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ORIGINAL ARTICLE

Clinical outcomes of nonvitamin K oral anticoagulants and acenocoumarol for stroke prevention in contemporary practice: A population-based propensity-weighted cohort study

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Aims: Acenocoumarol is a vitamin-K antagonist (VKA) primarily used in certain countries (e.g. India, Netherlands, Spain). The half-life of acenocoumarol is similar to that of non-VKA oral anticoagulants (NOAC), unlike warfarin, and this could affect comparative effectiveness and safety (CES). However, data on CES for NOAC come almost exclusively from studies using warfarin as the comparator. We aimed to assess outcomes of NOAC and acenocoumarol in people with non-valvular atrial fibrillation (NVAF) in real-world clinical practice.

Methods: This is a population-based retrospective cohort study. All new users of oral anticoagulants from November 2011 to December 2015 with NVAF were included (n = 41,560). Data were obtained by linking several health electronic records of the Valencia region, Spain. Incidence rates were estimated. We used the inverse probability of treatment weighted Cox analysis to control for indication bias when assessing the risk of effectiveness and safety outcomes for each NOAC compared with acenocoumarol. Several sensitivity analyses were performed.

Results: We did not find differences in the risk of mortality, ischaemic stroke or any gastrointestinal bleeding. However, we did find a decreased risk of intracranial haemorrhage for dabigatran (HR: 0.34, 95% CI 0.20–0.56) and rivaroxaban (HR: 0.55, 95% CI 0.35–0.85) as compared to acenocoumarol. In subanalyses, apixaban showed a higher risk of ischaemic stroke in high-risk persons (≥75 years and CHA2DS2-VASC score ≥ 2).

Conclusions: No differences in clinical outcomes were found between NOAC and acenocoumarol overall, although dabigatran and rivaroxaban showed a lower risk of intracranial haemorrhage. Findings on the potential inferiority of specific NOAC in high-risk subgroups should be studied further.

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Gabriel Sanfélix-Gimeno is the Principal Investigator in this study.

KEYWORDS

acenocoumarol, anticoagulants, atrial fibrillation, real-world data, stroke prevention

1 | INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOAC) have been established as an alternative for vitamin K antagonists (VKA) in stroke prevention for persons with atrial fibrillation (AF)[1] and their use increased rapidly following their introduction into the market.[2–4] A recent meta-analysis of clinical trials including all the NOAC currently available concluded that NOAC offered significant reductions in stroke, intracranial haemorrhage and mortality, with a similar risk of major bleeding but an increased risk of gastrointestinal bleeding compared with warfarin.[5] However, comparisons of clinical outcomes between NOAC and coumarinics different to warfarin have not been performed. Although warfarin is the most widely used VKA, alternatives such as acenocoumarol are primarily prescribed in certain countries including Spain and the Netherlands.[6,7] The differences in half-life between coumarinics might result in differences regarding the stability of anticoagulation, and therefore potentially affect efficacy and safety,[8,9] but the comparative effectiveness and safety of NOAC in relation to VKA different to warfarin is largely unknown.[10,11]

Furthermore, the results of clinical trials and close monitoring with selected groups of people do not necessarily translate into real-world settings, given the complexity of routine clinical practice. In fact, the results of studies in the US, Denmark and France, using data from routine practice, contradict or coincide only partially with those of the meta-analysis of trials regarding the risk of gastrointestinal bleeding,[12] major bleeding,[13] stroke[13,14] or death.[13] Additionally, there are few studies providing information on the effectiveness and safety of different OACS for certain subgroups of interest such as males/females,[15] or according to the baseline risk of stroke or bleeding.[16]

We sought to evaluate stroke, mortality and bleeding outcomes related to each NOAC agent—rivaroxaban, dabigatran and apixaban—as compared to acenocoumarol therapy in a universal health care setting for the whole cohort and in subgroups of interest, using a large population-based cohort with a maximum follow-up over four years.

What is already known about this subject

- Studies comparing NOAC to warfarin have established that NOAC are an effective and safe alternative for stroke prevention. Comparative evidence on alternative VKA is scarce.
- However, the differences in half-life between VKA might result in differences regarding stability of anticoagulation, and therefore potentially affect comparative efficacy and safety.
- There is no data in routine clinical care comparing NOAC with acenocoumarol, the most common anticoagulant alternative in some European and certain other countries.

What this study adds

- In this real-world study, we found that the effectiveness and safety profiles of NOAC and acenocoumarol are similar overall, as has been observed in the comparison with warfarin.
- However, in high-risk subgroups, our findings on the efficacy and safety of certain NOAC drugs might be of concern and should be studied further.
- Our work provides real-world evidence to facilitate decision making on oral anticoagulant treatment in settings where acenocoumarol is the VKA alternative.

2 | METHODS

2.1 | Study design

This is a population-based retrospective cohort study of all people with atrial fibrillation, who were newly prescribed acenocoumarol, apixaban, dabigatran or rivaroxaban from November 2011 to December 2015 in the Valencia region of Spain.

2.2 | Population and setting

The population covered by this study comprised all people in the Valencia Health System (VHS) in Spain, the public health system that covers about 97% of the region's population (approximately 5 million inhabitants). We constructed a cohort of all people with a diagnosis of atrial fibrillation or atrial flutter (ICD-9-CM: 427.31 and 427.32) who started treatment with oral anticoagulants (acenocoumarol, apixaban, dabigatran or rivaroxaban) for the prevention of thromboembolic events between November 2011 (date of the market launch of the first NOAC in Spain, dabigatran) and December 2015. The rest of the DOAC analysed were marketed during the follow-up period (June 2012 in the case of rivaroxaban and August 2013 for apixaban). One year of look-back period was used to define the baseline characteristics of the population and for excluding prevalent OAC users. We defined new users as those without anticoagulant treatment (those without any prescriptions—filled or not) in the 12 months preceding the first prescription (index date). We excluded people with

