NON-INTERVENTIONAL (NI) STUDY REPORT

Executive summary

Study Information

Title	**Apixaban drug utilization study in stroke prevention in atrial fibrillation (SPAF)**
Protocol number	B0661076
AEMPS Code	PFI-API-2016-01
Version identifier of the final study report	**1.0**
Date of last version of the final study report	**8 March 2017**
Active substance	Apixaban B01AF02
Medicinal product	Eliquis®
Research question and objectives	Evaluate the apixaban utilization according to the approved SPAF indication and recommendations by EMA. The study objectives are: Objective 1: To characterize patients using apixaban according to demographics, comorbidity, risk of thromboembolic events ($CHADS_2$ and CHA_2DS_2-Vasc scores), risk of bleeding events (HAS-BLED score), comedications and compare it with the profile of patients

	treated with VKA, dabigatran and rivaroxaban. Objective 2: Describe the level of appropriate usage according to the posology recommended in the apixaban SmPC. Objective 3: Describe the potential interactions with other drugs prescribed concomitantly according with the SmPC recommendations. Objective 4: Estimate the level of apixaban adherence by the medication possession ratio (MPR) and discontinuation rates and compare it with VKA, dabigatran and rivaroxaban cohort. Objective 5: To analyze INR (International Normalized Ratio) values during the last 12 months and to obtain TTR (Time in Therapeutic Range) values in patients previously treated with VKA and, during the whole study period for those in the cohort treated with VKA
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1 Investigators

Table 1. Members of the research team

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2 Rationale and background

We present a non-interventional (NI) post-authorization study on the use of apixaban in Catalonia – Spain public health care population.

The apixaban SPAF indication was commercialized in Spain for the first time in August 2013 as Eliquis®, 5 mg BID film-coated tablets[1].

Apixaban is a direct oral anticoagulant (DOAC), which inhibits factor Xa. Until now, most of the observational studies for apixaban were about cost-effectiveness. According to the study "Patterns of initiation of oral anticoagulants in patients with atrial fibrillation (AF) - quality

and cost implications" patients were characterized by prescription and comparing apixaban with other DOAC in the treatment of NVAF, and the authors found that DOAC are being incorporated quickly into clinical practice, especially among patients with low values of $CHADS_2$ score and HAS-BLED score.[2]

The EMA recommends additional monitoring for this drug and a pharmacovigilance plan which includes performing DUS and post marketing studies.

This DUS study assesses whether this drug has been used properly and in accordance with the approved indications and recommendations described in the summary of product characteristics (SmPC) and estimates possible misuse or overuse of apixaban.

3 Research question and objectives

Objective 1: To characterize patients using apixaban according to demographics, comorbidity, risk of thromboembolic events ($CHADS_2$ and CHA_2DS_2-Vasc scores)[3], risk of bleeding events (HAS-BLED score)[4], and comedications; and compare them with the profile of patients treated with VKA, dabigatran and rivaroxaban.

Objective 2: To describe the level of appropriate use according to the posology recommended in the apixaban SmPC.

Objective 3: To describe the potential interactions with other drugs prescribed concomitantly according with the SmPC recommendations.

Objective 4: To estimate the level of apixaban adherence by the medication possession ratio (MPR) and discontinuation rates and compare it with the VKA, dabigatran and rivaroxaban cohorts.

Objective 5: To analyze INR (International Normalized Ratio) values during the last 12 months and to obtain TTR (Time in Therapeutic Range) values in patients previously treated with VKA, and during the whole study period for those in the cohort treated with VKA.

4 Research methods

4.1 Study design

This DUS is a retrospective, observational, cohort study. DOAC and VKA users have been identified in the primary health care database SIDIAP (Information System for the Improvement of Research in Primary Care) in Catalonia, Spain.

4.1.1 Study cohorts

The study cohort included all individuals diagnosed with NVAF from source population who had a new prescription for apixaban, VKA (warfarin or acenocoumarol), dabigatran or rivaroxaban from August 2013 until December 2015, and a previously recorded diagnosis of NVAF. All patients enrolled in the cohort were subdivided in four main groups:

Group 1 - Patients treated with apixaban:

- 1a: patients who initiated apixaban as treatment-naïve (no prior prescription of VKA or DOAC during 12 months before index date).
- 1b: patients previously treated with VKA, dabigatran or rivaroxaban in the 12 months before index date.

Group 2 - Patients treated with VKA (acenocoumarol or warfarin):

- 2a: patients who initiated VKA as treatment-naïve (no prior prescription of VKA or DOAC during 12 months before index date)
- 2b: patients previously treated with a different VKA or DOAC in the 12 months before index date.

Group 3 - Patients treated with dabigatran:

- 3a: patients who initiated dabigatran as treatment-naïve (no prior prescription of VKA or DOAC during 12 months before index date).
- 3b: patients previously treated with VKA, rivaroxaban or apixaban in the 12 months before index date.

Group 4 - Patients treated with rivaroxaban:

- 4a: patients who initiated rivaroxaban as treatment-naïve (no prior prescription of VKA or DOAC during 12 months before index date).
- 4b: patients previously treated with VKA, dabigatran or apixaban in the 12 months before index date.

