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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

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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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2 3	1	Title Page					
4 5	2	AE Boost study: progeribing profile and the adherence with NOACs intoles in patients					
6 7	2	AF- React study, presenting prome and the adherence with NOACs make in patients					
8	3	With atrial fiormation, a retrospective longitudinal study from real-world data in					
9 10	4	Northern Portugal					
11 12	5	Authors					
13 14	6	Pinto, Susana Silva; ^{1, 2,3} Email: susyapinto@gmail.com					
15 16	7	¹ São Tomé Family Health Unit (ACeS Santo Tirso/Trofa), Portugal.					
17 18	8	² Department of Community Medicine, Information and Health Decision Sciences					
19	9	(MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal.					
20 21	10	³ CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of					
22 23	11	Medicine, University of Porto, Porto Portugal					
24	12						
25 26	13	Henriques, Teresa S.; ^{3,4} Email: teresasarhen@gmail.com					
27 28	14	³ CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of					
29 30	15	Medicine, University of Porto, Porto Portugal					
31	16	⁴ CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto, Porto,					
32 33	17	Portugal.					
34 35	18						
36 37	19	Teixeira, Andreia; ^{2, 3, 5} Email: andreiasofiat@hotmail.com					
38	20	² MEDCIDS - Department of Community Medicine, Information and Decision in					
39 40	21	Health; Faculty of Medicine, University of Porto, Porto Portugal					
41 42	22	³ CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of					
43	23	Medicine, University of Porto, Porto Portugal					
44 45	24	⁵ ADiT-LAB, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e					
46 47	25	Comercial Nun'Álvares, 4900-347 Viana do Castelo, Portugal					
48 49	26						
50	27	Monteiro, Hugo; ⁶ Email: hfmonteiro@arsnorte.min-saude.pt					
51 52	28	⁶ Regional Health Administration of Northern, Min. of Health Portugal.					
53 54	29						
55	30	Martins, Carlos. ^{3, 7} Email: carlosmartins20@gmail.com					
57	31	³ CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of					
58 59	32	Medicine, University of Porto, Porto Portugal					
60	33	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 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 > 60ml/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

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63 years old with GFR > 60 ml/min had the highest percentage of an adequate GFR range,

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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.

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Strengths and limitations of this study 2

- 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.
- .t wit gy. 32 Greater adherence to treatment with edoxaban than with apixaban seems to be • 3 related to the drugs' posology.

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85 INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is frequently 86 associated with chronic kidney disease (CKD) (1). The first part of the AF-React study 87 revealed that 41.1% of 63,526 AF patients had a glomerular filtration rate (GFR) \leq 60 88 89 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 90 the other hand, the development of AF can accelerate the progression of CKD (1). As 91 with the general population, AF in CKD patients is associated with an increased risk of 92 thromboembolism and stroke (3). The synergistic effect of these two conditions raises 93 serious issues concerning the balance between bleeding and thrombotic risk. 94 95 Anticoagulant treatment can be challenging, especially in stage 5 CKD, where the clinical benefit is still unclear (1). 96 Oral anticoagulation (OAC) is the most effective form of thromboprophylaxis in AF 97 patients with an increased risk of stroke. However, reducing stroke risk is directly 98 related to the appropriateness of OAC prescription and adherence to OAC intake in 99 100 these patients (4). Previous studies have shown that non-vitamin K antagonist oral anticoagulants 101 102 (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban are superior to 103 warfarin in preventing thromboembolic events in patients with non-valvular AF, providing increased safety and a reduction in the number of bleeding events overall (5-104 8). Therefore, they are currently recommended for AF patients at risk for stroke after 105 106 calculating the CHA₂DS₂-VASc score (9). 107 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 3 108 109 NOAC trials, are not well studied (3). 110 The 2020 ESC Guidelines (9) and 2021 EHRA practical guide (10) recommend dose 111 adjustment for apixaban, rivaroxaban, and edoxaban in stage 4 CKD and do not 112 recommend the use of dabigatran. For GFR \leq 50ml/min, dose adjustment is recommended for all NOACs. 113 This is particularly relevant since the kidneys are responsible for partially eliminating 114

all four available NOACs. Dabigatran has the greatest extent of renal elimination (80%),

