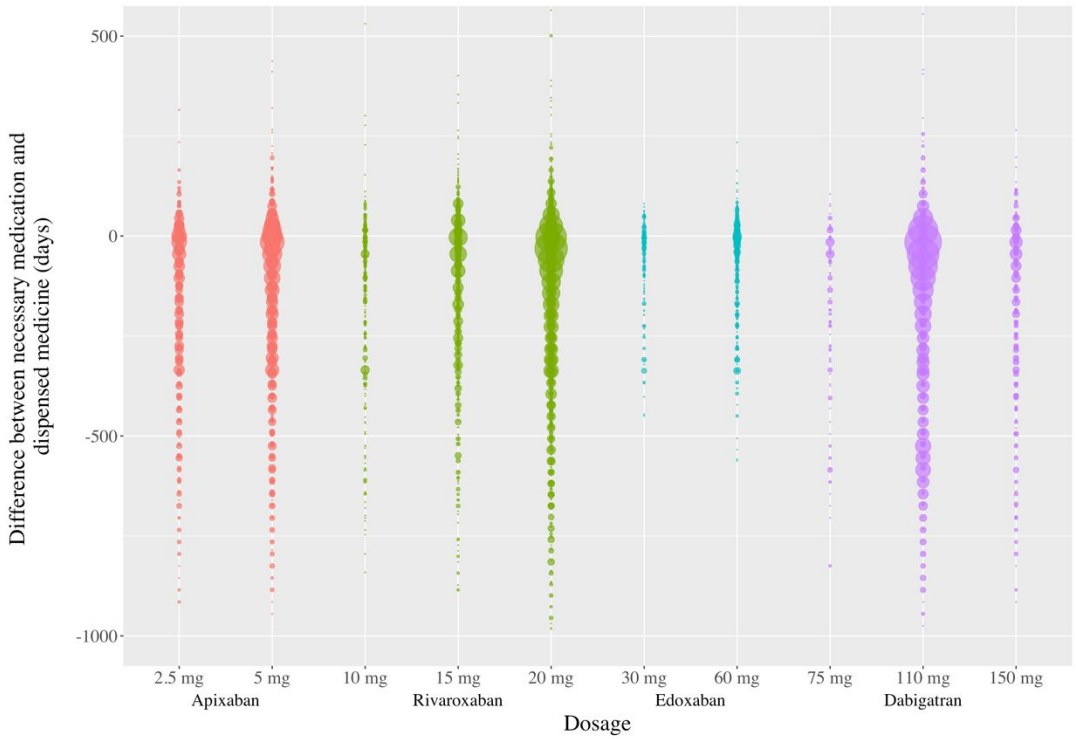

Figure 2. The difference between the number of pills needed to complete the therapy and the number of pills dispensed.

Table 1. The suitability of prescribed dose non-VKA oral anticoagulants (NOAC).

			Unsuitable		
	Contraindicated	Suitable	Not suitable for renal function		Not suitable for weight or age
			Lower dose	Higher dose	
Dabigatran (n = 3305)					
n	5	1657	1538	17	88
%	0.2	50.1	46.5	0.5	2.7
Rivaroxaban (n = 5802)					
n	5	4737	678	382	
%	0.1	81.6	11.7	6.6	
Apixaban (n = 4869)					
n	7	3830	975	10	47
%	0.1	78.7	20.0	0.2	1.0
Edoxaban (n = 531)					
n	2	436	50	25	18
%	0.4	82.1	9.4	4.7	3.4

Table 2. Analysis of ranges between GFR for monitoring renal function for prescribing non-VKA oral anticoagulants (NOAC) in three groups: patients > 75 years old; patients ≤ 75 years old and GFR > 60ml/min; and patients ≤ 75 years old and GFR < 60ml/min.

Months after the recommended deadline	Patients > 75 years old n (%)		Patients ≤ 75 years old and GFR > 60ml/min n (%)		Patients ≤ 75 years old and GFR < 60ml/min n (%)	
	GFR recordings	Patients	GFR recordings	Patients	GFR recordings	Patients
Before or 0 months	7166 (28)	4063 (23)	10028 (60)	5672 (48)	913 (29)	586 (25)
]0; 6] months	11247 (44)	7084 (39)	4267 (25)	3750 (32)	1297 (42)	950 (40)
]6; 12] months	4718 (18)	4169 (23)	1453 (9)	1452 (12)	577 (19)	530 (22)
]12;24] months	2296 (9)	2288 (13)	975 (6)	974 (8)	277 (9)	275 (12)
More than 24 months	392 (1)	392 (2)	34 (0)	24 (0)	39 (1)	29 (1)
Total	25819	17996	16757	11882	3103	2380

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13, 14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: analysis of a retrospective longitudinal study using real-world data from Northern Portugal (AF-React study)

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Stroke < NEUROLOGY, Primary Health Care, Anticoagulation < HAEMATOLOGY

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Title Page

Appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: analysis of a retrospective longitudinal study using real-world data from Northern Portugal (AF-React study)

Authors

Pinto, Susana Silva;[1, 2,3] Email: susyapinto@gmail.com

[1] São Tomé Family Health Unit (ACeS Santo Tirso/Trofa), Portugal.

[2] Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal.

[3] CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

Henriques, Teresa S.;[3, 4] Email: teresasarhen@gmail.com

[3] CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[4] CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto, Porto, Portugal.

Teixeira, Andreia;[2, 3, 5] Email: andreiasofiat@hotmail.com

[2] MEDCIDS - Department of Community Medicine, Information and Decision in Health; Faculty of Medicine, University of Porto, Porto Portugal

[3]CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[5]ADiT-LAB, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial Nun'Álvares, 4900-347 Viana do Castelo, Portugal

Monteiro, Hugo;[6] Email: hfmonteiro@arsnorte.min-saude.pt

[6]Regional Health Administration of Northern, Min. of Health Portugal.

Martins, Carlos.[3, 7] Email: carlosmartins20@gmail.com

[3]CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[7]#H4A Primary Health Care Research Network, Porto, Portugal

Corresponding Author

Susana Silva Pinto

susyapinto@gmail.com

Keywords

atrial fibrillation, anticoagulants, prevention, stroke; primary health care.

ABSTRACT

Objectives: This study aims to assess the appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients.

Design: Retrospective longitudinal study.

Setting: The study was conducted in the Regional Health Administration of Northern Portugal.

Participants: The authors selected a database of 21,854 patients with prescriptions from the same NOAC between January 2016 and December 2018 from all patients classified with the AF until December 2018.

Outcome measures: The appropriate dosages of NOAC for patients with AF according to three dosage suitability categories: contraindicated, unsuitable, and suitable, based on 2020 European Society of Cardiology guidelines of Atrial Fibrillation.

Results: Dabigatran had a lower percentage of suitable doses (n=1657, 50.1%) than other drugs, such as rivaroxaban (n=4737, 81.6%), apixaban (n=3830, 78.7%), and edoxaban (n=436, 82.1%). Most patients with an unsuitable dose were prescribed a lower dose than recommended based on their glomerular filtration rate (GFR). Among patients under 75 years old with GFR > 60 ml/min, 59.8% (n=10,028) had an adequate GFR range, while 27.8% (n=7,166) of GFR measurements from patients over 75 years old and 29.4% (n=913) of GFR measurements from patients under 75 years old with GFR < 60 ml/min were within an adequate time range. Adherence to NOACs varied across different drugs,

with 59.1% (n=540) adhering to edoxaban, 56.3% (n=5443) to rivaroxaban, 55.3% (n=3143) to dabigatran, and 53.3% (n=4211) to apixaban.

Conclusions: Dabigatran had the lowest percentage of suitable doses. Patients under 75 years old with GFR > 60ml/min had the highest percentage of an adequate GFR range, while other groups that require closer GFR monitoring had a lower percentage of an adequate GFR range. Adherence to NOACs differed among different drugs, with greater adherence to treatment with edoxaban and less adherence to apixaban.

Strengths and limitations of this study

- The main limitation of this real-world study is possible registration and codification bias, as the data are obtained from electronic health records created by family doctors.
- When assessing the appropriateness of the prescribed NOAC dose, only the most recent GFR, weight, and age criteria were considered.
- All NOAC dispensations were evaluated, regardless of whether the prescription was issued by a family doctor, hospital doctor from the National Health Service, or doctor from a private institution, for evaluation adherence to NOAC intake among AF patients.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is frequently associated with chronic kidney disease (CKD) (1). The first part of the AF-React study aimed to determine the prevalence of AF and to assess how these patients are being cared for: what anticoagulants are being prescribed and are they being prescribed as recommended. The renal function analyze revealed that 41.1% of 63,526 AF patients had a glomerular filtration rate (GFR) ≤ 60 ml/min (2). There is an intimate relationship between AF and CKD. On the one hand, kidney-specific mechanisms can alter the cardiac structure and predispose it to AF. On the other hand, the development of AF can accelerate the progression of CKD (1). As with the general population, AF in CKD patients is associated with an increased risk of thromboembolism and stroke (3). The synergistic effect of these two conditions raises serious issues concerning the balance between bleeding and thrombotic risk. Anticoagulant treatment can be challenging, especially in stage 5 CKD, where the clinical benefit is still unclear (1).