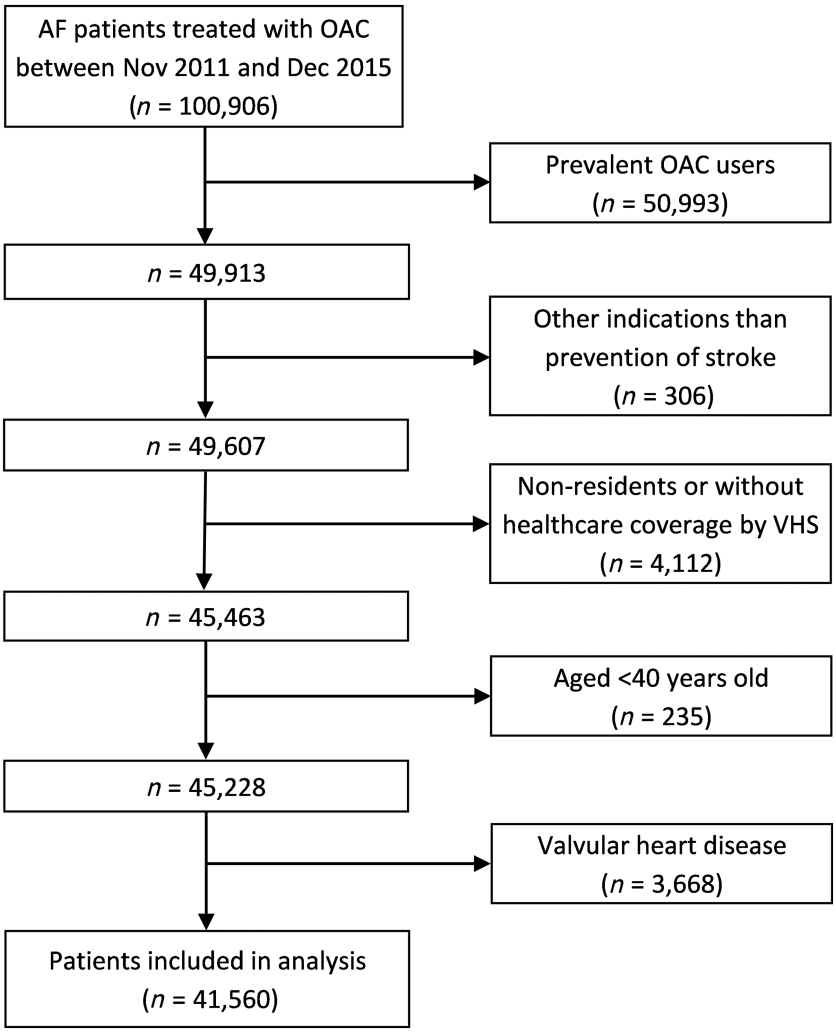

FIGURE 1 Overview of the study population. OAC, oral anticoagulants; VHS, Valencia health system

concomitant valvular heart disease (ICD-9: 394.x-397.x, 398.9, 42.4x, V42.2, V43.3, 35.1x, 35.2x).

Those with limitations of follow-up were also excluded: people without pharmaceutical/health coverage by the VHS, mainly Spanish government employees whose prescriptions are reimbursed by civil servant insurance mutualities, and thus not included in the electronic records of the Valencia Health System, and people not registered in the municipal census, such as non-residents or temporary residents (Figure 1).

The study protocol, observational in design and using retrospective anonymized non-identifiable data transferred from the Valencia Ministry of Health to the research team in line with Spanish laws and institutional requirements, was approved by the Ethics Committee for Clinical Research of the General Directorate of Public Health and the Centre for Public Health Research (CEIC DGSP-CSISP, ruling of 5 March 2014) including exemption from the patient consent requirement.

2.3 | Data sources

The main source of data was the VHS ambulatory Electronic Medical Record (EMR), which includes information on diagnoses, personal medical history, laboratory test results, lifestyle factors, as well as information on both physician prescriptions and dispensations from pharmacy claims. The information on hospitalizations was based on the Minimum Basic Dataset (MBDS) at hospital discharge, a synopsis of clinical and administrative information on all hospital discharges, including diagnoses and procedures. The Population Information System (SIP) provides information on the population covered by the VHS and registers certain demographic characteristics, including the geographical location of each person and the dates and causes of VHS discharge, including deaths. All these data sources are linked at an individual level through a single anonymized patient identifier. A detailed description of the sources of data can be found elsewhere.[17]

2.4 | Definitions of effectiveness and safety outcomes

The pre-specified effectiveness outcomes were: mortality, hospitalization for ischaemic stroke and transient ischaemic attack (TIA). The safety outcomes considered were: hospitalizations for gastrointestinal bleeding, major gastrointestinal bleeding (defined as a GI bleeding hospitalization needing a blood or blood components transfusion) and

intracranial haemorrhage. Only principal discharge diagnoses based on ICD9CM (see Table S1 for coding on clinical outcomes) were used to define endpoints. Out-of-hospital mortality was collected from the SIP system that, in turn, obtains the information from the mortality register. All outcomes were analysed separately and only the first event was considered for analysis. Persons were followed from the first prescription until the relevant event, health system disenrolment, death or end of follow-up (31 December 2015), whichever came first. All outcomes were analysed by the intention-to-treat approach, that is, all participants were analysed in their initial group (i.e. the treatment prescribed as initial OAC therapy), regardless of whether a switch to another OAC had occurred during the follow-up.

