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Comparison of medication adherence to different oral anticoagulants: population-based cohort study

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ABSTRACT

Objective Previous observational studies have yielded conflicting results on whether medication adherence differs between patients receiving warfarin and direct oral anticoagulants (DOACs). Importantly, no study has adequately accounted for warfarin dosing being continuously modified based on INR values while dosing of DOACs is fixed. We aimed to compare non-adherence between new users of apixaban, dabigatran, rivaroxaban and warfarin in a population-based cohort.

Methods New users of apixaban, dabigatran, rivaroxaban and warfarin from 2014 to 2019 living in the Icelandic capital area were included. Non-adherence was defined as proportion of days covered below 80%. Inverse probability weighting was used to yield balanced study groups and non-adherence was compared using logistic regression. Factors associated with non-adherence were estimated using multivariable logistic regression.

Results Overall, 1266 patients received apixaban, 247 dabigatran, 1566 rivaroxaban and 768 warfarin. The proportion of patients with non-adherence ranged from 10.5% to 16.7%. Dabigatran was associated with significantly higher odds of non-adherence compared with apixaban (OR 1.57, 95% CI 1.21 to 2.04, p<0.001), rivaroxaban (OR 1.45, 95% CI 1.12 to 1.89, p=0.005) and warfarin (OR 1.63, 95% CI 1.23 to 2.15, p<0.001). The odds of non-adherence were similar for apixaban, rivaroxaban and warfarin. Apart from the type of oral anticoagulants (OACs) used, female sex, hypertension, history of cerebrovascular accident and concomitant statin use were all independently associated with lower odds of non-adherence.

Conclusion Dabigatran was associated with higher odds of non-adherence compared with other OACs. Non-adherence was similar between apixaban, rivaroxaban and warfarin users. Female sex and higher comorbidity were associated with better medication adherence.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study was population-based and used robust propensity score-weighting model to account for indication bias.
⇒ The study accounted for all dose adjustments for both warfarin and direct oral anticoagulants during the study period, greatly increasing the accuracy of non-adherence calculations.
⇒ As data on dose adjustments for warfarin were only available from Landspitali University Hospital (the only university hospital in the capital area), the primary analysis was restricted to patients living in the capital area.
⇒ The propensity score-weighting model did not account for important socioeconomic factors that may affect risk of non-adherence, such as smoking, alcohol consumption, education level or household income.

INTRODUCTION

Based on the outcomes of large clinical trials, direct oral anticoagulants (DOACs) are currently recommended as first-line treatment for patients with atrial fibrillation and venous thromboembolism (VTE).[1–4] However, concerns have been raised that the efficacy of DOACs may be lower in clinical practice than reported in clinical trials,[5] possibly due to lower medication adherence. Warfarin treatment needs to be controlled by regular INR measurements, while no such monitoring is deemed necessary for DOACs. However, the regular monitoring of warfarin treatment may not only secure optimal therapeutic dosing, but may also serve as a safety marker ensuring that the drug is used correctly and that patients are adherent to their dosing regimen.

Results from observational studies comparing adherence between warfarin and DOACs have been ambiguous.[6–9] Importantly, previous studies have failed to account for dosing adjustments between prescriptions for warfarin.[6–9] This is important as warfarin dosing is continuously being modified according to INR values, while DOACs are prescribed at fixed doses. While patients are usually started on a standard dose when initiating warfarin treatment, the final maintenance dose can vary by as much as 40-fold.[10] Therefore, results from previous studies may

be unreliable. Indeed, a previous study from Sweden comparing the adherence and persistence of oral anticoagulants (OACs), excluded patients receiving warfarin when comparing adherence as 'the proportion of days covered could not be calculated for warfarin treatment due to the highly variable dosage regimens'.[11]

This study aimed to compare non-adherence between warfarin and DOAC users in a population-based cohort where all dose adjustments were taken into account.

METHODS

Study population

The Icelandic OAC database has been previously described in detail.[12] Briefly, data were collected on all patients receiving their first drug prescription for OAC from 1 March 2014 to 28 February 2019 using the Icelandic Medicine Registry, which contains a centralised record of all outpatient drug prescriptions in the country. The personal identification numbers of these patients were subsequently linked to the electronic medical record system of Landspitali University Hospital, and all four regional hospitals in Iceland (Akureyri, Akranes, Ísafjörður and Neskaupsstaður hospitals).

To yield an OAC naïve cohort, patients were excluded if they had filled an OAC prescription in the preceding 12 months before their eligibility in the study. Additionally, as the catchment area of the Landspitali Anticoagulation Management Center is limited to the capital area, we excluded patients with residence outside the capital area. Furthermore, patients were excluded if they had a mechanical heart valve, mitral stenosis, end-stage renal disease or treatment indication other than atrial fibrillation, VTE or ischaemic stroke (figure 1). Finally, patients with a follow-up of less than 30 days or who only had a single OAC prescription were excluded, as well as patients receiving warfarin who had missing data on dose adjustments.

Follow-up

Patients were followed from the filling of their first OAC prescription until 28 February 2019 or earlier if treatment was discontinued or switched to another OAC, if the patient had a major bleeding or thromboembolic event, or if death occurred. Adherence was calculated from the date of first prescription to the date of the last prescription before follow-up stopped. As the last OAC prescription before the end of follow-up was excluded from calculations, the calculated adherence was unaffected by abrupt treatment cessations.

Study outcomes

The primary study outcome was medication non-adherence, defined as proportion of days covered (PDC) below 80%. This cut-off has been shown to be optimal in stratifying adherent and non-adherent patients,[7 13] and has been widely used in previous studies.[7–9 13] Secondary outcomes were rates of any thromboembolic event or major bleeding, and factors associated with non-adherence.

Calculation of medication adherence

In Iceland, 75% of all warfarin treatment is regulated by the Icelandic Anticoagulation Management Center, which has a database containing information on every dose adjustment between visits for these patients. Using these data, we calculated the mean daily dose of warfarin for each patient (in mg). The PDC was subsequently calculated by dividing

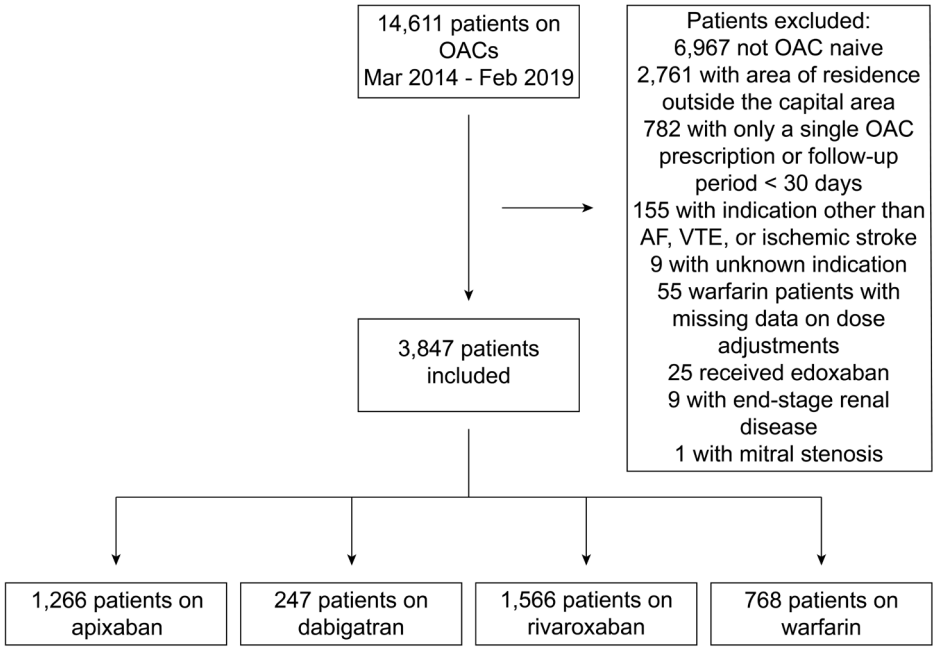

Figure 1 Flowchart for selection of study cohort. AF, atrial fibrillation; OAC, oral anticoagulant; VTE, venous thromboembolism.

the total amount of warfarin dispensed (in mg) by the predicted amount needed during the study period (in mg).