Oral anticoagulation (OAC) is the most effective form of thromboprophylaxis in AF patients with an increased risk of stroke. However, reducing stroke risk is directly related to the appropriateness of OAC prescription and adherence to OAC intake in these patients (4).

Previous studies have shown that non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban are superior to warfarin in preventing thromboembolic events in patients with non-valvular AF, providing increased safety and a reduction in the number of bleeding events overall (5–8). Therefore, they are currently recommended for AF patients at risk for stroke after calculating the CHA_2DS_2-VASc score (9).

However, the metabolism of NOACs largely depends on the kidneys for elimination, and patients with creatinine clearance <25 ml/min, who were excluded from all phase 3 NOAC trials, are not well studied (3).

The 2020 ESC Guidelines (9) and 2021 EHRA practical guide (10) recommend dose adjustment for apixaban, rivaroxaban, and edoxaban in stage 4 CKD and do not recommend the use of dabigatran. For GFR ≤ 50ml/min, dose adjustment is recommended for all NOACs.

This is particularly relevant since the kidneys are responsible for partially eliminating all four available NOACs. Dabigatran has the greatest extent of renal elimination (80%), while 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared via the kidneys (11).

Other conditions also influence the appropriate prescription of NOACs in AF patients. For dabigatran, a reduced dose should be prescribed if the patient is over 80 years old, has concomitant administration with verapamil, or has an increased risk of bleeding. For apixaban, a reduced dose is recommended for patients over 80 years old or with a body weight < 60 kg. For edoxaban, a reduced dose is recommended for patients with a body weight < 60 kg or with concomitant administration of dronedarone, cyclosporine, erythromycin, or ketoconazole (10).

Lowres et al. identified various factors associated with poor adherence to OAC intake. Medical factors include no prior history of stroke/TIA or low stroke risk, fewer comorbidities, high bleeding risk, paroxysmal AF, lack of AF symptoms, electrical cardioversion after commencing OAC and taking ≥2 dosages per day. Patient factors include younger age, lower health literacy, low AF knowledge, unawareness of associated stroke risk, poor OAC knowledge, concerns about bleeding and lifestyle changes, information overload, anger, depression, or anxiety from the AF diagnosis, low treatment satisfaction, busy work schedule, lack of health insurance coverage, and low ability to pay for medications (4).

This study aims to assess the appropriateness of the prescribing profile and adherence to the intake of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF.

METHODS

Data collection

This study was performed with the AF-React project database. The Department of Studies and Planning within the Regional Health Administration of Northern Portugal developed the AF-React project database, which includes data from 2016, 2017, and 2018. To identify patients with AF, the ICPC-2 code K78 for AF was utilized.

The AF-React study encompasses all adults (18 years or older) whose clinical records in Primary Health Care, under the purview of the Regional Health Administration of

Northern Portugal, included the K78 code prior to December 2018. For the purpose of this study, we focused on individuals who were prescribed the same NOAC (novel oral anticoagulant) within the study period of 2016 to 2018. So, a retrospective longitudinal study was conducted.

NOAC dosage suitability

In order to investigate the appropriate dosages of NOAC for patients with AF, we classified patients into one of three dosage suitability categories: contraindicated, unsuitable, and suitable. The patient's most recent GFR value was considered when making these classifications.

Regarding dabigatran (10), a GFR < 30 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if 1) the patient was not prescribed a 110mg dose when the GFR was between 50 and 30 ml/min, or a 150 mg dose when the GFR was above 50 ml/min, or 2) the patient was over 80 years old and not prescribed a 110 mg dose. Suitable dosage status was assigned if 1) the patient was prescribed a 110 mg dose when the GFR was between 50 and 30 ml/min, or a 150 mg dose when the GFR was above 50ml/min, and 2) the patient was over 80 years old and prescribed a 110 mg dose with a GFR above 30 ml/min.

For rivaroxaban (10), a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if the patient was not prescribed a 15 mg dose when the GFR was between 50 and 15 ml/min or a 20 mg dose when the GFR was above 50 ml/min. Suitable dosage status was assigned if the patient was prescribed a 15 mg dose when the GFR was between 50 and 15 ml/min or a 20 mg dose when the GFR was above 50 ml/min.

For apixaban, a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if 1) the patient was not prescribed a 2.5 mg dose when the GFR was between 30 and 15 ml/min, or a 5mg dose when the GFR was above 30 ml/min, or 2) the patient was over 80 years old or weighed less than 60 kg and not prescribed a 2.5 mg dose of apixaban. Suitable dosage status was assigned if 1) the patient was prescribed a 2.5mg dose when the GFR was between 30 and 15ml/min, or a 5 mg dose when the GFR was above 30 ml/min, or 2) the patient was over 80 years old or weighed

less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 2.5 mg dose of apixaban.

For edoxaban, a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable dosage status was assigned if 1) the patient was not prescribed a 30 mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50 ml/min, or 2) the patient weighed less than 60 kg and was not prescribed a 30mg dose of edoxaban. Suitable dosage status was assigned if 1) the patient was prescribed a 30 mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50 ml/min, or 2) the patient weighed less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 30 mg dose of edoxaban.

Monitoring renal function and prescribing NOAC

Regarding the monitoring of renal function and prescribing NOAC, the analysis was divided into three groups: patients over 75 years old (monitored every 6 months), patients 75 years old or younger with a GFR over 60 ml/min (monitored annually), and patients 75 years old or younger with a GFR under 60 ml/min (monitored according to the most recent GFR measurement). For each group, the number of patients with a GFR within the appropriate range (within 0 months or earlier), a GFR up to 6 months after the appropriate range, and a GFR after 6, 12, or 24 months after the appropriate range is provided.

Adherence to NOAC

To examine adherence to NOAC intake among AF patients who received the same NOAC during the study period, all NOAC dispensations were evaluated, regardless of whether the prescription was issued by a family doctor, hospital doctor from the National Health Service, or doctor from a private institution. Patients were considered adherent if they received at least 90% of the prescribed pills from the time of the AF diagnosis or the beginning of the study until the end (12).

Data analysis

The categorical variables were described using absolute and relative frequencies, n (%).

The statistical analysis was performed using software R (13).

Ethic issues

The Department of Studies and Planning of the Regional Health Administration of Northern Portugal (Ministry of Health, Portugal) processed the data. Anonymized data processing and editing were conducted on a secure platform, and the data were extracted from the server in compliance with legal regulations and with the approval of the Health Ethics Committee of the Regional Health Administration of Northern Portugal.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Data description

Out of a total of 63,526 patients diagnosed with atrial fibrillation/flutter (ICPC-2, K78 code) in the northern region of Portugal until December 2018, we identified 21,854 patients who were prescribed the same non-vitamin K antagonist oral anticoagulant (NOAC) during the study period. These NOACs included dabigatran (5,219 prescriptions), rivaroxaban (8,801 prescriptions), apixaban (7,052 prescriptions), and edoxaban (782 prescriptions). Understanding the temporal relationship between NOAC prescription and K78 coding is crucial to determine whether NOACs were prescribed after AF diagnosis. Of the 21,455 (98%) patients, 188,780 prescriptions were issued after the K78 code.

In the first part of the AF-React study, a primary limitation was identified: the assessment of AF was based on data coded in the clinical process in primary healthcare. Therefore, in this analysis, we examined how codification has evolved over the years (see Figure 1). Our findings indicate that the frequency of ICPC-2 K78 encoding has increased over time.

Additionally, since 2015, the number of AF diagnoses coded has decreased, suggesting that from this date, the ICPC-2 K78 coding is more closely related to new and accurate diagnoses rather than the detection of previous diagnostic coding errors.

NOAC dosage suitability

The appropriate dosage of NOAC is critical for anticoagulation to effectively prevent stroke. To evaluate the suitability of the prescribed dose, we analyzed 128,603 prescriptions from 16,282 patients with at least one GFR value (Table 1).

Table 1. The suitability of prescribed dose non-VKA oral anticoagulants (NOAC).

