Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report	31 Jan 2020
Study title	**TRE**atment Pattern of **N**OACs (non-vitamin K oral anticoagulants) in Outpatient Users in Colombian **D**atabases – TREND Colombia
Sponsor:	Bayer
Sponsor's study ID	20104
NCT number	NCT03474757
Indication	Non-valvular atrial fibrillation (NVAF)
Study objectives	**Primary objective(s):** • To provide a detailed description of SPAF patients who are prescribed NOACs (rivaroxaban, dabigatran and apixaban) for first time use in an outpatient setting • To assess the pattern of outpatient use of NOACs in SPAF patients **Secondary objective(s):** • To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in outpatient SPAF patients
Name of observed product	Rivaroxaban (Xarelto, BAY59-7939)
Active ingredient(s)	Rivaroxaban
Dose:	On the discretion of the treating physician
Route of administration:	Oral use
Duration of treatment:	On the discretion of the treating physician
Reference therapy 1	Dabigatran (Pradaxa)
[Dose]	On the discretion of the treating physician
[Route of administration]	Oral use
[Duration of treatment]	On the discretion of the treating physician
Reference therapy 2	Apixaban (Eliquis)
[Dose]	On the discretion of the treating physician
[Route of administration]	Oral use
[Duration of treatment]	On the discretion of the treating physician

Main inclusion criteria	• First prescription of NOACs (rivaroxaban, dabigatran and apixaban) in the outpatient setting. • NVAF Patients • aged ≥18 years • at least one year of enrollment in the Audifarma database • one year since first encounter with healthcare provider will be included in the study.
Study design	Population-based retrospective cohort study.
Methodology	This was a population-based descriptive study with the aim of characterizing first-time users of NOACs among patients with NVAF in Colombia and assessing use of these medications, including type and dose of the initial NOAC prescription. The study was carried out in Colombia, South America using primary care data from the Audifarma S.A, the main drug dispensing company within the Health System of Colombia. The study period started on 01 JUL 2009 and ended on 31 JUN 2017 (the latest date of data collection).
Statistical methods	The main summary measures were the number and percentage (for categorical variables) and the number and mean with standard deviation (SD)(for age) of patients in each NOAC cohort for each characteristic studied. Potential changes in the prevalence of patient/index NOAC characteristics over time were quantified with the calculation of odds ratios (ORs) with 95% confidence intervals (CIs).
Early termination	Not applicable
Substantial protocol changes	The study was conducted according to final Study Protocol from 06-Feb-2018, and included no substantial amendments.
Study period	Study Start Date: 28-Feb-2018 Study End Date: 30-Jul-2018
Study center(s)	The study was conducted at one study center in Colombia
Number of subjects	Planned: 15000 - 20000 Analyzed: 10528

Study endpoints	***Primary variable(s):*** • Baseline patient characteristics of SPAF patients in Colombia prescribed any of the three NOACs (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention: o Demographics: Age and sex distribution at index date (date of first prescription) o Comorbidities any time before, and including the index date o Co-medications (including prior anticoagulant use – naïve/non-naïve status) in the year before the index date o Healthcare use: number of PCP visits, outpatient visits and hospital admissions in the year before the index date • Outpatient patterns of rivaroxaban, dabigatran and apixaban use in SPAF patients: o Dose of index drug at index date o dose posology (including pack size) o Treatment duration o Proportion of naïve patients (defined as those with no outpatient use of any anticoagulant ever prior to index date) ***Secondary variable(s):*** • Time-trends in the characteristics of first-time use of NOACs in SPAF patients with regard to the primary endpoints (wherever possible): o Patient characteristics o Medical history 12 months prior to index date o Medication history 12 months prior to index date o Characteristics of prescriptions stratified per years before index date *Safety variable(s):* • Not applicable

Subject disposition and baseline

A total of 18,551 patients met the inclusion criteria. After creating mutually exclusive cohorts and retaining only patients with a diagnosis of NVAF, there were a total of 10,528 patients left for analysis: 2153 in the apixaban cohort, 3089 in the dabigatran cohort and 5286 in the rivaroxaban cohort.