As opposed to warfarin, the dosing of DOACs is fixed. Therefore, PDC for DOACs was calculated as the number of tablets dispensed during the study period divided by the total amount needed during that period. This accounted for patients being switched from standard to reduced dosing during the study period (or less commonly vice versa). Patients receiving rivaroxaban due to VTE were estimated to have received rivaroxaban 15 mg two times a day for 3 weeks, followed by 20 mg once a day as per the medication's monograph. Similarly, patients receiving apixaban due to VTE were estimated to have received dosing of 10 mg two times a day for 1 week, followed by 5 mg two times a day. All other doses were estimated to be once daily for rivaroxaban, and two times a day for apixaban and dabigatran.

Data acquisition

Information on thromboembolic and bleeding events during the study period, as well as prior bleeding and thromboembolic events, comorbidities and indication for treatment were gathered using relevant ICD-10 codes as previously described (online supplemental table 1).[12] Additionally, events were identified by searching the Icelandic death registry and by manually reviewing results from computed tomographies of the head and pulmonary arteries and all endoscopic procedures. To estimate the comorbidity burden of patients, Charlson comorbidity index and CHA_2DS_2-VASc scores were calculated for each patient using previously verified ICD-10 codes.[14 15]

Information on concomitant drug use was obtained from the Icelandic Medicine Registry (online supplemental table 2). Concomitant drug use was defined as filling a relevant drug prescription within 6 months of the start of a patient's follow-up.

Statistical analysis

Inverse probability weighting (IPW) was used to achieve balanced study groups. It assigns weights to patients based on propensity scores, therefore yielding a balanced pseudopopulation that includes the whole study population. The following variables were used in the model: age, sex, treatment indication, all variables in the Charlson comorbidity index (except for AIDS, which was too sporadic), bleeding or coagulation disorders, hypertension, history of VTE or gastrointestinal bleeding requiring hospital admission, and concomitant use of antihistamines, antihypertensives, antiplatelets, corticosteroids, non-steroidal anti-inflammatory drugs, proton pump inhibitors, selective serotonin receptor inhibitors and statins. Standardised mean difference was used to evaluate balance between study groups after weighting, with values below 0.1 being considered ideal and values below 0.2 being considered acceptable.[12 16] The model yielded acceptable balance for all variables, except treatment indication and the highly correlated variable history of VTE. Therefore, a sensitivity analysis including patients with atrial fibrillation only was performed. Additionally, to account for potential differences in medication adherence based on area of residence, a second analysis was performed which included patients receiving DOACs and living in all regions of Iceland. This analysis used the same statistical methods as described above except area of residence was included as a variable in the IPW model as well. Finally, as the average length of follow-up varied considerably between individual OACs, a sensitivity analysis was performed with follow-up limited to the first 18 months of treatment.

Non-adherence was compared using propensity score-weighted logistic regression that accounted for length of follow-up. Univariate analysis was performed to identify factors associated with non-adherence. Categorical variables were compared using the χ^2 test and continuous variables using analysis of variance. This analysis compared 32 variables. Therefore, to account for multiple testing, a p value of less than 0.0016 was considered significant. Multivariable analysis was performed including variables from the univariate analysis with significant association with non-adherence. For this analysis, the linearity assumption of continuous variables was assessed by visualising the logit of non-adherence in quantiles of OAC users and the goodness of fit was assessed using the Hosmer-Lemeshow test.

Statistical analysis was performed in R, V.4.2.1 (R Foundation for Statistical Computing), using RStudio, V.2022.07.1. All statistical tests were two-tailed. Apart from the univariate analysis, a p value of less than 0.05 was considered significant.

Patient and public involvement

There was no active patient involvement in this study.

RESULTS

Study population

In total, 14 611 patients received OAC during the study period. Of those, 6967 patients were excluded as they had filled an OAC prescription during the preceding 12 months, 2761 patients as they had permanent residence outside the capital area and 782 patients were excluded as they had a follow-up of less than 30 days or only filled a single OAC prescription during the follow-up period. Additionally, 254 patients were excluded for other reasons as listed in figure 1. The final study population consisted of 3847 patients. Thereof, 1266 patients had received apixaban, 247 dabigatran, 1566 rivaroxaban and 768 warfarin. The mean follow-up period was 1.4 years for patients receiving apixaban, 2.1 years for dabigatran, 2.0 years for rivaroxaban and 1.3 years for warfarin. Baseline characteristics of the study population are provided in table 1.

Comparison of medication non-adherence between users of individual OACs

Overall, the majority of patients had near-perfect adherence, with a median PDC of 100% for apixaban users

Table 1 Baseline characteristics of study population

Variables	Apixaban n=1266	Dabigatran n=247	Rivaroxaban n=1566	Warfarin n=768	SMD Before IPW	SMD After IPW
Age	73.6 (12.8)	71.2 (13.1)	69.4 (12.5)	65.3 (16.7)	0.313	0.060
Sex (male)	668 (52.8)	126 (51.0)	938 (59.9)	390 (50.8)	0.098	0.136
CHA_2DS_2-VASC score	3.0 (1.7)	2.7 (1.5)	2.4 (1.5)	2.4 (1.7)	0.200	0.050
Charlson comorbidity index	1.0 (1.4)	0.7 (1.2)	0.7 (1.2)	1.0 (1.4)	0.143	0.067
Ischaemic heart disease	95 (7.5)	14 (5.7)	103 (6.6)	43 (5.6)	0.045	0.034
Heart failure	125 (9.9)	18 (7.3)	110 (7.0)	62 (8.1)	0.056	0.048
Peripheral vascular disease	62 (4.9)	8 (3.2)	58 (3.7)	33 (4.3)	0.047	0.059
Cerebrovascular disease	190 (15.0)	26 (10.5)	104 (6.6)	61 (7.9)	0.151	0.040
Dementia	40 (3.2)	4 (1.6)	26 (1.7)	14 (1.8)	0.053	0.082
Chronic lung disease	85 (6.7)	14 (5.7)	75 (4.8)	61 (7.9)	0.072	0.028
Connective tissue disease	39 (3.1)	4 (1.6)	37 (2.4)	20 (2.6)	0.051	0.062
Peptic ulcer disease	36 (2.8)	7 (2.8)	24 (1.5)	21 (2.7)	0.046	0.069
Diabetes mellitus	70 (5.5)	6 (2.4)	60 (3.8)	33 (4.3)	0.084	0.134
Diabetes mellitus with end-organ damage	43 (3.4)	5 (2.0)	40 (2.6)	23 (3.0)	0.047	0.064
Hemiplegia	15 (1.2)	1 (0.4)	8 (0.5)	11 (1.4)	0.067	0.048
Moderate/severe renal disease	49 (3.9)	8 (3.2)	46 (2.9)	46 (6.0)	0.080	0.011
Any tumour	166 (13.1)	28 (11.3)	160 (10.2)	120 (15.6)	0.090	0.033
Metastatic cancer	7 (0.6)	1 (0.4)	15 (1.0)	6 (0.8)	0.039	0.061
Hypertension	861 (68.0)	174 (70.4)	972 (62.1)	359 (46.7)	0.267	0.059
Bleeding or coagulation disorder	10 (0.8)	1 (0.4)	9 (0.6)	8 (1.0)	0.042	0.042
Liver disease	12 (0.9)	1 (0.4)	14 (0.9)	7 (0.9)	0.034	0.028
History of gastrointestinal bleeding	74 (5.8)	14 (5.7)	58 (3.7)	36 (4.7)	0.058	0.063
History of VTE	135 (10.7)	23 (9.3)	284 (18.1)	553 (72.0)	0.843	0.288
Concomitant drug use						
Antihistamine	7 (0.6)	1 (0.4)	6 (0.4)	6 (0.8)	0.030	0.023
Antiplatelet	343 (27.1)	65 (26.3)	322 (20.6)	143 (18.6)	0.124	0.098
NSAID	246 (19.4)	53 (21.5)	353 (22.5)	179 (23.3)	0.052	0.081
PPI	528 (41.7)	89 (36.0)	569 (36.3)	316 (41.1)	0.075	0.083
SSRI	257 (20.3)	28 (11.3)	226 (14.4)	157 (20.4)	0.151	0.147
Statin	588 (46.4)	109 (44.1)	678 (43.3)	219 (28.5)	0.191	0.094
Steroid	252 (19.9)	45 (18.2)	297 (19.0)	187 (24.3)	0.079	0.057
Treatment indication					0.845	0.258
AF	1104 (87.2)	223 (90.3)	1307 (83.5)	229 (29.8)		
Ischaemic stroke	47 (3.7)	2 (0.8)	13 (0.8)	16 (2.1)		
VTE	115 (9.1)	22 (8.9)	246 (15.7)	523 (68.1)		

AF, atrial fibrillation; IPW, inverse probability weighting; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SMD, standardised mean difference; SSRI, selective serotonin receptor inhibitor; VTE, venous thromboembolism.