TABLE 1 Patient characteristics by oral anticoagulant medication. Values are numbers (percentages) unless stated otherwise

	All patients *n* = 41,560	Acenocoumarol *n* = 32,476	Apixaban *n* = 2,259	Dabigatran n = 3,380	Rivaroxaban n = 3,445	Standardized differences[a]	
						Before	After
Age; mean (SD)	74.62 (9.90)	74.82 (9.58)	75.03 (10.67)	72.30 (11.30)	74.72 (10.63)	–	–
Female	19,659 (47.30)	15,464 (47.62)	1,086 (48.05)	1,467 (43.40)	1,642 (47.66)	0.09	0.02
CHADS2 score[b]; mean (SD)	2.18 (1.27)	2.20 (1.24)	2.31 (1.39)	1.99 (1.37)	2.14 (1.32)	–	–
CHA2DS2-VASC score[c]; mean (SD)	3.78 (1.69)	3.83 (1.65)	3.89 (1.77)	3.39 (1.86)	3.71 (1.78)	–	–
HAS BLED score[d]; mean (SD)	2.91 (1.19)	2.93 (1.17)	3.04 (1.25)	2.74 (1.23)	2.89 (1.22)	–	–
Diagnosis							
Atrial fibrillation	39,144 (94.19)	30,537 (94.03)	2,150 (95.17)	3,183 (94.17)	3,274 (95.04)	0.05	0.01
Atrial flutter	2,416 (5.81)	1,939 (5.97)	109 (4.83)	197 (5.83)	171 (4.96)	–	–
Comorbidities							
Congestive heart failure	7,460 (17.95)	6,027 (18.56)	431 (19.08)	441 (13.05)	561 (16.28)	0.15	0.01
Hypertension	33,158 (79.78)	26,149 (80.51)	1,796 (79.50)	2,511 (74.29)	2,704 (78.49)	0.15	0.04
Diabetes	14,570 (35.06)	11,702 (36.03)	758 (33.55)	989 (29.26)	1,121 (32.54)	0.14	0.04
Liver disease	3,040 (7.31)	2,397 (7.38)	179 (7.92)	224 (6.63)	240 (6.97)	0.03	0.01
Renal disease	5,431 (13.07)	4,555 (14.03)	280 (12.39)	206 (6.10)	390 (11.32)	0.27	0.02
COPD	4,867 (11.71)	3,959 (12.19)	241 (10.67)	328 (9.70)	339 (9.84)	0.08	0.02
Previous ischaemic stroke or TIA	6,018 (14.48)	4,411 (13.58)	490 (21.69)	583 (17.25)	534 (15.50)	0.21	0.03
Dementia	2,933 (7.06)	2,205 (6.79)	214 (9.47)	212 (6.28)	302 (8.77)	0.10	0.02
Depression	5,689 (13.69)	4,464 (13.75)	326 (14.43)	396 (11.72)	503 (14.60)	0.06	0.01
Cancer	6,033 (14.52)	4,810 (14.81)	347 (15.36)	393 (11.63)	483 (14.02)	0.09	<0.01
Coronary disease	7,603 (18.29)	6,061 (18.66)	424 (18.77)	524 (15.50)	594 (17.24)	0.08	0.02
Thromboembolism	2,939 (7.07)	2,462 (7.581)	116 (5.13)	137 (4.05)	224 (6.50)	0.15	0.01
Intracranial haemorrhage	343 (0.83)	199 (0.61)	48 (2.13)	62 (1.83)	34 (0.99)	0.13	0.01
Gastrointestinal bleeding	1,786 (4.30)	1,404 (4.32)	119 (5.27)	117 (3.46)	146 (4.24)	0.04	0.04
Other bleeding	9,662 (23.25)	7,668 (23.61)	581 (25.72)	656 (19.41)	757 (21.97)	0.10	0.01
Medication use							
NSAIDs	7,641 (18.39)	5,964 (18.36)	385 (17.04)	702 (20.77)	590 (17.13)	0.06	<0.01
ASA	15,844 (38.12)	11,971 (36.86)	941 (41.66)	1,462 (43.25)	1,470 (42.67)	0.13	<0.01
Clopidogrel	1,876 (4.51)	1,402 (4.32)	122 (5.40)	177 (5.24)	175 (5.08)	0.05	<0.01
ASA + Clopidogrel	1,785 (4.29)	1,425 (4.39)	87 (3.85)	137 (4.05)	136 (3.95)	0.03	0.02
Other antiplatelets	1,298 (3.12)	1,022 (3.15)	64 (2.83)	109 (3.23)	103 (2.990)	–	–

COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack; NSAIDs, nonsteroidal anti-inflammatory drugs; ASA, acetylsalicylic acid.

[a]Maximum standardized pairwise difference, before and after inverse probability of treatment weighting. Variables with no information (cells with –) were not included in the models to obtain the weights. Age was included as a categorical variable in deciles and atrial fibrillation and flutter were included as a unique binary variable.

[b]Scores range from 0 to 6, reflecting baseline risk of stroke.

[c]Scores range from 0 to 9, reflecting baseline risk of stroke.

[d]Scores range from 0 to 9, reflecting baseline risk of bleeding.

2.5 | Covariates

We considered all available factors potentially related to the risk of thromboembolic events and bleeding. These included demographic and clinical characteristics, and healthcare resource utilization in the preceding 12 months (Table 1). Comorbidity was defined as the presence of an active diagnosis of the particular condition in the EMR within a 12-month period preceding the index date (Table S1 shows details on definitions of comorbidities). Concomitant medication (NSAID and antiplatelet) was defined as medication dispensed at least once during the 3-month pre-index period. Based on comorbidity information, concomitant medication and age, we calculated relevant patient-level risk scores for stroke (CHADS2, CHA2DS2-VASC) and bleeding (HAS-BLED).[18]

2.6 | Statistical analysis

The study population characteristics are presented as means for continuous variables and frequencies for categorical variables according to each specific OAC exposure group. To adjust for potential confounding, mainly due to indication bias, we used inverse probability of treatment weighting (IPTW) based on propensity scores, which allows adjustment without losing generalizability.[19] Propensity scores were calculated based on logistic regression that estimated the probability of being prescribed NOAC vs. VKA on the basis of all the covariates listed above, to generate patient-specific weights. Covariate balance between the weighted exposure cohorts was assessed using standardized mean differences. Standardized differences <0.10 suggest adequate balance.[20] We examined the distribution of propensity scores between treatment groups to ensure sufficient overlap.

The incidence of thromboembolic and haemorrhagic events was described using crude and weighted event rates per 1,000 person years along with 95% CIs separately for each outcome and for each treatment cohort. Cox proportional hazard models (crude, adjusted for sociodemographic, clinical, healthcare utilization, and IPTW) were used to assess the risk of several outcomes on the effectiveness and safety of each NOAC compared with acenocoumarol. To allow for a thorough prognostic evaluation, we supplemented the main analysis with subgroup analyses based on categories of age, gender, diagnosis of atrial fibrillation vs. flutter, CHA2DS-VASC2 and HAS-BLED.

