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Influence of the COVID-19 pandemic on patients receiving oral anticoagulants for the treatment of non-valvular atrial fibrillation

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ABSTRACT

Background: Frequent monitoring of patients declined during the COVID-19 pandemic, harming patients with chronic diseases who critically needed correct monitoring. We evaluated the impact of the COVID-19 pandemic in patients with non-valvular atrial fibrillation (NVAF) receiving treatment with vitamin K antagonists (VKA) or non-vitamin K antagonist oral anticoagulants (NOAC) in clinical practice in Spain.

Methods: This observational, retrospective study analyzed prevalent patients treated with NOAC/VKA on 14/03/2019 (pre-COVID-19 period) and 14/03/2020 (COVID-19 period), who were followed up to 12 months. The study also considered incident patients who started treatment with NOAC/VKA between 15/03/2019 and 13/03/2020 (pre-COVID-19 period) and from 15/03/2020 to 13/03/2021 (COVID-19 period). Demographic characteristics, comorbidities, effectiveness, treatment patterns, and healthcare resource utilization were considered.

Results: Prevalent patients amounted to 12,336 and 13,342 patients, whereas 1,612 and 1,602 incident patients were included in the pre-COVID-19 and COVID-19 periods, respectively. Prevalent patients treated with VKA had more strokes, thromboembolism, and major bleeding compared to those receiving NOAC, particularly during the COVID-19 period. NOAC patients had a 12 % lower risk of death than those on treatment with VKA (Hazard ratio = 0.88 [95 % CI: 0.81 – 0.95], p = 0.033). In addition, VKA patients were less persistent after 12 months than NOAC patients (pre-COVID-19 period: 52.1 % vs. 78.9 %, p < 0.001; COVID-19 period: 49.2 % vs. 80.3 %, p < 0.001), and required more healthcare visits and hospitalizations than those on treatment with NOAC.

Conclusion: Compared to VKA, NOAC seems to have reduced the incidence of severe events and the use of healthcare resources for NVAF, particularly during the pandemic.

1. Introduction

Atrial fibrillation (AF) is the most common type of supraventricular tachycardia in clinical practice [1]. AF is a disabling condition and causes up to 30 % of strokes [2]. It is estimated that 10–40 % of AF patients are hospitalized yearly. AF patients have a high risk of mortality due to sudden death, heart failure, or stroke [2]. According to the OFRECE study, the prevalence of AF in Spain is 4.4 % in people aged > 40 years [3], and most of them suffer from non-valvular atrial fibrillation (NVAF) [4,5].

The treatment of NVAF is based on preventing thromboembolisms and controlling the heart rate [2]. Anticoagulants have proven effective in preventing cardioembolic complications [6,7], with the vitamin K antagonists (VKA) and the new non-vitamin K antagonist oral anticoagulants being the most commonly used groups [1,8]. In clinical trials and real-life studies, VKA (acenocoumarol and warfarin) have demonstrated a reduction in the incidence of strokes with an acceptable risk of bleeding compared with aspirin in patients with AF and moderate-high risk of thromboembolic events [1,9]. NOACs have demonstrated a better risk–benefit profile than VKA in patients with NVAF and are associated with a lower risk of intracranial bleeding, one of the most severe complications [1,10–14].

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19) [15]. COVID-19 had many health, social, and economic consequences, including the pressure on healthcare systems [16], which resulted in organizational and functional changes in health centers and the clinical management of patients [17]. Remote monitoring of patients, especially those with chronic diseases like NVAF, has increased, leading to a decline in face-to-face visits [16–18]. However, NVAF patients on treatment with VKAs require frequent monitoring to avoid thromboembolic and bleeding events, particularly in those with labile international normalized ratios (INR) [19]. As a consequence, NOACs are recommended in NVAF patients, as they may reduce the monitorization requirements of VKA treatments during the COVID-19 pandemic [19,20].

Since the management of patients with NVAF was modified during the COVID-19 pandemic to reduce the virus exposure and the burden in healthcare centers, this study aims to evaluate the impact of the pandemic on patients with NVAF receiving anticoagulant treatment with VKA or NOAC in clinical practice in Spain.

2. Methods

2.1. Study design and data collection

This is an observational, retrospective study based on the electronic medical records (EMR) of the BIG-PAC® database, which gathers information from primary care centers and hospitals in seven public health areas from seven autonomous communities (1.8 million individuals) in Spain [21]. The BIG-PAC® database proved to be representative of the Spanish population [22].

EMR undergoes rigorous anonymization in the centers/hospitals of origin, in compliance with Organic Law 3/2018 of December 5th on the Protection of Personal Data and guarantee of digital rights [23].