(IQR 94.3%–100%), 99.7% for dabigatran users (IQR 90.8%–100%), 100% for rivaroxaban users (IQR 95.2%–100%) and 97.0% for warfarin users (IQR 85.4%–100%). The distribution of PDC for the overall population is provided in figure 2 and online supplemental figure 1. When patients were stratified by length of follow-up using 6 month intervals, the proportion of patients with non-adherence was around 15.2%–18.9% for patients with less than 18 months of follow-up, but 7.1%–8.1% for patients with longer than 18 months of follow-up (online supplemental figure 2).

Before propensity score-weighting, 16.7% of warfarin users (95% CI 14.0% to 19.3%), 16.2% of dabigatran users (95% CI 11.6% to 20.8%), 12.4% of rivaroxaban users (95% CI 10.8% to 14.0%) and 10.5% of apixaban users (95% CI 8.8% to 12.2%) were non-adherent (figure 3A).

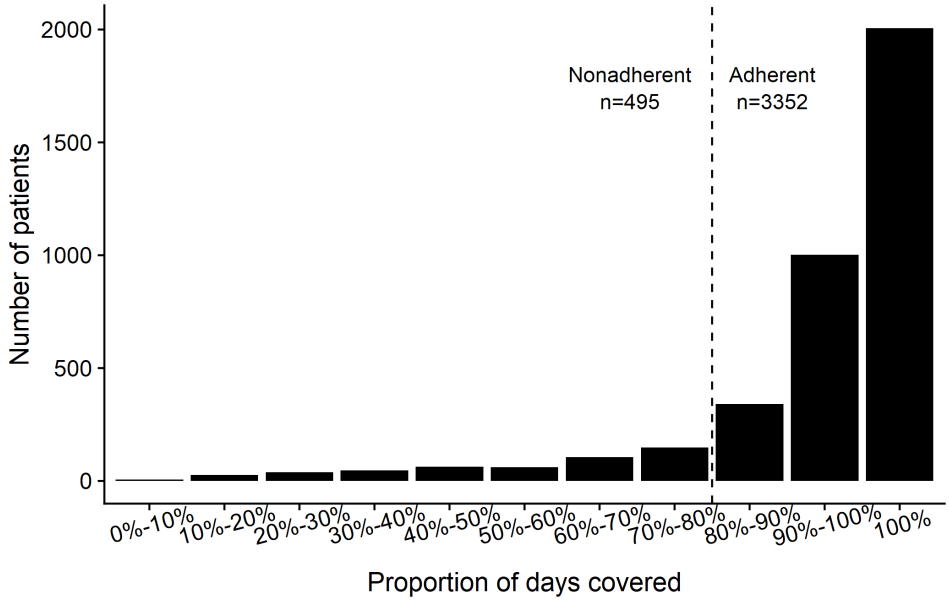

Figure 2 Bar graph demonstrating the distribution of proportion of days covered for the overall study population. Non-adherence was defined as proportion of days covered below 80%.

After adjusting for propensity score-weighting and length of follow-up, dabigatran was associated with significantly higher odds of non-adherence compared with apixaban (15.5% vs 11.9%, OR 1.57, 95% CI 1.21 to 2.04, p<0.001), rivaroxaban (15.5% vs 11.3%, OR 1.45, 95% CI 1.12 to 1.89, p=0.005) and warfarin (15.5% vs 11.1%, OR 1.63, 95% CI 1.23 to 2.15, p<0.001). The odds of non-adherence were similar between apixaban, rivaroxaban and warfarin users (figure 3B). The results were similar when the analysis was limited to 18 months of follow-up (online supplemental figure 3).

Patient characteristics associated with non-adherence

Patients who were found to be non-adherent were younger than adherent patients, had a lower CHA_2DS_2-VASc score and were more commonly males (table 2). Non-adherent patients were also less likely to have hypertension, history of cerebrovascular accident, or to have received concomitant statin treatment.

After multivariable logistic regression, dabigatran usage and male gender were both associated with higher odds of non-adherence. Meanwhile, hypertension, history of cerebrovascular accident and concomitant use of statins were all independently associated with lower odds of non-adherence (table 3).

Comparison of outcomes between adherent and non-adherent patients

Rates of thromboembolism (1.9 events per 100 person-years (events/100-py) vs 2.1 events/100-py, HR 0.86, 95% CI 0.31 to 2.37) and major bleeding (2.8 events/100-py vs 2.3 events/100-py, HR 0.97, 95% CI 0.55 to 1.73) were similar between adherent and non-adherent patients.

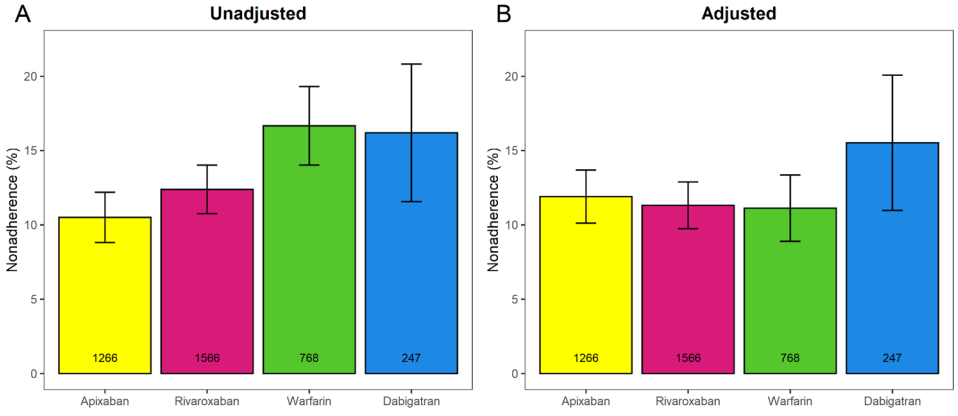

Figure 3 Bar graphs comparing the proportion of patients with non-adherence for the primary analysis (A) before and (B) after inverse probability weighting. Non-adherence was defined as proportion of days covered below 80%. Values are presented as means ± 95% confidence intervals.

Table 2 Univariate analysis comparing factors associated with non-adherence

	Adherent n=3352	Non-adherent n=495	P value
Age	70.6 (13.7)	66.5 (14.8)	<0.001
Sex (male)	1811 (54.0)	311 (62.8)	<0.001
CHA_2DS_2-VASC score	2.7 (1.6)	2.1 (1.6)	<0.001
Charlson comorbidity index	0.9 (1.4)	0.8 (1.2)	0.09
Ischaemic heart disease	224 (6.7)	31 (6.3)	0.80
Heart failure	282 (8.4)	33 (6.7)	0.22
Peripheral vascular disease	144 (4.3)	17 (3.4)	0.44
Cerebrovascular disease	357 (10.7)	24 (4.8)	<0.001
Dementia	77 (2.3)	7 (1.4)	0.28
Chronic lung disease	203 (6.1)	32 (6.5)	0.80
Connective tissue disease	90 (2.7)	10 (2.0)	0.47
Peptic ulcer disease	75 (2.2)	13 (2.6)	0.71
Diabetes mellitus	155 (4.6)	14 (2.8)	0.09
Diabetes mellitus with end-organ damage	102 (3.0)	9 (1.8)	0.17
Hemiplegia	31 (0.9)	4 (0.8)	1.00
Moderate/severe renal disease	129 (3.8)	20 (4.0)	0.94
Any tumour	411 (12.3)	63 (12.7)	0.83
Metastatic cancer	25 (0.7)	4 (0.8)	1.00
Hypertension	2113 (63.0)	253 (51.1)	<0.001
Bleeding or coagulation disorder	21 (0.6)	7 (1.4)	0.10
Liver disease	27 (0.8)	7 (1.4)	0.27
History of gastrointestinal bleeding	160 (4.8)	22 (4.4)	0.84
History of VTE	847 (25.3)	148 (29.9)	0.03
Concomitant drug use			
Antihistamine	16 (0.5)	4 (0.8)	0.54
Antiplatelet	786 (23.4)	87 (17.6)	0.004
NSAID	715 (21.3)	116 (23.4)	0.32
PPI	1319 (39.3)	183 (37.0)	0.34
SSRI	597 (17.8)	71 (14.3)	0.07
Statin	1431 (42.7)	163 (32.9)	<0.001
Steroid	684 (20.4)	97 (19.6)	0.72
Treatment indication			0.14
AF	2511 (74.9)	352 (71.1)	
Cryptogenic stroke	69 (2.1)	9 (1.8)	
VTE	772 (23.0)	134 (27.1)	