4.1.2 Setting

SIDIAP currently collects information from 279 primary health care centres managed by the Catalan health institute (ICS), which covers more than 5.8 million patients (approximately 80% of the Catalonia population, or more than 10% of the Spanish population).[6]

Our study population included all eligible subjects from the source population with a first-recorded prescription of apixaban, VKA, dabigatran or rivaroxaban for SPAF registered in SIDIAP database during the study period and diagnosed of NVAF.

The study period was defined as the time when apixaban became commercialized for the SPAF indication in Spain, August 2013, until December 2015.

4.2 Medication

Drug dispensings of drugs of interest were identified through ATC codes[5] from ECAP (electronic medical records in Primary Care of the ICS) prescriptions. We established two groups of doses according to the apixaban SmPC for the SPAF indication: 5mg/BID or 2.5mg/BID in the. Patients were followed-up until the prescription of other anticoagulant.

Co-medications were identified from prescription data at the index date and collected from the inclusion and up to one month after.

Medication adherence outcome

Definition of the therapeutic adherence: medication possession ratio (MPR), defined daily dose (DDD), TTR (Time in Therapeutic Range) and accumulative discontinuation rate.

4.3 Statistical methods

Sociodemographic characteristics for the four groups (apixaban, dabigatran, rivaroxaban and VKA) at the start date are provided. Comorbidities at the start date were identified by ICD-10 codes. Concurrent use of medications at the start date was quantified by the number and percentage of users. Risk of stroke and major haemorrhage event were assessed at the start date with $CHADS_2$, CHA_2DS_2Vasc and HAS-BLED.

Appropriate use of apixaban during the study period was assessed for two groups of patients depending on the recommended daily dose: 5 or 2.5 mg BID.

Apixaban, VKA, dabigatran and rivaroxaban user adherences were assessed during the study period through the MPR.

Detailed methodology for summary and statistical analyses of data collected in this study are documented in the Statistical Analysis Plan, which is dated, filed and maintained by the sponsor.

4.4 Quality control

IDIAP Jordi Gol is in charge of implementing their standard operating procedures to guide the conduct of the study.

5 Results

5.1 Participants

A total of 51,690 patients were included in the study; 47,197 (91.3%) were naïve patients and 4,493 (8.7%) were non-naïve. Numbers of patients included in each treatment group are described in Table2. In the group of DOAC, there are higher proportions of non-naïve patients, most of them were previously treated with VKA.

Table 2. Patients included in each treatment group

	Total	Apixaban (group 1)	Acenocoumarol (group 2, VKA)	Warfarin (group 2, VKA)	Dabigatran (group 3)	Rivaroxaban (group 4)
Type of treatment						
Naïve (groups a)	47,197 (91.3%)	4,712 (76.8%)	32,212 (99.4%)	2,286 (86.3%)	2,855 (75.0%)	5,132 (76.7%)
Non-naïve (groups b)	4,493 (8.7%)	1,423 (23.2%)	192 (0.6%)	363 (13.7%)	953 (25.0%)	1,562 (23.3%)
Total	**51,690**	**6,135**	**32,404**	**2,649**	**3,808**	**6,694**

5.2 Descriptive data

5.2.1 Descriptive data of the study population

In general, naïve patients were younger (32% of the naïve patients vs 46.2% of non-naïve patients where 80 years and older) and with less comorbidity (22.7% of the naïve patients had at least 3 comorbidities vs 39.5% of the non-naïve patients). Both groups had any concurrent medication at base line (100% naïve and 98.5% non-naïve patients). Among the naïve 17% had a $CHA_2DS_2VASc<2$ but only 6.1% of the non-naïve were under this score. More than half of the naïve patients had higher risk of bleeding (HAS-BLED score ≥3), 66.6%, and almost half of the non-naïve had these scores (47.2%). Both groups had a high prevalence of good renal function, glomerular filtration rate over 60 mL/min per 1.73 m^2 (59.7% and 55.8% of the naïve and non-naïve patients). Table 3 shows the sociodemographic characteristics of patients included in the apixaban group.

Table 3. Sociodemographic characteristics of patients included in group 1, apixaban

Categorical	N= 6,135	Naïve (n=4,712, 76.8%)	Non-naïve (n=1,423, 23.2%)
Sex			
Female	3,412 (55.6%)	2,661 (56.5%)	751 (52.8%)