	Contraindicated	Suitable	Unsuitable		
			Not suitable for renal function		Not suitable for weight or age
			Lower dose	Higher dose	
Dabigatran (n = 3305)					
n	5	1657	1538	17	88
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n	2	436	50	25	18
%	0.4	82.1	9.4	4.7	3.4

Approximately 89.1% (14,507) of patients maintained the same suitability dose status: 19 were contraindicated, 10,660 were suitable, and 3,828 were unsuitable. Notably, dabigatran had fewer suitable doses than other drugs: dabigatran - 50.1%; rivaroxaban - 81.6%; apixaban - 78.7%; and edoxaban - 82.1%. Most patients with an unsuitable dose were on a lower dose than recommended based on their GFR: dabigatran - 46.5%; rivaroxaban - 11.7%; apixaban - 20.0%; and edoxaban - 9.4%. For patients in an unsuitable dose condition due to weight and age: those on dabigatran who were over 80 years of age were prescribed a dose of 150mg (27 patients) or 75mg (61 patients); those on apixaban who were over 80 years of age or weighed less than 60 kilograms were

prescribed a dose of 5mg (47 patients); and those on edoxaban who weighed less than 60 kilograms were prescribed a dose of 60mg (18 patients).

Monitoring renal function and prescribing NOAC

Another crucial aspect of NOAC therapy to effectively prevent stroke is adequate renal monitoring by physicians. Analyzing renal function monitoring, we found that 19,877 patients had at least one GFR measurement during the 3-year study, resulting in 45,679 recordings. Of these, 25,819 (56.5%) measurements were from 10,792 (54.3%) patients over 75 years old, while 16,757 (36.7%) GFR recordings were from 8,469 (45.4%) patients younger than 75 years old with GFR levels above 60 ml/min. Only 1,737 (8.7%) patients 75 years or younger had 3,103 (6.8%) GFR values at most 60 ml/min.

Regarding the appropriate GFR ranges for monitoring renal function and prescribing NOAC, we found that 1) 7,166 (27.8%) GFR measurements from patients over 75 years old, 2) 10,028 (59.8%) GFR measurements from patients under 75 years old with GFR levels above 60 ml/min, and 3) 913 (29.4%) measurements from patients under 75 years old with GFR levels below 60 ml/min fell within the recommended time range. However, many GFR measurements did not have an adequate range. For those with an inadequate range of GFR, we documented the number of months beyond the recommended range, which is described in Table 2.

Table 2. Analysis of ranges between GFR for monitoring renal function for prescribing non-VKA oral anticoagulants (NOAC) in three groups: patients > 75 years old; patients ≤ 75 years old and GFR > 60ml/min; and patients ≤ 75 years old and GFR < 60ml/min.

Months after the recommended deadline	Patients > 75 years old n (%)		Patients ≤ 75 years old and GFR > 60ml/min n (%)		Patients ≤ 75 years old and GFR < 60ml/min n (%)	
	GFR recordings	Patients	GFR recordings	Patients	GFR recordings	Patients
Before or 0 months	7166 (28)	4063 (23)	10028 (60)	5672 (48)	913 (29)	586 (25)
]0; 6] months	11247 (44)	7084 (39)	4267 (25)	3750 (32)	1297 (42)	950 (40)
]6; 12] months	4718 (18)	4169 (23)	1453 (9)	1452 (12)	577 (19)	530 (22)
]12;24] months	2296 (9)	2288 (13)	975 (6)	974 (8)	277 (9)	275 (12)
More than 24 months	392 (1)	392 (2)	34 (0)	24 (0)	39 (1)	29 (1)
Total	25819	17996	16757	11882	3103	2380

Adherence to NOAC

To analyze adherence to NOAC intake in AF patients, we considered the NOAC dispensed due to adherence to therapy, regardless of whether the patient had a medical prescription for the medication.

Regarding dispensation analysis, 24,426 patients dispensed the same NOAC at the pharmacy during the study period. When we examined the relationship between dispensation and the K78 coding date, we found that 5,837 patients dispensed 25,890 NOAC before the K78 coding date, while 24,164 patients dispensed 295,551 NOAC after the K78 coding date. Additionally, 5,576 patients dispensed the same NOAC before and after the atrial fibrillation/flutter coding. Of the 24,164 patients who dispensed NOAC after the K78 coding date, 5,683 (23.5%) dispensed dabigatran, 9,667 (40.0%) dispensed rivaroxaban, 7,901 (32.7%) dispensed apixaban, and 913 (3.8%) dispensed edoxaban.

Figure 2 shows the difference between the number of pills required to complete the therapy and the number of pills actually dispensed.

Based on this analysis, there was greater adherence to treatment with edoxaban and less adherence with apixaban. Patients who were considered adherent had received at least 90% of the pills intended to be taken from the time of diagnosis of AF or the start of the study until the end (12). Approximately 59.1% of patients adhered to edoxaban, 56.3% to rivaroxaban, 55.3% to dabigatran, and 53.3% to apixaban. Furthermore, we compared the adherence to the NOAC of patients who were diagnosed with atrial fibrillation (K78) before the start of the study period with the adherence of those who were diagnosed with atrial fibrillation (K78) after the start of the study: apixaban - 44.1%; 57.1% (before; after, respectively), dabigatran - 56.0%, 54.0% (before; after, respectively), edoxaban - 8.1%, 67.1% (before; after, respectively) and rivaroxaban - 50, 7%, 60.2% (before; after, respectively).

We also analyzed which patients had received all the pills necessary to complete the entire treatment during the study period: edoxaban - 29.4%; rivaroxaban - 24.3%; apixaban - 22.6%; and dabigatran - 18.5%.

DISCUSSION

Summary

Dabigatran has the lowest percentage of suitable doses, with 46.5% of patients being medicated with an unsuitable lower dose. Patients who are 75 years old or younger and have a GFR greater than 60 ml/min, whose renal function should be monitored annually, have the highest percentage of an adequate range of GFR. Other groups that require closer GFR monitoring have a lower percentage of an adequate range of GFR. Adherence to NOACs varies with different drugs: There was greater adherence to treatment with edoxaban and less adherence to apixaban.

Comparison with existing literature

Antunes et al. evaluated the prescription of oral anticoagulation in four family health units in northern Portugal from January 2010 to December 2015. They found that 76.7% of

patients diagnosed with atrial fibrillation based on ICPC-2 coding were medicated with OAC (14). However, in the period from 2016 to 2018, there was an increase in prescriptions to 98%. This suggests an improvement in the anticoagulation of patients with atrial fibrillation in the northern region of Portugal over the years. These results contradict some European studies that showed resistance from family physicians to introduce anticoagulation after the diagnosis of atrial fibrillation (15–18) and contradict the findings of the study by Turakhia et al., which showed that the medical speciality that diagnoses AF influences the decision to anticoagulate or not (19).

The electronic clinical files of primary health care contain a list of health problems for which there is a follow-up plan, relevant diseases, and those that require continuous medical treatment. Accurate records ensure the adequacy of care and enable monitoring and evaluation of the care provided to the population (20). The use of the International Classification of Primary Care, 2nd edition (ICPC-2) is essential for this purpose. Data published in 2015 by the Central Administration of the Health System (CAHS) showed a growing codification of health problems at a national level, reflecting the increase in computerized clinical records and demand from users and healthcare providers (21). This study found that the ICPC-2 K78 encoding has become more frequent over the years, which is consistent with the CAHS data at the national level. In 2011, 20.6 million health problems were identified, and by 2013, this figure had increased to 30.2 million. The percentage of consultations with ICPC-2 coding in primary health care is high in Portugal (69.2% in 2011, 83.9% in 2012, and 84% in 2013) (21).

Sugrue et al. found that NOAC dosing was unsuitable in 14.8% of patients at the Mayo Clinic: 12.4% received an inappropriate lower dose, and 2.4% received an unsuitable high dose (22). Even the ORBIT-AF II Registry, a nationwide AF registry conducted in a community practice in the US, showed that an unsuitable dose of a NOAC was prescribed in only 12.5% of cases: underdosing in 9.3% of patients and overdosing in 3.3% of patients, respectively (23). However, a real-world registry in Spain reported higher rates of underdosing and overdosing on NOAC therapy: 17.5% and 14.9%, respectively (24). This study's results agree with those of the Mayo Clinic and ORBIT-AF II Registry studies, with underdosing in 15.1% of patients and overdosing in 1.8%. These findings are consistent with studies conducted in other countries. Nevertheless, due to the risks associated with unsuitable prescribing, greater attention is needed from Portuguese family doctors.