P<0.0016 was considered significant.
AF, atrial fibrillation; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SMD, standardised mean difference; SSRI, selective serotonin receptor inhibitor; VTE, venous thromboembolism.

Sensitivity analysis

A sensitivity analysis including patients with atrial fibrillation only was performed. This analysis included 1104 patients receiving apixaban, 223 receiving dabigatran, 1307 receiving rivaroxaban and 229 receiving warfarin. The mean follow-up period was 1.5 years for apixaban, 2.2 years for dabigatran, 2.2 years for rivaroxaban and 1.6 years for warfarin. IPW yielded an acceptable balance between all study groups (online supplemental table 3).

The crude proportion of patients with non-adherence was 9.9% for apixaban, 13.4% for rivaroxaban, 13.5% for warfarin and 16.6% for dabigatran (figure 4A). After propensity score-weighting, dabigatran was associated with higher odds of non-adherence compared with

Table 3 Logistic regression estimating factors associated with non-adherence

Variable	OR	95% CI	P value
Oral anticoagulant			
Not dabigatran	1 (Ref)	N/A	N/A
Dabigatran	1.44	1.00 to 2.04	0.046
Age	0.99	0.98 to 1.00	0.07
Sex (male)	1.34	1.05 to 1.72	0.02
CHA_2DS_2-VASc score	0.95	0.84 to 1.08	0.43
Cerebrovascular disease	0.56	0.33 to 0.90	0.02
Hypertension	0.76	0.60 to 0.97	0.03
Statin usage	0.77	0.62 to 0.95	0.02

apixaban (16.2% vs 10.5%, OR 2.05, 95% CI 1.51 to 2.81, p<0.001), rivaroxaban (16.2% vs 12.5%, OR 1.34, 95% CI 1.00 to 1.80, p=0.05) and warfarin (16.2% vs 7.6%, OR 2.75, 95% CI 1.63 to 3.37, p<0.001). Additionally, rivaroxaban was associated with higher odds of non-adherence compared with apixaban (OR 1.53, 95% CI 1.11 to 2.12, p=0.009) and warfarin (OR 2.05, 95% CI 1.41 to 2.01, p<0.001) (figure 4B).

Similar to the primary analysis, dabigatran use, younger age and male sex were all independently associated with higher odds of non-adherence, while a history of cerebrovascular accident and concomitant statin use were associated with lower odds of non-adherence. Similarly, rates of major bleeding (3.0 events/100-py vs 2.1 events/100-py, HR 0.83, 95% CI 0.43 to 1.58) and thromboembolism (1.5 events/100-py vs 1.6 events/100-py, HR 0.97, 95% CI 0.35 to 2.68) were similar between adherent and non-adherent patients.

A second analysis including patients receiving DOACs and living anywhere in the country was performed to account for potential differences due to area of residence. Comparison of the baseline characteristics of this population is provided in online supplemental table 4. Similar to the primary analysis, dabigatran was associated with higher odds of non-adherence compared with both apixaban (16.3% vs 11.5%, OR 1.81, 95% CI 1.47 to 2.23, p<0.001) and rivaroxaban (16.3% vs 11.6%, OR 1.53, 95% CI 1.25 to 1.88, p<0.001), while no differences were noted between apixaban and rivaroxaban. The odds of non-adherence were similar between patients who lived in the capital area and those who did not (OR 1.05, 95% CI 0.87 to 1.27).

DISCUSSION

In this population-based study, medication adherence for OACs was found to be good overall, with a median PDC around 100% for all medications. After accounting for patients' baseline characteristics, non-adherence was significantly more common among dabigatran users compared with patients receiving other OACs, while the odds of non-adherence were similar between apixaban, rivaroxaban and warfarin.

The higher odds of non-adherence for patients receiving dabigatran reported in the current study are consistent with several previous studies.[7 9 11 17–22] This lower adherence might be due to a combination of two factors. First, it is administered two times a day as opposed to warfarin and rivaroxaban which are given as a single daily dose. Previous studies on chronic cardiovascular medications have demonstrated that once a day dosing is associated with greater adherence compared with two times a day dosing.[23] However, apixaban is also administered two times a day but had similar odds of non-adherence as rivaroxaban and warfarin in the primary analysis. Additionally, apixaban was associated with lower odds of non-adherence than rivaroxaban when only patients with atrial fibrillation were analysed. Second, dabigatran's lower adherence has been speculated to be due to its frequent gastrointestinal side effects.[12 24] Supporting this, 12% of patients receiving dabigatran in the RE-LY trial reported dyspepsia and three times as many patients discontinued treatment due to gastrointestinal upset compared with warfarin.[25]

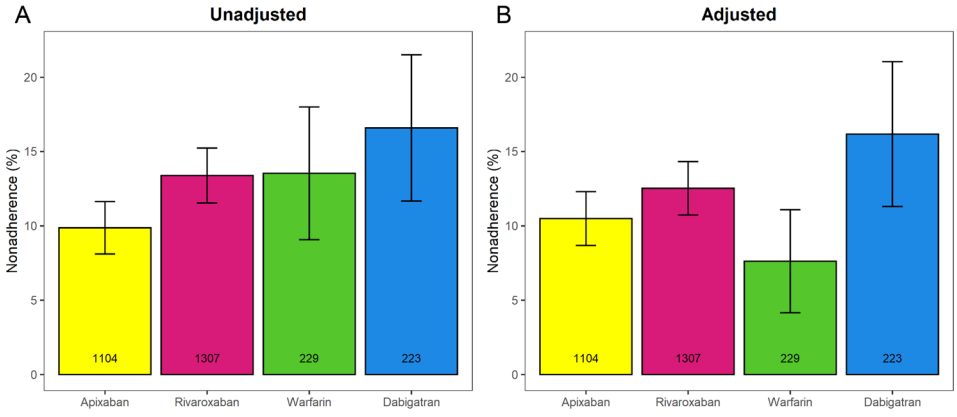

Figure 4 Bar graphs comparing the proportion of patients with non-adherence for patients with atrial fibrillation only (A) before and (B) after inverse probability weighting. Non-adherence was defined as proportion of days covered below 80%. Values are presented as means ± 95% confidence intervals.

Previous studies comparing adherence between warfarin and DOACs have yielded conflicting results.[6–9] This might, at least partly, be due to the inability of these studies to account for dosage adjustments being performed for warfarin according to patient's INR values. For example, while patients are usually put on a standard dose when initiating warfarin treatment, the final maintenance dose can vary by as much as 40-fold.[10] This can easily lead to false estimations of non-adherence if dose adjustments between drug prescriptions are not taken into account. In the current study, all dose adjustments during warfarin treatment were taken into account, greatly increasing the accuracy of the data. Similarly, the study accounted for patients on DOACs switching from high-dose treatment to reduced doses or, less commonly, vice versa.