Male	2,723 (44.4%)	2,051 (43.5%)	672 (47.2%)
Smoking habit			
Missing	230 (3.7%)	207 (4.4%)	23 (1.6%)
Non-smoker	4,050 (66.0%)	3,104 (65.9%)	946 (66.5%)
Ex-smoker	542 (8.8%)	459 (9.7%)	83 (5.8%)
Smoker	1,313 (21.4%)	942 (20.0%)	371 (26.1%)
Alcoholic habit			
Missing	2,515 (41.0%)	2,162 (45.9%)	353 (24.8%)
No intake	2,559 (41.7%)	1,749 (37.1%)	810 (56.9%)
Moderate intake	1,012 (16.5%)	765 (16.2%)	247 (17.4%)
Risk consumption	49 (0.8%)	36 (0.8%)	13 (0.9%)
MEDEA			
Missing - Urban area	280 (4.6%)	190 (4.0%)	90 (6.3%)
Rural area	898 (14.6%)	685 (14.5%)	213 (15.0%)
Quintile 1 - Urban area	940 (15.3%)	716 (15.2%)	224 (15.7%)
Quintile 2 - Urban area	970 (15.8%)	754 (16.0%)	216 (15.2%)
Quintile 3 - Urban area	1,081 (17.6%)	825 (17.5%)	256 (18.0%)
Quintile 4 - Urban area	1,038 (16.9%)	807 (17.1%)	231 (16.2%)
Quintile 5 - Urban area	928 (15.1%)	735 (15.6%)	193 (13.6%)
Glomerular Filtration Rate (mL/min per 1.73 m^2)			
Missing	1,249 (20.4%)	1,030 (21.9%)	219 (15.4%)
≥ 60	3,605 (58.8%)	2,873 (61.0%)	732 (51.4%)
45 - 59	798 (13.0%)	537 (11.4%)	261 (18.3%)
30 - 44	400 (6.5%)	228 (4.8%)	172 (12.1%)
< 30	83 (1.4%)	44 (0.9%)	39 (2.7%)
Age groups (years)			
18-39	58 (0.9%)	56 (1.2%)	2 (0.1%)
40-49	141 (2.3%)	131 (2.8%)	10 (0.7%)

50-59	426 (6.9%)	388 (8.2%)	38 (2.7%)
60-69	1,390 (22.7%)	1,219 (25.9%)	171 (12.0%)
70-79	2,241 (36.5%)	1,770 (37.6%)	471 (33.1%)
≥80	1,879 (30.6%)	1,148 (24.4%)	731 (51.4%)
BMI groups (kg/m²)			
Missing	1,685 (27.5%)	1,424 (30.2%)	261 (18.3%)
18.5 - 25 (Normal)	676 (11.0%)	423 (9.0%)	253 (17.8%)
< 18.5 (Underweight)	18 (0.3%)	12 (0.3%)	6 (0.4%)
25 - 30 (Overweight)	1,722 (28.1%)	1,229 (26.1%)	493 (34.6%)
> 30 (Obese)	2,034 (33.2%)	1,624 (34.5%)	410 (28.8%)
Continuous			
Age (years)			
Valid n	6,135	4,712	1,423
Mean (SD)	73.2 (11.0)	71.8 (11.1)	78.1 (8.7)
Median (IQR)	74.0 (67.0 - 81.0)	73.0 (66.0 - 79.0)	80.0 (74.0 - 84.0)
Minimum - maximum	19 , 101	19 , 99	36 , 101
BMI (kg/m²)			
Valid n	4,450	3,288	1162
Missing	1,685 (27.5%)	1,424 (30.2%)	261 (18.3%)
Mean (SD)	30.1 (5.3)	30.5 (5.2)	28.9 (5.4)
Median (IQR)	29.6 (26.4 - 33.1)	29.9 (26.9 - 33.5)	28.3 (25.3 - 31.6)
Minimum, maximum	16.6 , 58.4	16.6 , 50.5	16.7 , 58.4

*MEDEA, socioeconomic index. BMI, body mass index. SD, standard deviation. IQR, interquartile range

Table 4. Comorbidities of patients included in group 1, apixaban

	N= 6,135	Naïve (n=4,712, 76.8%)	Non-naïve (n=1,423, 23.2%)
Any comorbidity			
Yes	5,011 (81.7%)	3,695 (78.4%)	1,316 (92.5%)

no. comorbidities			
0	1,124 (18.3%)	1,017 (21.6%)	107 (7.5%)
1	2,012 (32.8%)	1,703 (36.1%)	309 (21.7%)
2	1,530 (24.9%)	1,138 (24.2%)	392 (27.5%)
≥ 3	1,469 (23.9%)	854 (18.1%)	615 (43.2%)
Comorbidity type			
Heart failure	866 (14.1%)	385 (8.2%)	481 (33.8%)
Peripheral artery disease	323 (5.3%)	189 (4.0%)	134 (9.4%)
Ischemic heart disease	802 (13.1%)	460 (9.8%)	342 (24.0%)
Acute myocardial infarction	246 (4.0%)	140 (3.0%)	106 (7.4%)
Hypertension	4,295 (70.0%)	3,172 (67.3%)	1,123 (78.9%)
Diabetes mellitus	1,986 (32.4%)	1,404 (29.8%)	582 (40.9%)
Deep vein thrombosis and pulmonary embolism	83 (1.4%)	45 (1.0%)	38 (2.7%)
Liver disease	348 (5.7%)	270 (5.7%)	78 (5.5%)
Renal disease	927 (15.1%)	562 (11.9%)	365 (25.7%)
Cerebrovascular disease	891 (14.5%)	490 (10.4%)	401 (28.2%)
Cancer	1,606 (26.2%)	1,202 (25.5%)	404 (28.4%)
Chronic obstructive pulmonary disease	1,206 (19.7%)	839 (17.8%)	367 (25.8%)

Table 5. Risk of stroke and haemorrhage of patients in group 1, apixaban

	N= 6,135	Naïve (n=4,712, 76.8%)	Non-naïve (n=1,423, 23.2%)
$CHADS_2$			
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
0	880 (14.3%)	831 (17.6%)	49 (3.4%)
1	1,609 (26.2%)	1,426 (30.3%)	183 (12.9%)
2	1,804 (29.4%)	1,409 (29.9%)	395 (27.8%)
3	969 (15.8%)	621 (13.2%)	348 (24.5%)

