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Treatment Changes among Users of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation

Maja Hellfritsch¹, Steen Elkjær Husted², Erik Lerkevang Grove^{3,4}, Lotte Rasmussen¹, Birgitte Klindt Poulsen⁵, Søren Paaske Johnsen⁶, Jesper Hallas¹ and Anton Pottegård¹

¹Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark, ²Department of Internal Medicine, Hospital Unit West, Herning, Denmark, ³Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark, ⁴Faculty of Health, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark, ⁵Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark and ⁶Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

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Abstract: Patients with atrial fibrillation discontinuing anticoagulant therapy are left unprotected against ischaemic stroke. Further, switching between oral anticoagulants may be associated with a transiently increased risk of bleeding or thromboembolism. However, there is a paucity of real-life data on pattern of switching and discontinuation of oral anticoagulants. To address this, we conducted a nationwide drug utilization study including all registered Danish atrial fibrillation patients initiating a non-VKA oral anticoagulant (NOAC) between August 2011 and February 2016. We assessed changes in anticoagulant treatment, including switching between oral anticoagulants and discontinuation of NOACs, and explored patient characteristics predicting these changes. We identified 50,632 patients with atrial fibrillation initiating NOAC therapy within the study period. The majority initiated dabigatran (49.9%) and one-third had previously used VKA. Within 1 year, 10.1% switched to VKA, 4.8% switched to another NOAC and 14.4% discontinued treatment. The frequencies of switching to VKA and discontinuation were highest among NOAC users of young age (<55 years) and with low CHA₂DS₂-VASc score (=0). However, the majority of patients (87.3%) stopping NOAC treatment had a CHA₂DS₂-VASc score ≥1. We conclude that switching from VKA to NOAC, and to a lesser extent from NOAC to VKA, is common, as is early treatment discontinuation. The majority of treatment changes are observed in patients at increased risk of stroke. More research is warranted on the risks of bleeding and thromboembolism associated with switching and discontinuation of NOACs as well as the underlying reasons why these treatment changes occur.

Non-vitamin K antagonist oral anticoagulants (NOACs) were introduced as stroke prophylaxis in patients with atrial fibrillation (AF) in 2011 [1]. Since then, the uptake of NOAC in western countries, including Denmark, has been massive [2,3]. Further, many patients are switched from a vitamin K antagonist (VKA) to a NOAC [4,5]. While switching from VKA to NOAC is generally assumed to be safe [6], switching from NOAC to VKA was associated with an increased risk of both bleeding and thromboembolism in post hoc analyses of randomized, clinical trials [7,8]. So far, only few studies have provided real-life data on the extent of anticoagulant switching from NOAC to VKA, and the rates have differed substantially [4,9–11].

The benefits of NOACs on certain safety outcomes, for example lower risk of intracerebral haemorrhage [12], are the main reason why several scientific societies recommend NOAC over VKA [1,13]. However, the expected clinical benefit of NOAC may be offset by subsequent switches to VKA or discontinuation. The aim of this study was to establish whether switching and discontinuation of oral anticoagulants occurs at an extent that should lead to such concerns. We therefore conducted a nationwide, register-based drug

utilization study and explored switching and discontinuation during NOAC therapy including frequency, patient characteristics and predictors among AF patients initiating NOAC therapy in Denmark during 2011–2016.

Materials and Methods

Using nationwide registries, we identified patients with AF initiating NOAC therapy and assessed their baseline characteristics, including prior VKA use. We tabulated treatment changes using descriptive statistics and analysed potential predictors for discontinuation or switching between oral anticoagulants by use of multivariable modelling.

Data sources. We obtained data from three registries: the Danish National Prescription Registry [14] ('Prescription Registry'), the Danish National Patient Registry [15] ('Patient Registry') and the Civil Registration System [16]. The registries are described in detail in Appendix S1. Definitions of drugs, diseases, operations, procedures and risk scores used in this study are detailed in Appendix S2.

Virtually, all medical care in Denmark is furnished by the national health authorities, allowing true population-based studies covering all inhabitants of Denmark. Data were linked using the personal identification number ('CPR number'), a unique identifier assigned to all Danish citizens at birth or upon immigration [16].

Study drugs. We included the three NOACs with market authorization in Denmark during the study period: dabigatran etexilate (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®).

Author for correspondence: Maja Hellfritsch, Clinical Pharmacology and Pharmacy, University of Southern Denmark, J.B. Winsløvs Vej 19, 2., DK-5000 Odense C, Denmark (e-mail mmhellfritsch@health.sdu.dk).