Non-adherence in the current study was found to be 10.5%–16.7%. This is comparable to previous studies from Scandinavia that have reported non-adherence ranging from 4.3% to 23.2%,[11 26] but considerably lower than the reported non-adherence for OACs in American studies which has ranged from 24.6% to 61.5%.[7 9 22 27–30] This difference may be due to the different study settings. Most studies from the USA have gathered data on drug prescriptions from either Veteran Health Administration pharmacies[27] or insurance claims[9 22 28–30] which may be more prone to missing prescriptions compared with the centralised nationwide prescription database used in the current study. Additionally, the observed difference may, at least partly, be explained by increased social disparity in the American population, as patients with low socioeconomic status may not afford to fill their drug prescriptions on time.

Apart from the type of OAC received, female gender, hypertension, history of cerebrovascular accident and concomitant statin use were all associated with lower odds of non-adherence. This suggests that patients with higher comorbidity burden are at reduced risk of non-adherence, which is reassuring as those patients are likely at higher risk of complications following inadequate drug consumption.

In the current study, thromboembolism and major bleeding rates were not significantly different between adherent and non-adherent patients after accounting for baseline characteristics. In comparison, a previous study demonstrated that among patients with a CHA_2DS_2-VASc score of 2 or higher, poor adherence was associated with higher rates of the composite outcome of ischaemic stroke, systemic embolism and all-cause mortality.[9] Similarly, these patients had lower rates of major bleeding compared with adherent patients. Another study demonstrated that poor adherence to dabigatran was associated with higher likelihood of all-cause mortality and stroke, but not myocardial infarction or major bleeding.[27] The reason for the differences between previous studies and the current one is likely due to the fact that our study was based on an 'on treatment' analysis, where all thromboembolic and major bleeding events were manually verified and events excluded if the patients had not been receiving OACs in the preceding 2 days. Previous studies have not manually verified outcome events and are therefore more representative of an 'indication-to-treat' analysis.[9 27]

The current study has several strengths. It is population-based using previously verified databases, such as the Icelandic Medicine Registry, which includes data on all outpatient drug prescriptions in the country. The study also has minimal missing data. Additionally, to our best knowledge, it is the first study to account for all dose adjustments for warfarin and DOACs during the study period when estimating non-adherence.

The study also has several limitations. First, as data on dose adjustments for warfarin were only available from Landspitali (the only university hospital in the capital area), the primary analysis was restricted to patients living in the capital area. This is important as treatment adherence in rural areas may differ from the catchment area of university hospitals. However, a sensitivity analysis of patients receiving DOACs and living in all regions of Iceland demonstrated no difference in non-adherence between patients who lived in the capital area and those who did not. Second, although a robust propensity score-weighting model was used to account for indication bias, data were missing on socioeconomic factors such as smoking, alcohol consumption, education level and household income. These variables may be associated with medication non-adherence. In fact, lower household income and decreased socioeconomic status have both been associated with lower self-reported overall medication adherence.[31] Importantly, patients with low socioeconomic status may also be more likely to receive warfarin. However, even though the cost of warfarin is lower than for DOACs in Iceland, DOACs are reimbursed, which likely substantially reduces the magnitude of this bias compared with many other populations. Third, adherence was calculated based on the assumption that all filled OAC prescriptions were consumed. How closely this resembles the true medication adherence of patients is unknown. Fourth, our study did not account for hospital admissions. In Iceland, patients are provided medications during their hospital stay, a lengthy stay may therefore lead to inaccurate calculation of non-adherence. However, the current study did censor the follow-up period to the first major bleeding or thromboembolic event, which likely attenuates this risk. Fifth, analysis of the data is complicated by the fact that while warfarin and DOACs were both considered first-line treatment at the start of the study period, during the 2016 update of the European Society of Cardiology (ESC) guidelines, DOACs were recommended over warfarin for patients with atrial fibrillation.[32] Meanwhile, warfarin and DOACs were both recommended as first-line treatment for pulmonary embolism by the ESC guidelines throughout the study period.[4 33] Therefore, proportionally higher proportion of patients were started on warfarin during the first half of the study period and patients receiving warfarin were

more often being treated for VTE than patients receiving DOACs. Having said that, the IPW model accounted for treatment indication, and a subanalysis including only patients with atrial fibrillation demonstrated similar results as the primary analysis. Therefore, the results are unlikely to be explained by in-group differences in treatment indication. Sixth, the length of follow-up varied from 1.3 years for patients receiving warfarin to 2.1 years for patients receiving dabigatran. This is important as non-adherence may be affected by treatment length. In fact, we found that for patients with follow-up less than 18 months, non-adherence ranged from 15.2% to 18.9%, compared with 7.1%–8.1% for patients with more than 18 months of follow-up. However, a sensitivity analysis limited to the first 18 months of follow-up yielded similar results as the primary analysis. Additionally, length of follow-up was accounted for in the logistic regression when comparing non-adherence between groups. Therefore, the results are unlikely to be explained by differences in length of follow-up. Finally, the current study did not include data on time in therapeutic range (TTR) for warfarin patients. This is important as TTR is routinely used to assess the quality of warfarin management. However, previous studies from Iceland using the same population have demonstrated TTR of 77%–79%.[34 35]

In conclusion, after accounting for baseline patient characteristics, dabigatran was associated with higher odds of non-adherence compared with apixaban, rivaroxaban and warfarin. The odds of non-adherence were similar for patients receiving warfarin, apixaban and rivaroxaban. Apart from the type of OAC received, female sex, hypertension, history of cerebrovascular accident and concomitant statin use were all associated with lower odds of non-adherence.

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Contributors ABI, ESB, JPH, SHL and PTO designed the study. ABI and ESB were involved in obtaining funding for the study. ABI, ASA, ER, DAP, IER and BRG performed the data acquisition. ABI performed the statistical analysis and visualised the data with help from JPH and SHL. ABI wrote the first draft of the manuscript. All other coauthors critically reviewed the manuscript and approved the final manuscript before submission. ABI and ESB act as co-guarantors for the study.

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Competing interests PTO and BRG together with the Landspitali University Hospital and the University of Iceland hold a patent for the Fiix-prothrombin measurement. All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Icelandic Bioethics Committee (VSN-18-111-V1). The need for informed consent was waived by the Icelandic Bioethics Committee as all data was anonymised and no active patient participation was needed.

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Data availability statement Data are available upon reasonable request. Technical appendix and statistical code are available from ABI (abingason@gmail.com) upon request. Study dataset is available with license from the National Bioethics Committee (vsn@vsn.is).

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Supplementary Table 1: ICD-10 codes used

	ICD-10 codes
Major bleeding outcomes	
Gastrointestinal bleeding (specific search)	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2, I85.0, I98.3
Gastrointestinal bleeding (sensitive search)	C15, C15.3, C15.4, C15.5, C15.8, C15.9, C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, C21, C21.0, C21.1, C21.2, C21.8, D37.1, D37.2, D37.3, D37.4, D37.5, I85, I85.0, I85.1, I98.3, K29, K29.2, K29.3, K29.4, K29.5, K29.6, K29.7, K29.8, K29.9, K50, K50.0, K50.1, K50.8, K50.9, K51, K51.0, K51.2, K51.3, K51.4, K51.5, K51.8, K51.9, K55.0, K55.1, K55.8 K55.9, K57.1, K57.3, K57.5, K57.9, K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2
Intracranial hemorrhage	I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9, S06.3, S06.4, S06.5, S06.6
Other bleeding	D50.0, D62, H11.3, H35.6, H43.1, J94.2, M25.0, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N95.0, R04, R04.0, R04.1, R04.2, R04.8, R04.9, R31, R58
Thromboembolic outcomes	
Ischemic stroke	I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6,I63.8, I63.9, I64
Transient ischemic attack	G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9
Myocardial infarction	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8
Deep venous thrombosis	I63.6, I67.6, I80.2, I80.3, I80.8, I80.9, I81, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9