2.2. Study population

Patients with NVAF constituted the study population. They were recorded as AF based on the International Classification of Diseases, 10th edition, Clinical modification (ICD-10-CM code I48.91), without mitral valve heart disease (ICD-10-CM codes I05.0, I05.1, I05.2, I05.8, I08.0, I08.8, I08.9, I34.0, I34.8, Q20.0, Q20.1, Q20.3, Q20.4, Q20.5, Q20.8, Q21.0 - Q21.3, Q21.8, Q21.9, I27.83, Z95.2, Z95.3) [24].

Inclusion criteria involve patients aged ≥ 18 with a diagnosis of atrial fibrillation (AF) according to ICD-10 CM. They needed to be active in the database before 13/03/2021, enrolled in the chronic prescription program (≥2 prescriptions), and regularly monitored (≥2 health records). Exclusion criteria comprised AF with mitral valve heart disease, transfers, nursing home residents, AF secondary to reversible causes, recent surgeries, valvular AF with end-stage kidney disease, VKA to NOAC switch, and COVID-19 diagnosis (ICD-10-CM code B97.21) (Table S2).

2.2.1. Subgroups

The study considered prevalent and incident patients with NAVF diagnosis whose index date varied in the study periods (pre-COVID-19 period and COVID-19 period) (Fig. S1). Prevalent patients were those on treatment with an oral anticoagulant treatment (NOAC/VKA), whose index date was when they entered the study: 14/03/2019 (pre-COVID-19 period) and 14/03/2020 (COVID-19 period). They were followed until the discontinuation of the anticoagulant treatment, the end of the study period (12 months), or death, whichever occurred first.

Incident patients were those who started a new oral anticoagulant treatment (NOAC/VKA) between 15/03/2019 and 13/03/2020 (pre-COVID-19 period) and from 15/03/2020 to 13/03/2021 (COVID-19 period). Their index date was the treatment initiation date. Incident patients were analyzed at the index date and did not have a prescription for anticoagulants (NOAC/VKA) 12 months before the index date (Fig. S1).

2.3. Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital of Terrassa (Barcelona) (code: 02-21-399-089) on 29th June 2021. The patient consent was not necessary, according to Article 5 of Royal Decree 957/2020, of November 3rd, which regulates observational studies with medicines for human use.

2.4. Study variables

2.4.1. Demographic variables and comorbidities at the baseline

Demographic variables and comorbidities are listed in Table 1. These variables were estimated in the last 12 months before the index date in prevalent patients.

2.4.2. Treatments

The management of patients was obtained from drug dispensing records. Drug prescription was made according to clinical practice. The Anatomical Therapeutic Chemical Classification System (ATC) [25] was used to identify drugs (VKA: acenocoumarol [B01AA07] and warfarin [B01AA03]) and NOAC: rivaroxaban [B01AF01], apixaban [B01AF02], edoxaban [B01AF03] and dabigatran [B01AE07]). Concomitant medications included antiplatelets (B01AC), antidiabetics (A10), beta-blockers (C07), renin-angiotensin system-acting agents (C09), and lipid-lowering agents (C10). Anticoagulant treatment and concomitant medications were analyzed in prevalent and incident patients.

The time in therapeutic range (TTR) was determined in prevalent patients on treatment with VKA using the Rosendaal method. The TTR was used to estimate the percentage of patients outside the therapeutic range (INR: 2–3) and was considered inadequate when the percentage of INR values was < 65 % throughout 6 months [26].

For prevalent and incident patients, treatment persistence/duration of medicaments was estimated from the index date (start date) up to 1 year, or up to the development of a new event (hemorrhagic/ischemic stroke, bleeding), the switch to another anti-platelet/anticoagulant treatment other than that that motivated inclusion (in the succeeding 30 days), or treatment abandonment (≥60 days without renewing the medication) or death, whichever occurred first. Treatment persistence was obtained at 6 and 12 months of follow-up. The date of interruption was 30 days from the date of the last prescription.

2.4.3. Effectiveness, safety, and mortality

The effectiveness of the study treatments was estimated in prevalent patients in terms of the number of severe events (strokes and episodes of systemic thromboembolism). In contrast, safety was determined as the incidence of major bleeding. These events were identified from the first 30 days after initiating anticoagulant medication (NOAC or VKA) until the date of treatment discontinuation, using the ICD-10-CM codes (Supplementary Table S1).

Mortality rates were estimated as the percentage of patients who died at the end of the study. The survival time was defined as the time between the start of the treatment (index date) and the patient's death.

