Comparative analysis of patient characteristics and real-world outcomes in Spanish patients with atrial fibrillation treated with direct oral anticoagulants versus vitamin K antagonists

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PURPOSE

- Atrial fibrillation (AF) affects approximately 60 million people worldwide, and the prevalence is expected to rise with an ageing population[1–3]
- European Society of Cardiology guidelines recommend direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) for patients with AF who are at risk of ischemic stroke (IS) and thromboembolism due to their risk-benefit profile[4]
- In Spain, VKAs remain widely used due to prior authorisation and reimbursement restrictions on DOACs,[5–7] although DOAC use has increased over the past decade[8]
- Real-world evidence is needed to better understand the clinical outcomes and prescribing patterns of VKAs and DOACs in Spain
- This study evaluated the real-world effectiveness and safety of DOACs versus VKAs in patients with nonvalvular AF in Spain, including a comparison of individual DOACs

METHODS

- This retrospective, observational cohort analysis used electronic medical record data from the BIG-PAC® database from 1 January 2017 to 31 December 2023
  - The BIG-PAC® database contains approximately 1.9 million health records in Spain, with integrated inpatient and outpatient data, and is representative of the Spanish population
- To be eligible for inclusion, patients (≥18 years of age) must have had at least 1 VKA (eg, warfarin, acenocoumarol, phenprocoumon) or DOAC (eg, edoxaban, apixaban, dabigatran, rivaroxaban) prescription during the study period (first prescription = index date), a confirmatory diagnosis of AF, and ≥12 months of database activity before the index date
- Patients with deep vein thrombosis, pulmonary embolism, or mechanical heart valves within 12 months prior to the index date and patients with hip or knee replacements within 6 weeks prior to the index date were excluded
  - Patients with a medical record of any prior VKA or DOAC on the index date were also excluded
- VKA and DOAC cohorts were identified based on index treatment
  - Additionally, individual DOAC cohorts, including patients who received edoxaban, apixaban, dabigatran, or rivaroxaban, were identified based on index treatment
- Inverse probability of treatment weighting (IPTW) was performed for the VKA and DOAC cohorts, as well as for each DOAC cohort, to adjust for confounding prior to comparative effectiveness and safety analyses
  - All-cause mortality, major bleeding (MB) events, IS, and systemic embolism (SE) were compared between the VKA and DOAC cohorts and between the individual DOAC cohorts, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated to assess outcomes

RESULTS

- A total of 15,348 patients were included in the study, with 7084 (46.2%) in the VKA cohort and 8264 (53.8%) in the DOAC cohort (**Figure 1**)
  - The mean age was slightly higher in the DOAC cohort (76.0 years) than in the VKA cohort (74.4 years; **Table 1**)
  - Among the 8264 patients in the DOAC cohort, apixaban was the most frequently prescribed treatment (n = 4367; 52.8%)
- At baseline, hypertension, coronary artery disease, and prior bleeding events were more frequently reported in the DOAC cohort than in the VKA cohort (**Table 1**)
- Compared with VKAs, DOACs had significantly lower risks of all-cause mortality (*P* <0.001), MB events (*P* <0.001), and SE (*P* = 0.015) within the total observation time (**Figure 2A**)
- Compared with edoxaban, apixaban had a higher risk of IS and dabigatran had a higher risk of IS and combined risk of IS or SE (IS/SE; **Figures 2B** and **2C**); no significant differences in outcomes were observed between edoxaban and rivaroxaban (**Figure 2D**)
- Risk of all-cause mortality, MB events, and SE within the total observation time did not differ significantly between the edoxaban cohort and the other DOAC cohorts (**Figures 2B-2D**)

Comparative analyses of real-world data from the Spanish BIG-PAC® database demonstrated that DOACs had significantly lower risks of all-cause mortality and MB events, with a similar risk of IS, compared with VKAs.

When evaluating outcomes within the DOAC cohort, the risk of IS was significantly lower for edoxaban compared with apixaban and dabigatran, and the risks of all-cause mortality and MB events were similar between edoxaban and all other DOACs.