Stamellou and Floege highlighted the importance of regular checks of renal function in patients receiving NOACs to avoid overdosing, especially in situations that may cause acute-on-chronic kidney injury. In such patients, apixaban may be the safest licensed NOAC because of its relatively low renal elimination. In more advanced CKD, i.e., stage 4 and particularly in stage 5, NOACs are not recommended due to the lack of RCT data and concerns of overdosing with the risk of bleeding and anticoagulant-related nephropathy (25). A prudent approach is to check renal function at the initiation of treatment with NOACs, after three months, and then every year, except for high-risk patients (elderly >75 years, patients with low body mass) who require monitoring at least every six months (26). In patients with declining renal function, the current position of EHRA is to estimate the recheck intervals individually using a simple calculation: if creatinine clearance (CrCl) is ≤60 mL/min, the recheck interval in months is CrCl/10 (11).

Cayuelas et al. assessed compliance with kidney function monitoring recommendations in NVAF patients starting NOAC therapy (27). Compliance with kidney function monitoring recommendations was 61%, similar to the group of patients younger than 75 years with a GFR > 60ml/min in this study. Patients younger than 75 years with a GFR > 60ml/min had the highest rate of adequate GFR range, at about 60%, followed by patients ≤75 years old with a GFR <60ml/min at 29.4%, and patients >75 years old at 27.8%. Another noteworthy finding is the low percentage of patients with a GFR range assessed beyond the appropriate 12-month interval in patients >75 years old and in patients ≤75 years old with a GFR <60ml/min (10.4% and 10.2%, respectively). Family doctors appear to follow an annual pattern for monitoring renal function in all patients receiving NOACs, without individualizing the interval for monitoring renal function according to the criteria mentioned here. Therefore, patients who receive annual GFR evaluations have the highest rate of adequate renal monitoring. More training for individualized tracking of patients with other conditions may help Portuguese family doctors improve these results.

There was greater adherence to treatment with edoxaban and less adherence to apixaban, likely due to differences in drug posology, with edoxaban taken once daily and apixaban taken twice daily. Brízido et al. evaluated adherence to NOACs and its determinants in a population of AF patients from the outpatient general cardiology list at a tertiary centre in Portugal. The median adherence was 91% (IQR 74-100%) for rivaroxaban, 87% (IQR 74-100%) for apixaban, 82% (IQR 48-100%) for dabigatran, and 96% (IQR 83-100%) for edoxaban. There were no statistically significant differences between the NOACs (p

= 0.102). Half of the patients (51%) were classified as non-compliant, which is consistent with the findings of this study. It was found that in all NOACs, with the exception of dabigatran, adherence was higher in patients diagnosed after the start of the study than in those diagnosed before the start of the study who had a longer duration of therapy. Therefore, there appears to be greater adherence in the immediate period after the diagnosis than in a later period. Therapy duration, NOACs taken twice daily, and higher out-of-pocket costs were independent predictors of non-compliance (12).

In another real-world analysis of adherence to NOACs, rivaroxaban and apixaban had favourable profiles compared to dabigatran, and rivaroxaban appeared to have higher overall adherence among the NOACs, although edoxaban was not included in this analysis. (28) A systematic review and meta-analysis of observational studies found that up to 30% of patients with AF are non-adherent to NOAC therapy (29). Although we analyzed data on drug dispensing in pharmacies, there may be the possibility of patients forgetting to take medication, which is more likely to occur with twice-daily drugs (apixaban and dabigatran), so once medications usage by the patients were not verified.

Limitations

The primary limitation of the AF-React study is that it relies on AF assessment data coded during the clinical process in primary healthcare. While there are some defects in the coding, it appears that the ICPC-2 K78 encoding has become more common over the years, and since 2015, there has been a decrease in the number of AF diagnoses coded. This suggests that the increase in K78 encoding is related to real new diagnoses rather than simply detecting coding errors in previous diagnoses.

When assessing the appropriateness of the prescribed NOAC dose, only the most recent GFR, weight, and age criteria were considered. Unfortunately, other relevant NOAC dosage criteria were not available in the database. It is also important to consider frailty when assessing the appropriate range of GFR to monitor renal function and prescribe NOACs. However, this data was not available for analysis.

CONCLUSIONS

The AF-React study enabled an analysis of the appropriateness of NOAC dosage prescriptions, the appropriate range of GFR for monitoring renal function and prescribing NOACs, and adherence to NOAC intake in AF patients. As such, the study provides highly relevant conclusions for Portugal. In the future, it will be necessary to improve the appropriate prescribing of NOAC doses and understand the reasons for inadequate monitoring of renal function in AF patients receiving NOACs. Additionally, further studies are needed to identify reasons for non-adherence to NOAC treatment in AF patients.

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AUTHOR STATEMENT

SSP and CM contributed to the conception of the work. All authors contributed to the design of the study. HM contributed to the data acquisition process. SPP, ASCT, and TSH contributed to the analysis and interpretation of the data. SSP drafted the manuscript, and HM, ASCT, TSH, and CM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

DATA AVAILABILITY STATEMENT

No additional data available.

ETHICS APPROVAL

The Health Ethics Committee of the Regional Health Administration of Northern Portugal approved the study protocol (Nº133/2018).

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

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Figure 1. ICPC-2 K78 codification over the years.

Figure 2. The difference between the number of pills needed to complete the therapy and the number of pills dispensed.

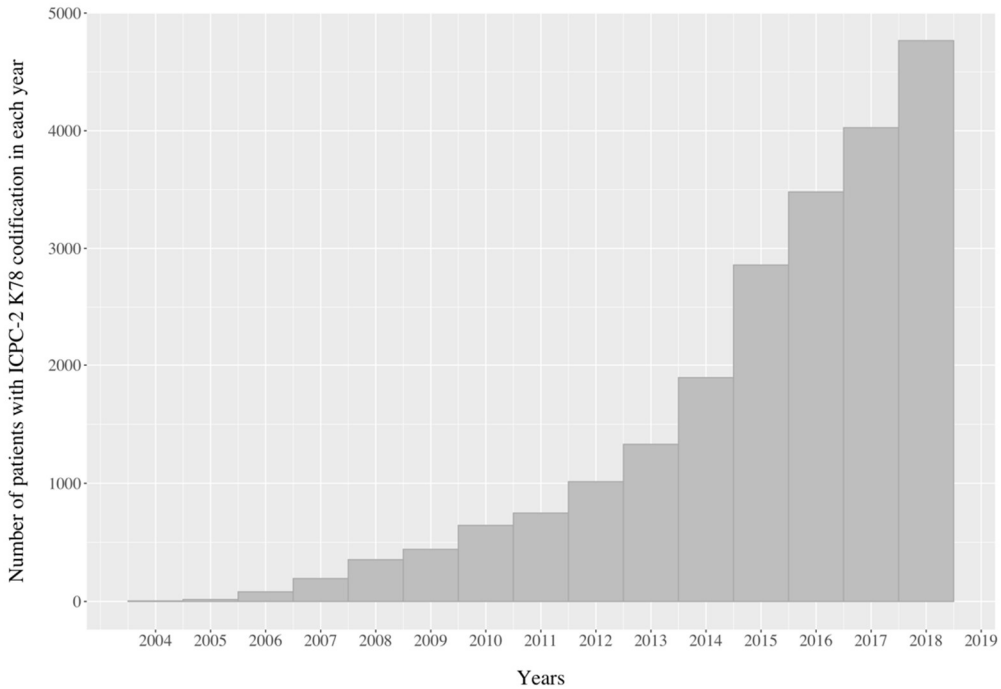

Figure 1.