2.4.4. Use of healthcare resources

The use of healthcare resources was analyzed for 12 months during the two study periods, including primary care visits, nurse visits, specialist visits (hematology, cardiology), emergencies, and hospitalizations for ischemic and hemorrhagic events.

2.5. Statistical analysis

Search criteria were based on computer statements (SQL script), and the data were carefully reviewed through exploratory analyses. Data

Table 1
Demographic characteristics and comorbidities of prevalent patients.

Study groups	Pre-COVID-19 period	COVID-19 period	Total	*p*
Number of patients, n (%)	12,336 (48.0)	13,342 (52.0)	25,678 (100.0)	
Sociodemographic characteristics				
Age, years, mean (SD)	77.1 (9.8)	77.3 (9.8)	77.2 (9.8)	0.082
Age ranges, n (%)				
18–49 years	127 (1.0)	131 (1.0)	258 (1.0)	
50–64 years	1240 (10.1)	1324 (9.9)	2564 (10.0)	
65–74 years	3288 (26.7)	3485 (26.1)	6773 (26.4)	
75–84 years	4881 (39.6)	5229 (39.2)	10,110 (39.4)	
≥ 85 years	2800 (22.7)	3173 (23.8)	5973 (23.3)	
Gender male, n (%)	6710 (54.4)	7217 (54.1)	13,927 (54.2)	0.628
Time from diagnosis, days[†]				<0.001
Mean (SD)	1510.4 (857.2)	1664.7 (976.9)	1590.6 (924.6)	
Median (P25-P75)	1582.0 (730.0—2354.0)	1704.5 (766.0—2641.0)	1634.0 (750.0—2472.0)	
Clinical variables				
BMI, kg/m^2, mean (SD)	30.1 (5.1)	29.2 (5.3)	29.6 (5.2)	<0.001
Hemoglobin levels, g/dL, mean (SD)	14.2 (1.8)	14.1 (1.8)	14.2 (1.8)	<0.001
Associated comorbidities, n (%)				
Arterial hypertension	8730 (70.8)	9734 (73.0)	18,464 (71.9)	<0.001
Diabetes	4078 (33.1)	4412 (33.1)	8490 (33.1)	0.985
Dyslipidemia	6334 (51.3)	7524 (56.4)	13,858 (54.0)	<0.001
Obesity	3334 (27.0)	3892 (29.2)	7226 (28.1)	<0.001
Active Smoker	922 (7.5)	1137 (8.5)	2059 (8.0)	0.002
Alcohol consumption	378 (3.1)	414 (3.1)	792 (3.1)	0.857
Stroke	1322 (10.7)	1503 (11.3)	2825 (11)	0.160
Hemorrhagic ictus	77 (0.6)	87 (0.7)	164 (0.6)	0.779
Ischemic ictus	1220 (9.9)	1397 (10.5)	2617 (10.2)	0.124
Transient ischemic attack	482 (3.9)	540 (4.0)	1022 (4.0)	0.566
Peripheric arterial disease	1031 (8.4)	1174 (8.8)	2205 (8.6)	0.207
Cardiac failure	3597 (29.2)	4023 (30.2)	7620 (29.7)	0.081
Renal failure	1226 (9.9)	1333 (10.0)	2559 (10.0)	0.888
Asthma	981 (8.0)	1103 (8.3)	2084 (8.1)	0.356
COPD	2119 (17.2)	2357 (17.7)	4476 (17.4)	0.302
Dementia	416 (3.4)	439 (3.3)	855 (3.3)	0.715
Depression	1186 (9.6)	1402 (10.5)	2588 (10.1)	0.017
Neoplasia	1107 (9.0)	1287 (9.6)	2394 (9.3)	0.064
Liver failure	677 (5.5)	744 (5.6)	1421 (5.5)	0.757
Scales				
Charlson comorbidity index, mean (SD)	1.9 (1.7)	2.0 (1.7)	2.0 (1.7)	<0.001
$CHAS_2DS_2$-VASc, mean (SD)	2.8 (1.4)	2.9 (1.4)	2.8 (1.4)	0.001
HAS-BLED, mean (SD)	3.0 (0.9)	3.1 (0.9)	3.1 (0.9)	<0.001

[†] Time from diagnosis of NVAF to the index date Values expressed as a percentage or mean (SD). p: statistical significance. BMI: body mass index; COPD: Chronic obstructive pulmonary disease; P: percentile; SD: standard deviation.

validation was carried out to ensure the quality of the results.