Pulmonary embolism	I26, I26.0, I26.9
Arterial thromboembolism	I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9
Other thrombosis (sensitive search)	G08, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, G95.1, H34.9, I65, I65.0, I65.1, I65.2, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.8, I66.9, I67, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.7, I67.8, I67.9, I68.8, I76, I79.0, I79.1, I82.0
Treatment indication	
Atrial fibrillation	I48, I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Venous thromboembolism	I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Ischemic stroke	G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, I69, I69.3, I69.8, 169.9
Mechanical heart valve	Z95.2, Z95.3, Z95.4
Comorbidities	
Prior history of gastrointestinal bleeding	K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2, I85.0, I98.3
Venous thromboembolism	I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Ischemic heart disease	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8
Heart failure	I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9
Peripheral vascular disease	I70, I70.0, I70.1, I70.2, I70.8, I70.9, I71, I71.0, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I72, I72.0, I72.1, I72.2, I72.3, I72.4, I72.8, I72.9,

	I73.0, I73.1, I73.8, I73.9, I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I77, I77.0, I77.1, I77.2, I77.3, I77.4, I77.5, I77.6, I77.8, I77.9
Cerebral accident	I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6,I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8
Hemiplegia	G81, G81.0, G81.1, G81.9, G82, G82.0, G82.1, G82.2, G82.3, G82.4, G82.5
Dementia	F00, F00.0, F00.1, F00.2, F00.39, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05, F05.0, F05.1, F05.8, F05.9, G30, G30.0, G30.1, G30.8, G30.9
Chronic lung disease	J40, J41, J41.0, J41.1, J41.8, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9, J45, J45.0, J45.1, J45.8, J45.9, J46, J47, J60, J61, J62, J62.0, J62.8, J63, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.8, J64, J65, J66, J66.0, J66.1, J66.2, J66.8, J67, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	D86, D86.0, D86.1, D86.2, D86.3, D86.8, D86.9, M05, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9, M08, M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9, M09, M09.0, M09.1, M09.2, M09.8, M30, M30.0, M30.1, M30.2, M30.3, M30.8, M31, M31.0, M31.1, M31.2, M31.3, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M32, M32.0, M32.1, M32.2, M32.8, M32.9, M33, M33.0, M33.1, M33.8, M33.9, M34, M34.0, M34.1, M34.2, M34.8, M34.9, M35, M35.0, M35.1, M35.2, M35.3, M35.4, M35.5, M35.6, M35.7, M35.8, M35.9, M36, M36.0, M36.1, M36.2, M36.3, M36.4, M36.8
Peptic ulcer disease	K22.1, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9
Mild liver disease	B18, B18.0, B18.1, B18.2, B18.8, B18.9, K70.0, K70.1, K70.2, 70.3, K70.9, K71, K71.0, K71.1, K71.2, K71.3, K71.4, K71.5, K71.6, K71.7, K71.8, K71.9, K73, K73.0, K73.1, K73.2, K73.8, K73.9, K74, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K76.1, K76.2, K76.3, K76.4, K76.8, K76.9

Moderate or severe liver disease	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K72.0, K72.1, K72.9, K76.6, I85, I85.0, I85.9, I86.4, I98.2
Moderate or severe renal disease	I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, N00, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N1, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N03, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N07, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N11, N11.0, N11.1, N11.8, N11.9, N14, N14.0, N14.1, N14.2, N14.3, N14.4, N17, N17.0, N17.1, N17.2, N17.8, N17.9, N18, N18.0, N18.8, N18.9, N19, Q61, Q61.0, Q61.1, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q61.9
Diabetes mellitus without signs of end-organ damage	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes mellitus with end-organ damage	E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8
Tumor	C00-C75, C81-C85, C88, C90-C96
Metastasis	C76-C80
HIV/AIDS	B20, B20.0, B20.1, B20.2, B20.3, B20.4, B20.5, B20.6, B20.7, B20.8, B20.9, B21, B21.0, B21.1, B21.2, B21.3, B21.7, B21.8, B21.9, B22, B22.0, B22.1, B22.2, B22.7, B23, B23.0, B23.1, B23.2, B23.8, B24
Hypertension	I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9
Bleeding or coagulation disorders	D65, D66, D67, D68.0, D68.1, D68.2, D68.3, D68.4, D68.5, D68.6, D68.8, D68.9, D69.1, D69.3, D69.4, D69.5, D69.6
End-stage renal disease	N18.5, N18.6
Mitral stenosis	I05.0, I34.2

Supplementary Table 2: ATC codes for concomitant drug use.

Drug class	ATC codes
Antihistamines	A02BA
Antiplatelets	B01AC
Corticosteroids	H02AB
NSAIDs	M01A
PPIs	A02BC
SSRIs	N06AB
Statins	C10AA
Antihypertensive medications	
Alpha adrenergic blockers	C02A, C02B, C02C
Beta blockers	C07A, C07B
Calcium channel blockers	C08, C09BB, C09DB, C07FB
Medications affecting the RAAS	C09
Thiazides	C03A, C09BA, C09DA, C07B, C07D, C08G
Other diuretics	C02L, C03B, C03D, C03EA, C03X, C07C, C07D
Vasodilators	C02D, C04, C05, C07E

NSAIDs = Nonsteroidal anti-inflammatory drugs, PPIs = Proton pump inhibitors, RAAS = Renin-angiotensin-aldosterone system, SSRIs = Selective serotonin receptor inhibitors.

Supplementary Table 3: Baseline characteristics of sensitivity analysis of patients with atrial fibrillation

Variables	Apixaban n=1104	Dabigatran n=223	Rivaroxaban n=1307	Warfarin n=229	SMD Before IPW	SMD After IPW
Age	74.3 (11.8)	71.8 (11.8)	70.9 (11.1)	75.6 (10.1)	0.253	0.056
Sex (male)	589 (53.4)	116 (52.0)	813 (62.2)	132 (57.6)	0.118	0.145
CHA_2DS_2-VASC score	2.9 (1.6)	2.7 (1.5)	2.5 (1.5)	3.3 (1.7)	0.278	0.064
Charlson comorbidity index	1.0 (1.4)	0.7 (1.2)	0.7 (1.2)	1.4 (1.7)	0.291	0.092
Ischemic heart disease	88 (8.0)	12 (5.4)	96 (7.3)	27 (11.8)	0.120	0.069
Heart failure	113 (10.2)	15 (6.7)	99 (7.6)	39 (17.0)	0.178	0.090
Peripheral vascular disease	54 (4.9)	8 (3.6)	52 (4.0)	19 (8.3)	0.108	0.049
Cerebrovascular disease	150 (13.6)	21 (9.4)	86 (6.6)	31 (13.5)	0.139	0.044
Dementia	34 (3.1)	4 (1.8)	16 (1.2)	4 (1.7)	0.065	0.106
Chronic lung disease	74 (6.7)	12 (5.4)	60 (4.6)	21 (9.2)	0.100	0.046
Connective tissue disease	29 (2.6)	4 (1.8)	31 (2.4)	6 (2.6)	0.031	0.040
Peptic ulcer disease	32 (2.9)	6 (2.7)	19 (1.5)	13 (5.7)	0.119	0.049
Diabetes mellitus	58 (5.3)	6 (2.7)	55 (4.2)	14 (6.1)	0.092	0.093
Diabetes mellitus with end-organ damage	33 (3.0)	5 (2.2)	37 (2.8)	13 (5.7)	0.091	0.028
Hemiplegia	11 (1.0)	0 (0.0)	6 (0.5)	3 (1.3)	0.097	0.106

Moderate/severe renal disease	42 (3.8)	7 (3.1)	38 (2.9)	30 (13.1)	0.199	0.032
Any tumor	141 (12.8)	25 (11.2)	120 (9.2)	36 (15.7)	0.108	0.045
Metastatic cancer	6 (0.5)	1 (0.4)	8 (0.6)	0 (0.0)	0.059	0.090
Hypertension	776 (70.3)	166 (74.4)	881 (67.4)	165 (72.1)	0.084	0.126
Bleeding or coagulation disorder	10 (0.9)	1 (0.4)	8 (0.6)	2 (0.9)	0.033	0.064
Liver disease	12 (1.1)	0 (0.0)	11 (0.8)	2 (0.9)	0.077	0.169
History of gastro-intestinal bleeding	63 (5.7)	10 (4.5)	47 (3.6)	21 (9.2)	0.125	0.022
History of VTE	20 (1.8)	1 (0.4)	38 (2.9)	30 (13.1)	0.289	0.126
Concomitant drug use						
Antihistamine	5 (0.5)	1 (0.4)	6 (0.5)	3 (1.3)	0.046	0.025
Antiplatelet	302 (27.4)	58 (26.0)	293 (22.4)	88 (38.4)	0.181	0.041
NSAID	208 (18.8)	48 (21.5)	287 (22.0)	28 (12.2)	0.142	0.135
PPI	458 (41.5)	81 (36.3)	453 (34.7)	109 (47.6)	0.150	0.055
SSRI	202 (18.3)	23 (10.3)	170 (13.0)	47 (20.5)	0.167	0.136
Statin	528 (47.8)	105 (47.1)	621 (47.5)	102 (44.5)	0.034	0.101
Steroid	215 (19.5)	39 (17.5)	230 (17.6)	47 (20.5)	0.047	0.109