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3 ⊿	116	while 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are				
5	117	cleared via the kidneys (11).				
7 8	118	Other conditions also influence the appropriate prescription of NOACs in AF patients.				
9	119	For dabigatran, a reduced dose should be prescribed if the patient is over 80 years old,				
10 11	120	has concomitant administration with verapamil, or has an increased risk of bleeding. For				
12 13	121	apixaban, a reduced dose is recommended for patients over 80 years old or with a body				
14 15	122	weight < 60 kg. For edoxaban, a reduced dose is recommended for patients with a body				
16	123	weight < 60 kg or with concomitant administration of dronedarone, cyclosporine,				
17 18	124	erythromycin, or ketoconazole (10).				
19 20	125	Lowres et al. identified various factors associated with poor adherence to OAC intake.				
21 22	126	Medical factors include no prior history of stroke/TIA or low stroke risk, fewer				
23 24	127	comorbidities, high bleeding risk, paroxysmal AF, lack of AF symptoms, electrical				
25	128	cardioversion after commencing OAC and taking ≥ 2 dosages per day. Patient factors				
20	129	include younger age, lower health literacy, low AF knowledge, unawareness of				
28 29	130	associated stroke risk, poor OAC knowledge, concerns about bleeding and lifestyle				
30 31	131	changes, information overload, anger, depression, or anxiety from the AF diagnosis,				
32	132	low treatment satisfaction, busy work schedule, lack of health insurance coverage, and				
33 34	133	low ability to pay for medications (4).				
35 36	134	This study aims to assess the appropriateness of the prescribing profile and adherence to				
37 38	135	the intake of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with				
39 40	136	AF.				
41 42	137					
43 44 45	138	METHODS				
46 47	139	Data collection				
48 49	140	This study was performed with the $\Delta F_{-}R_{-}$ eact project database. The Department of				
50 51	1/1	Studies and Planning within the Regional Health Administration of Northern Portugal				
52	142	developed the AF-React project database which includes data from 2016 2017 and				
55 54	143	2018. To identify patients with AF, the ICPC-2 code K78 for AF was utilized.				
55 56						
57 58	144	The AF-React study encompasses all adults (18 years or older) whose clinical records in				
59	145	Primary Health Care, under the purview of the Regional Health Administration of				
00	146	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.

151 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

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3 1	177	or weighed less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 2.5 mg
4 5 6	178	dose of apixaban.
7 8	179	For edoxaban, a GFR < 15 ml/min was classified as contraindicated for use. Unsuitable
9	180	dosage status was assigned if 1) the patient was not prescribed a 30 mg dose when the
10 11	181	GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR was above 50
12 13	182	ml/min, or 2) the patient weighed less than 60 kg and was not prescribed a 30mg dose
14 15	183	of edoxaban. Suitable dosage status was assigned if 1) the patient was prescribed a 30
16	184	mg dose when the GFR was between 50 and 15 ml/min, or a 60 mg dose when the GFR
17 18	185	was above 50 ml/min, or 2) the patient weighed less than 60 kg, had a GFR above 15
19 20	186	ml/min, and was prescribed a 30 mg dose of edoxaban.
21	187	
22 23	107	
24 25	188	Monitoring renal function and prescribing NOAC
26 27	189	Regarding the monitoring of renal function and prescribing NOAC, the analysis was
28	190	divided into three groups: patients over 75 years old (monitored every 6 months),
29 30	191	patients 75 years old or younger with a GFR over 60 ml/min (monitored annually), and
31 32	192	patients 75 years old or younger with a GFR under 60 ml/min (monitored according to
33 34	193	the most recent GFR measurement). For each group, the number of patients with a GFR
35	194	within the appropriate range (within 0 months or earlier), a GFR up to 6 months after
36 37	195	the appropriate range, and a GFR after 6, 12, or 24 months after the appropriate range is
38 39	196	provided.
40 41	197	
42	157	
43 44	198	Adherence to NOAC
45 46	199	To examine adherence to NOAC intake among AF patients who received the same
47 48	200	NOAC during the study period, all NOAC dispensations were evaluated, regardless of
49 50	201	whether the prescription was issued by a family doctor, hospital doctor from the
51	202	National Health Service, or doctor from a private institution. Patients were considered
52 53	203	adherent if they received at least 90% of the prescribed pills from the time of the AF
54 55	204	diagnosis or the beginning of the study until the end (12).
56 57	205	
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60		

