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Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011–2013

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Aims Non-vitamin K antagonist oral anticoagulation (NOAC) agents have been approved for stroke prophylaxis in atrial fibrillation (AF). We investigated 'real-world' information on how these drugs are being adopted.

Methods and results Using Danish nationwide administrative registers, we identified all oral anticoagulation-naïve AF patients initiating oral anticoagulation from 22 August 2011 through 31 October 2013. Using logistic regression analysis, baseline characteristics and temporal utilization trends were compared between initiators of warfarin vs. one of the N OACs: dabigatran, rivaroxaban, or apixaban. We identified 18 611 oral anticoagulation-naïve AF patients of which 9902 (53%) initiated warfarin treatment, 7128 (38%) dabigatran, 1303 (7%) rivaroxaban, and 278 (1%) apixaban. Overall, 40% of newly initiated patients were started on dabigatran within the first 4 months of when the drug came on market. By October, 2013, 40% were being started on warfarin and dabigatran, respectively, and another 20% were started on either rivaroxaban or apixaban. Rivaroxaban and apixaban users generally had a higher predicted risk of stroke and bleeding compared with warfarin and dabigatran users. Older age, female gender, and prior stroke were some of the factors associated with NOAC use vs. warfarin, whereas chronic kidney disease, myocardial infarction, and heart failure showed the opposite association.

Conclusion Among oral anticoagulation-naïve AF patients initiated on oral anticoagulation in Denmark, warfarin initiation has declined since the introduction of dabigatran in August 2011. Dabigatran is the most frequently used alternative option to warfarin; however, use of rivaroxaban and apixaban is increasing. Patients initiated with rivaroxaban or apixaban in general have a higher predicted stroke and bleeding risks compared with warfarin or dabigatran initiators.

Keywords Atrial fibrillation • Oral anticoagulation • Warfarin • Dabigatran • Rivaroxaban • Apixaban

Introduction

Warfarin has long been the treatment of choice for stroke prophylaxis in atrial fibrillation (AF)—the most common cardiac dysrhythmia with a lifetime prevalence of ~25% for subjects >40 years.[1] While warfarin is effective for preventing thromboembolic complications, it is associated with several treatment-related drawbacks (e.g. continuous monitoring and interactions with other drugs and food) which has encouraged the development of non-vitamin K antagonist oral anticoagulation (NOAC) agents.[2] Albeit the increased risk of stroke and systemic thromboembolism associated with AF, oral anticoagulation (OAC) therapy has shown efficacy for preventing these disabling outcomes,[3] yet at the expense of increased risk of bleeding.[4–6] Dabigatran, apixaban, and rivaroxaban are all examples

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What's new?

- Non-vitamin K antagonist oral anticoagulants are rapidly being adopted for non-valvular atrial fibrillation.
- Patients prescribed apixaban or rivaroxaban generally have more co-morbidities than patients prescribed dabigatran or warfarin.
- Dabigatran is dosed according to guidelines.
- Older age, female gender, and prior stroke are associated with new oral anticoagulant usage.
- Chronic kidney disease, myocardial infarction, and heart failure are associated with warfarin usage.

of NOACs and have all shown at least non-inferiority to warfarin in terms of stroke and systemic thromboembolism prevention.[7–10] Furthermore, some studies have shown the NOACs to be superior and with a more beneficial safety profile.[7,8,10] While the NOACs have proven efficacious in clinical trials, there are very limited real world data available on how NOACs are currently being used and to what degree the NOACs replace warfarin. Current treatment guidelines recommend the initiation of one of the NOACs instead of warfarin in non-valvular AF,[11] yet little is known whether this clinical practice is followed among medical providers.

In order to address these gaps in knowledge, we used Danish nationwide registries to examine changes and temporal trends in OAC use among OAC-naïve AF patients after approval of NOACs on 22 August 2011. The following questions were addressed: (i) how many patients are initiated on one of the NOACs compared with warfarin; (ii) is there a temporal prescription pattern of the NOACs compared with warfarin throughout the study period; and (iii) what characterizes those AF patients who initiate the NOACs compared with those who initiate warfarin.