In sensitivity analyses, we used the first dispensation date (instead of the first prescription) as index date to initiate the ascertainment of clinical outcomes, given that a non-trivial number of patients (n = 520) had a distance between these two dates equal to or greater than 30 days. Second, we repeated the IPTW analysis after trimming the extreme weights, eliminating those patients with a PS above the 97.5th percentile and those with a PS below the 2.5th percentile. Third, given that a high mortality rate would significantly overestimate effect sizes, we performed an analysis using the method of Fine and Gray[21] to account for the competing risk of death. Last, we reanalysed the data using an "on-treatment" approach, where patients were censored if they discontinued treatment (defined as exceeding a gap of 90 days without any refills) or switched to another oral anticoagulant. A grace period of 14 days was used after discontinuation or switching to start the follow-up.

All statistical analyses were conducted using STATA 14® (StataCorp, College Station, TX, USA), and the 5% level of significance was considered.

3 | RESULTS

After applying the exclusion criteria, we identified a study population of 41,560 persons who had not been taking oral anticoagulants within the previous year and who were starting treatment with either NOAC (dabigatran, apixaban or rivaroxaban) or acenocoumarol. Distribution by type of oral anticoagulant was as follows: 78.2% received acenocumarol, 5.4% apixaban, 8.1% dabigatran and 8.3% rivaroxaban. The average time of population follow-up (with respect to all-cause mortality) was 1.8 years, with the dabigatran group having the longest mean follow-up (2.1 years) and the apixaban group having the shortest mean follow-up (almost 1 year). Median continuous follow-up was 1.84 years (interquartile range 0.15–3.87 years) for acenocoumarol; 0.83 years (interquartile range 0.06–2.07 years) for apixaban; 2.10 years (interquartile range 0.15–4.03 years) for dabigatran and 1.53 years (interquartile range 0.10–3.14 years) for rivaroxaban.

The mean age of the cohort was 74.6 years old, with 47% being females (Table 1). People treated with dabigatran were to some extent younger (mean age: 72 years old) than those treated with another NOAC or acenocoumarol. Additionally, people treated with dabigatran had a lower prevalence of heart failure (13.1%), hypertension (74.3%), diabetes (29.3%) and renal disease (6.1%). Those treated with apixaban had a higher prevalence of a previous stroke (21.7%). The mean CHA2DS2-VASc score was the highest in those treated with apixaban (3.9), somewhat lower for acenocumarol (3.8) and rivaroxaban (3.7), and the lowest for those treated with dabigatran (3.4). A similar pattern was observed for the mean HAS-BLED score, which was the highest for people on apixaban (3.0), slightly lower for acenocoumarol (2.9) and rivaroxaban (2.9), and the lowest for dabigatran (2.7).

After inverse probability weighting, the standardized differences were less than 0.04, resulting in a cohort with a comparable distribution of baseline covariates between treatment groups.

3.1 | Effectiveness outcomes

3.1.1 | Stroke

During follow-up, the weighted incidence of ischaemic stroke was 10.17 per 1,000 person-years for acenocoumarol, and ranged between 10.58 (dabigatran) and 17.17 (apixaban) for NOAC (Table 2). In the Cox regression models, after adjustment by IPTW, neither apixaban (HR: 1.35; CI

TABLE 2 Incidence rates (crude and weighted) of effectiveness and safety outcomes according to oral anticoagulant medication

	Person-time	Events	Crude rate[a]	Weighted rate[b]
Ischaemic stroke				
Acenocoumarol	61,325	627	10.22 (9.45–11.06)	10.17 (9.40–11.01)
Apixaban	2,064	35	16.96 (12.18–23.62)	17.17 (12.41–24.43)
Dabigatran	7,133	75	10.51 (8.39–13.19)	10.58 (8.48–13.39)
Rivaroxaban	5,297	59	11.14 (8.63–14.38)	11.02 (8.58–14.39)
TIA				
Acenocoumarol	61,869	140	2.26 (1.92–2.67)	2.26 (1.92–2.68)
Apixaban	2,082	7	3.36 (1.60–7.05)	3.32 (1.61–8.04)
Dabigatran	7,187	16	2.23 (1.36–3.63)	2.28 (1.42–3.91)
Rivaroxaban	5,334	9	1.69 (0.88–3.24)	1.68 (0.89–3.58)
Mortality				
Acenocoumarol	62,058	4,539	73.14 (71.04–75.30)	74.16 (72.03–76.37)
Apixaban	2,087	166	79.56 (68.33–92.63)	79.77 (68.56–93.33)
Dabigatran	7,214	426	59.05 (53.70–64.93)	59.65 (54.32–65.64)
Rivaroxaban	5,342	412	77.12 (70.02–84.94)	78.09 (70.90–86.18)
Gastrointestinal bleeding				
Acenocoumarol	61,582	482	7.83 (7.16–8.56)	7.98 (7.30–8.74)
Apixaban	2,079	12	5.77 (3.28–10.16)	5.83 (3.36–11.06)
Dabigatran	7,149	59	8.25 (6.39–10.65)	8.15 (6.34–10.66)
Rivaroxaban	5,299	39	7.36 (5.38–10.07)	7.53 (5.55–10.49)
Major gastrointestinal bleeding				
Acenocoumarol	61,790	256	4.14 (3.67–4.68)	4.25 (3.77–4.82)
Apixaban	2,082	5	2.40 (1.00–5.77)	2.53 (1.06–7.64)
Dabigatran	7,186	22	3.06 (2.02–4.65)	3.06 (2.03–4.82)
Rivaroxaban	5,322	18	3.38 (2.13–5.37)	3.52 (2.25–5.84)
Intracranial haemorrhage				
Acenocoumarol	61,764	430	6.96 (6.33–7.65)	7.02 (6.39–7.73)
Apixaban	2,081	10	4.80 (2.59–8.93)	4.72 (2.59–9.59)
Dabigatran	7,206	16	2.22 (1.36–3.62)	2.20 (1.37–3.79)
Rivaroxaban	5,328	21	3.94 (2.57–6.04)	3.95 (2.61–6.27)

TIA, transient ischaemic attack

[a]Rate expressed per 1,000 person-years.