CONCLUSIONS

In this analysis of patients with AF in the Spanish BIG-PAC® database, DOACs had significantly lower risks of all-cause mortality, MB events, and SE compared with VKAs

When comparing edoxaban with other DOACs, edoxaban had a significantly lower risk of IS compared with apixaban and dabigatran and a had a similar risk of all-cause mortality and MB events compared with apixaban, dabigatran, and rivaroxaban

These findings indicate that real-world DOAC use for IS prevention in Spanish patients with AF had a more favourable safety profile, with similar effectiveness, relative to VKA use

FIGURES & TABLES

Figure 1. Patient attrition.

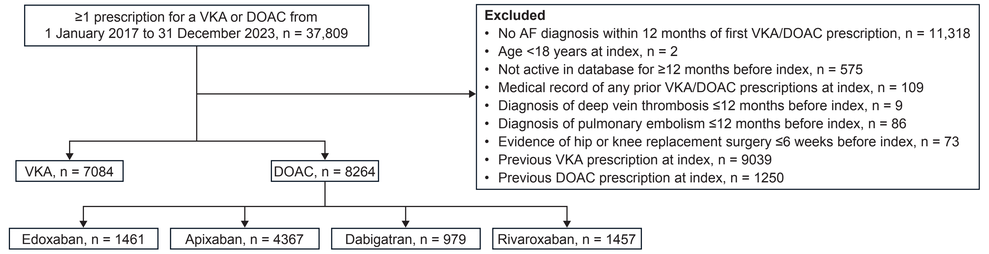
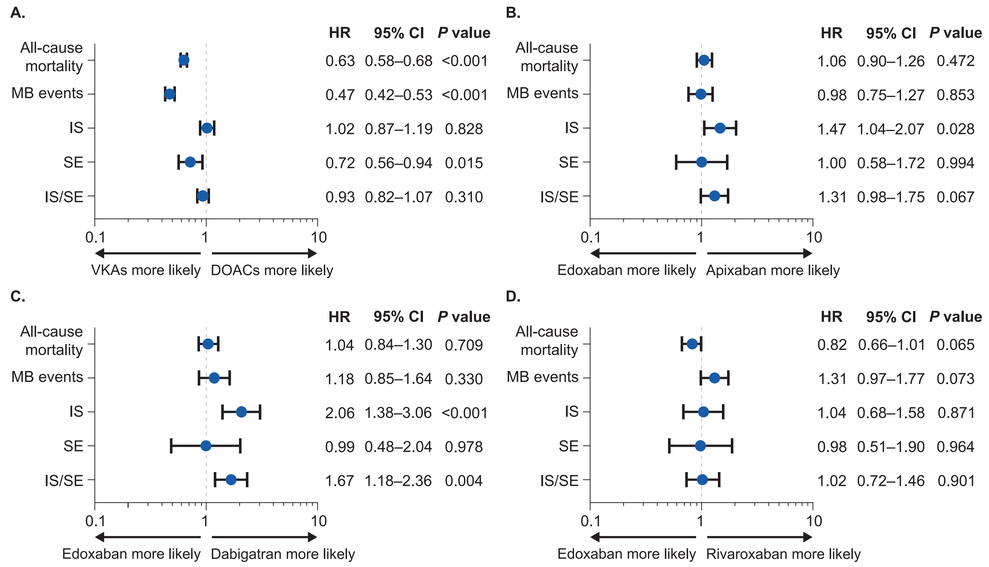


Table 1. Baseline patient characteristics and comorbidities.