Results

Primary variable(s)

Baseline patient characteristics of SPAF patients in Colombia prescribed any of the three NOACs (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention:

Demographics: Age and sex distribution at index date (date of first prescription)

The sex distribution of patients was broadly similar between NOAC cohorts with males accounting for more than half: apixaban 56.0%, dabigatran 54.9% and rivaroxaban 59.0%. The mean age was also similar across cohorts: apixaban 78.5 years, dabigatran 76.5 years and rivaroxaban 76.0 years. The apixaban cohort had the highest percentage of anticoagulant naïve patients (70.5%) compared with dabigatran (64.7%) and rivaroxaban (65.8%).

Comorbidities any time before, and including the index date

The frequencies of most comorbidity, including hypertension, PAD, obesity, diabetes, asthma, COPD, rheumatoid arthritis, cancer and severe renal disease, were broadly similar across NOAC cohorts. Hypertension was recorded in the vast majority (>80% in each cohort), heart failure in about one third of patients in each cohort and diabetes mellitus in about one fifth of patients in each cohort. Heart failure, myocardial infarction, IHD, VTE and hyperlipidemia were all more prevalent among the rivaroxaban cohort. The dabigatran cohort had the highest percentage of patients with a previous record of ischemic stroke and urogenital bleeding but also the lower percentage of patients with a previous record of gastrointestinal bleeding. A previous record of VTE occurred more frequently among patients starting on rivaroxaban (6.3%) compared with those starting on apixaban (2.5%) or dabigatran (3.5%).

Co-medications (including prior anticoagulant use – naïve/non-naïve status) in the year before the index date

The most frequently prescribed medications in the year before starting NOAC therapy were beta-blockers, statins, low-dose aspirin, proton pump inhibitors and diuretics. For several medications, including low-dose aspirin, NSAIDS, antiarrhythmics, antihypertensives, diuretics, and statins, the highest level of previous use was among patients in the rivaroxaban cohort. The apixaban cohort had the lowest level of previous anticoagulant use as well as previous antiarrhythmic drugs use. The frequency of previous use of antidiabetics, PPIs, ranitidine, antipsychotics and antidepressants was similar between the cohorts.

There was a significant percentage of patients in each cohort with polypharmacy. Close to 60% of patients in each cohort received between 5 and 9 different medications (including their NOAC) in the 2 months before the index date, and about a quarter of patients in each cohort received at least 10 different medications during this time period.

Table 1. Polypharmacy among patients with NVAF newly prescribed a NOAC.

	Apixaban N=2153		Dabigatran N=3089		Rivaroxaban N=5286	
	n	**%**	**n**	**%**	**n**	**%**
Polypharmacy[†]						
None	473	22.0	722	23.4	1007	19.1
1–4	428	19.9	620	20.1	1077	20.4
5–9	704	32.7	1016	32.9	1785	33.8
≥10	548	25.5	731	23.7	1417	26.8

[†]Number of different medications (including NOACs) in the 2 months before the index date.

Healthcare use: including number of PCP visits, outpatient visits and hospital admissions in the year before the index date

In each NOAC cohort, around 40% of patients had fewer than 10 healthcare visits in the year before the index date. About a third of patients in each cohort had between 10 and 19 healthcare visits during this time period, while approximately 10% in each cohort had ≥30 healthcare visits.

Table 2. Healthcare visits among patients with NVAF newly prescribed a NOAC.

	Apixaban N=2153		Dabigatran N=3089		Rivaroxaban N=5286	
	n	**%**	**n**	**%**	**n**	**%**
Healthcare visits[*]						
<3	546	25.4	829	26.8	1280	24.2
4–9	303	14.1	496	16.1	780	14.8
10–19	708	32.9	1002	32.4	1768	33.4
20–29	338	15.7	459	14.9	855	16.2
≥30	258	12.0	303	9.8	603	11.4

[*]Health care visits in the year before the index date.