[b]Inverse probability of treatment weighted, expressed per 1,000 person-years.

95% 0.96–1.91), dabigatran (HR: 1.03; CI 95% 0.81–1.31) or rivaroxaban (HR: 1.03; CI 95% 0.78–1.35) showed differences as compared to acenocoumarol (Table 3, Figure 2). In subgroup analyses (Figure 2), results were consistent for all the subgroups, except for people older than 75 years old and those with CHA2DS2-VASC ≥ 2, in which apixaban showed a higher risk of stroke (HR: 1.68; CI 95% 1.14–2.46, and HR: 1.56; CI 95% 1.10–2.22, respectively).

3.1.2 | Transient ischaemic attack (TIA)

The weighted incidence of TIA was 2.26 per 1,000 person-years for acenocoumarol, ranging between 1.68 (rivaroxaban) and 3.32 (dabigatran) among NOAC drugs (Table 2). No statistically significant differences were observed in crude or adjusted analysis in the risk of TIA for any of the NOAC drugs assessed, compared to acenocoumarol. After IPTW adjustment, the relative risks were as follows: HR: 1.20 (CI 95% 0.56–2.58), HR: 1.05 (CI 95% 0.62–1.78) and HR: 0.69 (CI 95% 0.35–1.37) for apixaban, dabigatran and rivaroxaban, respectively (Table 3, Figure 2). Results remained similar for all the subgroups assessed (Figure 2).

3.1.3 | Mortality

The weighted incidence of all-cause mortality was 74.16 per 1,000 person-years for acenocoumarol, and ranged between 59.65 (dabigatran) and 79.77 (apixaban) for NOAC drugs (Table 2). In the Cox regression

TABLE 3 Hazard ratios (95% CI) for effectiveness and safety outcomes in atrial fibrillation patients starting treatment with oral anticoagulant medications as compared to acenocoumarol

	HR (95% CI)		
	Unadjusted	Adjusted (all covariates)	Adjusted (IPW)
Ischaemic stroke			
Apixaban	1.469 (1.042–2.071)[a]	1.325 (0.939–1.870)	1.353 (0.958–1.911)
Dabigatran	1.036 (0.815–1.316)	1.022 (0.803–1.302)	1.032 (0.810–1.315)
Rivaroxaban	1.076 (0.823–1.406)	1.033 (0.789–1.351)	1.028 (0.785–1.346)
TIA			
Apixaban	1.299 (0.605–2.790)	1.202 (0.561–2.574)	1.199 (0.557–2.579)
Dabigatran	0.998 (0.595–1.675)	1.021 (0.603–1.728)	1.054 (0.623–1.784)
Rivaroxaban	0.724 (0.368–1.422)	0.695 (0.354–1.364)	0.699 (0.355–1.375)
Mortality			
Apixaban	1.047 (0.895–1.223)	0.927 (0.791–1.087)	0.919 (0.783–1.079)
Dabigatran	0.806 (0.730–0.890)[a]	0.906 (0.819–1.003)	0.906 (0.818–1.003)
Rivaroxaban	1.057 (0.956–1.170)	1.018 (0.917–1.130)	1.023 (0.921–1.136)
Gastrointestinal bleeding			
Apixaban	0.603 (0.339–1.071)	0.566 (0.318–1.008)	0.562 (0.315–1.005)
Dabigatran	1.072 (0.818–1.405)	1.217 (0.926–1.599)	1.182 (0.898–1.557)
Rivaroxaban	0.906 (0.653–1.256)	0.929 (0.668–1.291)	0.936 (0.673–1.301)
Major gastrointestinal bleeding			
Apixaban	0.459 (0.189–1.115)	0.425 (0.175–1.029)	0.438 (0.180–1.066)
Dabigatran	0.768 (0.497–1.188)	0.932 (0.600–1.448)	0.913 (0.585–1.425)
Rivaroxaban	0.761 (0.471–1.228)	0.798 (0.492–1.293)	0.816 (0.504–1.322)
Intracranial haemorrhage			
Apixaban	0.472 (0.194–1.151)	0.438 (0.180–1.066)	0.595 (0.316–1.119)
Dabigatran	0.748 (0.482–1.163)	0.913 (0.585–1.425)	0.337 (0.204–0.557)[a]
Rivaroxaban	0.772 (0.479–1.245)	0.816 (0.504–1.322)	0.550 (0.354–0.855)[a]

TIA, transient ischaemic attack; HR, Hazard Ratio; IPW, Inverse probability of treatment weighting.
[a]$p < 0.05$

models, after adjustment by IPTW (Table 3, Figure 2), no differences in risk of mortality were observed either for apixaban (HR: 0.92; CI 95% 0.78–1.08), dabigatran (HR: 0.91; CI 95% 0.82–1.00) or rivaroxaban (HR: 1.02; CI 95% 0.92–1.14). In subgroup analyses (Figure 2), results were consistent overall; however, in people with a diagnosis of atrial fibrillation (excluding flutter), and in males, dabigatran showed a lower risk of mortality compared with acenocoumarol (HR: 0.90; CI 95% 0.81–0.99 and HR: 0.85; CI 95% 0.74–0.98, respectively).

3.2 | Safety outcomes

3.2.1 | Gastrointestinal bleeding

The weighted incidence of gastrointestinal (GI) bleeding was 7.98 per 1,000 person-years for acenocoumarol, ranging between 5.83 per 1,000 person-years (apixaban) and 8.15 per 1,000 person-years (dabigatran) for NOAC (Table 2). In adjusted Cox regression models (Table 3, Figure 3), none of the NOAC drugs showed statistically significant differences in the risk of GI bleeding as compared to acenocoumarol after IPTW (HR: 0.56; CI 95% 0.31–1.00, HR: 1.18; CI 95% 0.90–1.56, HR: 0.94; CI 95% 0.67–1.30 for apixaban, dabigatran and rivaroxaban, respectively). However, when subgroups were assessed (Figure 3), apixaban showed a decreased risk of GI bleeding in older people (≥ 75 years old).