Methods

Data sources

Using a unique and personal identifier, we linked Danish nationwide administrative registries on an individual level. Information regarding prescription fills, hospitalizations, ambulatory visits, and vital status was collected. The Danish National Patient Registry holds information regarding contacts to the hospital system and records one primary and if appropriate one or more secondary diagnoses codes according to the International Classification of Diseases (ICD) version 8 (before 1994) and 10 (from 1994). Prescription filling data were drawn from the Danish Registry of Medicinal Product Statistics (the National Prescription Register), which contains information on all prescriptions dispensed in Danish pharmacies since 1995 (coded according to the Anatomical Therapeutic Chemical (ATC) classification system): date of prescription fill, strength, and number of tablets dispensed. All pharmacies are required by Danish legislation to provide information that ensures complete and accurate registration.[12]

Study patients and time index

In this study, we included OAC-naïve AF patients who were 30–100 years and initiated with OAC from 22 August 2011 to October 2013. 'OAC-naïve' was defined from no previous prescription claim for an OAC (since 1995). The diagnosis of AF have been validated in the Danish Patient Registry and found to have a positive predictive value of 99% among hospitalized patients.[13] Patients were excluded if they had valvular AF, had undergone hip or knee arthroplastic surgery within 5 weeks, or had a history of pulmonary embolism or deep vein thrombosis within six months.

OAC treatment initiation patterns were assessed through prescription fillings and comprised the following groups: vitamin K antagonists (nearly 100% being warfarin), dabigatran, rivaroxaban, or apixaban. The date of treatment initiation was used as the index date (baseline), and all patients had been diagnosed with AF within this date.

In the study period, 4488 patients were initiated on OAC treatment but were first registered with a diagnosis of AF subsequently. As the

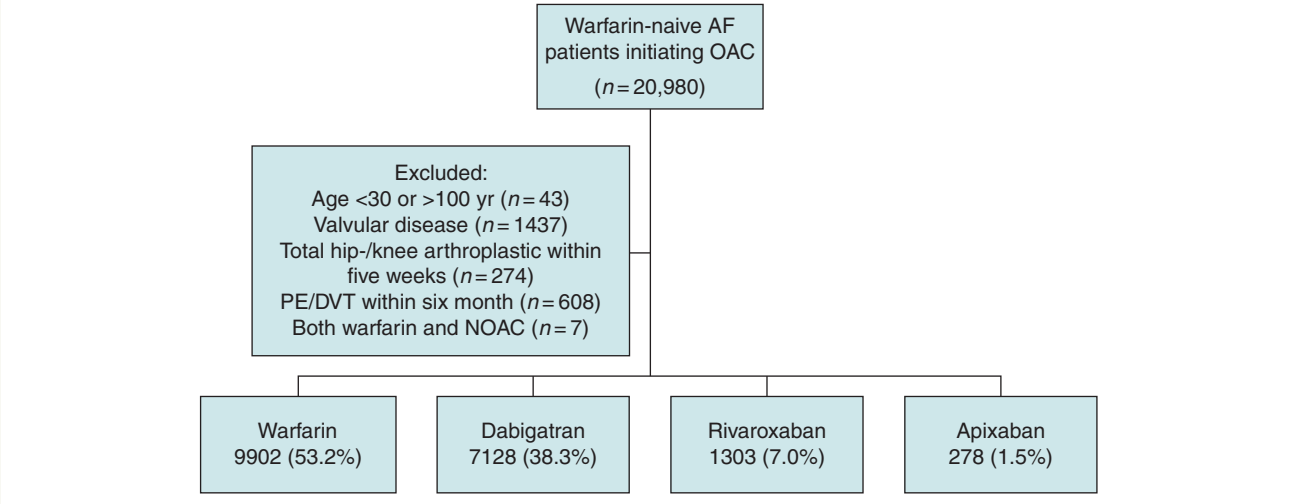

Figure 1 Patient selection process. AF, atrial fibrillation; OAC, oral anticoagulation; PE/DVT, pulmonary embolism/deep vein thrombosis.

inclusion criterion was OAC treatment initiation in patients diagnosed with AF, these 4488 patients were not included in the study.