Outpatient patterns of rivaroxaban, dabigatran and apixaban use in SPAF patients - Dose of index drug at index date and Treatment duration

Among patients starting on apixaban, 38% started on the standard 10 mg daily dose, with over half prescribed a reduced dose of 5 mg/day and 8.5% were prescribed a further reduced dose of 2.5 mg/day. Just under half of patients (44.6%) had a first episode of continuous apixaban use that lasted more than 180 days.

Among patients starting on dabigatran, 30.9% of patients were prescribed the standard dose of 300mg/day, while nearly half of the patients (49.5%) were prescribed a reduced dose of 220 mg/day with the remaining patients (19.6%) receiving a dose of 150mg/day or less. Approximately half of patients (51.4%) had a first episode of continuous use that lasted more than 180 days while 27.2% had a first episode of continuous use that lasted for at least a year.

Among patients starting on rivaroxaban, a daily dose of 20 mg (standard daily dose) was the most frequent prescribed (56.9%), followed by a reduced daily dose of 15 mg (37.4%). Just over half (52.7%) had a first episode of continuous use that lasted more than 180 days.

Approximately, half of patients were still prescribed their index NOAC at 6 months (apixaban 44.6%, dabigatran 51.4% and rivaroxaban 52.7%). As shown in Table 18, irrespective of the index NOAC, the majority of the NOAC prescriptions had either no gap between them (i.e. they were immediately next to each other or were overlapping prescriptions) or a small gap (0–7 days) between them during follow-up.

Dose posology (including pack size)

The most frequent posology for apixaban was twice daily (83.0% of patients) in line with the drug label..

	Apixaban N=2153		Apixaban (prescription at least one year after the index date) N=1331	
	n	%	n	%
Apixaban tablet strength (mg)				
2.5	1152	53.5	671	50.4
5	1001	46.5	660	49.6
Dose frequency per day (based on the recorded posology for first prescription)				
Once daily	365	17.0	246	18.4
Twice daily	1788	83.0	1085	81.5
Length of the index prescription (days)				
1–15	26	1.2	19	1.4
16–30	1852	86.0	1120	84.2
31–60	269	12.5	188	14.1
61–90	4	0.2	3	0.2
≥91	2	0.1	1	0.1

As with apixaban, although the most frequent posology for dabigatran was twice daily, this applied to 82.5% of patients, in-line with the instructions on the drug label.

	Dabigatran N=3089		(prescription at least one year after the index date) N=2459	
	n	%	n	%
Dabigatran tablet strength (mg)				
75	87	2.8	72	2.9
110	1860	60.2	1496	60.8
150	1142	37.0	891	36.2
Dose frequency per day (based on the recorded posology for first prescription)				
Once daily	542	17.5	458	18.6
Twice daily	2547	82.5	2001	81.4
Length of the index prescription (days)				
1–15	23	0.7	20	0.8
16–30	330	10.7	279	11.3
31–60	253	8.2	211	8.6

61–90	1530	49.5	1217	49.5
≥91	953	30.9	732	29.8

Rivaroxaban was mostly prescribed once daily (97.2%), which is the correct posology for stroke prevention in AF.

	Rivaroxaban N=5286		**Rivaroxaban (prescription at least one year after the index date) N=3825**	
	n	**%**	**n**	**%**
Rivaroxaban tablet strength (mg)				
2.5	9	0.2	6	0.2
10	233	4.4	182	4.8
15	2028	38.4	1408	36.8
20	3016	57.1	2229	58.3
Dose frequency per day (based on the recorded posology for first prescription)				
Once daily	5140	97.2	3724	97.3
Twice daily	146	2.8	101	2.9
Length of the index prescription (days)				
1–15	62	1.2	36	1.0
16–30	5096	96.4	3688	96.4
31–60	125	2.4	98	2.6
61–90	1	0.0	1	0
≥91	2	0.0	2	0

Proportion of naïve patients (defined as those with no outpatient use of any anticoagulant ever prior to index date)

There was a higher percentage of patients who were anticoagulant naïve among the apixaban cohort (70.5%) compared with the dabigatran cohort (64.7%) and the rivaroxaban cohort (65.8%).