2 3	207	Data anglusia
4	207	Data analysis
5 6 7	208	The categorical variables were described using absolute and relative frequencies, n (%).
7 8 9	209	The statistical analysis was performed using software R (13).
10 11	210	
12 13 14	211	Ethic issues
15	212	The Department of Studies and Planning of the Regional Health Administration of
17	213	Northern Portugal (Ministry of Health, Portugal) processed the data. Anonymized data
18 19	214	processing and editing were conducted on a secure platform, and the data were extracted
20 21	215	from the server in compliance with legal regulations and with the approval of the Health
22 23	216	Ethics Committee of the Regional Health Administration of Northern Portugal.
24 25	217	
26 27 28	218	Patient and public involvement
29 30	219	Patients and the public were not involved in developing the research question.
31 32	220	
33 34 25	221	RESULTS
36	222	Data description
37 38	222	
39	223	Out of a total of 63,526 patients diagnosed with atrial fibrillation/flutter (ICPC-2, K78
40 41	224	code) in the northern region of Portugal until December 2018, we identified 21,854
42 43	225	patients who were prescribed the same non-vitamin K antagonist oral anticoagulant
44	226	(NOAC) during the study period. These NOACs included dabigatran (5,219
45 46	227	prescriptions), rivaroxaban (8,801 prescriptions), apixaban (7,052 prescriptions), and
47 48	228	edoxaban (782 prescriptions). Understanding the temporal relationship between NOAC
49 50 51 52 53	229	prescription and K78 coding is crucial to determine whether NOACs were prescribed
	230	after AF diagnosis. Of the 21,455 (98%) patients, 188,780 prescriptions were issued
	231	after the K78 code.
54 55	232	In the first part of the AF-React study, a primary limitation was identified: the
56 57	233	assessment of AF was based on data coded in the clinical process in primary healthcare.
58	234	Therefore, in this analysis, we examined how codification has evolved over the years
60	235	(see Figure 1). Our findings indicate that the frequency of ICPC-2 K78 encoding has

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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.

241 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).

41 25

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

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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%.

297 DISCUSSION

298 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.

307 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

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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

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patients \leq 75 years old with a GFR \leq 60ml/min at 29.4%, and patients \geq 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 <60 ml/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).

388 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

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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.

1		
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10 11 12	415	
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17	418	design of the study. HM contributed to the data acquisition process. SPP, ASCT, and
19 20	419	TSH contributed to the analysis and interpretation of the data. SSP drafted the
21 22	420	manuscript, and HM, ASCT, TSH, and CM critically revised the manuscript. All
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43 44 45	430	
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48 49	432	Patients and the public were not involved in this research's design, conduct, reporting,
50 51	433	or dissemination plans.
52 53	434	
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50 57 58	436	Not required.
59 60	437	

Page 18 of 26

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438 ETHICS APPROVAL

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

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PROVENANCE AND PEER REVIEW

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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.

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			Unsuitable	e	
			Not suitable for renal		
	Contraindicated	Suitable	function		Not suitable for
			Lower	Higher	weight or age
Debisstran	(n - 2205)		dose	dose	
Dabigatran	$\frac{(n-3303)}{5}$	1657	1520	17	00
[] 0/_	3 0 2	1037	1558	1/	88 27
70 Riveroveba	0.2	30.1	40.3	0.5	2.1
Rivaloxada	$\frac{\ln(1-3002)}{5}$	1737	678	387	
11 0/2	01	47 <i>5</i> 7 81.6	11 7	562	
Apixaban (r	1 = 4869	01.0	11./	0.0	
n	7	3830	975	10	47
%	01	787	20.0	02	10
Edoxaban (1	n = 531)	1011	20.0		
n	2	436	50	25	18
%	0.4	82.1	9.4	4.7	3.4

Table 1	. The	suitability	of pres	cribed of	dose non-	VKA	oral	anticoagula	nts (NOAC).
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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
\leq 75 years old and GFR > 60ml/min; and patients \leq 75 years old and GFR < 60ml/min.

Months after the recommended deadline	Patients > 7 n (%)	5 years old	Patients \leq 7 and GFR > n (%)	5 years old 60ml/min	Patients \leq 75 years old and GFR \leq 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	

<u>319 17996 16757 11882 3103</u>

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

	Item No	Recommendation	Page No
Title and abstract	1	(<i>a</i>) Indicate the study's design with a commonly used term in the title or the	1
		abstract	
		(b) Provide in the abstract an informative and balanced summary of what was	2, 3
		done and what was found	
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	6
		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	6
		participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	7,8
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	7, 8
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
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,	7, 8
		describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	8
		confounding	
		(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	
		(<u>e</u>) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	9
		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(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)	9
-		and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
			1
		(c) Summarise follow-up time (eg, average and total amount)	

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Main results	16	(<i>a</i>) 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	1
		(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	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N
Discussion			
Key results	18	Summarise key results with reference to study objectives	1
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	1 1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 11 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	1 1 1 1 1
Other informati	on		
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	1

*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.