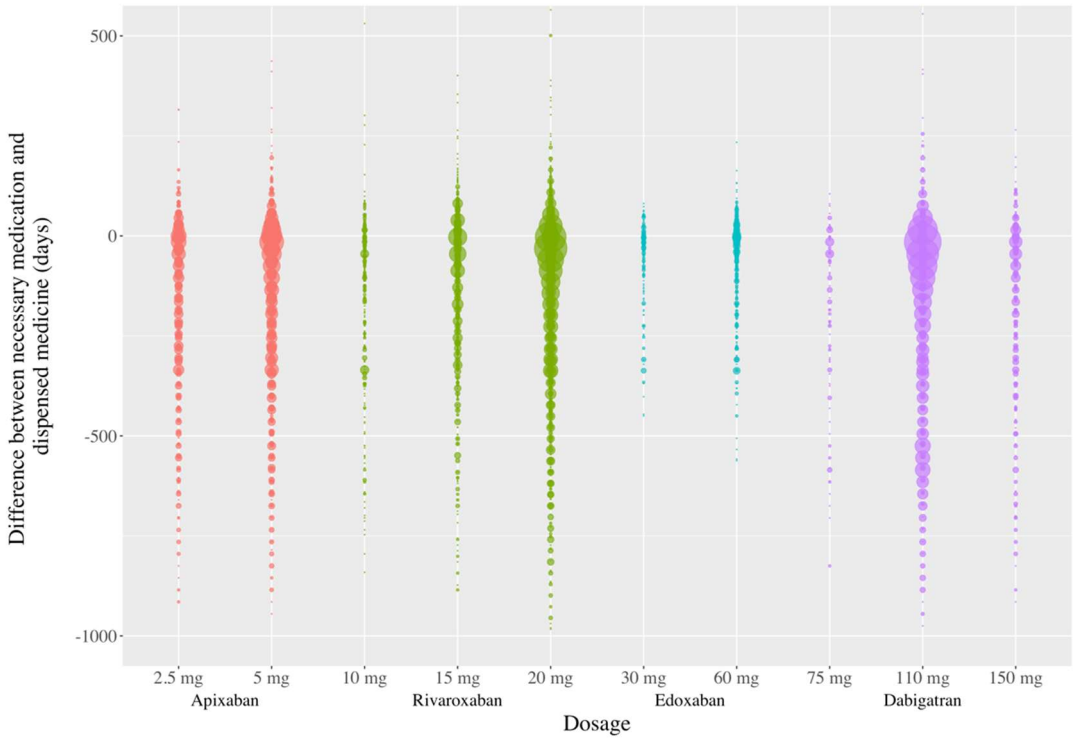

Figure 2.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13, 14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: analysis of a retrospective longitudinal study using real-world data from Northern Portugal (AF-React study)

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Keywords:	Stroke < NEUROLOGY, Primary Health Care, Anticoagulation < HAEMATOLOGY

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Appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: analysis of a retrospective longitudinal study using real-world data from Northern Portugal (AF-React study)

Authors

Pinto, Susana Silva;[1, 2,3] Email: susyapinto@gmail.com

[1] São Tomé Family Health Unit (ACeS Santo Tirso/Trofa), Portugal.

[2] Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal.

[3] CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

Henriques, Teresa S.;[3, 4] Email: teresasarhen@gmail.com

[3] CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[4] CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto, Porto, Portugal.

Teixeira, Andreia;[2, 3, 5] Email: andreiasofiat@hotmail.com

[2] MEDCIDS - Department of Community Medicine, Information and Decision in Health; Faculty of Medicine, University of Porto, Porto Portugal

[3]CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[5]ADiT-LAB, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial Nun'Álvares, 4900-347 Viana do Castelo, Portugal

Monteiro, Hugo;[6] Email: hfmonteiro@arsnorte.min-saude.pt

[6]Regional Health Administration of Northern, Min. of Health Portugal.

Martins, Carlos.[3, 7] Email: carlosmartins20@gmail.com

[3]CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

[7]#H4A Primary Health Care Research Network, Porto, Portugal

Correspondence to:
Susana Silva Pinto
susyapinto@gmail.com

Keywords

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ABSTRACT

Objectives: This study aimed to assess the appropriateness of prescribing profiles and intake adherence with non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation (AF).

Design: Retrospective longitudinal study.

Setting: The study was conducted in the Regional Health Administration of Northern Portugal.

Participants: The authors selected a database of 21,854 patients with prescriptions for NOACs between January 2016 and December 2018 from all patients classified with the AF until December 2018.

Outcome measures: The appropriate dosages of NOAC for patients with AF according to three dosage categories: contraindicated, inconsistent, and consistent with the guidelines, based on 2020 European Society of Cardiology guidelines of Atrial Fibrillation.

Results: Dabigatran had a lower percentage of guideline-consistent doses (n=1657, 50.1%) than other drugs such as rivaroxaban (n=4737, 81.6%), apixaban (n=3830, 78.7%), and edoxaban (n=436, 82.1%). Most patients with an inconsistent dose were prescribed a lower dose than recommended based on their glomerular filtration rate (GFR). Among patients younger than 75 years with GFR >60 ml/min, 59.8% (n=10,028) had an adequate GFR range, while 27.8% (n=7,166) of GFR measurements from patients older than 75 years old and 29.4% (n=913) of GFR measurements from patients younger than 75 years with GFR <60 ml/min were within an adequate time range. Adherence to NOACs varied across different drugs, with 59.1% (n=540) adhering to edoxaban, 56.3%

(n=5443) to rivaroxaban, 55.3% (n=3143) to dabigatran, and 53.3% (n=4211) to apixaban.

Conclusions: Dabigatran had the lowest percentage of guideline-consistent doses. Patients younger than 75 years with GFR >60ml/min had the highest percentage with an adequate GFR range, while other groups that require closer GFR monitoring had lower percentages within an adequate GFR range. Adherence to NOACs differed among different drugs, with greater adherence to treatment with edoxaban and less adherence to apixaban.

Strengths and limitations of this study

- All NOAC dispensations were evaluated, regardless of whether the prescription was issued by a family doctor, hospital doctor from the National Health Service, or doctor from a private institution, for evaluation adherence to NOAC intake among AF patients.
- The main limitation of this real-world study is possible registration and codification bias, as the data are obtained from electronic health records created by family doctors.
- When assessing the appropriateness of the prescribed NOAC dose, only the most recent GFR, weight, and age criteria were considered.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is frequently associated with chronic kidney disease (CKD) (1). The first part of the AF-React study aimed to determine the prevalence of AF and to assess how these patients are being cared for: what anticoagulants are being prescribed and are they being prescribed as recommended. The renal function analyze revealed that 41.1% of 63,526 AF patients had a glomerular filtration rate (GFR) ≤ 60 ml/min (2). There is an intimate relationship between AF and CKD. On the one hand, kidney-specific mechanisms can alter the cardiac structure and predispose it to AF. On the other hand, the development of AF can accelerate the progression of CKD (1). As with the general population, AF in CKD patients is associated with an increased risk of thromboembolism and stroke (3). The synergistic effect of these two conditions raises serious issues concerning the balance between bleeding and thrombotic risk. Anticoagulant treatment can be challenging, especially in stage 5 CKD, where the clinical benefit is still unclear (1).

Oral anticoagulation (OAC) is the most effective form of thromboprophylaxis in AF patients with an increased risk of stroke. However, reducing stroke risk is directly related to the appropriateness of OAC prescription and adherence to OAC intake in these patients (4).

Previous studies have shown that non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban are superior to warfarin in preventing thromboembolic events in patients with non-valvular AF, providing increased safety and a reduction in the number of bleeding events overall (5–8). Therefore, they are currently recommended for AF patients at risk for stroke after calculating the CHA_2DS_2-VASc score (9).

However, the metabolism of NOACs largely depends on the kidneys for elimination, and patients with creatinine clearance <25 ml/min, who were excluded from all phase 3 NOAC trials, are not well studied (3).

The 2020 ESC Guidelines (9) and 2021 EHRA practical guide (10) recommend dose adjustment for apixaban, rivaroxaban, and edoxaban in stage 4 CKD and do not recommend the use of dabigatran. For GFR ≤ 50ml/min, dose adjustment is recommended for all NOACs.

This is particularly relevant since the kidneys are responsible for partially eliminating all four available NOACs. Dabigatran has the greatest extent of renal elimination (80%), while 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared via the kidneys (11).

Other conditions also influence the appropriate prescription of NOACs in AF patients. For dabigatran, a reduced dose should be prescribed if the patient is over 80 years old, has concomitant administration with verapamil, or has an increased risk of bleeding. For apixaban, a reduced dose is recommended for patients over 80 years old or with a body weight < 60 kg. For edoxaban, a reduced dose is recommended for patients with a body weight < 60 kg or with concomitant administration of dronedarone, cyclosporine, erythromycin, or ketoconazole (10).

Lowres et al. identified various factors associated with poor adherence to OAC intake. Medical factors include no prior history of stroke/TIA or low stroke risk, fewer comorbidities, high bleeding risk, paroxysmal AF, lack of AF symptoms, electrical cardioversion after commencing OAC and taking ≥2 dosages per day. Patient factors include younger age, lower health literacy, low AF knowledge, unawareness of associated stroke risk, poor OAC knowledge, concerns about bleeding and lifestyle changes, information overload, anger, depression, or anxiety from the AF diagnosis, low treatment satisfaction, busy work schedule, lack of health insurance coverage, and low ability to pay for medications (4).

This study aims to assess the appropriateness of the prescribing profile and adherence to the intake of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF.