Secondary variable(s)

Time-trends in the characteristics of first-time use of NOACs in SPAF patients with regard to the primary study endpoints (wherever possible):

Demographics: Age and sex distribution

Among new users of apixaban, the majority in 2013 were female yet the majority in later study years were male (55.6% in 2016). The percentage of patients over 80 years of age increased from 33.3% in 2013 to 50.3% in 2016. The proportion of patients aged <60 years also increased over study years from 2.8% in 2013 to 6.4% in 2016, as did the percentage of patients who were anticoagulant naïve (50.0% in 2013 and 70.6% in 2016).

Among new users of dabigatran, males accounted for less than half of patients in 2011 (48.1%) but for more than half in later study years (56.0% in 2016). The percentage of patients over 80 years of age decreased from 56.8% in 2011 to 30.5% in 2016, while the percentage of patients aged <60 years almost doubled rising from 4.9% in 2011 to 9.6% in 2016. The percentage of patients who were anticoagulant naïve increased significantly from 57.3% in 2011 to 73.8% in 2016, OR 2.07 (95% CI: 1.56–2.75)

Among new users of rivaroxaban, males increasingly accounted for the majority of patients across study years (55.8% in 2012 and 62.1% in 2016). The percentage of patients over 80 years of age decreased from 44.2% in 2012 to 37.5% in 2016, OR 0.39 (95% CI: 0.22–0.67), while the percentage of patients aged <60 years more than doubled increasing from 5.2% in 2012 to 11.2% in 2016. The percentage of patients who were anticoagulant naïve increased from 54.2% in 2012 to 69.4% in 2016, OR 1.91 (95% CI: 1.49–2.46).

Medical history 12 months prior to index date

Among new users of apixaban several comorbidities became less prevalent over study years (2016 vs. 2014): hypertension (OR: 0.65, 95% CI: 0.42–0.98), heart failure (OR: 0.69, 95% CI: 0.52–0.93), ventricular arrhythmias (OR: 0.51, 95% CI: 0.30–0.88), TIA (OR: 0.38, 95% CI: 0.16–0.89), diabetes mellitus (OR: 0.64, 95% CI: 0.46–0.89) and severe renal disease (OR: 0.46, 95% CI: 0.33–0.68). The percentage of patients with dyslipidaemia and the percentage of those with the other comorbidities evaluated remained stable.

Similarly to apixaban, among new users of dabigatran, several comorbidities became less prevalent over study years (2016 vs. 2012): myocardial infarction (OR: 0.46, 95% CI: 0.22–0.96), heart failure (OR: 0.55, 95% CI: 0.41–0.72), hypertension (OR: 0.47, 95% CI: 0.33–0.66), ventricular arrhythmias (OR: 0.26, 95% CI: 0.15–0.44), ischaemic stroke (OR: 0.33, 95% CI: 0.21–0.54), TIA (OR: 0.23, 95% CI: 0.04–0.81), asthma (OR: 0.36, 95% CI: 0.15–0.86), COPD (OR: 0.53, 95% CI: 0.46–0.78) and severe renal disease (OR: 0.44, 95% CI: 0.29–0.65). The percentage of patients with obesity, diabetes mellitus and rheumatoid arthritis remained stable over study years.

