All-cause mortality, stroke, and bleeding in patients with atrial fibrillation and valvular heart disease

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Original Article

Title: All-cause mortality, stroke, and bleeding in patients with atrial fibrillation and valvular heart disease

Brief title: Outcomes in atrial fibrillation and valvular heart disease

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Abstract

Aims: To compare the risk of all-cause mortality, stroke and bleeding in patients with atrial fibrillation (AF) and valvular heart disease (VHD) treated with vitamin K antagonist (VKA) or factor Xa-inhibitors (FXa-I; rivaroxaban and apixaban).

Methods and Results: We crosslinked data from Danish nationwide registries identifying patients with AF and VHD (VHD; aortic stenosis/insufficiency, mitral insufficiency, bioprosthetic heart valves, mitral-, and aortic valve repair) initiating VKA or FXa-I between January 2014 and June 2017. Outcomes were all-cause mortality, stroke, and bleeding. Using cause-specific Cox regression, we reported the standardized absolute 2-year risk of the outcomes and absolute risk differences (ARD).

We identified 1,115 (41.7%), 620 (23.1%), and 942 (35.2%) patients initiating treatment with VKA, rivaroxaban, and apixaban. The standardized absolute risk (95% CI) of all-cause mortality associated with VKA treatment was 34.1% (30.4% to 37.8%) with corresponding ARD for FXa-I of -2.7% (-6.7% to 1.4%). The standardized absolute risk of stroke for VKA was 3.8% (2.2% to 5.4%) with corresponding ARD for FXa-I of –0.1% (-2.0% to 1.8%). The standardized risk of bleeding for VKA was 10.4% (7.2% to 12.9%) with corresponding ARD for FXa-I of –2.0% (-5.1% to 1.1%). The risk of bleeding was significantly reduced in subgroup analyses of apixaban compared with VKA (ARD: -3.9% (-7.0% to -0.9%)) and rivaroxaban (ARD: -5.6% (-9.5% to -1.7%))

Conclusion: In this nationwide cohort study, there were no significant differences in the risks of all-cause mortality, stroke, and bleeding in patients with AF and VHD treated with VKA compared with FXa-I.

Keywords

Atrial fibrillation, anticoagulation, bleeding, mortality, stroke, valvular heart disease.

Introduction

Since 2011, four non-vitamin K antagonist oral anticoagulants (NOAC) have been approved for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) defined as atrial fibrillation and absence of mitral stenosis or mechanical heart valves in European guidelines, whereas American guidelines also require absence of prosthetic heart valves and mitral valve repair (1-3).

Valvular heart disease (VHD) alone is associated with an increased risk of stroke (4). In patients with NVAF, 90% of the thrombi formed in the left atrium are likely to be formed in the left atrial appendage. However, in patients with AF and VHD, especially rheumatic mitral stenosis, approximately 40% of the thrombi are formed outside the left atrial appendage (5). Whether these findings translate into altered risks of stroke and bleeding in patients with NVAF and VHD when treated with NOAC or vitamin K antagonist (VKA) remains to be determined.

Meta-analyses based on the four pivotal phase III RCTs that led to approval of NOAC for stroke prevention therapy for AF showed that when pooling the results there was a reduced risk of stroke and no difference in the risk of major bleeding when comparing NOAC to VKA in patients with NVAF and VHD (6-8). However, the RCTs used different inclusion and exclusion criteria, making extrapolation of trial results to "real-world" populations difficult (9-12). Outside the trials, only few studies have investigated the safety and efficacy of NOAC compared with VKA and found no increased risk of stroke and major bleeding associated with NOAC in these patients (13-16).

The purpose of our study was to compare the risk of all-cause mortality, stroke/SE, and bleeding in oral anticoagulation (OAC) naïve patients with AF and VHD, excluding mechanical heart valves and/or mitral stenosis, treated with either VKA or factor Xa-inhibitors (FXa-I; rivaroxaban and apixaban).

Methods

Data collection

All Danish residents have a unique personal identification number, and by using this number, we crosslinked individual-level information from the following Danish nationwide administrative registries: The Danish Civil Registration System: Contains data on date of birth and civil status (17). The Danish National Patient Registry: Contains data on the activity of Danish hospitals (18). The Danish National Prescription Registry: Contains data on all prescription drugs dispensed from pharmacies (19).