METHODS

Data collection

This study was performed with the AF-React project database. The Department of Studies and Planning within the Regional Health Administration of Northern Portugal developed the AF-React project database, which includes data from 2016, 2017, and 2018. To identify patients with AF, the ICPC-2 code K78 for AF was utilized.

The AF-React study encompasses all adults (18 years or older) whose clinical records in Primary Health Care, under the purview of the Regional Health Administration of

Northern Portugal, included the K78 code prior to December 2018. For the purpose of this study, we focused on individuals who were prescribed the same NOAC (novel oral anticoagulant) within the study period of 2016 to 2018. So, a retrospective longitudinal study was conducted.

NOAC dosage

In order to investigate the appropriate dosages of NOAC for patients with AF, we classified patients into one of three dosage categories: contraindicated, inconsistent, and consistent with the guidelines. The patient's most recent GFR value was considered when making these classifications.

Regarding dabigatran (10), a GFR < 30 ml/min was classified as contraindicated for use. Inconsistent with the guidelines dosage status was assigned if 1) the patient was not prescribed a 110mg dose when the GFR was between 50 and 30 ml/min, or a 150 mg dose when the GFR was above 50 ml/min, or 2) the patient was over 80 years old and not prescribed a 110 mg dose. Consistent with the guidelines dosage status was assigned if 1) the patient was prescribed a 110 mg dose when the GFR was between 50 and 30 ml/min, or a 150 mg dose when the GFR was above 50ml/min, and 2) the patient was over 80 years old and prescribed a 110 mg dose with a GFR above 30 ml/min.

For rivaroxaban (10), a GFR < 15 ml/min was classified as contraindicated for use. Inconsistent with the guidelines dosage status was assigned if the patient was not prescribed a 15 mg dose when the GFR was between 50 and 15 ml/min or a 20 mg dose when the GFR was above 50 ml/min. Consistent with the guidelines dosage status was assigned if the patient was prescribed a 15 mg dose when the GFR was between 50 and 15 ml/min or a 20 mg dose when the GFR was above 50 ml/min.

For apixaban, a GFR < 15 ml/min was classified as contraindicated for use. Inconsistent with the guidelines dosage status was assigned if 1) the patient was not prescribed a 2.5 mg dose when the GFR was between 30 and 15 ml/min, or a 5mg dose when the GFR was above 30 ml/min, or 2) the patient was over 80 years old or weighed less than 60 kg and not prescribed a 2.5 mg dose of apixaban. Consistent with the guidelines dosage status was assigned if 1) the patient was prescribed a 2.5mg dose when the GFR was between 29 and 15ml/min, or a 5 mg dose when the GFR was above 30 ml/min, or 2) the patient

was over 80 years old or weighed less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 2.5 mg dose of apixaban.

For edoxaban, a GFR < 15 ml/min was classified as contraindicated for use. Inconsistent with the guidelines dosage status was assigned if 1) the patient was not prescribed a 30 mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50 ml/min, or 2) the patient weighed less than 60 kg and was not prescribed a 30mg dose of edoxaban. Consistent with the guidelines dosage status was assigned if 1) the patient was prescribed a 30 mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50 ml/min, or 2) the patient weighed less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 30 mg dose of edoxaban.

Monitoring renal function and prescribing NOAC

Regarding the monitoring of renal function and prescribing NOAC, the analysis was divided into three groups: patients over 75 years old (monitored every 6 months), patients 75 years old or younger with a GFR over 60 ml/min (monitored annually), and patients 75 years old or younger with a GFR under 60 ml/min (monitored according to the most recent GFR measurement). For each group, the number of patients with a GFR within the appropriate range (within 0 months or earlier), a GFR up to 6 months after the appropriate range, and a GFR after 6, 12, or 24 months after the appropriate range is provided.

Adherence to NOAC

To examine adherence to NOAC intake among AF patients who received the same NOAC during the study period, all NOAC dispensations were evaluated, regardless of whether the prescription was issued by a family doctor, hospital doctor from the National Health Service, or doctor from a private institution. Patients were considered adherent if they received at least 90% of the prescribed pills from the time of the AF diagnosis or the beginning of the study until the end (12).

Data analysis

The categorical variables were described using absolute and relative frequencies, n (%). The statistical analysis was performed using software R (13).

Ethical issues

The Department of Studies and Planning of the Regional Health Administration of Northern Portugal (Ministry of Health, Portugal) processed the data. Anonymized data processing and editing were conducted on a secure platform, and the data were extracted from the server in compliance with legal regulations and with the approval of the Health Ethics Committee of the Regional Health Administration of Northern Portugal.

Patient and public involvement

None.

RESULTS

Data description

Out of a total of 63,526 patients diagnosed with atrial fibrillation/flutter (ICPC-2, K78 code) in the northern region of Portugal until December 2018, we identified 21,854 patients who were prescribed non-vitamin K antagonist oral anticoagulants (NOACs) during the study period. These NOACs included dabigatran (5,219 prescriptions), rivaroxaban (8,801 prescriptions), apixaban (7,052 prescriptions), and edoxaban (782 prescriptions). Understanding the temporal relationship between NOAC prescription and K78 coding is crucial to determine whether NOACs were prescribed after AF diagnosis. Of the 21,455 (98%) patients, 188,780 prescriptions were issued after the K78 code.

In the first part of the AF-React study, a primary limitation was identified: the assessment of AF was based on data coded in the clinical process in primary healthcare. Therefore, in this analysis, we examined how codification has evolved over the years (see Figure 1). Our findings indicate that the frequency of ICPC-2 K78 encoding has increased over time. Additionally, since 2015, the number of AF diagnoses coded has decreased, suggesting

that from this date, the ICPC-2 K78 coding is more closely related to new and accurate diagnoses rather than the detection of previous diagnostic coding errors.

NOAC dosage

The appropriate dosage of NOAC is critical for anticoagulation to effectively prevent stroke. To evaluate the prescribed dose, we analyzed 128,603 prescriptions from 16,282 patients with at least one GFR value (Table 1).

Table 1. The prescribed dose non-VKA oral anticoagulants (NOAC)

	Contraindicated according to guidelines	Consistent with the guidelines	Inconsistent with the guidelines		
			Inconsistent with the guidelines for renal function		Inconsistent with the guidelines for weight or age
			Lower dose	Higher dose	
Dabigatran (n = 3305)					
N	5	1657	1538	17	88
%	0.2	50.1	46.5	0.5	2.7
Rivaroxaban (n = 5802)					
N	5	4737	678	382	
%	0.1	81.6	11.7	6.6	
Apixaban (n = 4869)					
N	7	3830	975	10	47
%	0.1	78.7	20.0	0.2	1.0
Edoxaban (n = 531)					
n	2	436	50	25	18
%	0.4	82.1	9.4	4.7	3.4

Approximately 89.1% (14,507) of patients maintained the same dose status: 19 were contraindicated, 10,660 were consistent with the guidelines, and 3,828 were inconsistent with the guidelines. Notably, dabigatran had fewer consistent with the guidelines doses than other drugs: dabigatran - 50.1%; rivaroxaban - 81.6%; apixaban - 78.7%; and edoxaban - 82.1%. Most patients with an inconsistent with the guidelines dose were on a lower dose than recommended based on their GFR: dabigatran - 46.5%; rivaroxaban - 11.7%; apixaban - 20.0%; and edoxaban - 9.4%. For patients in an inconsistent with the guidelines dose condition due to weight and age: those on dabigatran who were over 80 years of age were prescribed a dose of 150mg (27 patients) or 75mg (61 patients); those

on apixaban who were over 80 years of age or weighed less than 60 kilograms were prescribed a dose of 5mg (47 patients); and those on edoxaban who weighed less than 60 kilograms were prescribed a dose of 60mg (18 patients).

Monitoring renal function and prescribing NOAC

Another crucial aspect of NOAC therapy to effectively prevent stroke is adequate renal monitoring by physicians. Analyzing renal function monitoring, we found that 19,877 patients had at least one GFR measurement during the 3-year study, resulting in 45,679 recordings. Of these, 25,819 (56.5%) measurements were from 10,792 (54.3%) patients over 75 years old, while 16,757 (36.7%) GFR recordings were from 8,469 (45.4%) patients younger than 75 years old with GFR levels above 60 ml/min. Only 1,737 (8.7%) patients 75 years or younger had 3,103 (6.8%) GFR values at most 60 ml/min.