AF = atrial fibrillation, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

Supplementary Table 4: Baseline characteristics of sensitivity analysis of patients receiving direct oral anticoagulants and living in all regions of Iceland

Variables	Apixaban	Dabigatran	Rivaroxaban	SMD	
	n=1805	n=386	n=2608	Before IPW	After IPW
Age	73.4 (12.6)	71.3 (12.9)	69.4 (12.6)	0.210	0.035
Sex (male)	956 (53.0)	212 (54.9)	1534 (58.8)	0.079	0.053
CHA_2DS_2-VASC score	2.9 (1.6)	2.7 (1.4)	2.4 (1.5)	0.247	0.048
Charlson comorbidity index	0.9 (1.4)	0.7 (1.1)	0.6 (1.1)	0.167	0.025
Ischemic heart disease	130 (7.2)	33 (8.5)	167 (6.4)	0.054	0.023
Heart failure	152 (8.4)	33 (8.5)	149 (5.7)	0.074	0.012
Peripheral vascular disease	84 (4.7)	13 (3.4)	88 (3.4)	0.044	0.028
Cerebrovascular disease	249 (13.8)	32 (8.3)	144 (5.5)	0.190	0.038
Dementia	47 (2.6)	5 (1.3)	30 (1.2)	0.072	0.058
Chronic lung disease	102 (5.7)	19 (4.9)	98 (3.8)	0.060	0.019
Connective tissue disease	43 (2.4)	6 (1.6)	48 (1.8)	0.040	0.036
Peptic ulcer disease	40 (2.2)	10 (2.6)	31 (1.2)	0.069	0.020
Diabetes mellitus	91 (5.0)	18 (4.7)	82 (3.1)	0.064	0.018
Diabetes mellitus with end-organ damage	56 (3.1)	9 (2.3)	53 (2.0)	0.045	0.027
Hemiplegia	20 (1.1)	3 (0.8)	11 (0.4)	0.053	0.089

Moderate/severe renal disease	61 (3.4)	8 (2.1)	58 (2.2)	0.054	0.037
Any tumor	214 (11.9)	39 (10.1)	230 (8.8)	0.067	0.030
Metastatic cancer	9 (0.5)	1 (0.3)	21 (0.8)	0.051	0.062
Hypertension	1241 (68.8)	272 (70.5)	1595 (61.2)	0.131	0.049
Bleeding or coagulation disorder	11 (0.6)	1 (0.3)	12 (0.5)	0.036	0.041
Liver disease	14 (0.8)	1 (0.3)	14 (0.5)	0.049	0.014
History of gastro-intestinal bleeding	81 (4.5)	19 (4.9)	74 (2.8)	0.072	0.029
History of VTE	201 (11.1)	29 (7.5)	507 (19.4)	0.237	0.151
Concomitant drug use					
Antihistamine	10 (0.6)	3 (0.8)	15 (0.6)	0.018	0.065
Antiplatelet	499 (27.6)	108 (28.0)	531 (20.4)	0.119	0.080
NSAID	392 (21.7)	81 (21.0)	669 (25.7)	0.074	0.063
PPI	754 (41.8)	140 (36.3)	978 (37.5)	0.075	0.059
SSRI	352 (19.5)	47 (12.2)	375 (14.4)	0.134	0.065
Statin	850 (47.1)	180 (46.6)	1087 (41.7)	0.073	0.021
Steroid	373 (20.7)	75 (19.4)	518 (19.9)	0.021	0.020
Treatment indication				0.246	0.126
AF	1561 (86.5)	351 (90.9)	2118 (81.2)		
Ischemic stroke	68 (3.8)	8 (2.1)	35 (1.3)		
VTE	176 (9.8)	27 (7.0)	455 (17.4)		
Area of residence				0.325	0.111
Capital Area	1266 (70.1)	247 (64.0)	1566 (60.0)		

Eastern	64 (3.5)	10 (2.6)	74 (2.8)	
Northern	119 (6.6)	41 (10.6)	419 (16.1)	
Southern	220 (12.2)	77 (19.9)	352 (13.5)	
Western	97 (5.4)	10 (2.6)	150 (5.8)	
Westfjords	39 (2.2)	1 (0.3)	47 (1.8)	

AF = atrial fibrillation, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

Supplementary Figure 1: Violin plot demonstrating the distribution of the proportion of days covered for the study population stratified by oral anticoagulant received.

Supplementary Figure 2: Bar graph comparing the proportion of patients with nonadherence when stratified by length of follow-up.

Supplementary Figure 3: Bar graphs comparing the proportion of patients with nonadherence when follow-up was limited to 18 months A) before and B) after inverse probability weighting. Nonadherence was defined as proportion of days covered below 80%.