Study covariates

Concomitant pharmacotherapy was assessed by prescription fillings 180 days before the index date. Comorbidities were obtained through previous in-hospital ICD-10 diagnosis codes, i.e. since 1994. The ICD-10 codes applied to this study for defining comorbidities are listed in Supplementary material online, *Table S1* and have been used in previous studies.[14,15] $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke/transient ischaemic attack/systemic thromboembolism), CHA_2DS_2–VASc [adding vascular disease, age 65–75, and sex category (female)], and HAS-BLED [hypertension, abnormal renal/liver function, stroke history, bleeding history, labile INR (international normalized ratio), elderly (>65 years), Drug consumption/alcohol abuse] scores were calculated. Identification and validation of the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores in similar cohorts have been described in detail previously and, as in the previous studies, we had no information on labile INR.[4,16,17]

Statistical analysis

Baseline characteristics were compared using the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables, we tested for homogeneity among all four treatment groups. Temporal trends in prescription patterns were shown graphically and we performed the Cochran–Armitage test to examine for a trend over time. A multivariate logistics regression model was used to examine factors associated with initiation of an NOAC compared with warfarin. Using backward

Table 1 Baseline characteristics according to OAC treatment choice

Variable	Overall (*n* = 18 611)	Warfarin (*n* = 9902)	Dabigatran (*n* = 7128)	Rivaroxaban (*n* = 1303)	Apixaban (*n* = 278)	*P*-value
Age, mean (SD)	72.0 (11.0)	71.5 (11.1)	71.9 (10.8)	74.7 (11.1)	75.5 (10.1)	<0.001
Female (%)	8422 (45.3)	4285 (43.3)	3316 (46.5)	679 (52.1)	142 (51.1)	<0.001
$CHADS_2$ score, mean (SD)	1.5 (1.2)	1.5 (1.2)	1.4 (1.2)	1.7 (1.3)	1.5 (1.2)	<0.001
CHA_2DS_2-VASc score, mean (SD)	2.8 (1.6)	2.8 (1.6)	2.7 (1.6)	3.1 (1.6)	3.0 (1.5)	<0.001
HAS-BLED score, mean (SD)	2.0 (1.1)	2.0 (1.1)	2.0 (1.1)	2.2 (1.1)	2.2 (1.1)	<0.001
Co-morbidities (%)						
Stroke/thromboembolism	2935 (15.8)	1394 (14.1)	1202 (16.9)	287 (22.0)	52 (18.7)	<0.001
Myocardial infarction	1483 (8.0)	940 (9.5)	437 (6.1)	83 (6.4)	23 (8.3)	<0.001
Ischaemic heart disease	3602 (19.3)	2138 (21.6)	1164 (16.3)	242 (18.6)	58 (20.9)	<0.001
Peripheral artery disease	362 (2.0)	224 (2.3)	106 (1.5)	25 (1.9)	7 (2.5)	0.004
Heart failure	2634 (14.2)	1591 (16.1)	848 (11.9)	167 (12.8)	28 (10.1)	<0.001
Chronic kidney disease	601 (3.2)	472 (4.8)	78 (1.1)	41 (3.2)	10 (3.6)	<0.001
Liver failure	177 (1.0)	115 (1.2)	45 (0.6)	15 (1.2)	2 (0.7)	0.004
Bleeding	967 (5.2)	503 (5.1)	366 (5.1)	72 (5.5)	26 (9.4)	0.016
Alcohol abuse	619 (3.3)	311 (3.1)	247 (3.5)	54 (4.1)	7 (2.5)	0.19
Hypertension	8362 (44.9)	4549 (45.9)	3103 (43.5)	593 (45.5)	117 (42.1)	0.013
Diabetes mellitus	2277 (12.2)	1283 (13.0)	813 (11.4)	152 (11.7)	29 (10.4)	0.014
Concomitant pharmacotherapy (%)						
ADP receptor inhibitors	1565 (8.4)	823 (8.3)	585 (8.2)	126 (9.7)	31 (11.2)	0.12
Aspirin	7762 (41.7)	4296 (43.4)	2798 (39.3)	551 (42.3)	117 (42.1)	<0.001
Dipyridamole	601 (3.2)	373 (3.8)	182 (2.6)	43 (3.3)	3 (1.1)	<0.001
NSAIDs	2824 (15.2)	1532 (15.5)	1063 (14.9)	187 (14.4)	42 (15.1)	0.63
Adrenergic α-antagonists	312 (1.7)	186 (1.9)	108 (1.5)	17 (1.3)	1 (0.4)	0.06
Non-loop-diuretics	6098 (32.8)	3266 (33.0)	2297 (32.2)	446 (34.2)	89 (32.0)	0.48
Beta-blockers	7812 (42.0)	4359 (44.0)	2788 (39.1)	542 (41.6)	123 (44.2)	<0.001
Calcium channel blockers	5005 (26.9)	2759 (27.9)	1854 (26.0)	331 (25.4)	61 (21.9)	0.006
Renin–angiotensin system inhibitors	7732 (41.6)	4130 (41.7)	2944 (41.3)	541 (41.5)	117 (42.1)	0.96
Loop diuretics	3229 (17.4)	1912 (19.3)	1049 (14.7)	217 (16.7)	51 (18.4)	<0.001
Statins	6365 (34.2)	3516 (35.5)	2323 (32.6)	437 (33.5)	89 (32.0)	<0.001
Digoxin	1479 (8.0)	781 (7.9)	553 (7.8)	120 (9.2)	25 (9.0)	0.30
Amiodarone	200 (1.1)	133 (1.3)	49 (0.7)	11 (0.8)	7 (2.5)	<0.001