3.2.2 | Major gastrointestinal bleeding

The weighted incidence of major GI bleeding was 4.25 per 1,000 person-years for acenocoumarol, ranging between 2.53 (apixaban) and 3.52 (rivaroxaban) for NOAC treatment (Table 2). In IPTW adjusted Cox regression models (Table 3, Figure 3), none of the NOAC drugs showed statistically significant differences in risk of major GI bleeding as compared to acenocoumarol (HR: 0.44; CI 95% 0.18–1.07, HR: 0.91;CI 95% 0.58–1.42, HR: 0.82; CI 95% 0.50–1.32 for apixaban, dabigatran and rivaroxaban, respectively). In subgroup analyses, results were consistent with those of the main analysis (Figure 3).

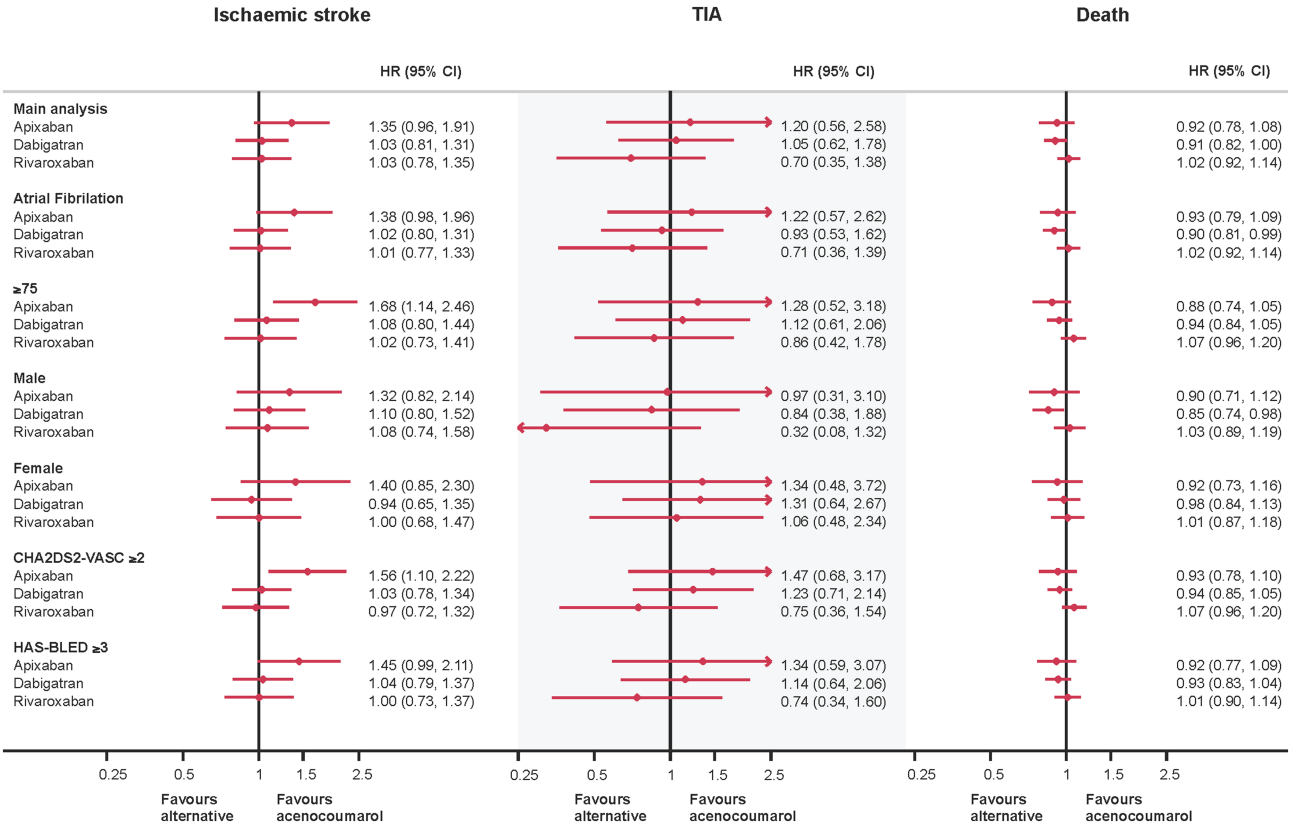

FIGURE 2 Effectiveness outcomes of apixaban, dabigatran and rivaroxaban compared to acenocoumarol in subgroup analyses. TIA, transient ischaemic attack; HR, hazard ratio; CI, confidence interval

3.3 | Intracranial haemorrhage

The weighted incidence of intracranial haemorrhage was 7.02 per 1,000 person-years for acenocoumarol, and ranged between 2.20 (dabigatran) and 4.72 (apixaban) for NOAC (Table 2). IPTW Cox regression models showed a reduced risk of intracranial haemorrhage for dabigatran and rivaroxaban (HR: 0.34; CI 95%: 0.20–0.56 and HR: 0.55; CI 95%: 0.35–0.85, respectively), and no statistically significant differences for apixaban (HR: 0.59; CI 95%: 0.32–1.12) as compared to acenocoumarol (Table 3, Figure 3). Results were consistent in all subgroups analysed, except for males, in which only dabigatran showed a decreased risk (Figure 3).

3.4 | Sensitivity analyses

When we used the date of first dispensation claim as index date, instead of the first prescription date, results were consistent for the main cohort and for all the subgroups studied (Figure S1, Figure S2).

When we performed additional sensitivity analyses (IPTW with trimming, on treatment and competing risk of death), results were also very consistent with the main analysis. In the case of apixaban, a lower risk of gastrointestinal bleeding was also observed (Figure S3).