Study design and population

We conducted an observational study of all OAC naïve patients with AF and VHD, i.e. aortic stenosis, aortic insufficiency, mitral insufficiency, bioprosthetic heart valves, mitral-, and aortic valve repairs, treated with VKA or FXa-I between the 1st of January 2014 and the 30th of June 2017. Inclusion date was defined as the date of first dispensed OAC drug. Exclusion criteria were as follows: History of deep vein thrombosis or pulmonary embolism within 6 months, total hip or knee arthroplasty within 5 weeks, age < 30 years or > 100 years, valvular AF (mechanical heart valves and/or mitral stenosis), use of edoxaban or dabigatran, and dispensation of two different OAC on the same day. Exclusion of edoxaban and dabigatran was done due to a limited number of patients initiating treatment with these OAC in the study period and to ensure positivity (see Supplementary Figure 1 for temporal trends in OAC initiation). Patients were followed from inclusion date until death, event, emigration, switch or discontinuation of OAC treatment, 30th of June 2017, or 2 years of follow-up, whichever came first.

Comorbidities and comedication

Comorbidities registered in the prior 10 years of inclusion date were identified using International Classification of Disease (ICD)-10 codes (see Supplementary Table 1). We compared the risk of stroke using CHA_2DS_2-VASc and the risk of bleeding using HAS-BLED (see Supplementary Methods for definitions). Prescription drugs dispensed within 180 days of inclusion date were registered as comedication.

Outcomes

The outcomes of interest were all-cause mortality, hospitalization from stroke/SE (ischaemic stroke, unspecified stroke, systemic embolism, or transient ischemic attack), and bleeding (intracranial bleeding, gastrointestinal bleeding, urinary tract bleeding, intraspinal bleeding, retroperitoneal bleeding, pericardial bleeding, intraocular bleeding, chronic bleeding anemia, or anemia following acute bleeding). Separate analyses of the risk of intracranial bleeding and gastrointestinal bleeding were also performed (see Supplementary Table 1 for list of included diagnosis codes). A validation study found a positive predictive value of intracerebral bleeding and ischemic stroke of 74% and 97%, respectively (20). The definition of bleeding has been used in similar databases and found to have a positive predictive value of 89 to 99% (21).

Statistical analyses

We explored temporal trends in initiation of NOAC and VKA by identifying the first redeemed OAC drug from the ATC codes registered in the Danish National Prescription Registry. The target parameters (estimands) of our primary analysis are the differences in average 2-year risks of all-cause mortality, stroke, and bleeding between VKA or FXa-I. For the all-cause mortality endpoint, a Cox regression model was employed. The model was adjusted for sex, age (<65, 65-69, 70-74, 75-79, 80-84, 85-89, and ≥90), calendar year of treatment initiation, ischemic

heart disease, peripheral artery disease, vascular disease, heart failure, hypertension, previous stroke, previous bleeding, diabetes, chronic kidney disease, liver disease, cancer, chronic obstructive pulmonary disease, and alcohol abuse. Based on the model, we calculated predicted 2-year risks of all-cause mortality and reported average 2-year risks and differences thereof. We refer to the average 2-year risks as standardized risks with respect to the risk factor distribution of all patients (22).

To deal with the competing risk of death without stroke (similar for bleeding), we modelled the absolute 2-year risks of stroke (similar for bleeding) using separate cause-specific Cox regression models (see the formula of Benichou and Gail in Supplementary Figure 2 and results of Cox-regressions in Supplementary Table 2) (23). In the analyses of stroke, we adjusted for the CHA_2DS_2-VASc risk factors and in the analyses of bleeding, we adjusted for the HAS-BLED risk factors (International normalized ratio (INR) not included). We used the following age groups: <65, 65-69, 70-74, 75-79, 80-84, 85-89, and ≥90 in all analyses instead of the age groups used in the CHA_2DS_2-VASc and HAS-BLED risk scores. Based on the cause-specific Cox regression models, we computed the predicted absolute 2-year risk of stroke (similar for bleeding) for each patient and all available treatment options. Reported were the average standardized absolute 2-year risks for each treatment option and differences thereof as average treatment effects.