4	569 (9.3%)	288 (6.1%)	281 (19.7%)
5	240 (3.9%)	116 (2.5%)	124 (8.7%)
6	64 (1.0%)	21 (0.4%)	43 (3.0%)
CHA_2DS_2VASc			
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
0 or 1 (women)	480 (7.8%)	457 (9.7%)	23 (1.6%)
1	375 (6.1%)	344 (7.3%)	31 (2.2%)
2	993 (16.2%)	877 (18.6%)	116 (8.2%)
3	1,436 (23.4%)	1,179 (25.0%)	257 (18.1%)
4	1,385 (22.6%)	1,058 (22.5%)	327 (23.0%)
5	777 (12.7%)	464 (9.8%)	313 (22.0%)
6	466 (7.6%)	238 (5.1%)	228 (16.0%)
7	169 (2.8%)	77 (1.6%)	92 (6.5%)
8	52 (0.8%)	16 (0.3%)	36 (2.5%)
9	2 (0.0%)	2 (0.0%)	0 (0.0%)
HAS - BLED			
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
0	540 (8.8%)	519 (11.0%)	21 (1.5%)
1	1,335 (21.8%)	1,186 (25.2%)	149 (10.5%)
2	2,592 (42.2%)	2,131 (45.2%)	461 (32.4%)
3	1,226 (20.0%)	722 (15.3%)	504 (35.4%)
4	372 (6.1%)	141 (3.0%)	231 (16.2%)
5	65 (1.1%)	13 (0.3%)	52 (3.7%)
6	5 (0.1%)	0 (0.0%)	5 (0.4%)
≥7	0 (0.0%)	0 (0.0%)	0 (0.0%)
Continuous			
$CHADS_2$			
Valid n	6,135	4,712	1,423
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

Mean (SD)	2.0 (1.4)	1.7 (1.3)	2.8 (1.4)
Median (IQR)	2.0 (1.0 - 3.0)	2.0 (1.0 - 2.0)	3.0 (2.0 - 4.0)
Minimum - maximum	0 , 6	0 , 6	0 , 6
CHA_2DS_2VASc			
Valid n	6,135	4,712	1,423
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (SD)	3.3 (1.8)	3.0 (1.7)	4.4 (1.6)
Median (IQR)	3.0 (2.0 - 4.0)	3.0 (2.0 - 4.0)	4.0 (3.0 - 5.5)
Minimum, maximum	0 , 9	0 , 9	0 , 8
HAS - BLED			
Valid n	6,135	4,712	1,423
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (SD)	2.0 (1.1)	1.7 (1.0)	2.7 (1.1)
Median (IQR)	2.0 (1.0 - 3.0)	2.0 (1.0 - 2.0)	3.0 (2.0 - 3.0)
Minimum, maximum	0 , 6	0 , 5	0 , 6

*SD, standard deviation. IQR, interquartile range

Table 6. Concurrent medication of patients in group 1, apixaban

	N= 6,135	Naïve (n=4,712, 76.8%)	Non-naïve (n=1,423, 23.2%)
Any co-medication			
Yes	6,118 (99.7%)	4,712 (100.0%)	1,406 (98.8%)
Proton pump inhibitors	4,308 (70.2%)	3,362 (71.3%)	946 (66.5%)
Drugs used in diabetes	1,404 (22.9%)	955 (20.3%)	449 (31.6%)
Insulins	418 (6.8%)	256 (5.4%)	162 (11.4%)
Blood glucose lowering drugs	1,254 (20.4%)	874 (18.5%)	380 (26.7%)
Platelet aggregation inhibitors	985 (16.1%)	856 (18.2%)	129 (9.1%)
Clopidogrel	107 (1.7%)	88 (1.9%)	19 (1.3%)
Acetylsalicylic acid	889 (14.5%)	773 (16.4%)	116 (8.2%)