Descriptive-univariate analyses were performed, and qualitative data were described using absolute and relative frequencies (N, %). Means and standard deviations (SD) were used to describe quantitative variables with symmetric distributions, whereas medians and interquartile ranges (IQR) were estimated for quantitative variables with asymmetric distributions. 95 % Confidence intervals (CI) were calculated for population parameter estimation.

Bivariate analyses were developed to compare prevalent and incident cases in both study periods regarding demographic variables, comorbidities, and treatments; ANOVA and the chi-square tests were used for independent groups. Cox proportional risk models were used to determine the time elapsed until death in prevalent cases (hazard ratio [HR], with censored data). The results were estimated as percentages (incidence rate; accumulated risk).

The SPSSWIN version 27 statistical program was used, and values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Study population

Out of the database population, 34,061 patients with NVAF, aged 18 years and above, were considered. According to the inclusion/exclusion criteria, 28,892 patients were included in the study. Most were prevalent patients (n = 25,678), whereas 3,214 were incident patients (Fig. S2).

About half of prevalent patients (48 %) entered in the pre-COVID-19 period (n = 12,336), whereas 13,342 patients (52 %) were considered in the COVID-19 period. Regarding incident patients, 1,612 patients and 1,602 patients were included in the pre-COVID-19 period and COVID-19 period, respectively (Fig. S2).

3.2. Clinical characteristics of prevalent patients

Prevalent patients had an average age of 77.2 years (SD: 9.8), and 54.2 % of patients were male. The median time from diagnosis of NVAF to the index date was higher during the COVID-19 period (1,704.5 days) in comparison to the pre-COVID-19 period (1,582.0 days; $p < 0.001$). In general, the study population analyzed during the pandemic had more comorbidities; arterial hypertension, dyslipidemia, and diabetes were identified as the most frequent disorders. Charlson comorbidity index [27] and $CHAS_2DS_2$-VASc and HAS-BLED [28] scores were also higher in NVAF patients during COVID-19, compared to those in the previous period ($p \leq 0.001$ in all comparisons) (Table 1). Therefore, during the pandemic, NVAF patients had more disability and a higher risk of thromboembolic complications and hemorrhages than those recorded in the previous period.

3.3. Clinical effectiveness and safety in prevalent patients

Most patients with NVAF were on treatment with VKA, and this group of medications decreased from the pre-COVID-19 period (75.1 %) to the COVID-19 period (69.9 %). The incidence rate of severe events was slightly higher in the COVID-19 period vs. the pre-COVID-19 period (7.7 % vs. 7.0 %, respectively) (Table 2). However, the incidence of severe events was superior in patients with VKA vs. those on treatment with NOAC ($p < 0.001$) (Fig. 1). Patients on treatment with VKA had more strokes and major bleeding in comparison to those receiving NOAC in both periods of the study ($p < 0.001$ in all comparisons). In addition, VKA patients had more episodes of thromboembolism than NOAC patients during the pandemic ($p < 0.001$). However, there was no difference in the time to these episodes between both groups of treatment ($p > 0.05$ in all comparisons) (Table 2).

Regarding patients on treatment with VKA, during the pre-COVID-19 period, more patients had poor anticoagulation control compared to those during the COVID-19 period (44.7 % vs. 41.9 %) (Table 2).

Mortality rates were higher during the pandemic, particularly in patients with VKA, than in those with NOAC (pre-COVID-19 period: 4.8 % vs. 3.8 % [$p = 0.035$] and COVID-19 period: 5.6 % vs. 4.7 % [$p = 0.033$]). During the COVID-19 period, the risk of death in patients on treatment with NOAC was 12 % lower in comparison to those on treatment with VKA (HR = 0.88 [95 % CI: 0.81 – 0.95], p = 0.033) (Fig. S3). In addition, the time to death was shorter during the pandemic compared to that during the pre-COVID-19 period (231.5 days vs. 248.5 days), being even shorter in NOAC vs. VKA patients (205.5 days vs. 241.5 days, p = 0.045) (Table 2).

3.4. Duration and persistence of anticoagulant treatment in prevalent patients

The duration of treatment was similar to the follow-up length (365 days [13 months]) in both study periods. However, on average, the treatment was longer in patients on therapy with NOAC compared to VKA patients (pre-COVID-19 period: 340.0 days [SD: 67.8] vs. 315.0 days [SD: 81.0], p < 0.001; COVID-19 period: 343.0 days [SD: 64.4] vs. 310.0 days [SD: 84.5], p < 0.001). Patients with NOAC were more persistent at 12 months than those receiving VKA (pre-COVID-19 period: 78.9 % vs. 52.1 %, $p < 0.001$; COVID-19 period: 80.3 % vs. 49.2 %, $p < 0.001$). Discontinuation was similar in both study periods (pre-COVID-19 period: 41.3 % and COVID-19 period: 41.5 %), and the most frequent cause of discontinuation was treatment abandonment (Table S3).