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 ³CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal ⁴CI-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 ³CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal ⁵ADiT-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 ⁶Regional Health Administration of Northern, Min. of Health Portugal. Martins, Carlos.^{3,7} Email: carlosmartins20@gmail.com ³CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of Medicine, University of Porto, Porto Portugal

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⁷#H4A Primary Health Care Research Network, Porto, Portugal **Corresponding Author**Susana Silva Pinto
susyapinto@gmail.com

39 Keywords

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

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42 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.

46 **Design:** Retrospective longitudinal study.

47 Setting: The study was conducted in the Regional Health Administration of Northern48 Portugal.

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

52 Outcome measures: The appropriate dosages of NOAC for patients with AF according
53 to three dosage suitability categories: contraindicated, unsuitable, and suitable, based on
54 2020 European Society of Cardiology guidelines of Atrial Fibrillation.

55 **Results:** Dabigatran had a lower percentage of suitable doses (n=1657, 50.1%) than other 56 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 57 recommended based on their glomerular filtration rate (GFR). Among patients under 75 58 years old with GFR > 60 ml/min, 59.8% (n=10,028) had an adequate GFR range, while 59 27.8% (n=7,166) of GFR measurements from patients over 75 years old and 29.4% 60 (n=913) of GFR measurements from patients under 75 years old with GFR < 60 ml/min 61 were within an adequate time range. Adherence to NOACs varied across different drugs, 62

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with 59.1% (n=540) adhering to edoxaban, 56.3% (n=5443) to rivaroxaban, 55.3% 63 (n=3143) to dabigatran, and 53.3% (n=4211) to apixaban. 64

Conclusions: Dabigatran had the lowest percentage of suitable doses. Patients under 75 65

years old with GFR > 60 ml/min had the highest percentage of an adequate GFR range, 66

67 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 68

.h ed. adherence to treatment with edoxaban and less adherence to apixaban. 69

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73 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.

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85 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 CHA₂DS₂VASc 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 $GFR \le 50$ ml/min, dose adjustment is recommended for all NOACs.
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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 tothe intake of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF.

46 139 METHODS
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140 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.

152 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

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178 less than 60 kg, had a GFR above 15 ml/min, and was prescribed a 2.5 mg dose of179 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.

189 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.

198 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).

207 Data analysis

2 3 4	208	The categorical variables were described using absolute and relative frequencies, n (%).
5 6 7	209	The statistical analysis was performed using software R (13).
7 8 9	210	
10 11 12	211	Ethic issues
12	212	The Department of Studies and Planning of the Regional Health Administration of
14 15	213	Northern Portugal (Ministry of Health, Portugal) processed the data. Anonymized data
16 17	214	processing and editing were conducted on a secure platform, and the data were extracted
18	215	from the server in compliance with legal regulations and with the approval of the Health
19 20 21	216	Ethics Committee of the Regional Health Administration of Northern Portugal.
22 23	217	
24 25 26	218	Patient and public involvement
20	219	Patients and/or the public were not involved in the design, or conduct, or reporting, or
28 29 30	220	dissemination plans of this research.
31 32	221	
33 34	222	RESULTS
35 36 37	223	Data description
38	224	Out of a total of 63,526 patients diagnosed with atrial fibrillation/flutter (ICPC-2, K78
40	225	code) in the northern region of Portugal until December 2018, we identified 21,854
41 42	226	patients who were prescribed the same non-vitamin K antagonist oral anticoagulant
43 44	227	(NOAC) during the study period. These NOACs included dabigatran (5,219
45	228	prescriptions), rivaroxaban (8,801 prescriptions), apixaban (7,052 prescriptions), and
46 47	229	edoxaban (782 prescriptions). Understanding the temporal relationship between NOAC
48 49	230	prescription and K78 coding is crucial to determine whether NOACs were prescribed
50	231	after AF diagnosis. Of the 21,455 (98%) patients, 188,780 prescriptions were issued after
51 52 53	232	the K78 code.
54	233	In the first part of the AF-React study, a primary limitation was identified: the assessment
56	234	of AF was based on data coded in the clinical process in primary healthcare. Therefore,
57 58	235	in this analysis, we examined how codification has evolved over the years (see Figure 1).
59 60	236	Our findings indicate that the frequency of ICPC-2 K78 encoding has increased over time.

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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.