As with patients in the apixaban and dabigatran cohorts, among new users of rivaroxaban there was a reduction in the percentage of patients with certain comorbidities over study years (2016 vs. 2012): myocardial infarction (OR: 0.54, 95% CI: 0.33–0.88), heart failure (OR: 0.45, 95% CI: 0.35–0.57), hypertension (OR: 0.54, 95% CI: 0.38–0.77), ventricular arrhythmias (OR: 0.28, 95% CI: 0.19–0.44), VTE (OR: 0.51, 95% CI: 0.33–0.79), ischaemic stroke (OR: 0.30, 95% CI:0.21–0.43), TIA (OR: 0.42, 95% CI: 0.23–0.78), intracranial bleeding (OR: 0.16, 95% CI: 0.05–0.46), diabetes mellitus (OR: 0.70, 95% CI:0.53–0.93), COPD (OR: 0.58, 95% CI: 0.43–0.80), rheumatoid arthritis (OR: 0.34, 95% CI:

0.17–0.64) and severe renal disease (OR: 0.60, 95% CI: 0.44–0.82). The percentage of patients with obesity remained stable over study years.

Medication history 12 months prior to index date

Among new users of apixaban, there was a reduction between 2014 and 2016 in the use of low-dose aspirin (OR: 0.70, 95% CI: 0.53–0.93), antiarrhythmics (OR: 0.66, 95% CI: 0.45–0.96), diuretics (OR: 0.67 (95% CI: 0.51–0.89) and statins (OR: 0.69, 95% CI: 0.52–0.93).

Among new users of dabigatran there was a decrease in the use of several medications between 2012 and 2016: antiplatelet agents (OR: 0.75, 95% CI: 0.58–0.98), antiarrhythmics (OR: 0.40, 95% CI: 0.27–0.58), antihypertensive agents (OR: 0.60, 95% CI: 0.45–0.80), beta-blockers (OR: 0.60, 95% CI: 0.46–0.78), diuretics (OR: 0.62, 95% CI: 0.47–0.81), and H_2RAs (OR: 0.55, 95% CI: 0.34–0.89). The use of antidepressants and antipsychotics was stable across study years, while the use of NSAIDs (OR: 1.63, 95% CI: 1.08–2.46) and antidiabetics increased (OR: 1.64, 95% CI: 1.11–2.43).

Among new users of rivaroxaban, there was a decrease in the use of several medication across study years (2012 to 2016): antiplatelet agents (OR: 0.74, 95% CI: 0.58–0.95), antiarrhythmic drugs (OR: 0.63, 95% CI: 0.47–0.84), antihypertensives (OR: 0.59, 95% CI: 0.43–0.80), beta-blockers (OR: 0.74, 95% CI: 0.58–0.96), ACE inhibitors (OR: 0.61, 95% CI: 10.46–0.82), diuretics (OR: 0.58, 95% CI: 0.45–0.75), statins (OR: 0.62, 95% CI: 0.48–0.80), PPIs (OR: 0.72, 95% CI: 0.56–0.92), antipsychotics (OR: 0.57, 95% CI: 0.32–0.99) and strong CYP3A4 inducers (OR: 0.52, 95% CI: 0.34–0.81).

Characteristics of index prescriptions per year

Among new users of apixaban, 5 mg tablets were the most commonly prescribed in the early study years but this was replaced by 2.5 mg tablets being the most commonly prescribed from 2015. Across study years, the most common dosing frequency was twice daily and the most common length of the index apixaban prescription was between 16 and 30 days. Across study years, about a third of patients had a first continuous episode of apixaban use that lasted more than a year.

Among new users of dabigatran, 110 mg tablets were the most commonly prescribed across study years, although 150 mg tablets became increasingly issued. Twice daily was the most common dosing frequency across study years. A substantial percentage (between 39% and 45%) of patients had a first continuous episode of use that lasted more than a year.

Among new users of rivaroxaban, 20 mg tablets were the most commonly issued across study years, although 15 mg tablets became increasingly issued over time. The most common dosing frequency was always once a day. More than 40% of new users of dabigatran had a first continuous episode of use that lasted more than a year.

Overall conclusions

The increasing use of NOACs in patients with NVAF in Colombia likely reflects the growing confidence in NOACs among PCPs in Colombia. The characteristics of these patients and characteristics of NOAC prescribing, including the observation that a large percentage of patients are prescribed a reduced dose, are in line with those seen in comparable European and American cohorts.

Publication(s) based on the study

None at the time of this report.