Other platelet aggregation inhibitors	18 (0.3%)	17 (0.4%)	1 (0.1%)
Heparins	161 (2.6%)	113 (2.4%)	48 (3.4%)
Iron preparations	625 (10.2%)	473 (10.0%)	152 (10.7%)
Cardiovascular medications	5,284 (86.1%)	3,907 (82.9%)	1,377 (96.8%)
Cardiac glycosides	517 (8.4%)	190 (4.0%)	327 (23.0%)
Antiarrhythmics, Class I and III	726 (11.8%)	502 (10.7%)	224 (15.7%)
Cardiac stimulants excluding cardiac glycosides	5 (0.1%)	3 (0.1%)	2 (0.1%)
Vasodilators used in cardiac diseases	498 (8.1%)	279 (5.9%)	219 (15.4%)
Other cardiac preparations	88 (1.4%)	54 (1.1%)	34 (2.4%)
Diuretics	2,131 (34.7%)	1,360 (28.9%)	771 (54.2%)
Peripheral vasodilators	82 (1.3%)	56 (1.2%)	26 (1.8%)
Pentoxifylline	81 (1.3%)	55 (1.2%)	26 (1.8%)
Beta blocking agents	2,075 (33.8%)	1,335 (28.3%)	740 (52.0%)
Calcium channel blockers	1,197 (19.5%)	846 (18.0%)	351 (24.7%)
Antihypertensives	244 (4.0%)	158 (3.4%)	86 (6.0%)
Agents acting on the renin-angiotensin system	3,469 (56.5%)	2,540 (53.9%)	929 (65.3%)
Angiotensin-converting-enzyme inhibitors	1,981 (32.3%)	1,475 (31.3%)	506 (35.6%)
Angiotensin II receptor antagonists	1,500 (24.4%)	1,074 (22.8%)	426 (29.9%)
Renin-inhibitors	11 (0.2%)	4 (0.1%)	7 (0.5%)
Lipid-modifying agents	2,801 (45.7%)	2,010 (42.7%)	791 (55.6%)
Statins	2,657 (43.3%)	1,906 (40.4%)	751 (52.8%)
Other lipid-modifying agents	239 (3.9%)	171 (3.6%)	68 (4.8%)
Hormone replacement therapy	39 (0.6%)	30 (0.6%)	9 (0.6%)
Systemic corticosteroids	234 (3.8%)	171 (3.6%)	63 (4.4%)
Immunosuppressants	37 (0.6%)	27 (0.6%)	10 (0.7%)
Drugs for musculoskeletal system	1,805 (29.4%)	1,735 (36.8%)	70 (4.9%)
Non-steroidal anti-inflammatory drugs	1,805 (29.4%)	1,735 (36.8%)	70 (4.9%)

Acetylsalicylic acid (other analgesics and antipyretics)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other antirheumatic agents	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antidepressants	1,362 (22.2%)	1,049 (22.3%)	313 (22.0%)
Selective serotonin reuptake inhibitors	958 (15.6%)	742 (15.7%)	216 (15.2%)
Drugs for obstructive airway diseases	1,010 (16.5%)	691 (14.7%)	319 (22.4%)

5.2.2 Descriptive data of patients treated with vitamin K antagonists

In this group we can find 67.8% of the whole cohort of study (n=35053), being the majority naïve patients (n=34,498, 98.4%) and under acenocumarol treatment (92.4%). There were more men than women treated with VKA (52.1%). More than half of VKA-treated were older than 70 years (68.8%). The median of the BMI was around 30. One quarter of the VKA-treated had 3 or more comorbidities being hypertension and diabetes mellitus the two principal comorbidities. Almost 60% presented a glomerular filtration rate ≥60 mL/min per 1.73 m^2. The acenocoumarol naïve patients had a CHA_2DS_2VASc score median of 3.0 (IQR 2.0 - 4.0) meanwhile the non-naïve under acenocoumarol treatment had a median CHA_2DS_2VASc score of 4.0 (IQR 3.0 - 5.0). Among the acenocoumarol naïve patients the HAS-BLED score median was 2.0 (IQR 2.0-3.0) vs 2.5 (IQR 2.0-3.0) in the non-naïve treated patients.

5.2.3 Descriptive data of patients treated with dabigatran

Patients treated with dabigatran (7.4% of the total) showed a high proportion of naïve patients (75%) with similar proportions of men and women. The naïve patients had a median age of 71.0 (63.0 - 79.0), meanwhile the non-naïve patients had 78.0 (71.0 - 83.0) years of median age. 71.1% of the naïve patients had at least one comorbidity and 91.3% of the non-naïve patients had. The CHA_2DS_2VASc score median was lower for the naïve patients (3.0 IQR 2.0 - 4.0) than for the non-naïve (4.0 IQR 3.0-5.0), as well as for the HAS-BLED score (median

2.0 IQR 1.0 - 2.0 vs 3.0 IQR 2.0 - 3.0). 14.3% of the naïve patients were taking acetylsalicylic acid but only 6.4% of the non-naïve were.

5.2.4 Descriptive data of patients treated with rivaroxaban

A total of 6,694 patients were treated with rivaroxaban, being 76.7% of them naïve. There was a slightly higher proportion of women than men (51.7% vs 48.3%). 58.1% of the patients treated with rivaroxaban had a BMI of 25 or higher. Among the non-naïve patients 90.7% had any comorbidity and 39.7%, 3 or more comorbidities albeit only 15.1% of the naïve had 3 or more comorbidities. The non-naïve patients had a higher proportion of heart failure (29.3% vs 6.3% among the naïve), ischemic heart disease (23.4% vs 9.6%), renal disease (19.9% vs 9%) and cerebrovascular disease (24.8% vs 6.7%), being in both, naïve and non-naïve patients hypertension the most prevalent comorbidity. The mean of CHA_2DS_2VASc of the naïve patients was 2.7 (SD 1.7) and for the non-naïve patients the mean was 4.1 (SD 1.7), the mean of the HAS-BLED score was 1.6 (SD 1.0) for the naïve patients and of 2.6 (SD 1.1) for the non-naïve ones. 17.0% of the naïve patients were under treatment with platelet aggregation inhibitors vs only 7.8% of the non-naïve patients and also 29.3% were treated with non-steroidal anti-inflammatory drugs vs only 5.8% of the non-naïve patients. Half of the non-naïve were under treatment with statins (50.4%) and a third of the naïve were (37.7%) treated too.

5.3 Main results

5.3.1 Results for objective 1

Comparisons between apixaban patients' profiles with the profiles of patients treated with VKA, dabigatran and rivaroxaban; according to sociodemographic characteristics, comorbidities, risk of stroke and bleeding and co-medications.