4 | DISCUSSION

In a large real-world cohort of people with atrial fibrillation in Spain, we compared the effectiveness and safety of most available NOAC with that of acenocoumarol, a coumarinic primarily used as an oral anticoagulant in several countries including Spain, whose differences in half-life with warfarin could theoretically affect effectiveness and safety, but whose comparative performance in contemporary clinical practice is largely unknown. We found no significant differences overall in the effectiveness and safety profiles of NOAC compared to acenocoumarol. However, dabigatran and rivaroxaban showed a lower risk of intracranial haemorrhage compared to acenocoumarol. In general, results were consistent in subgroup analyses. However, we did find certain differences in efficacy and safety outcomes according to NOAC drugs, compared to acenocoumarol. Apixaban showed a higher risk of ischaemic stroke in high risk people (older and with higher CHA2DS2-VASC scores), but a lower risk of gastrointestinal bleeding in older people, while dabigatran showed a decreased risk of death among males and when those with a flutter diagnosis were excluded.

People starting therapy with dabigatran were younger and healthier (lower prevalence of comorbidities and lower risk as measured by CHA2DS2-VASC score), whereas those prescribed apixaban were the oldest and had the highest risk as assessed by CHA2DS2-VASC and HAS-BLED scores. Previous studies on comparative effectiveness and

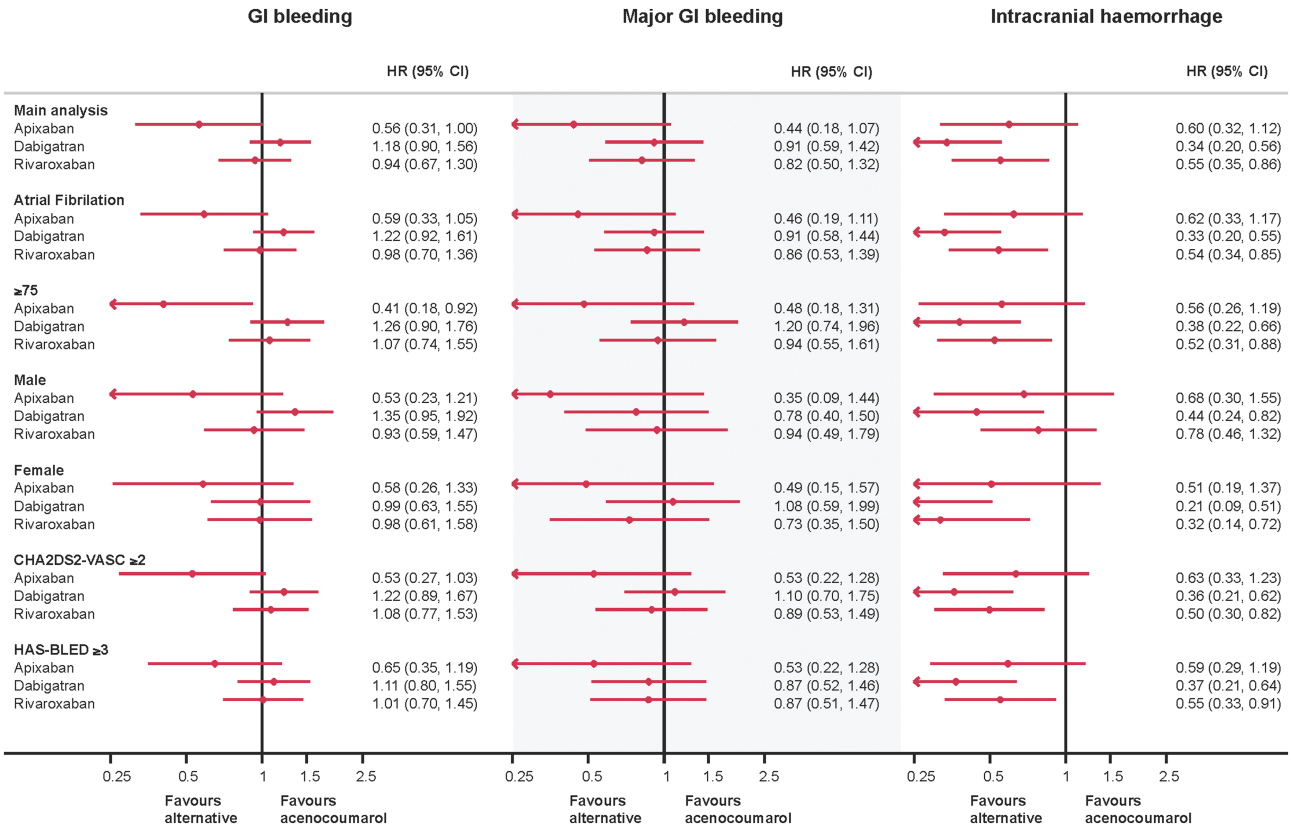

FIGURE 3 Safety outcomes of apixaban, dabigatran and rivaroxaban compared to acenocoumarol in subgroup analyses. GI, gastrointestinal

safety found similar patterns of differential OAC prescribing.[13] The methodological design of the present study accounted for this selective prescribing, expected in routine clinical practice, by using propensity scores, which resulted in a cohort with a comparable distribution of observed variables between treatment groups.

4.1 | Effectiveness outcomes

Regarding effectiveness, the profile of NOAC did not differ from that of acenocoumarol for the whole cohort in the present study. Our results coincide with those of previous studies in routine care comparing the risk of stroke between NOAC and warfarin or fluindione.[13,14,16]

However, in subgroup analyses, apixaban showed a higher risk of ischaemic stroke in high-risk people (older and with higher CHA2DS2-VASC scores). This trend towards a higher risk of ischaemic stroke for apixaban was also observed in our sensitivity analyses for the whole cohort, although it did not reach statistical significance.

A recent study using data of a large cohort in the US also found that apixaban users had a higher risk of ischaemic stroke and a lower risk of bleeding compared to warfarin users, although risk strata were not assessed,[22] coinciding partially with our results. The authors suggest that the lower risk of haemorrhagic events comes at the cost of an increased risk of ischaemic strokes, which is also a plausible explanation in our case.