Characteristic	VKAs (n = 7084)	DOACs (n = 8264)	DOACs (n = 8264)			
			Edoxaban (n = 1461)	Apixaban (n = 4367)	Dabigatran (n = 979)	Rivaroxaban (n = 1457)
Female sex, n (%)	3909 (55.2)	4634 (56.1)	812 (55.6)	2447 (56.0)	541 (55.3)	834 (57.2)
Age, years						
Mean (SD)	74.4 (10.9)	76.0 (11.2)	76.0 (11.0)	77.0 (11.0)	77.0 (11.0)	73.7 (12.1)
Median (min, max)	75.5 (21.5, 100.4)	77.2 (23.5, 102.8)	77.0 (25.0, 101.0)	78.0 (23.0, 103.0)	78 (27.0, 101.0)	75.1 (24.4, 102.1)
Alcohol consumption, n (%)	104 (1.5)	108 (1.3)	21 (1.4)	54 (1.2)	15 (1.5)	18 (1.2)
Currently smoking, n (%)	458 (6.5)	411 (5.0)	62 (4.2)	220 (5.0)	47 (4.8)	82 (5.6)
History of smoking, n (%)	1079 (15.2)	1166 (14.1)	211 (14.4)	608 (13.9)	135 (13.8)	212 (14.6)
Observation time, days						
Mean (SD)	550.0 (580.1)	516.3 (487.9)	466.8 (460.9)	509.7 (481.6)	563.3 (514.8)	554.4 (509.2)
Median (min, max)	299.0 (1.0, 2552.0)	376.0 (0, 2553.0)	325.0 (1.0, 2535.0)	368.0 (0, 2553.0)	439.0 (2.0, 2545.0)	426.0 (6.0, 2523.0)
CCI score, mean (SD)	1.03 (1.21)	1.15 (1.31)	1.08 (1.28)	1.23 (1.36)	1.19 (1.29)	0.96 (1.20)
CHA_2DS_2-VASc score, mean (SD)	2.75 (1.42)	3.06 (1.54)	3.07 (1.56)	3.12 (1.52)	3.14 (1.52)	2.83 (1.55)
HAS-BLED score, mean (SD)	1.57 (0.99)	1.76 (1.03)	1.73 (1.02)	1.83 (1.05)	1.70 (0.97)	1.62 (1.01)
Baseline comorbidities, n (%)*						
Hypertension	4682 (66.1)	5899 (71.4)	1040 (71.2)	3138 (71.9)	697 (71.2)	1024 (70.3)
Diabetes	2694 (38.0)	3119 (37.7)	575 (39.4)	1641 (37.6)	376 (38.4)	527 (36.2)
Coronary artery disease	942 (13.3)	1455 (17.6)	296 (20.3)	745 (17.1)	181 (18.5)	233 (16.0)
Congestive heart failure	871 (12.3)	1207 (14.6)	264 (18.1)	601 (13.8)	125 (12.8)	217 (14.9)
Renal disease	689 (9.7)	773 (9.4)	129 (8.8)	475 (10.9)	70 (7.2)	99 (6.8)
Prior bleeding events	676 (9.5)	1046 (12.7)	172 (11.8)	589 (13.5)	123 (12.6)	162 (11.1)
Baseline treatments, n (%)						
Antiplatelet agents	2781 (39.3)	2921 (35.3)	521 (35.7)	1574 (36.0)	376 (38.4)	450 (30.9)
Oral antidiabetics	2679 (37.8)	3106 (37.6)	574 (39.3)	1634 (37.4)	375 (38.3)	523 (35.9)
Nonsteroidal anti-inflammatory drugs	2088 (29.5)	2330 (28.2)	404 (27.7)	1259 (28.8)	256 (26.1)	411 (28.2)
Selective serotonin reuptake inhibitors	968 (13.7)	1122 (13.6)	194 (13.3)	585 (13.4)	149 (15.2)	194 (13.3)
Systematic glucocorticoids	897 (12.7)	990 (12.0)	186 (12.7)	532 (12.2)	111 (11.3)	161 (11.1)
Insulin	507 (7.2)	507 (6.1)	80 (5.5)	309 (7.1)	46 (4.7)	72 (4.9)
Antihypertensives	431 (6.1)	396 (4.8)	72 (4.9)	222 (5.1)	45 (4.6)	57 (3.9)
Prior VKAs	N/A	355 (4.3)	75 (5.1)	178 (4.1)	41 (4.2)	61 (4.2)

CCI, Charlson Comorbidity Index; max, maximum; min, minimum; N/A, not available; SD, standard deviation.
*Reported for comorbidities occurring in ≥10% of patients in any cohort.

Figure 2. Comparative effectiveness of all DOACs versus VKAs (A) and of apixaban (B), dabigatran (C), and rivaroxaban (D) versus edoxaban within the total observation time.



Baseline characteristics were balanced across cohorts by IPTW.

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DISCLOSURES

RS-B: participated in advisory committees for Daiichi Sankyo, Inc.; **RW**, **CC**, **MU**, and **XY:** employees of Daiichi Sankyo, Inc.; **SK:** employee of Cytel, Inc.; **IH**, **LLB**, and **MGM:** employees of Atrys Health S.A.; **XG-M:** participated in advisory committees for and received honoraria from Daiichi Sankyo, Inc.

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