241 NOAC dosage suitability

242 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).

				Unsuit	able
			Not suital	ble for renal	
	Contraindicated	Suitable	fun	oction	Not suitable for
			Lower	Higher	weight or age
			dose	dose	
Dabigatran (n = 3305)				
n	5	1657	1538	17	88
%	0.2	50.1	46.5	0.5	2.7
Rivaroxaban	n (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	$1 = 5\overline{31}$				
n	2	436	50	25	18
%	0.4	82.1	9.4	4.7	3.4

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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).

259 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.

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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 > 7 n (%)	5 years old	Patients ≤ 75 years old and GFR > 60ml/min n (%)		Patients \leq 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

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289 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 293 pharmacy during the study period. When we examined the relationship between 294 dispensation and the K78 coding date, we found that 5,837 patients dispensed 25,890 295 NOAC before the K78 coding date, while 24,164 patients dispensed 295,551 NOAC after 296 297 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 298 299 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. 300

Figure 2 shows the difference between the number of pills required to complete thetherapy 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%.

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DISCUSSION

321 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.

330 Comparison with existing literature

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

Page 15 of 27

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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.

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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 $\leq 60 \text{ mL/min}$, 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 \leq 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 \leq 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

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= 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. to beet terien only

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11	444	
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14	445	AUTHOR STATEMENT
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16 17	446	SSP and CM contributed to the conception of the work. All authors contributed to the
18	447	design of the study. HM contributed to the data acquisition process. SPP, ASCT, and
19 20	448	TSH contributed to the analysis and interpretation of the data. SSP drafted the
21	449	manuscript, and HM, ASCT, TSH, and CM critically revised the manuscript, All
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23 24	450	authors gave final approval and agreed to be accountable for all aspects of the work,
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60	466	ETHICS APPROVAL

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3 4	467	The Health Ethics Committee of the Regional Health Administration of Northern
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11 12 13	471	Not commissioned; externally peer-reviewed.
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	583	Figure 1. ICPC-2 K78 codification over	the years
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Figure 2. The difference between the number of pills needed to complete the therapy and the number of pills dispensed.

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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	(<i>a</i>) 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	2,3
		done and what was found	
Introduction			1
Background/rationale	2	Explain the scientific background and rationale for the investigation being	5,6
		reported	
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	6
		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	6
		participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	7, 8
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	7, 8
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
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,	7, 8
		describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	8
		confounding	
		(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	
		(<i>e</i>) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	9
1	-	eligible, examined for eligibility, confirmed eligible, included in the study.	
		completing follow-up, and analysed	
		(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)	9
1		and information on exposures and potential confounders	
		and information on exposures and potential comounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(b) Indicate number of participants with missing data for each variable of interest(c) Summarise follow-up time (eg. average and total amount)	

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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 		
		(<i>c</i>) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
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 informat	ion		
Funding	22	Give the source of funding and the role of the funders for the present study and, if	16
		applicable, for the original study on which the present article is based	

*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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3 4	1	Appropriateness of prescribing profiles and intake adherence with non-vitamin K					
5	2	antagonist oral anticoagulants in patients with atrial fibrillation: analysis of a					
6 7	3	retrospective longitudinal study using real-world data from Northern Portugal (AF					
8 9	4	React study)					
10	F	Authors					
11 12	5	Authors					
13 14	6	Pinto, Susana Silva; ^{1, 2,3} Email: susyapinto@gmail.com					
15	7	¹ São Tomé Family Health Unit (ACeS Santo Tirso/Trofa), Portugal.					
16 17	8	² Department of Community Medicine, Information and Health Decision Sciences					
18 10	9	(MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal.					
20	10	³ CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of					
21 22	11	Medicine, University of Porto, Porto Portugal					
23	12						
25	13	Henriques, Teresa S.; ^{3, 4} Email: teresasarhen@gmail.com					
26 27	14	³ CINTESIS@RISE - Center for Health Technology and Services Research: Faculty of					
28 20	15	Medicine, University of Porto, Porto Portugal					
30	16	⁴ CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto, Porto,					
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35	10	Teiveira Andreia ^{2,3,5} Email: andreiasofiat@hotmail.com					
36 37	20	² MEDCIDS Department of Community Medicine Information and Decision in					
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44	24	³ ADi1-LAB, Instituto Politecnico de Viana do Castelo, Rua Escola Industrial e					
46 47	25	Comercial Nun'Alvares, 4900-347 Viana do Castelo, Portugal					
48 40	26						
49 50	27	Monteiro, Hugo; ⁶ Email: hfmonteiro@arsnorte.min-saude.pt					
51 52	28	⁶ Regional Health Administration of Northern, Min. of Health Portugal.					
53	29						
54 55	30	Martins, Carlos. ^{3, 7} Email: carlosmartins20@gmail.com					
56 57	31	³ CINTESIS@RISE - Center for Health Technology and Services Research; Faculty of					
58	32	Medicine, University of Porto, Porto Portugal					
59 60	33	⁷ #H4A Primary Health Care Research Network, Porto, Portugal					