With regard to differences by risk scores (apixaban showing a higher stroke risk with higher scoring), the only previous study assessing the effectiveness of NOAC according to baseline risk (CHA2DS2-VASC score) found that apixaban showed no advantage compared to warfarin when assessing the risk of stroke, and observed a non-significant trend of higher risk for apixaban in high-risk people.[16]

Regarding mortality, we found that the risk was similar for the three NOAC drugs as compared to acenocoumarol for the whole cohort. A recent systematic review found that dabigatran had a lower risk of mortality compared to warfarin (six studies included, in which five reported lower risk).[10] This was also observed in sensitivity analysis but not in the main analysis for the whole cohort in our study; however, we did find that dabigatran had a lower risk of mortality compared to acenocoumarol among males (but not among females). The only previous study assessing OAC effectiveness and safety by gender also found a differential effect of dabigatran, reporting a reduced risk of major bleeding in men, but did not assess mortality risk,[15] although both events could be potentially related. Our findings of dabigatran showing a lower mortality risk among males should be confirmed by new studies.

Results shown for subgroups must be interpreted with caution given that we evaluated multiple subgroups.

4.2 | Safety outcomes

With regard to the safety profile, we did find differences in certain outcomes between specific NOAC drugs and acenocoumarol. The most recent meta-analysis of trials concluded that all available NOAC had an increased risk of gastrointestinal bleeding as compared to warfarin.[5] In contrast, our results showed that compared to acenocoumarol, all NOAC had a similar risk for this outcome, with apixaban showing a decreased risk in older people (≥ 75 years old). We also found a lower risk of GI bleeding in the whole cohort in certain sensitivity analyses. These coincide with several studies in real-world settings regarding no difference in risk for dabigatran and rivaroxaban.[10,12] In line with our results, two studies have also found that apixaban had a lower risk of GI bleeding.[10]

Regarding intracranial haemorrhage, the meta-analysis of trials by Ruff et al.[5] found that apixaban, dabigatran and rivaroxaban had a lower risk compared to warfarin, whereas in our study, dabigatran and rivaroxaban but not apixaban, showed that advantage in safety. Various real-world studies[10] coincide with the results of Ruff et al. However, the results of one recent real-world study assessing intracranial haemorrhage in a large European cohort,[13] coincide with ours, showing that dabigatran and rivaroxaban but not apixaban have a lower risk of intracranial haemorrhage as compared to VKA, with dabigatran showing the lowest risk.

4.2.1 | Limitations

Some limitations must be acknowledged. First, VID databases gather real-world clinical practice data containing information as registered by health professionals during routine clinical practice, which are not specifically prepared for research. In this sense, studies based on real-world clinical information like VID may be subject to well-known information biases due to absent registration or differing data-recording practices, an inherent problem in any study using data from routine clinical practice. Nevertheless, diagnostic accuracy for hospital discharge diagnoses due to acute conditions (such as our main clinical outcomes) is expected to be very high, and prescription and dispensation information (the essential data for defining exposure) is also very accurate as it is used for billing purposes. Second, despite accounting for many relevant covariates in the adjustment, we missed some potentially relevant information such as that on time in therapeutic range among acenocoumarol users, or other cardiovascular medication use (statins, ACE inhibitors, etc.), and thus we cannot rule out residual confounding. Third, given the characteristics of the study (observational, based on retrospective real-world data) we could expect the presence of indication bias. We have addressed this problem by adjusting the propensity of being prescribed each drug. Nevertheless, the fact that reverse causation cannot be ruled out, even with the use of this method, must be acknowledged. However, after performing several sensitivity analyses, conclusions from the main analysis remain unchanged, suggesting a limited potential for further adjustment and confirming the robustness of our findings. Last, there are also limitations regarding subgroup analyses, such as false positives derived from a large amount of comparisons and false negatives derived from inappropriate power.

One of the main strengths of this study is the large sample size and long follow-up period of people with atrial fibrillation starting oral anticoagulant treatment, and who received acenocoumarol (instead of warfarin) as the VKA option. Coumarinics different to warfarin have not been studied in phase III trials. Differences in half-life with warfarin could theoretically affect effectiveness and safety, but their comparative performance in either randomized controlled trials or contemporary clinical practice was largely unknown until now. Furthermore, a wide range of sociodemographic and clinical data were available for this study, reducing the likelihood of biases. We also assessed subgroups that had been understudied to date, such as a higher baseline risk of stroke or bleeding, or differences by gender. We indeed found differences in the effectiveness and safety profiles by subgroups for certain OAC drugs. Nonetheless, future studies assessing the effectiveness and safety of NOAC compared to acenocoumarol are warranted in order to confirm our results, which must be interpreted in the context of observational data. It is important to bear in mind that evidence from observational studies, like the present one, reflect with an acceptable degree of accuracy the performance of the different options of anticoagulant treatment in everyday clinical practice.

5 | CONCLUSIONS

Our study is the first to assess the long-term effectiveness and safety of NOAC as compared to acenocoumarol in a large real-world population-based cohort, providing evidence to facilitate decision making for most of the treatment options available. Our results suggest that overall, NOAC are effective and safe options compared to acenocoumarol. However, efficacy and safety concerns regarding specific NOAC in higher-risk subgroups might affect the choice of certain drugs. Nevertheless, further study is needed to assess if these findings are replicable in other settings.

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analysis, or decisions regarding the dissemination of findings, the development of the manuscript or its publication.

COMPETING INTERESTS

S.P. has received fees for participation in scientific meetings and courses sponsored by Novartis and Ferrer International. G.S.G. participated in an advisory meeting of Boehringer Ingelheim in 2014. A.G.S. is a former employee of Boehringer Ingelheim. C.R.-B., Y.S.-T. and I.H. have reported that they have no relationships relevant to the contents of this paper to disclose. None of the sponsors were involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review or approval of the manuscript, or in the decision to submit it for publication.

CONTRIBUTORS

G.S.G. and S.P. conceived and designed the study. C.R.-B. wrote the first draft of the manuscript. G.S.G. and C.R.-B. are guarantors and take full responsibility for the integrity of the data and the accuracy of the data analysis. Y.S.-T., A.G.S., C.R.-B., I.H., S.P. and G.S.G. participated in the study design and methodology. Y.S.-T. performed the analysis. All authors participated in interpretation of data, and contributed to the critical revision of the manuscript for important intellectual content. All authors agree to be accountable for all aspects of the work and have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were obtained from the Ministry of Health of the Valencian Government. Restrictions apply to the availability of these data, which were used under license for this study. The authors have no authorization to share the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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