ADP, adenosine diphosphate; AF, atrial fibrillation; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism; CHA_2DS_2VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal- or liver function, stroke, bleeding history, labile international normalized ratio, elderly (age >65 years), drug consumption or alcohol abuse; NSAID, non-steroidal anti-inflammatory drugs.

selection, only covariates associated with a *P*-value of <0.05 were kept in the model. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using SAS software (versions 9.2 and 9.3, SAS Institute).

Results

After applying selection criteria, 18 611 AF patients were included in this study (*Figure 1* for selection process); every month 715 (interquartile range 665–755) patients were included. Baseline patient characteristics stratified according to OAC treatment patterns are shown in *Table 1* and, baseline characteristics according to the initial dose of NOAC treatment are shown in Supplementary material online, *Table S2*. The overall mean age was 72.0 [standard deviation (SD) 11.0] years and was similar for warfarin and dabigatran users (71.5 and 71.9 years, respectively). In comparison, users of rivaroxaban and apixaban were older (74.7 and 75.5 years, respectively). Users of rivaroxaban and apixaban were generally characterized by higher predicted risk of stroke and bleeding (CHA_2DS_2-VASc score and HAS-BLED score) compared with those initiated on warfarin or dabigatran. The CHA_2DS_2-VASc score was generally higher for the patients initiated with reduced NOAC dose than for patients initiated with standard dose, and for dabigatran and apixaban more females received the reduced dose.

Temporal utilization pattern

The temporal utilization pattern of anticoagulation therapy is illustrated in *Figure 2*. At the start of the study period (August 2011), warfarin was the drug of choice for patients with AF who initiated OAC. By January 2012, 59% of patients were initiated on warfarin, where after this trend levelled out and by January 2013 49% of patients were initiated on warfarin. By October 2013, this number was 40% (*P* for decreasing trend over time <0.001). The decrease in warfarin initiation was especially explained by an uptake in dabigatran in the first 4 months following August 2011 (going from 0 to ~40%). In the study period, a significant increase in the uptake of dabigatran was seen (*P* for trend <0.001); however, from November 2011 to October 2013 the proportion initiating dabigatran was slightly decreasing (*P* for trend 0.01). From the beginning of 2012, there was a modest uptake in the use of rivaroxaban (1% in March 2012 to 10% in January 2013). Similarly, from January 2013 to October 2013, we saw an equally modest uptake in apixaban use (from <1 to 9%). *Figure 3* shows temporal trends in dabigatran dose use according to the age cut-off of 80 years as indicated by the drug label.