Regarding the appropriate GFR ranges for monitoring renal function and prescribing NOAC, we found that 1) 7,166 (27.8%) GFR measurements from patients over 75 years old, 2) 10,028 (59.8%) GFR measurements from patients under 75 years old with GFR levels above 60 ml/min, and 3) 913 (29.4%) measurements from patients under 75 years old with GFR levels below 60 ml/min fell within the recommended time range. However, many GFR measurements did not have an adequate range. For those with an inadequate range of GFR, we documented the number of months beyond the recommended range, which is described in Table 2.

Table 2. Analysis of ranges between GFR for monitoring renal function for prescribing non-VKA oral anticoagulants (NOAC) in three groups: patients >75 years old; patients ≤75 years old and GFR >60ml/min; and patients ≤75 years old and GFR <60ml/min

Months after the recommended deadline	Patients > 75 years old n (%)		Patients ≤ 75 years old and GFR > 60ml/min n (%)		Patients ≤ 75 years old and GFR < 60ml/min n (%)	
	GFR recordings	Patients	GFR recordings	Patients	GFR recordings	Patients
Before or 0 months	7166 (28)	4063 (23)	10028 (60)	5672 (48)	913 (29)	586 (25)
]0; 6] months	11247 (44)	7084 (39)	4267 (25)	3750 (32)	1297 (42)	950 (40)
]6; 12] months	4718 (18)	4169 (23)	1453 (9)	1452 (12)	577 (19)	530 (22)
]12;24] months	2296 (9)	2288 (13)	975 (6)	974 (8)	277 (9)	275 (12)
More than 24 months	392 (1)	392 (2)	34 (0)	24 (0)	39 (1)	29 (1)
Total	25819	17996	16757	11882	3103	2380

Adherence to NOAC

To analyze adherence to NOAC intake in AF patients, we considered the NOAC dispensed due to adherence to therapy, regardless of whether the patient had a medical prescription for the medication.

Regarding dispensation analysis, 24,426 patients dispensed the same NOAC at the pharmacy during the study period. When we examined the relationship between dispensation and the K78 coding date, we found that 5,837 patients dispensed 25,890 NOAC before the K78 coding date, while 24,164 patients dispensed 295,551 NOAC after the K78 coding date. Additionally, 5,576 patients dispensed the same NOAC before and after the atrial fibrillation/flutter coding. Of the 24,164 patients who dispensed NOAC after the K78 coding date, 5,683 (23.5%) dispensed dabigatran, 9,667 (40.0%) dispensed rivaroxaban, 7,901 (32.7%) dispensed apixaban, and 913 (3.8%) dispensed edoxaban.

Figure 2 shows the difference between the number of pills required to complete the therapy and the number of pills actually dispensed.

Based on this analysis, there was greater adherence to treatment with edoxaban and less adherence with apixaban. Patients who were considered adherent had received at least 90% of the pills intended to be taken from the time of diagnosis of AF or the start of the study until the end (12). Approximately 59.1% of patients adhered to edoxaban, 56.3% to rivaroxaban, 55.3% to dabigatran, and 53.3% to apixaban. Furthermore, we compared the adherence to the NOAC of patients who were diagnosed with atrial fibrillation (K78) before the start of the study period with the adherence of those who were diagnosed with atrial fibrillation (K78) after the start of the study: apixaban - 44.1%; 57.1% (before; after, respectively), dabigatran - 56.0%, 54.0% (before; after, respectively), edoxaban - 8.1%, 67.1% (before; after, respectively) and rivaroxaban - 50, 7%, 60.2% (before; after, respectively).

We also analyzed which patients had received all the pills necessary to complete the entire treatment during the study period: edoxaban - 29.4%; rivaroxaban - 24.3%; apixaban - 22.6%; and dabigatran - 18.5%.

DISCUSSION

Summary

Dabigatran has the lowest percentage of consistent with the guidelines doses, with 46.5% of patients being medicated with an inconsistent with the guidelines lower dose. Patients who are 75 years old or younger and have a GFR greater than 60 ml/min, whose renal function should be monitored annually, have the highest percentage of an adequate range of GFR. Other groups that require closer GFR monitoring have a lower percentage of an adequate range of GFR. Adherence to NOACs varies with different drugs: There was greater adherence to treatment with edoxaban and less adherence to apixaban.

Comparison with existing literature

Antunes et al. evaluated the prescription of oral anticoagulation in four family health units in northern Portugal from January 2010 to December 2015. They found that 76.7% of

patients diagnosed with atrial fibrillation based on ICPC-2 coding were medicated with OAC (14). However, in the period from 2016 to 2018, there was an increase in prescriptions to 98%. This suggests an improvement in the anticoagulation of patients with atrial fibrillation in the northern region of Portugal over the years. These results contradict some European studies that showed resistance from family physicians to introduce anticoagulation after the diagnosis of atrial fibrillation (15–18) and contradict the findings of the study by Turakhia et al., which showed that the medical speciality that diagnoses AF influences the decision to anticoagulate or not (19).

The electronic clinical files of primary health care contain a list of health problems for which there is a follow-up plan, relevant diseases, and those that require continuous medical treatment. Accurate records ensure the adequacy of care and enable monitoring and evaluation of the care provided to the population (20). The use of the International Classification of Primary Care, 2nd edition (ICPC-2) is essential for this purpose. Data published in 2015 by the Central Administration of the Health System (CAHS) showed a growing codification of health problems at a national level, reflecting the increase in computerized clinical records and demand from users and healthcare providers (21). This study found that the ICPC-2 K78 encoding has become more frequent over the years, which is consistent with the CAHS data at the national level. In 2011, 20.6 million health problems were identified, and by 2013, this figure had increased to 30.2 million. The percentage of consultations with ICPC-2 coding in primary health care is high in Portugal (69.2% in 2011, 83.9% in 2012, and 84% in 2013) (21).

Sugrue et al. found that NOAC dosing was inconsistent with the guidelines in 14.8% of patients at the Mayo Clinic: 12.4% received an inappropriate lower dose, and 2.4% received an inconsistent with the guidelines high dose (22). Even the ORBIT-AF II Registry, a nationwide AF registry conducted in a community practice in the US, showed that an inconsistent with the guidelines dose of a NOAC was prescribed in only 12.5% of cases: underdosing in 9.3% of patients and overdosing in 3.3% of patients, respectively (23). However, a real-world registry in Spain reported higher rates of underdosing and overdosing on NOAC therapy: 17.5% and 14.9%, respectively (24). This study's results agree with those of the Mayo Clinic and ORBIT-AF II Registry studies, with underdosing in 15.1% of patients and overdosing in 1.8%. These findings are consistent with studies conducted in other countries. Similar to studies carried out in other countries, in Portugal, taking into account that this study included patients from primary healthcare in the

northern region, the same prescription profile can be considered throughout the entire National Health Service. So, due to the risks associated with inconsistent with the guidelines prescribing, greater attention is needed from Portuguese family doctors, emphasizing the need for collaboration with health planners to implement a medical educational agenda. This agenda aims to enhance the knowledge and practices related to anticoagulation, possibly addressing issues such as proper prescription, monitoring, and management of anticoagulant therapy.

Stamellou and Floege highlighted the importance of regular checks of renal function in patients receiving NOACs to avoid overdosing, especially in situations that may cause acute-on-chronic kidney injury. In such patients, apixaban may be the safest licensed NOAC because of its relatively low renal elimination. In more advanced CKD, i.e., stage 4 and particularly in stage 5, NOACs are not recommended due to the lack of RCT data and concerns of overdosing with the risk of bleeding and anticoagulant-related nephropathy (25). A prudent approach is to check renal function at the initiation of treatment with NOACs, after three months, and then every year, except for high-risk patients (elderly >75 years, patients with low body mass) who require monitoring at least every six months (26). In patients with declining renal function, the current position of EHRA is to estimate the recheck intervals individually using a simple calculation: if creatinine clearance (CrCl) is ≤60 mL/min, the recheck interval in months is CrCl/10 (11).

Cayuelas et al. assessed compliance with kidney function monitoring recommendations in NVAF patients starting NOAC therapy (27). Compliance with kidney function monitoring recommendations was 61%, similar to the group of patients younger than 75 years with a GFR > 60ml/min in this study. Patients younger than 75 years with a GFR > 60ml/min had the highest rate of adequate GFR range, at about 60%, followed by patients ≤75 years old with a GFR <60ml/min at 29.4%, and patients >75 years old at 27.8%. Another noteworthy finding is the low percentage of patients with a GFR range assessed beyond the appropriate 12-month interval in patients >75 years old and in patients ≤75 years old with a GFR <60ml/min (10.4% and 10.2%, respectively). Family doctors appear to follow an annual pattern for monitoring renal function in all patients receiving NOACs, without individualizing the interval for monitoring renal function according to the criteria mentioned here. Therefore, patients who receive annual GFR evaluations have the highest rate of adequate renal monitoring. More training for individualized tracking of patients with other conditions may help Portuguese family doctors improve these results.