Regarding naïve patients, there were more women than men in apixaban group compared with the rest of groups. Apixaban-treated patients were older than the patients treated with other DOAC, but younger than acenocoumarol-treated patients. Dabigatran and rivaroxaban patients had less comorbidity than apixaban patients, and acenocumarol-treated had more comorbidities than apixaban patients. The risk of stroke and bleeding in apixaban-naïve patients was higher than for the rest of DOAC. When compared with apixaban, VKA patients were more frequently co-treated with heparins. Regarding cardiovascular drugs, in general they were more frequently used in VKA patients than in other groups. The OR for co-treatment with immunosuppressants with warfarin vs apixaban was 5.86 (95%CI, 3.81-9.30).
About non-naïve patients apixaban-treated were older than the rest of the patients. Apixaban non-naïve patients were 80 or older than the rest non-naïve patients. The risk of stroke and bleeding in apixaban-non-naïve was higher than for the rest of DOAC and for VKA. VKA patients were also more frequently co-treated with heparins, and acenocoumarol patients used more clopidogrel than the rest of groups.

5.3.2 Results for objective 2

In this section we describe the number and percentages of patients treated with the two doses of apixaban recommended in the SmPC, 2.5 mg or 5 mg BID.

The recommended dose was 2.5 mg if the patient had two of these three conditions: a) Serum creatinine ≥ 1.5 mg/dL; b) age ≥ 80 and c) body weight ≤ 60 kg or if he had severe renal impairment (creatinine clearance below 30 mL/min).

For the patients with a recommended dose of 2.5 mg BID of apixaban, 81.1% were prescribed with this dose. For the patients with a recommended dose of 5 mg BID, 51.8% received this dose. For 40.4% of the patients we did not have both the real dose and data enough for calculating the recommended dose.

When we analysed naïve patients (n=3,924), when the dosage recommended was 2.5 mg BID, 79.5% of patients initiated apixaban prescription correctly. When the dosage

recommended was 5 mg BID, 42.6% of patients were initially prescribed with 5 mg BID. We did not know apixaban dose prescribed in 1,924 (49.0%) naïve patients.

For non-naïve patients (n=1,222), when the dosage recommended was 2.5 mg BID, 82.5% of patients initiated apixaban prescription correctly. When the dosage recommended was 5 mg BID, 68.9% of patients were initially prescribed with 5 mg BID. We did not know the first dose prescribed of apixaban in 119 (9.7%) of these patients.

5.3.3 Results for objective 3

Potentially interacting drugs were prescribed in 28.8% of apixaban-naïve patients and in 26.7% of non-naïve patients. None of the patients had more than two potentially interacting drugs. Simvastatin was the most frequent prescribed potentially interacting drug (25.1%) followed by the calcium channel blocker diltiazem, which was prescribed in 3.8% of patients.

5.3.4 Results for objective 4

The therapeutic adherence was assessed through pharmacy invoice data for patients who initiated treatment between August 2013 and December 2014 (n=25,624), in order to analyse data of at least one year after initiation (2015). There were 23,259 naïve and 2,365 non-naïve patients for this period with less than one year of follow-up to assess adherence for 66.2% of the naïve patients and 43.0% for the non-naïve ones.

For apixaban 854 patients (32.5% naïve and 64.6% non-naïve) had at least one year of follow-up to assess adherence. The adherence was considered good in 61.1% of naïve patients and in 64.2% of non-naïve. For dabigatran 30.8% of naïve and 55.6% of non-naïve had at least one year of follow-up to assess adherence (n=758), and it was considered good in 46.1% of naïve and 42.8% of non-naïve patients. Regarding rivaroxaban, 30.7% of naïve and 60.6% of non-naïve had at least one year of follow-up to assess adherence (n=1,022), and it was considered good in 71.7% of naïve and 72.7% of non-naïve. Among the patients treated with VKA (n=19110) both, naïve and non-naïve patients showed a 34.3% of at least

one year of follow-up to assess adherence, it was considered good in only 9.5% taking into account that the adherence to VKA cannot be properly evaluated with DDDs.

With reference to discontinuation rates of treatments, which were also assessed in the period spanning August 2013 to December 2014, for naïve patients, 45.7% in apixaban group, 35.1% in dabigatran group and 42.1% in rivaroxaban group discontinued treatments after one month of initiation. For non-naïve patients, discontinuation rates after one month were lower (8.4%, 10% and 7.35 for apixaban, dabigatran and rivaroxaban respectively). In VKA the discontinuation rates after one month of treatment start were similar in naïve (6,8%) and non-naïve patients (8,7%). After one year of treatment start, the proportions of naïve patients discontinuing treatment were similar in the DOAC three groups (67.5%, 69.2% and 69.3%, respectively) and 65.6% for the naïve patients under VKA treatment. In naïve patients there are higher DOAC discontinuation rates in the first months of treatment, afterwards the discontinuation rates are lower compared to VKA.

When comparing “good adherence” between apixaban and the rest of treatments in naïve and non-naïve patients, in naïve patients, dabigatran showed worse adherence than apixaban (OR 0.67, 95%CI 0.55-0.82). When analysing only the first year of treatment, discontinuation was higher with apixaban than with dabigatran (Median ratio 1.83, 95% CI 1.07-2.87), whereas not significant differences were seen in apixaban vs rivaroxaban treated patients.