Correspondence to: Susana Silva Pinto susyapinto@gmail.com Keywords atrial fibrillation, anticoagulants, prevention, stroke; primary health care. 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%

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> (n=5443) to rivaroxaban, 55.3% (n=3143) to dabigatran, and 53.3% (n=4211) to 65 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 to perteries only apixaban.

> > For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

72 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.

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82 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 CHA₂DS₂VASc 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 $GFR \le 50$ ml/min, dose adjustment is recommended for all NOACs.

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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).

133 This study aims to assess the appropriateness of the prescribing profile and adherence to134 the intake of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF.

46 136 METHODS
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137 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

150 In order to investigate the appropriate dosages of NOAC for patients with AF, we 151 classified patients into one of three dosage categories: contraindicated, inconsistent, and 152 consistent with the guidelines. The patient's most recent GFR value was considered when 153 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

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was over 80 years old or weighed less than 60 kg, had a GFR above 15 ml/min, and wasprescribed 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.

186 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. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

195 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).

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204 Data analysis

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

206 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.

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215 Patient and public involvement

216 None.

RESULTS

219 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 accuratediagnoses rather than the detection of previous diagnostic coding errors.

236 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).

	U,		Inco	onsistent with	the guidelines	
	Contraindicated according to	Consistent with the	Inconsistent with the guidelines for renal function		Inconsistent with the guidelines for	
	guidennes	guidennes	Lower dose	Higher dose	weight or age	
Dabigatran	n (n = 3305)					
N	5	1657	1538	17	88	
%	0.2	50.1	46.5	0.5	2.7	
Rivaroxaba	an $(n = 5802)$					
Ν	5	4737	678	382		
%	0.1	81.6	11.7	6.6		
Apixaban ((n = 4869)					
Ν	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 1. The prescribed dose non-VKA oral anticoagulants (NOAC)

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).

255 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.

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Table 2. Analysis of ranges between GFR for monitoring renal function for prescribing

278 non-VKA oral anticoagulants (NOAC) in three groups: patients >75 years old; patients

 $279 \leq 75$ 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 \leq 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

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283 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 287 pharmacy during the study period. When we examined the relationship between 288 dispensation and the K78 coding date, we found that 5,837 patients dispensed 25,890 289 NOAC before the K78 coding date, while 24,164 patients dispensed 295,551 NOAC after 290 the K78 coding date. Additionally, 5,576 patients dispensed the same NOAC before and 291 292 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 293 rivaroxaban, 7,901 (32.7%) dispensed apixaban, and 913 (3.8%) dispensed edoxaban. 294
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%. CLICN

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 Page 15 of 27

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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

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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 $\leq 60 \text{ mL/min}$, the recheck interval in months is CrCl/10 (11).

Cavuelas 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 \leq 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 \leq 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.

Page 17 of 27

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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.

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413 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.

427 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 reasons studies are needed to identify reasons for non-adherence to NOAC treatment in AF patients.

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	 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462

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3 4	463	The Health Ethics Committee of the Regional Health Administration of Northern
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579	Figure 1. ICPC-2 K78 codification by year
580	Figure 2. The difference between the number of pills needed to complete the therapy and
581	the number of pills dispensed
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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	(<i>a</i>) 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	2,3
		done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being	5,6
		reported	
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	6
		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	6
		participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	7, 8
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	7,8
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
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,	7, 8
		describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	8
		confounding	
		(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			
Particinants	13*	(a) Report numbers of individuals at each stage of study—eq numbers potentially	9
i uitioipuilto	15	eligible examined for eligibility confirmed eligible included in the study	
		completing follow-up and analysed	
		(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 (eq demographic clinical social)	9
Descriptive data	17	and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interact	
		(c) Summarise follow-up time (eq. average and total amount)	
Outcomo doto	15*	C) Summarise follow-up time (eg, average and total amount)	NA
Juicome data	13*	Report numbers of outcome events or summary measures over time	

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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 informati	ion		
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.