There was greater adherence to treatment with edoxaban and less adherence to apixaban, likely due to differences in drug posology, with edoxaban taken once daily and apixaban taken twice daily. Brízido et al. evaluated adherence to NOACs and its determinants in a population of AF patients from the outpatient general cardiology list at a tertiary centre in Portugal. The median adherence was 91% (IQR 74-100%) for rivaroxaban, 87% (IQR 74-100%) for apixaban, 82% (IQR 48-100%) for dabigatran, and 96% (IQR 83-100%) for edoxaban. There were no statistically significant differences between the NOACs (p = 0.102). Half of the patients (51%) were classified as non-compliant, which is consistent with the findings of this study. It was found that in all NOACs, with the exception of dabigatran, adherence was higher in patients diagnosed after the start of the study than in those diagnosed before the start of the study who had a longer duration of therapy. Therefore, there appears to be greater adherence in the immediate period after the diagnosis than in a later period. Therapy duration, NOACs taken twice daily, and higher out-of-pocket costs were independent predictors of non-compliance (12).

In another real-world analysis of adherence to NOACs, rivaroxaban and apixaban had favourable profiles compared to dabigatran, and rivaroxaban appeared to have higher overall adherence among the NOACs, although edoxaban was not included in this analysis. (28) A systematic review and meta-analysis of observational studies found that up to 30% of patients with AF are non-adherent to NOAC therapy (29). Although we analyzed data on drug dispensing in pharmacies, there may be the possibility of patients forgetting to take medication, which is more likely to occur with twice-daily drugs (apixaban and dabigatran), so once medications usage by the patients were not verified.

Limitations

The primary limitation of the AF-React study is that it relies on AF assessment data coded during the clinical process in primary healthcare. While there are some defects in the coding, it appears that the ICPC-2 K78 encoding has become more common over the years, and since 2015, there has been a decrease in the number of AF diagnoses coded. This suggests that the increase in K78 encoding is related to real new diagnoses rather than simply detecting coding errors in previous diagnoses.

When assessing the appropriateness of the prescribed NOAC dose, only the most recent GFR, weight, and age criteria were considered. Unfortunately, other relevant NOAC dosage criteria were not available in the database, namely, the concomitant use of other

drugs. It is also important to consider frailty when assessing the appropriate range of GFR to monitor renal function and prescribe NOACs. However, this data was not available for analysis.

CONCLUSIONS

The AF-React study enabled an analysis of the appropriateness of NOAC dosage prescriptions, the appropriate range of GFR for monitoring renal function and prescribing NOACs, and adherence to NOAC intake in AF patients. As such, the study provides highly relevant conclusions for Portugal. In the future, it will be necessary to improve the appropriate prescribing of NOAC doses and understand the reasons for inadequate monitoring of renal function in AF patients receiving NOACs. Additionally, further studies are needed to identify reasons for non-adherence to NOAC treatment in AF patients.

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CONTRIBUTORS

SSP and CM contributed to the conception of the work. All authors contributed to the design of the study. HM contributed to the data acquisition process. SPP, ASCT, and TSH contributed to the analysis and interpretation of the data. SSP drafted the manuscript, and HM, ASCT, TSH, and CM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

DATA AVAILABILITY STATEMENT

No additional data available.

ETHICS APPROVAL

The Health Ethics Committee of the Regional Health Administration of Northern Portugal approved the study protocol (Nº133/2018).

PROVENANCE AND PEER REVIEW

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Figure 1. ICPC-2 K78 codification by year

Figure 2. The difference between the number of pills needed to complete the therapy and the number of pills dispensed

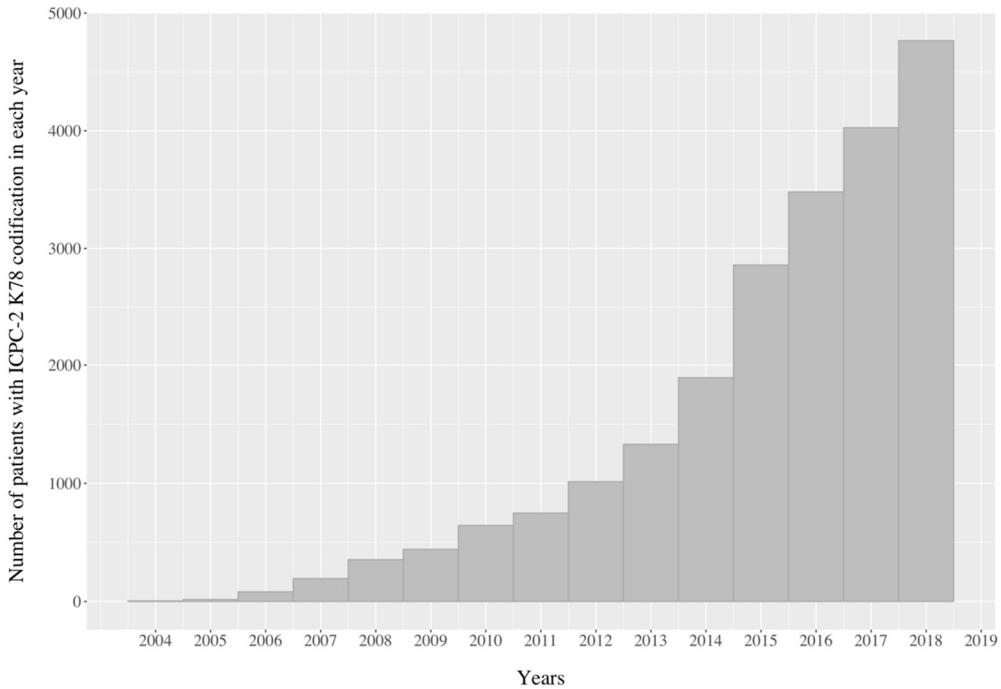

Figure 1.

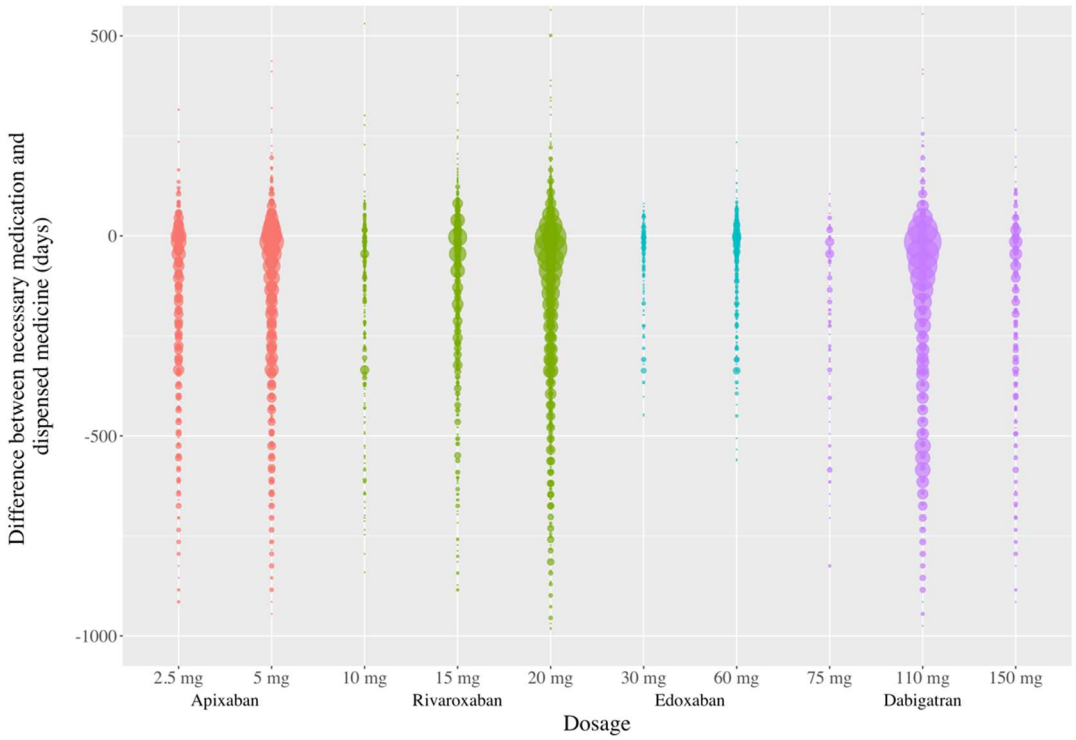

Figure 2.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13, 14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.