We conducted three subgroup analyses: (i) With each OAC analysed separately for the outcomes to address the clinical question "which NOAC should we choose?". (ii) Subgroup of patients with bioprosthetic heart valves as information about these patients have been requested in the guidelines (1). (iii) Patients treated with standard and reduced dose of FXa-I (Supplementary Table 3), as there was no randomization of standard and reduced dose of rivaroxaban and apixaban in the trials (9, 10).

Supplementary Data includes three sensitivity analyses: (i) Intention-to-treat analysis not censoring for switching or discontinuation of treatment. (ii) Including patients initiating treatment between the 1st of January 2014 and the 30th of June 2016. (iii) Excluding patients with chronic kidney disease and liver disease (Supplementary Table 4).

The level of statistical significance was set at 5%. The statistical analyses were performed with SAS version 9.4 and R Studio version 3.4.1.

Ethics

Retrospective registry-based studies do not require approval from the Research Ethics Committee System. The Danish Data Protection Agency approved use of data for this study (ref.no: 2007-58-0015/GEH-2014-012 I-Suite no: 02720).

Results

Study population, baseline characteristics, and follow-up

Figure 1 shows the final study population comprising 2,677 OAC naïve patients with AF and VHD. Overall, 1,115/2,677 (41.7%) and 1,562/2,677 (58.3%) patients were initiated with VKA and FXa-I. Of the FXa-I patients, 620/2,677 (23.1%) and 942/2,677 (35.2%) were initiated with rivaroxaban and apixaban.

Table 1 shows the baseline characteristics of our study population. The VKA group had the lowest median age (77) and the highest prevalence of males (56.6%). The apixaban group had the highest median age (81) and the lowest prevalence of males (46.1%). A total of 684/1,115 (61.3%), 382/620 (61.6%), and 587/942 (62.3%) patients had aortic stenosis in the VKA, rivaroxaban, and apixaban group. Mean CHA_2DS_2-VASc score was lowest for VKA 3.5 (SD: 1.6), followed by rivaroxaban 3.6 (SD: 1.6), and apixaban 3.9 (SD: 1.6). Mean HAS-BLED score was for VKA 2.6 (SD: 1.2), rivaroxaban 2.6 (SD: 1.2), and apixaban 2.7 (SD: 1.2). 1,661/2,677 (62%) patients did not achieve 2 years of follow-up either due to switch or discontinuation of OAC treatment or due to date of inclusion being less than 2 years from 30th of June 2017.

Outcomes

All-cause mortality

During follow-up, 236/1,115 (21.2%) of VKA treated and 344/1,562 (22.0%) of FXa-I treated patients died. Figure 2 illustrates the standardized absolute risk of all-cause mortality during 2 years of follow-up. The standardized absolute 2-year risk of all-cause mortality was 34.1% (95%CI: 30.4% to 37.8%) for patients treated with VKA and 31.4% (95%CI: 28.4% to 34.4%)

for patients treated with FXa-I. When compared, there was a non-significant absolute 2-year risk difference of -2.7% (95%CI: -6.7% to 1.4%; P=0.196) (Figure 3).

Stroke/SE

During follow-up, 27/1,115 (2.4%) of VKA treated and 42/1,562 (2.7%) of FXa-I treated patients experienced a stroke. Figure 2 illustrates the standardized absolute risk of stroke/SE during 2 years of follow-up. The standardized absolute 2-year risk of stroke/SE was 3.8% (95%CI: 2.2% to 5.4%) for patients treated with VKA and 3.7% (95%CI: 2.5% to 4.9%) for patients treated with FXa-I. When compared, there was a non-significant absolute 2-year risk difference of -0.1% (95%CI: -2.0% to 1.8%; P=0.926) (Figure 3).

Bleeding

During follow-up, 65/1,115 (5.8%) of VKA treated and 74/1,562 (4.7%) of FXa-I treated patients experienced a bleeding event. Figure 2 illustrates the standardized absolute risk of bleeding during 2 years of follow up. The standardized absolute 2-year risk of bleeding was 10.4% (95%CI: 7.2% to 12.9%) for patients treated with VKA and 8.0% (95%CI: 6.0% to 10.1%) for patients treated with FXa-I. When compared, there was a non-significant absolute 2-year risk difference of -2.0% (95%CI -5.1% to 1.1%; P=0.201) (Figure 3). Furthermore, no significant differences between VKA and FXa-I was found regarding ICB and gastrointestinal bleeding.