In non-naïve, compared with apixaban, dabigatran showed worse adherence too (OR 0.44, 95% CI 0.34-0.57). Discontinuation were higher with both dabigatran (OR 0.78, 95% CI 0.72-0.87) and rivaroxaban (OR 0.94, 95% CI 0.93-0.94) in comparison with apixaban.

Figure 1. Kaplan-Meier curves for treatment discontinuation of all anticoagulants in naïve patients

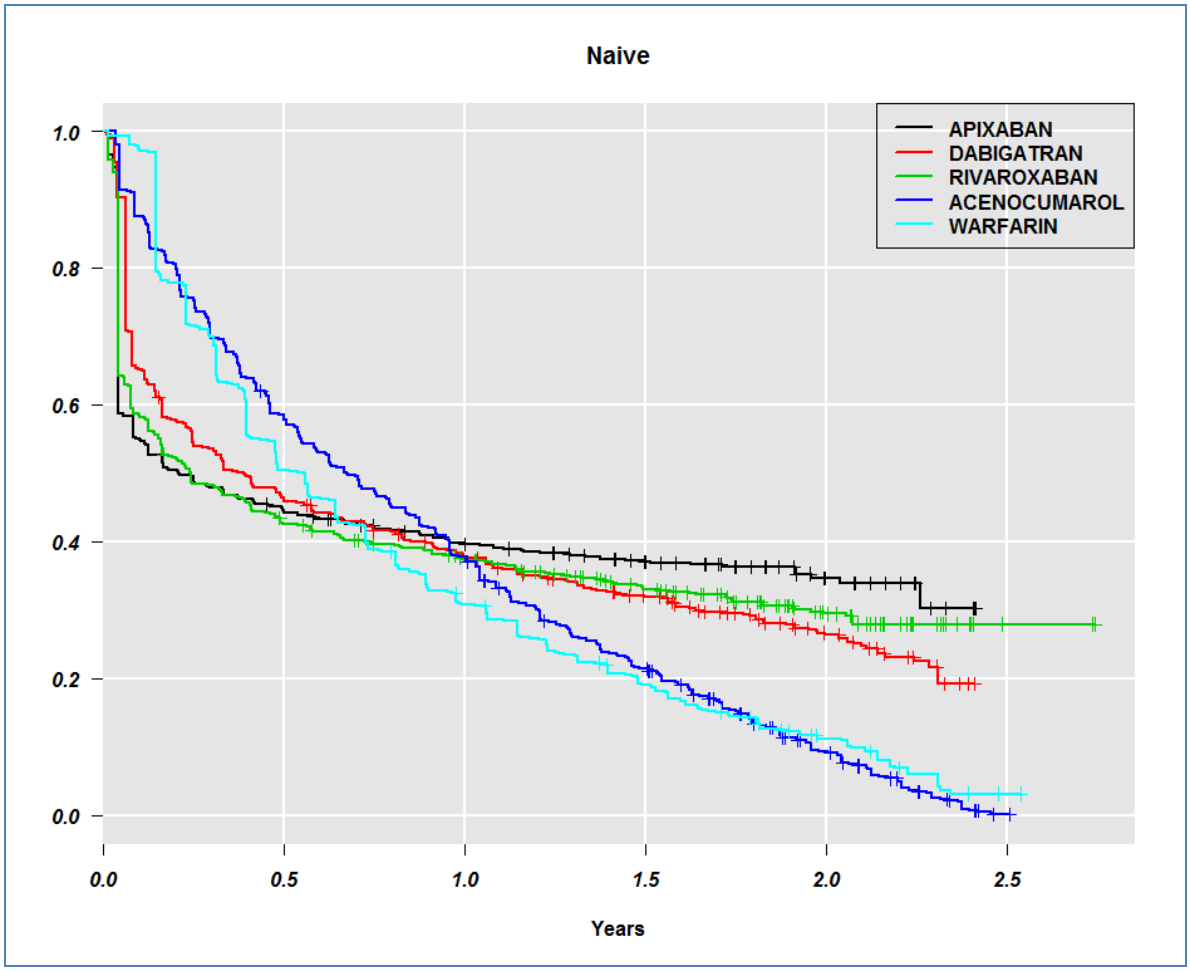
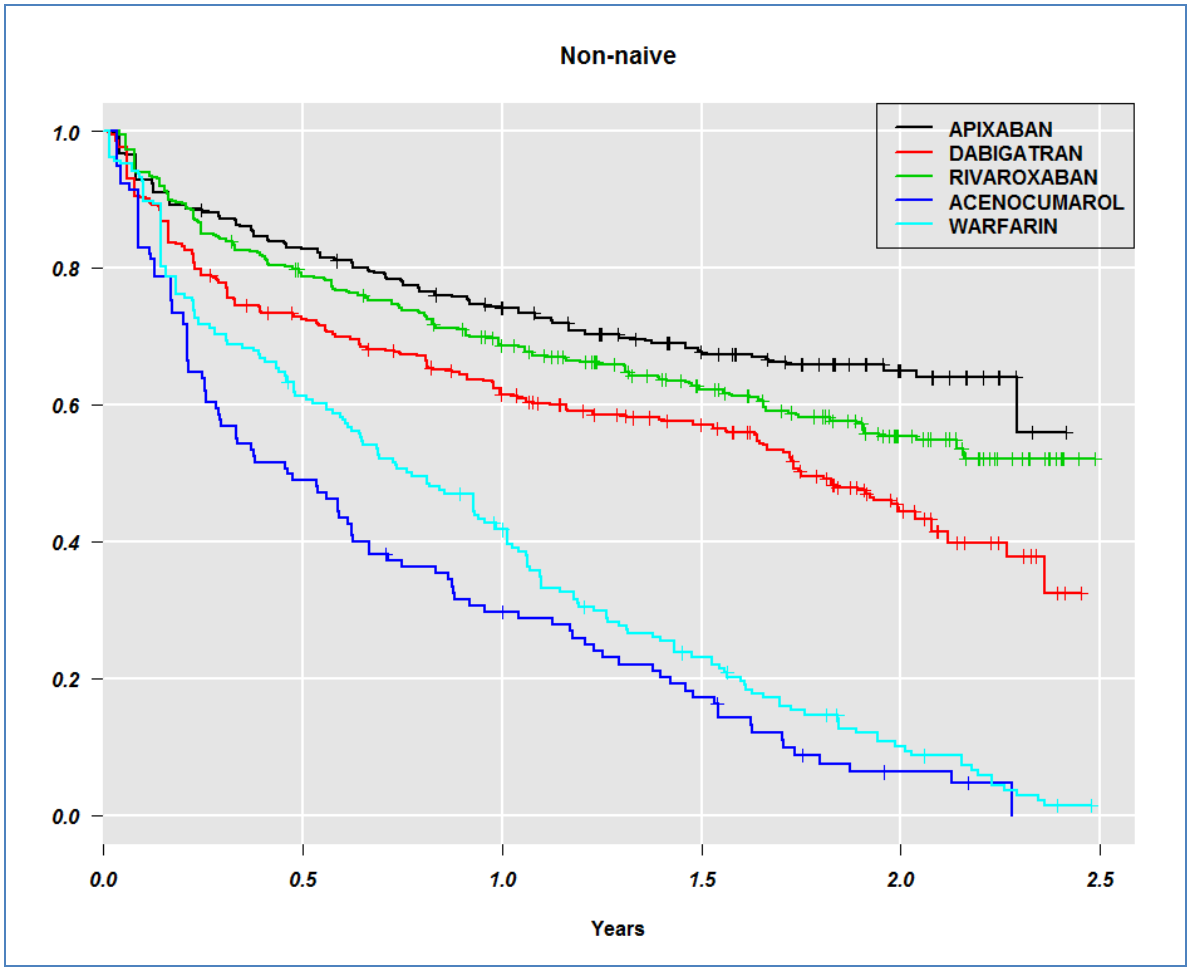