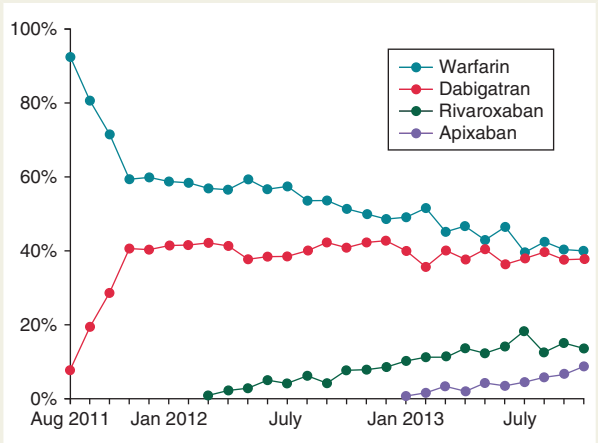

Figure 2 Temporal initiation patterns of oral anticoagulation options for AF.

Factors associated with initiation of a non-vitamin K antagonist oral anticoagulation vs. warfarin

Figure 4 displays the CHA_2DS_2VASc scores by treatment groups and *Figure 5* shows the HAS-BLED scores. *Table 2* shows the results for the adjusted associations with initiation of an NOAC vs. warfarin. Patients initiated on an NOAC were more likely to be older and have certain co-morbidities (more often stroke, bleeding, and alcohol abuse; and less often ischaemic heart disease, heart failure, chronic kidney disease, and liver failure). The factor most strongly associated with warfarin use was a history of chronic kidney disease. Compared with warfarin, those patients initiated on one of the NOACs had a comparable predicted thromboembolic risk [odds ratio (OR) per increase in CHA_2DS_2-VASc score 1.02,

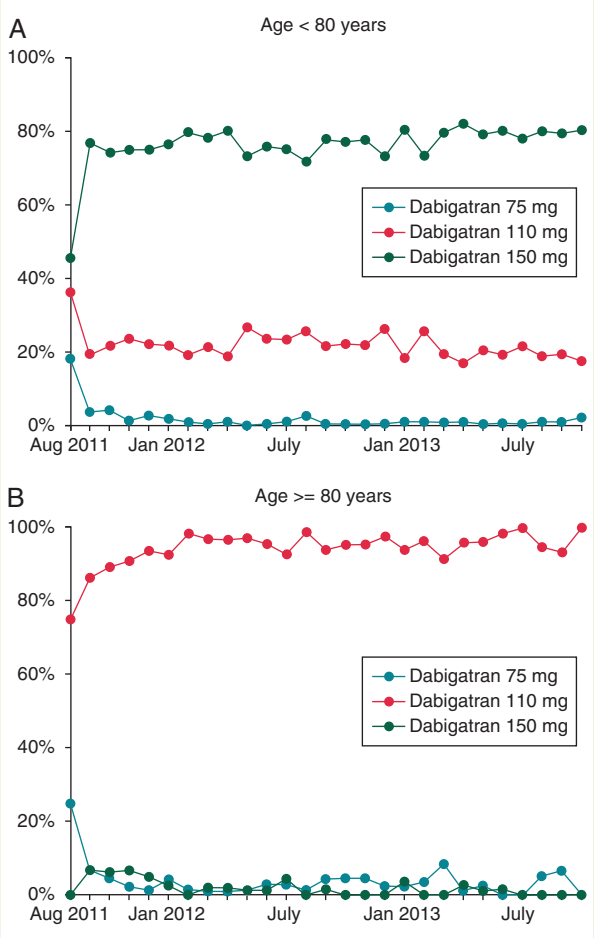

Figure 3 Temporal initiation patterns of dabigatran by age and dose.