Subgroup and sensitivity analyses

Table 2 shows the results of the subgroup analyses. In analysis (i) the absolute 2-year risk difference of bleeding was significantly reduced with -3.9% (95%CI: -7.0% to -0.9%; P= 0.012) in the apixaban group compared with the VKA group and with -5.6% (95%CI: -9.5% to -1.7%; P=0.005) in the apixaban group compared with the rivaroxaban group. Other results

were comparable to the main analysis. In analysis (ii) we included 389 patients with a bioprosthetic heart valve and results were comparable to the main analysis.

Supplementary Table 3 shows the subgroup analyses of patients treated with standard and reduced dose of FXa-I and results were comparable to the main analysis. Supplementary Table 4 shows the results of the sensitivity analysis. Results of analysis (i) showed a significantly reduced absolute 2-year risk difference in bleeding and gastrointestinal bleeding associated with FXa-I. Analyses (ii) and (iii) were comparable to the main analysis.

Discussion

In the present study, we estimated absolute risks instead of relative risks to provide easy-to-interpret results for both physicians and patients. Within the limitations of our observational study, the main findings were (i) In patients with AF and VHD, there were no significant differences in the risk of all-cause mortality, stroke/SE, or bleeding when comparing VKA to FXa-I. (ii) Patients treated with VKA and rivaroxaban had a significantly higher risk of bleeding when compared to apixaban. (iii) Considering the small population size and a limited number of events, patients with a bioprosthetic heart valve were not at increased risk of all-cause mortality, stroke/SE, or bleeding when comparing VKA to FXa-I.

Differences in patient characteristics between our study and post hoc analyses

The comparative safety and efficacy of FXa-I and VKA in patients with AF and VHD have been investigated in post hoc analyses based on the ARISTOTLE and ROCKET-AF trial (9, 10). Of note, there was a marked age discrepancy between our study population and the study population included in the post hoc analyses. Patients treated with apixaban had a median age of 81 years in our study and 71 years reported in the post hoc analysis (10). Similarly, for rivaroxaban the median age was 80 years in our study compared with 75 years in the post hoc analysis (9). Mean CHA_2DS_2-VASc score was 3.5, 3.6, and 3.9 in the VKA, rivaroxaban and apixaban group compared to 3.5 in the post-hoc analyses of ROCKET-AF trial and 2.2 ($CHADS_2$) in the ARISTOTLE trial.

The distribution of the types of VHD in our study population differed markedly from patients in the post hoc analyses. In our cohort, 60% or more of patients had aortic stenosis in all OAC-groups making it the most common type of VHD, whereas 73% or more of patients had mitral regurgitation in the post hoc analyses. The post hoc analyses reported that the identification of VHD in the RCTs relied on the clinical sites and was a combination of cardiovascular disease

history, echocardiographic history with available data, and prior invasive procedures with available data (9-12). This along with the older patient groups in our cohort might explain the discrepancy in the distribution of VHD between our cohort and the post hoc analyses.

Stroke/SE and ICB with FXa-I

We found no significantly reduced risk of stroke/SE in patients treated with FXa-I compared with VKA. Results from meta-analyses have suggested that apixaban significantly lowers the risk of stroke/SE when compared to VKA, whereas it has been found that rivaroxaban did not significantly lower the risk of stroke/SE (6, 8). The age discrepancy, pooling of apixaban and rivaroxaban in our main analysis, and higher proportion of patients treated with a standard dose of apixaban and rivaroxaban in the post hoc analyses compared to our study might explain why we did not find a significantly reduced risk of stroke/SE in the FXa-I group. Our results are consistent with another cohort of "real-world" NVAF patients that did not find a significantly lower risk of stroke/SE when comparing NOAC to VKA (24). We found a non-significant trend towards higher risk of ICB associated with FXa-I treatment, but few events were observed, and the trend was mainly driven by rivaroxaban and not apixaban (Table 2), which is consistent with findings from meta-analyses (6-8).