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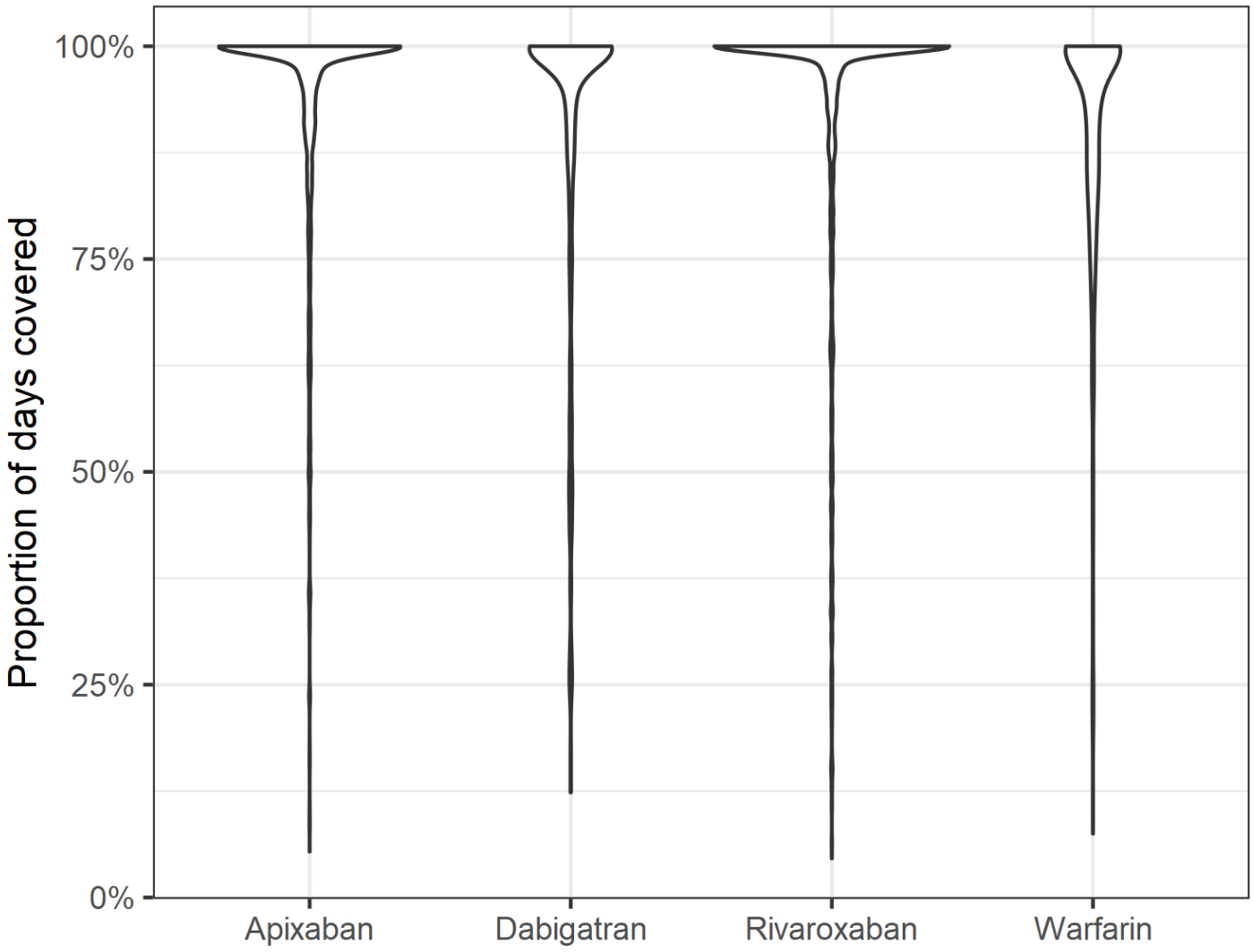
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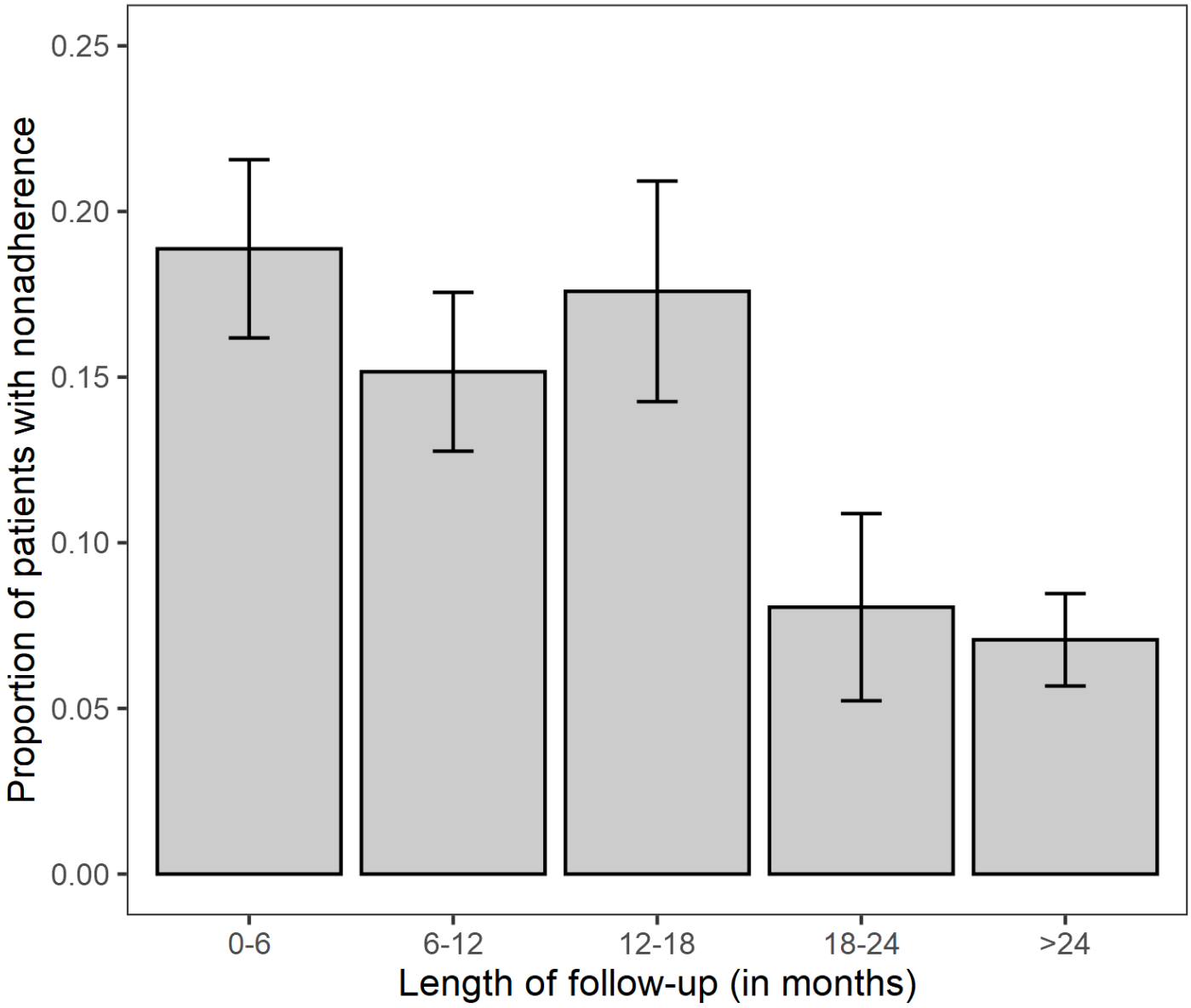
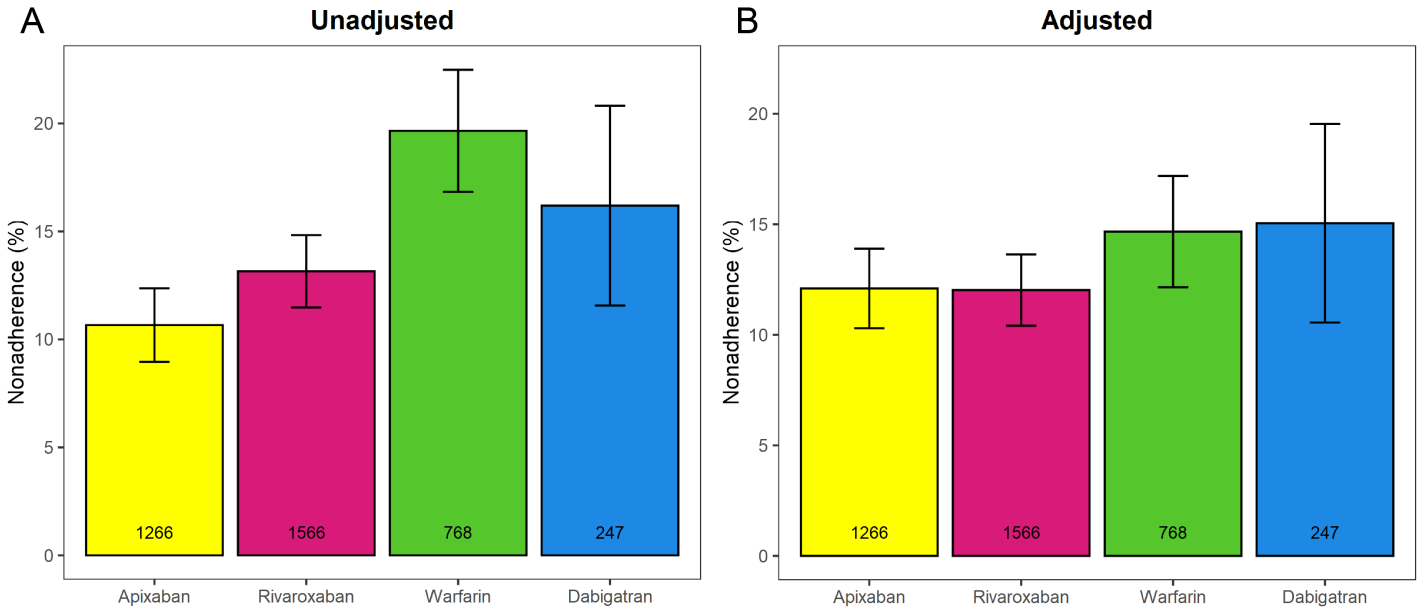
50%
25%
0%
Apixaban
Dabigatran
Rivaroxaban
Warfarin


0.25
0.20
0.15
0.10
0.05
0.00
Proportion of patients with nonadherence
0-6
6-12
12-18
18-24
>24
Length of follow-up (in months)


A
Unadjusted
Nonadherence (%)
0
5
10
15
20
1266
1566
768
247
Apixaban
Rivaroxaban
Warfarin
Dabigatran
B
Adjusted
Nonadherence (%)
0
5
10
15
20
1266
1566
768
247
Apixaban
Rivaroxaban
Warfarin
Dabigatran