Figure 2. Kaplan-Meier curves for treatment discontinuation of all anticoagulants in non-naïve patients



5.3.5 Results for objective 5

Those patients (n=20335) who had at least three different determinations of INR within at least three months (one determination per month) where analysed in order to obtain TTR values (only 58.0% of VKA-treated patients).

In the naïve treated with acenocoumarol 50.4% patients had TTR ≥ 60% and 62.4% of those treated with warfarin did.

In the non-naïve group 113 (58.9%) of acenocoumarol patients and 158 (43.5%) of warfarin-treated had at least three INR determinations in three months.

Of the patients who had been previously treated with VKA before the study period (3,938), 76 (5.3%) of the apixaban-treated, 77 (8.1%) of the patients with dabigatran and 124 (7.9%) of the patients treated with rivaroxaban had at least three determinations during three months when they were receiving VKA. The mean TTR values were 47.3% for apixaban, 51.6% for dabigatran and 53.5% for rivaroxaban, respectively.

6 Limitations

As an observational study conducted with electronic health records there are missing or incomplete information (like the missing values for the first dose prescribed). In our database there is not an association between GP's prescriptions and dispensings associated to these prescriptions. We do not have access to electronic health records from the hospitals where some first prescriptions of DOAC are filled by specialist physicians working there (mainly cardiologists). [6]

The strengths of our study are the large number of patients included, representativeness for the general population, complete socio-demographic and health records, long follow-up, and real clinical practice data.

7 Conclusions

- VKA are more commonly prescribed than OAC in our setting (67.8% of anticoagulated patients initiate VKA after AF diagnosis).
- Non-naïve patients are generally older, with more comorbidity and comedications prescribed, and with higher risks of stroke and bleeding than naïve patients.

- Apixaban and DOAC's use is generally low in naïve patients.
  The proportion of non-naïve patients is similar between DOAC (~25%).
- Apixaban-naïve patients have more comorbidity and risk of stroke and bleeding than the others DOAC, but similar to VKA.
- In the non-naïve group of apixaban, there were fewer differences compared with the others DOAC.
- There were 52.9% of apixaban patients who receive the 2.5 mg/12h dosage, even if they do not fully meet criteria for the lower dose.
- In naïve patients there are higher DOAC discontinuation rates in the first months of treatment, afterwards the discontinuation rates are lower compared to VKA.
- Non-naïve patients showed lower discontinuation rates than naïve patients.

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