Bleeding risk between OAC

We found that when analysing outcomes separately for rivaroxaban and apixaban that patients treated with apixaban had a significantly lower risk of bleeding, including gastrointestinal bleeding, when compared to rivaroxaban. In another cohort study from our research group, it has been found that patients with AF with and without VHD treated with rivaroxaban had a significantly higher risk of major bleeding when compared to patients treated with apixaban in both standard and reduced doses (25). Noteworthy, we found that patients in the apixaban group more frequently had a history of bleeding compared with patients treated with

rivaroxaban, suggesting that these patients are at a higher risk of bleeding. This finding is consistent with findings from Haastrup et al. that have highlighted the selective prescribing of apixaban to patients at high risk of bleeding (26). Noseworthy et al. found that apixaban when compared to rivaroxaban in a propensitiy-score-matched cohort was associated with a significantly lower risk of major bleeding even when stratifying for HAS-BLED and CHA_2DS_2-VASc score (27).

FXa-I in patients with bioprosthetic heart valves

In a subgroup analysis of patients with bioprosthetic heart valves, we found no significant differences regarding any of the outcomes investigated. However, only 389 patients were included in this subgroup analysis and few events were observed, thus yielding broad confidence intervals. In a meta-analysis (6), three studies (10, 12, 28) with a total of 280 patients with bioprosthetic heart valves were evaluated regarding the risk of stroke and only two studies (10, 28) regarding the risk of major bleeding. Results from the meta-analysis showed no significant difference in the risk of stroke or bleeding between patients treated with NOAC or VKA.

Limitations

This study included a small number of patients, which resulted in low statistical power, as illustrated by the broad confidence intervals. This could result in potential type 2 errors**.** The study design of observational studies only allows estimation of causation as associations, and thus it is not possible to comment on the causal relationship between the treatment and outcomes. Another limitation is that we cannot rule out either confounding by indication or residual confounding. Especially underreporting of diagnosis codes are often seen in registries and may have underestimated the comorbidities of the patients, and thus also the potential to adjust for these in our analyses. Selection bias is another potential bias, and it is possible that

patients who were able to maintain a high time in therapeutic range continued treatment with VKA and did not switch to a NOAC as shown in a previous study (29). This leaves a more selected population treated with VKA with higher compliance. There is a potential for detection bias regarding the outcomes. It is possible that patients treated with VKA were more often in contact with healthcare professionals with regular INR-monitoring and were more likely to be diagnosed with a bleeding episodes. Last, the heart valve diagnoses were from ICD-10 codes and not echocardiographic images thus making it impossible to stratify by VHD degree.

Conclusions

In this observational study, we found no significant differences in the risk of all-cause mortality, stroke/SE, or bleeding in patients with AF and VHD treated with VKA compared to FXa-I. Anticoagulation with FXa-I appears to be safe in patients with AF and VHD.

When FXa-I was separated by specific OAC, apixaban was associated with a significantly reduced risk of bleeding compared with VKA and rivaroxaban.

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Table 1. Baseline characteristics of oral anticoagulant naïve patients.

	VKA	Rivaroxaban	Apixaban	P-value
No.	**1,115**	**620**	**942**	
Males (%)	631 (56.6)	308 (49.7)	434 (46.1)	< 0.001
Age (median [IQR])	77.0 [70.0, 83.0]	80.0 [71.0, 87.0]	81.00 [74.0, 87.8]	< 0.001
CHA_2DS_2-VASc (mean [SD])	3.5 [1.6]	3.6 [1.6]	3.9 [1.6]	< 0.001
HAS-BLED (mean [SD])	2.6 [1.2]	2.6 [1.2]	2.7 [1.2]	0.023
Standard dose (%)	-	387 (62.4)	446 (47.3)	0.041
Reduced dose (%)	-	233 (37.6)	496 (52.7)	< 0.001
Valvular disease, No. (%)				
Aortic stenosis	684 (61.3)	382 (61.6)	587 (62.3)	0.901
Aortic insufficiency	247 (22.2)	155 (25.0)	223 (23.7)	0.388
Bioprosthetic mitral valve	26 (2.3)	< 3	4 (0.4)	< 0.001
Bioprosthetic aortic valve	191 (17.1)	71 (11.5)	103 (10.9)	< 0.001
Mitral insufficiency	338 (30.3)	157 (25.3)	244 (25.9)	0.029
Mitral valve repair	95 (8.5)	18 (2.9)	24 (2.5)	< 0.001
Aortic valve repair	4 (0.4)	< 3	4 (0.4)	0.669
Comorbidities, No. (%)				
Previous stroke/SE	132 (11.8)	109 (17.6)	165 (17.5)	< 0.001
Ischemic heart disease	415 (37.2)	173 (27.9)	315 (33.4)	< 0.001
Heart failure	334 (30.0)	167 (26.9)	290 (30.8)	0.245
Peripheral artery disease	64 (5.7)	28 (4.5)	52 (5.5)	0.541
Hypertension	830 (74.4)	448 (72.3)	692 (73.5)	0.610
Diabetes mellitus	155 (13.9)	67 (10.8)	108 (11.5)	0.104
Previous bleeding	174 (15.6)	93 (15.0)	185 (19.6)	0.019
Chronic kidney disease	138 (12.4)	31 (5.0)	80 (8.5)	< 0.001
Abnormal liver function	20 (1.8)	5 (0.8)	10 (1.1)	0.158
Alcohol abuse	33 (3.0)	12 (1.9)	20 (2.1)	0.311
Cancer	190 (17.0)	107 (17.3)	165 (17.5)	0.960