3.5. Use of medications in incident and prevalent patients

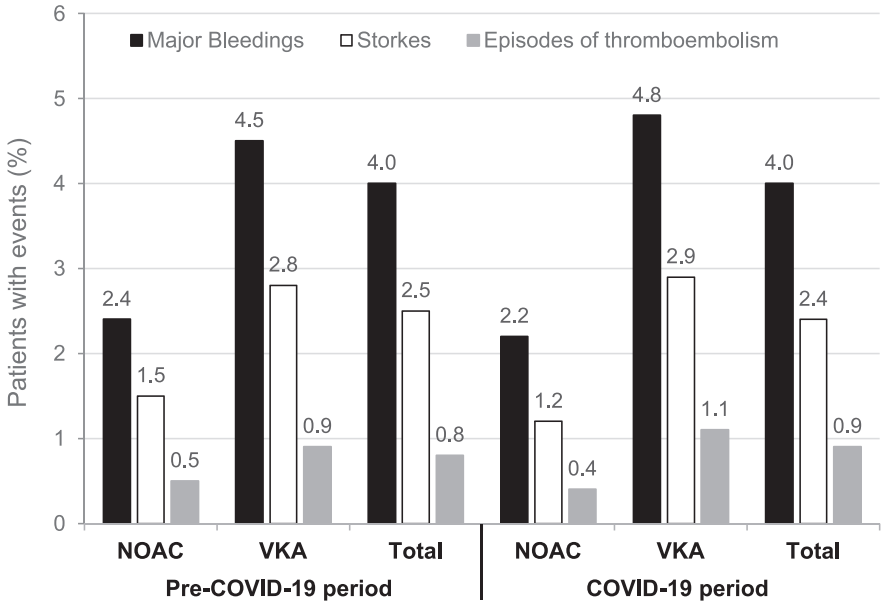
NVAF patients were on treatment with an average of at least 3 concomitant medications. Prevalent patients were on treatment with more concomitant medications than incident patients in both study periods (pre-COVID-19 period: 3.6 medications [SD: 1.3] vs. 3.3 medications [SD: 1.5], p < 0.001; COVID-19 period: 3.7 medications [SD: 1.3] vs. 3.4 medications [SD: 1.5]; $p < 0.001$). The most common concomitant medications were renin-angiotensin system acting agents, followed by beta-blockers and nonsteroidal anti-inflammatory drugs (Table S4).

During the COVID-19 period, the number of patients treated with VKA decreased from 76.2 % to 67.4 %. Most of them received acenocoumarol, particularly in incident patients. The doses of VKA were

Table 2
Clinical effectiveness and safety analysis per study period and type of anticoagulant in prevalent patients.

Study groups	Pre-COVID-19 period			*p*	COVID-19 period			*p*
	NOAC	VKA	Total		NOAC	VKA	Total	
Number of patients, n (%)	3068 (24.9)	9268 (75.1)	12,336 (100.0)	<0.001	4012 (30.1)	9330 (69.9)	13,342 (100.0)	<0.001
Total number of events, n (%)	135 (4.4)	760 (8.2)	895 (7.3)		153 (3.8)	824 (8.8)	977 (7.3)	
Strokes, n (%)	46 (1.5)	260 (2.8)	306 (2.5)	<0.001	49 (1.2)	275 (2.9)	324 (2.4)	<0.001
Episodes of thromboembolism, n (%)	16 (0.5)	83 (0.9)	99 (0.8)	0.051	16 (0.4)	102 (1.1)	118 (0.9)	<0.001
Major bleedings, n (%)	73 (2.4)	417 (4.5)	490 (4.0)	<0.001	88 (2.2)	447 (4.8)	535 (4.0)	<0.001
Mean events per patient (SD)	0.1 (0.3)	0 (0.2)	0.1 (0.3)	<0.001	0.1 (0.3)	0 (0.2)	0.1 (0.3)	<0.001
Time to episode								
Strokes								
Mean (SD)	145.4 (90.2)	141.9 (97.1)	143.5 (93.9)	0.756	147.9 (77.4)	144.6 (82.1)	146.5 (79.4)	0.700
Median (P25-P75)	183.0 (57—222)	137.0 (41—236.3)	165.0 (51.5—226.5)		158.0 (81—204)	163.5 (74—204.8)	158.0 (77—204)	
Episodes of thromboembolism								0.067
Mean (SD)	146.4 (92.5)	125.1 (78.4)	132.8 (83.8)	0.294	179.3 (89.3)	147.2 (99.7)	159.4 (96.8)	
Median (P25-P75)	140.0 (64—228)	96.5 (72.3—185.5)	125.0 (67—208)		190.0 (114—236.5)	145.0 (56.8—226.5)	165.0 (86—232.5)	
Major bleedings								0.143
Mean (SD)	156.4 (114.2)	158.9 (111.9)	158.2 (112.2)	0.888	209.5 (116.2)	194.3 (110.1)	200.1 (112.6)	
Median (P25-P75)	123.0 (51.5—268)	155.0 (53—249)	151.5 (53—249.8)		226.0 (101—316)	199.0 (93.5—299.5)	206.0 (95—309)	
Values								
TTR < 65 %, n (%)	–	3883 (41.9)	–	–	–	4171 (44.7)	–	–
Mortality								
Rate, n (%)	118 (3.8)	446 (4.8)	564 (4.6)	0.035	190 (4.7)	526 (5.6)	716 (5.4)	0.033
Time to death, days				0.150				0.045
Mean (SD)	209.7 (97.8)	230.4 (92.6)	225.3 (94.3)		196.2 (104.4)	226.4 (93.2)	217.3 (97.6)	
Median (P25-P75)	222.0 (125—296)	254.0 (144.0—310.0)	248.5 (144.0 – 309.0)		205.5 (110.0—293.8)	241.5 (157—308)	231.5 (141.3 – 304.0)	