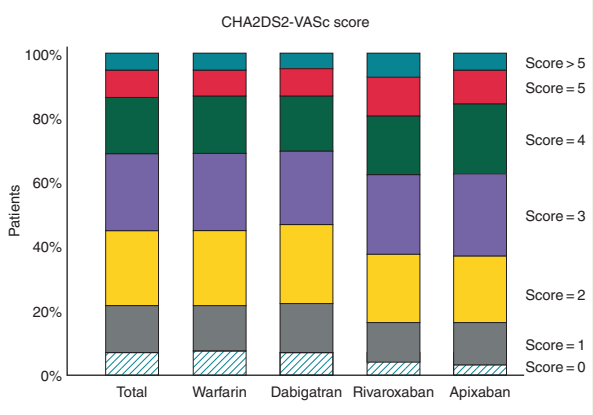

Figure 4 Distribution of CHA_2DS_2-VASc scores by groups.

Figure 5 Distribution of HAS-BLED scores by groups.

1.00–1.03] and a comparable predicted bleeding risk (OR per increase in HAS-BLED score 0.99, 0.96–1.02).

Discussion

This study examined contemporary utilization patterns of OAC therapy in patients with AF who were previously OAC-naïve. Our analysis yielded three major findings. First, warfarin initiation has decreased after the introduction of the NOACs to the market from 100% before August 2011 to ~40% in October, 2013. Secondly, this decline in warfarin initiation is explained mainly by a steep uptake in dabigatran just after the introduction of this drug to the market. The use of rivaroxaban and later apixaban has been increasing but at a slower rate than dabigatran. Thirdly, older age, female gender, and prior stroke were some of the factors associated with NOAC vs. warfarin use, whereas chronic kidney disease, myocardial infarction, and heart failure showed the opposite association. Yet, and importantly, the predicted thromboembolic risk and bleeding risk was similar between users of warfarin vs. those who were initiated on an NOAC.

Dabigatran was the first NOAC to be introduced as an alternative to warfarin in AF and our results show that this drug has been adopted quickly among AF patients who are naïve to OAC treatment. Interestingly, our results are quite different from that of a recent US registry report from the ORBIT-AF registry (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation).[18] In ORBIT-AF, adoption of dabigatran over warfarin was associated with younger age, less comorbidity, and lower risk of stroke and bleeding. In turn, the adoption of dabigatran was modest in ORBIT-AF (8% of patients). These findings are contrary to ours being that we found dabigatran initiation to be associated with similar age and a comparable risk of stroke and bleeding compared with warfarin. Moreover, our results showed a rapid uptake in dabigatran use (40% of patients initiated during the first 4 months of drug availability). These differences could potentially be explained by differences in guideline recommendations, although guidelines encourage the use of NOACs over warfarin.[3] Other European studies have shown similar numbers for the uptake of dabigatran.[3,19–21]

Contrary to the uptake of dabigatran, rivaroxaban and apixaban were adopted relatively slower among patients naïve to OAC treatment. At the end of the study period, these two drugs were initiated in about one in five of the patients vs. 40% on warfarin and 40% on dabigatran. In Denmark, dabigatran was approved for use from 22 August 2011, rivaroxaban from 6 February 2012, and apixaban from 10 December 2012. Our results showed that these newest drugs were used in patients with a higher predicted risk of stroke and bleeding. In addition, users of rivaroxaban and apixaban were significantly older than those who were started on either warfarin or dabigatran. To our knowledge, this study is the first to document the pattern of use of all of the currently available NOACs and the comparison against warfarin.