Table 1. Baseline characteristics of oral anticoagulant naïve patients (continued).

	VKA	Rivaroxaban	Apixaban	P-value
Chronic obstructive pulmonary disease	145 (13.0)	96 (15.5)	135 (14.3)	0.345
Comedication, No. (%)				
ADP receptor antagonists	162 (14.5)	93 (15.0)	149 (15.8)	0.717
Aspirin	504 (45.2)	267 (43.1)	390 (41.4)	0.219
Non-steroidal-anti-inflammatory-drugs	111 (10.4)	69 (11.1)	107 (11.4)	0.551
Beta-blockers	488 (43.8)	235 (37.9)	404 (42.9)	0.050
Calcium channel blockers	342 (30.7)	174 (28.1)	284 (30.1)	0.511
Renin-angiotensin system inhibitors	538 (48.3)	285 (46.0)	444 (47.1)	0.652
Loop diuretics	396 (35.5)	184 (29.7)	318 (33.8)	0.047
Digoxin	**61 (5.5)**	**33 (5.3)**	**57 (6.1)**	**0.788**

Abbreviations: ADP: Adenosine diphosphate. SE: Systemic embolism. VKA: Vitamin K antagonist.

Table 2. Subgroup analyses.

Outcomes by oral anticoagulant

	2-year absolute risk	2-year absolute risk difference	2-year absolute risk difference
All-cause mortality			
VKA	34.1% (30.4% to 37.8%)	REF	-
RIVAROXABAN	31.0% (26.7% to 35.2%)	-3.1% (-8.4% to 2.1%)	REF
APIXABAN	31.7% (28.1% to 35.2%)	-2.4% (-6.7% to 1.9%)	0.7% (-4.2% to 5.5%)
Stroke/systemic embolism			
VKA	3.8% (2.2% to 5.4%)	REF	-
RIVAROXABAN	3.7% (1.7% to 5.6%)	-0.1% (-2.6% to 2.3%)	REF
APIXABAN	3.7% (2.3% to 5.2%)	-0.1% (-2.0% to 2.1%)	0.1% (-2.2% to 2.4%)
Bleeding			
VKA	9.9% (7.1% to 12.7%)	REF	-
RIVAROXABAN	11.5% (8.0% to 15.1%)	1.7% (-2.8% to 6.1%)	REF
APIXABAN	6.0% (3.8% to 8.1%)	**-3.9% (-7.0% to -0.9%)**[b1]	**-5.6% (-9.5% to -1.7%)**[b2]
Gastrointestinal bleeding			
VKA	5.4% (3.3% to 7.6%)	REF	-
RIVAROXABAN	5.8% (3.2% to 8.4%)	0.4% (-2.9% to 3.6%)	REF
APIXABAN	2.8% (1.3% to 4.2%)	**-2.7% (-4.9% to -0.5%)**[b3]	**-3.1% (-5.9% to -0.2%)**[b4]
Intracranial bleeding			
VKA	1.0% (0.1% to 1.8%)	REF	-
RIVAROXABAN	3.0% (1.0% to 5.0%)	2.0% (-0.1% to 4.1%)	REF
APIXABAN	1.2% (0.2% to 2.2%)	0.2% (-1.0% to 1.5%)	-1.8% (-3.9% to 0.4%)

Table 2. Subgroup analyses (continued)