Values are expressed as a percentage or mean (SD). p: statistical significance (5%). NOAC: non-Vitamin K antagonist oral anticoagulants; P: percentile; SD: standard deviation; TTR: time in therapeutic range (Rosedaal method), VKA: vitamin K antagonists.



Study groups	Pre-COVID-19 period			COVID-19 period		
	NOAC	VKA	Total	NOAC	VKA	Total
Number of patients, n (%)	3068 (24.9)	9268 (75.1)	12336 (100.0)	4012 (30.1)	9330 (69.9)	13342 (100.0)
Episodes of thromboembolism (%)	0.5	0.9	0.8	0.4	1.1	0.9
Strokes (%)	1.5	2.8	2.5	1.2	2.9	2.4
Major bleedings (%)	2.4	4.5	4.0	2.2	4.8	4.0

Fig. 1. Incidence of events in prevalent patients in both study periods. NOAC: non-vitamin K antagonist oral anticoagulants VKA: vitamin K antagonists.

higher in prevalent patients compared to incident patients ($p < 0.001$ for both comparisons). The median duration of treatment was longer in the period before the pandemic (365 days vs. 357 days), especially in prevalent patients ($p < 0.001$ for both comparisons). Discontinuations were more frequent in incident patients (pre-COVID-19 period: 32.7 % vs. 15.9 %, $p < 0.001$; COVID-19 period: 40.0 % vs. 17.7 %; $p < 0.001$). In line with previous results, treatment abandonment was the most frequent reason for discontinuation. It should be noted that discontinuations were more common in patients treated with VKA (pre-COVID-19 period: 18.0 %; COVID-19 period: 19.4 %) in comparison to those with NOAC (pre-COVID-19 period: 12.4 %; COVID-19 period: 12.5 %) (Table S4).

The consumption of NOAC rose during the pandemic, from 23.8 % to 32.6 %. This increase was higher in incident patients (15.6 % to 53.8 %) than in prevalent patients (24.9 % to 30.1 %). Apixaban was the most prescribed NOAC, followed by dabigatran, rivaroxaban and edoxaban. In general, the initial daily dose of NOAC was similar in both study periods, slightly higher in prevalent patients than in incident patients. The median duration of the treatment was 365 days in both periods of the study, although it was longer in prevalent than in incident patients (pre-COVID-19 period: 198 days vs. 365 days, $p < 0.001$; COVID-19 period: 254 days vs. 365 days; $p < 0.001$). Discontinuations were similar before and after the pandemic, but they were more frequent in incident patients than in prevalent patients (pre-COVID-19 period: 33.1 % vs. 10.7 %, $p < 0.001$; COVID-19 period: 24.7 % vs. 9.8 %; $p < 0.001$). They were mainly associated with treatment abandonment (Table S4).

3.6. *Use of healthcare resources in prevalent patients*

In general, the attendance to medical visits (primary care, nursing,

Table 3
Use of healthcare resources in prevalent patients.