Our analysis also identified certain factors associated with NOAC initiation vs. warfarin. Older patients, females, and those with a prior stroke were more often started on one of the NOACs, whereas chronic kidney disease, myocardial infarction, and heart failure showed the opposite association. This trend is in line with what the subgroup analyses of the NOAC trials showed (interaction with history of myocardial infarction in the RE-LY study)[9] and what current guidelines recommend for the use of NOACs (dose modification as a function of kidney disease for dabigatran and caution for rivaroxaban and apixaban).[3] This is in contrast with the ORBIT-AF registry which showed that dabigatran generally was not optimally dosed according to age and kidney function.[18] Importantly, our study also showed that CHA_2DS_2-VASc and HAS-BLED scores were similar for patients put on warfarin vs. an NOAC. Hence, by predicted risk schemes, clinicians are prescribing NOACs to patients who are similar to those who are prescribed warfarin. However separately, the rivaroxaban and apixaban initiated patients were older, had more comorbidities, and higher predicted stroke and bleeding risks. For future studies, it would be important to assess the use of NOACs among those previously treated with warfarin that had fluctuating INR values and had little time in therapeutic range. For this scenario, NOACs could potentially be even more cost-effective than earlier shown.[22]

This was an observational study and had several limitations. First, identification of patients with AF was based on discharge diagnosis coding; however, these have previously been validated with very

Table 2 Factors associated with initiation of an NOAC vs. warfarin

	OR (95% CI)	Chi square	P
Male gender	0.88 (0.83–0.94)	15.9	<0.001
Age, 5-year increments	1.04 (1.03–1.06)	30.8	<0.001
Calendar years, 1-year increments	1.64 (1.57–1.71)	508.7	<0.001
History of			
Stroke/thromboembolism	1.41 (1.29–1.53)	62.0	<0.001
Myocardial infarction	0.78 (0.68–0.90)	12.0	<0.001
Ischaemic heart disease	0.88 (0.80–0.97)	6.2	0.01
Heart failure	0.81 (0.74–0.89)	19.7	<0.001
Chronic kidney disease	0.33 (0.27–0.40)	114.5	<0.001
Liver failure	0.61 (0.44–0.85)	8.8	0.003
Bleeding	1.16 (1.01–1.33)	4.3	0.04
Alcohol abuse	1.29 (1.09–1.53)	8.7	0.003
Concomitant pharmacotherapy			
Dipyridamole	0.58 (0.49–0.70)	34.7	<0.001
Beta-blockers	0.90 (0.84–0.95)	11.8	<0.001
Calcium channel blockers	0.90 (0.84–0.96)	9.3	0.002
Renin–angiotensin system inhibitors	1.09 (1.02–1.16)	7.2	0.007
Loop diuretics	0.84 (0.78–0.92)	15.2	<0.001
Amiodarone	0.70 (0.51–0.95)	5.3	0.02

The model also included the following variables, which did not reach a P–value of <0.05: diabetes mellitus, hypertension, peripheral artery disease, and concomitant use of adenosine diphosphate receptor inhibitors, aspirin, non-steroidal anti-inflammatory drugs, adrenergic α-antagonists, statins, other diuretics, and digoxin.

good results.[13] Secondly, we did not have information on some clinical variables important for stroke and bleeding such as body mass index, smoking, haemoglobin, exact alcohol consumption, and blood pressure. Thirdly, our results are based on prescription filling patterns and adherence to the drugs was assumed. Fourthly, a significant number of patients were not included due to an initiation of OAC before the diagnosis of AF was registered in the hospital records, and some AF patients are handled purely in general practice where no information on obtained diagnoses were available. This is probably due to those patients diagnosed by the general practitioner, then started on OAC, and then finally referred to the hospital system for further care (~2 months delay in diagnosis). Finally, in this study period dabigatran was initiated much more often than rivaroxaban and apixaban and therefore the NOAC results were primary driven by dabigatran initiators.

In conclusion, in a contemporary setting among patients with AF who are initiated on an OAC, warfarin initiation has declined since the introduction of dabigatran in August 2011. Dabigatran is the most frequently used alternative option to warfarin; however, use of rivaroxaban and apixaban is increasing. This study identified various factors associated with NOAC use and showed that NOACs are generally used according to guidelines. Patients initiated with rivaroxaban or apixaban in general have a higher predicted stroke and bleeding risks compared with warfarin or dabigatran initiators. Future comparative studies are needed to assess the real-life comparative effectiveness of these drugs for stroke prevention in AF.

Supplementary material

Supplementary material is available at *Europace* online.

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