Bioprosthetic heart valves		
All-cause mortality[a]		
VKA	18.7% (9.6% to 27.8%)	REF
FXa-I	26.1% (15.7% to 36.4%)	7.4% (-5.3% to 20.0%)
Stroke/systemic embolism		
VKA	2.2% (0.0% to 4.5%)	REF
FXa-I	4.2% (0.9% to 7.5%)	2.1% (-1.7% to 5.8%)
Bleeding[a]		
VKA	15.7% (4.2% to 27.3%)	REF
FXa-I	4.4% (0.0% to 10.8%)	-11.4% (-24.3% to 1.6%)
Gastrointestinal bleeding		
VKA	N/A	N/A
FXa-I	N/A	N/A
Intracranial bleeding		
VKA	N/A	N/A
FXa-I	N/A	N/A

Abbreviations: N/A: Not analyzed. Ref: Reference. (95% CI).

[a]Due to limited population size and few events, adjustment for liver disease was omitted in all-cause mortality and bleeding. Also, we used the following age groups: >75, 75-79, 80-84 and ≥85

[b1,2,3,4] P-values [b1]: 0.012 ; [b2] : 0.005 ; [b3]: 0.018 ; [b4]: 0.036

Legends

Figure 1:

Title: Flow chart

Legend: Selection of study population from 1st of January 2014 to 30th of June 2017.

Abbreviations: AF: Atrial fibrillation. DVT: Deep vein thrombosis. FXa-I: Factor Xa-inhibitor. OAC: Oral anticoagulation. PE: Pulmonary embolism. VHD: Valvular heart disease. VKA: Vitamin K antagonists.

Figure 2:

Title: Risk of all-cause mortality, stroke/systemic embolism, and bleeding

Legend: Standardized absolute risk of all-cause mortality for patients treated with FXa-I or VKA. Shadowed areas indicate 95 % confidence intervals.

Abbreviations: FXa-I: Factor Xa-inhibitor. VKA: Vitamin K antagonist.

Figure 3:

Title: Standardized absolute 2-year risks

Legend: Adjusted 2-year standardized absolute risk of all-cause mortality, stroke/SE, bleeding, and according to sites of bleeding for patients treated with FXa-I or VKA. CI: Confidence interval. Ref: Reference