	Pre-COVID-19 period			*p*	COVID-19 period			*p*
	NOAC	VKA	Total		NOAC	VKA	Total	
Number of patients, n (%)	3068 (24.9)	9268 (75.1)	12,336 (100)		4012 (30.1)	9330 (69.9)	13,342 (100.0)	
Total healthcare visits, mean (SD)	19.4 (15.8)	24.2 (15.9)	23.0 (16.0)	<0.001	18.2 (15.8)	24.3 (15.1)	22.5 (15.5)	<0.001
Primary care visits	9.4 (7.0)	8.9 (6.8)	9.0 (6.9)	<0.001	8.9 (6.9)	9.0 (6.4)	9.0 (6.6)	0.498
Nursing visits	7.9 (10.2)	12.6 (11.3)	11.4 (11.2)	<0.001	7.4 (10.6)	12.7 (10.8)	11.1 (11.0)	<0.001
Specialist visit	2.1 (4.2)	2.8 (3.0)	2.6 (3.3)	<0.001	1.8 (4.4)	2.6 (2.6)	2.4 (3.3)	<0.001
Hematology	0 (0.1)	0 (0.1)	0 (0.1)	0.534	0 (0.1)	0 (0.1)	0 (0.1)	0.139
Cardiology	2.1 (4.2)	2.8 (3.0)	2.6 (3.3)	<0.001	1.8 (4.4)	2.6 (2.6)	2.4 (3.3)	<0,001
Emergency visits, mean (SD)	0.4 (2.1)	0.4 (2.6)	0.4 (2.5)	0.882	0.4 (3.4)	0.5 (3.6)	0.5 (3.5)	0.016
Hospitalizations								
Patients admitted to hospitals, n (%)	210 (6.8)	676 (7.3)	886 (7.2)	0.404	228 (5.7)	809 (8.7)	1037 (7.8)	<0.001
Hospital stays per patient, mean (SD)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.187	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	<0.001

Values are expressed as a percentage or mean (SD). p: statistical significance (5%). NOAC: non-Vitamin K antagonist oral anticoagulants; SD: standard deviation; VKA: vitamin K antagonists.

and specialist visits) decreased during the pandemic. However, there was a slight increase in emergency visits and hospitalizations (Table 3).

Regarding the anticoagulant treatment, it was observed that patients with VKA had more medical visits per year than those on treatment with NOAC (pre-COVID-19 period: 24.2 visits [SD: 15.9] vs. 19.4 visits [SD: 15.8], $p < 0.001$; COVID-19 period: 24.3 visits [SD: 15.1] vs. 18.2 visits [SD: 15.8], $p < 0.001$). It should be noted that nursing visits were the most frequent, especially in VKA patients (pre-COVID-19 period: 12.6 visits [SD: 11.3] vs. 7.9 visits [SD: 10.2], $p < 0.001$; COVID-19 period: 12.7 visits [SD: 10.8] vs. 7.4 visits [SD: 10.6], $p < 0.001$). In addition, patients on treatment with VKA required more specialist visits, particularly to the cardiologist (pre-COVID-19 period: 2.8 visits [SD: 3.0] vs. 2.1 visits [SD: 4.2], $p < 0.001$; COVID-19 period: 2.6 visits [SD: 2.6] vs. 1.8 visits [SD: 4.4], $p < 0.001$). During the pre-COVID-19 period, there were no differences in attendance in the emergency room ($p = 0.882$) and hospitalizations ($p = 0.404$). However, during the pandemic, patients receiving VKA visited the emergency room more frequently (0.5 visits [SD: 3.6] vs. 0.4 visits [SD: 3.4]); $p = 0.016$) than those on treatment with NOAC. Similarly, VKA patients required more hospitalizations compared to NOAC patients (8.7 % vs. 5.7 %); $p < 0.001$) (Table 3).

4. Discussion

Our study showed that during the COVID-19 pandemic, the anticoagulant treatment with NOAC increased at the expense of VKA use in patients with NVAF. Prevalent patients treated with VKA had more strokes, episodes of thromboembolism and major bleedings, and a higher mortality rate than those receiving NOAC. In addition, NOAC patients were more persistent in the treatment after 12 months than VKA. NOAC patients also required fewer healthcare resources than patients treated with VKA.

Previous studies referred to the difficulties of monitoring patients on treatment with VKA during the COVID-19 pandemic. Barcellona et al. reported that after around 2 months, the number of patients treated with NOAC increased by 20 % in patients with long-term anticoagulation therapy with VKA in a Thrombosis Center in Italy [29]. Moreover, during the first 8 weeks of the pandemic, 133 patients were switched from VKA to NOAC in two hospitals in the UK. After 1 month of follow-up, most of them (90 %) were very satisfied or satisfied with their treatment, and 96 % of patients continued their treatment with NOAC, as side effects were minor or tolerable [30]. In addition, 164,000 patients in the UK were prescribed warfarin (VKA) between December 2019 and February 2020, and 12.2 % were switched to NOAC between March and May 2020 [31]. These changes in medication were in line with European clinical guidelines [17,19,32,33]. Papakonstantinou et al. indicated that in the time of COVID-19, anticoagulation therapy with NOAC seemed to be the safest approach in NVAF and that shifting to NOAC should be considered in those receiving VKA who are suitable for these treatments [19]. In line with this, we observed that the use of VKA in incident patients decreased from 84.4 % to 46.2 % during the pre-COVID-19 and the COVID-19 periods, respectively, whereas the prescriptions of NOAC increased from 15.6 % to 53.8 %. Of note-apixaban was the most frequently prescribed NOAC in these groups of patients.

A key aspect of our study is the analysis of the clinical results of NVAF patients receiving anticoagulation treatments before and after the COVID-19 pandemic in Spain. Our results showed that using NOAC reduced the incidence of severe events, particularly during the pandemic. In this regard it has been previously reported that in comparison to patients on treatment with acenocoumarol (VKA), those treated with apixaban (NOAC) had a lower incidence of systemic embolisms and strokes (3.7 % vs. 2.0 % respectively; $p < 0.001$), fewer minor bleedings (7.2 % vs. 10.9 %, respectively; $p < 0.001$) and major bleedings (4.6 % vs. 2.4 %, respectively; $p < 0.001$) [10]. However, our results cannot be directly compared with the study mentioned above, as they analyzed the effectiveness of these anticoagulants in naive patients, whereas we considered patients who were already on treatment with these medications. Another contribution of our study is the use of a large database representative of the Spanish population. It allows us to describe patients' clinical characteristics and treatment patterns with NVAF in medical practice.

4.1. Study limitations

Our study is not without limitations. The BIG-PAC® database is administrative and presents limitations when it is used for observational studies. EMR may have some missing information, particularly if patients attended healthcare facilities outside of the area of influence of BIG-PAC®. Other limitations involve the categorization of the disease, the possible classification bias of patients, disease recording, or possible variations in the clinical practice of healthcare professionals, and the management of patients. In this sense, using ICD-10-CM coding does not allow for differentiation of the type of permanent, persistent, or paroxysmal AF. In addition, some variables that could influence the results (socioeconomic level of patients, possible variations in left ventricle ejection fraction values, variations in the pharmacological dose prescribed, etc.) were unavailable. Furthermore, during the pandemic, the organization of primary care centers was modified to reduce contacts [34,35], leading to an increase in medical appointments made by phone or email, and we could not compare the percentage of remote consultations during the pre-COVID-19 and COVID-19 periods, as they were not differentiated from regular visits. Another limitation is that the analysis was conducted during a specific timeframe corresponding to the COVID-19 pandemic, a period marked by widespread lockdown implementations in most countries. Consequently, the findings may not hold the same validity under different circumstances beyond these specific conditions. Despite these limitations, our study provides more information about the use of anticoagulant treatments in patients with NVAF, their effectiveness, and the associated consumption of healthcare resources in Spain.

5. Conclusions

During the COVID-19 pandemic, the consumption of NOAC as anticoagulation therapy increased in patients with NVAF. Patients treated with NOAC had a lower incidence of strokes and major bleeding than patients with VKA. Our results suggest that NOAC reduced the use of healthcare resources and might reduce the direct healthcare costs in NVAF patients. Therefore, NOAC should be considered a convenient alternative to VKA in times of health crisis, such as the COVID-19 pandemic.

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CRediT authorship contribution statement

Josep Comín Colet: Writing – review & editing, Visualization, Validation, Methodology. **Antoni Sicras Mainar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Joel Salazar-Mendiguchía:** Writing – review & editing, Visualization, Validation, Methodology. **María Isabel del Campo Alonso:** Writing – review & editing, Visualization, Validation. **Ainara Echeto:** Writing – review & editing, Visualization, Validation. **David Vilanova Larena:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization. **Olga Delgado Sánchez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ASM is an employee of Atrys Health SA, who was paid consultant to BMS in connection with this manuscript. DVL, JSM, MICA and AE are employees of Bristol Myers Squibb and have BMS stocks. JCC and ODS declare to have received fees as coordinator investigators of this study by Bristol Myers Squibb.

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Appendix A. Supplementary data

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