Figure 1

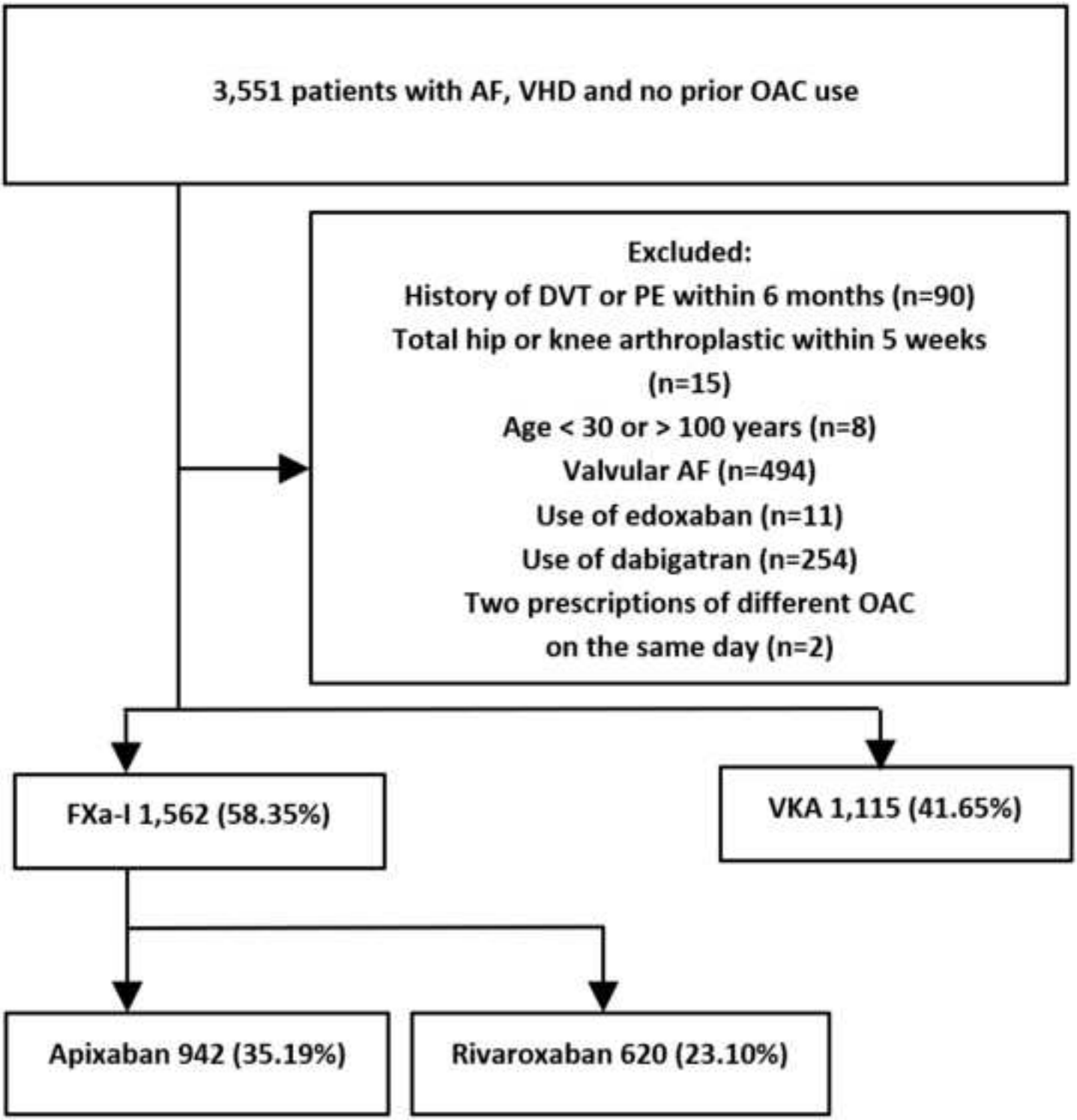

Figure 2

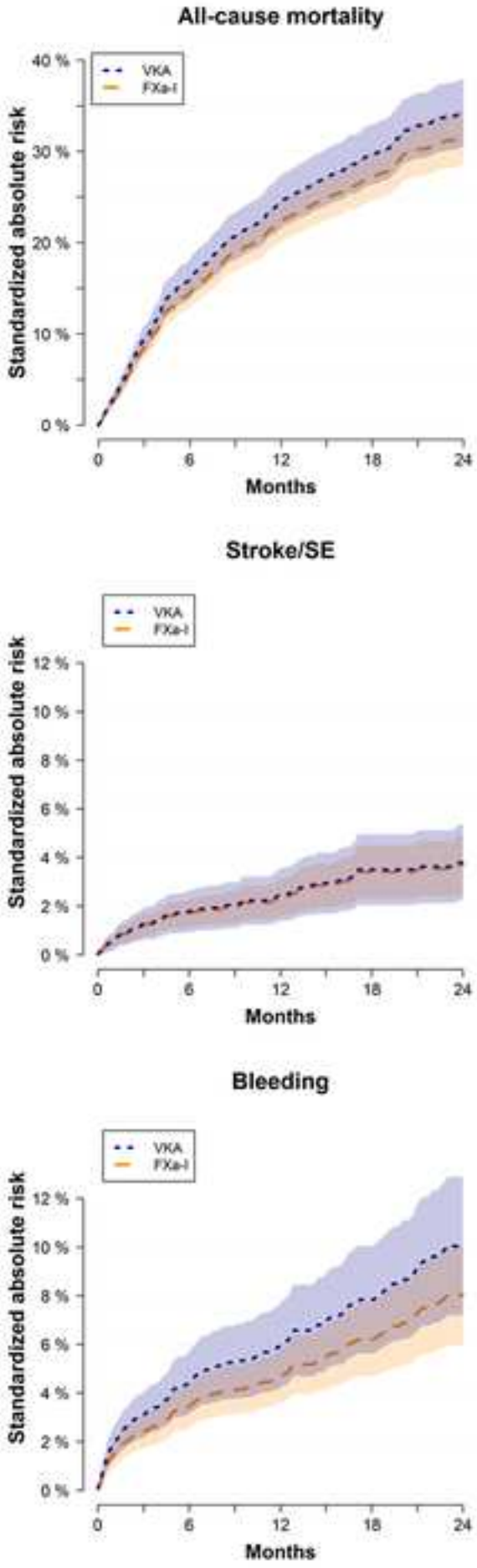

Figure 3