Dabigatran was marketed for AF in Denmark on 1 August 2011, rivaroxaban on 1 February 2012 and apixaban on 1 December 2012. 'Low-dose' treatment was defined as doses ≤ 110 mg twice daily for dabigatran, ≤ 15 mg once daily for rivaroxaban and ≤ 2.5 mg twice daily for apixaban. VKA consisted of warfarin and phenprocoumon, which are the only VKAs marketed in Denmark. During the study period, warfarin constituted 97% of the total sale of VKAs [17].

Study population. We identified all Danish individuals filling a prescription for a NOAC from August 2011 through February 2016. The index date was defined as the date of the first filling of a NOAC for a given patient. As we focused on NOAC use in AF patients, we required that patients were registered with a diagnosis of AF in the Patient Registry prior to or up to 60 days after the first NOAC prescription. The 60-day period was chosen to ensure inclusion of patients diagnosed with AF in primary care, as they will often initiate anticoagulant therapy before being registered with an AF diagnosis at the hospital [2]. The diagnosis of AF in the Patient Registry is highly valid with a positive predictive value of 98% [18,19]. We further excluded individuals potentially using NOAC for other indications registered in the Patient Registry, that is individuals with any history of venous thromboembolic disease at any time prior to the date of NOAC initiation, as well as individuals with hip or knee replacement procedures within two weeks before and five weeks after the first dispensing of a NOAC. Lastly, each patient had to have been a resident in Denmark for a minimum of 5 years and had to be ≥ 18 years old at the time of filling the first NOAC prescription.

Analyses. We divided the analyses into three subheadings collectively describing and exploring treatment changes during NOAC treatment in AF patients. All analyses were specified by previous use of VKA and by type of NOAC. Previous use of VKA was defined as having filled at least one VKA prescription within 2 years prior to the index date. All calculations were performed using STATA Release 14.0 (StataCorp, College Station, TX, USA).

Baseline characteristics of NOAC initiators. We assessed baseline characteristics of all AF patients initiating a NOAC during the study period. The following characteristics were included: (a) age at index date and sex; (b) chronic diseases associated with an increased risk of bleeding and/or thromboembolism (including registration of the following diagnoses within 5 years prior to index date: alcohol abuse, cancer, chronic renal failure, diabetes, ischaemic heart disease, liver failure, peripheral arterial disease, any previous bleeding and ischaemic stroke/transient ischaemic attack); (c) prescriptions for platelet inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors (SSRIs) filled within 180 days before index date; (d) type of NOAC and start dose; (e) CHAD₂DS₂-VASc score [20] (Appendix S3); and finally (f) HAS-BLED score [21] (Appendix S3).

To assess medication changes in relation to initiation of NOAC treatment, we further assessed the use of platelet inhibitors, NSAIDs and SSRIs within 180 days after index date.

Treatment changes during NOAC therapy. We considered a patient as treated with a given NOAC from the day of filling a prescription and for the subsequent number of days corresponding to the number of tablets in a package for rivaroxaban (used once daily) or half the number of tablets in a package for dabigatran and apixaban (used twice daily). Finally, a 30-day grace period was added to account for minor non-compliance and irregular prescription refills.

Following patients from their index date, we determined the proportion of patients who had (i) switched to another NOAC, defined as filling a prescription for a NOAC different from the one first filled; (ii) switched to VKA, defined as filling a prescription for VKA; or

(iii) discontinued anticoagulant treatment, defined as the first period without a prescription for the same or another oral anticoagulant lasting >60 days beyond the end of supply of the latest prescription (including the grace period). Follow-up was terminated upon switches to VKA and discontinuations but was continued when switching to another NOAC. Furthermore, study individuals were censored upon death, migration and end of the study period.

Distribution and prediction of treatment changes by baseline characteristics. For each subgroup, we determined the proportion of patients with a switch from NOAC to VKA and the proportion of patients with discontinuation within 1 year after filling the first NOAC prescription. To contribute to this analysis, a minimum follow-up of 1 year after the index date was thus required. Further, we entered all baseline characteristics into a multivariate logistic regression model, to assess whether any characteristics were associated with these specific treatment changes.

Ethics. The study was approved by the Danish Health Data Authority. According to Danish law, approval from an Ethics Committee is not required for purely register-based studies [22].

Results

We identified 94,023 individuals initiating a NOAC within the study period. After exclusions (Figure S1), 50,632 eligible patients were included. The number of new NOAC users increased every year in the study period. Overall, dabigatran was the most commonly used NOAC (49.9%, $n = 25,243$) (table 1), whereas rivaroxaban and apixaban were initiated by 24.9% ($n = 12,627$) and 25.2% ($n = 12,753$) of the patients, respectively. In 2015, initiation of apixaban was more common (49.0%) than initiation of rivaroxaban (35.7%) and dabigatran (15.4%).

Baseline characteristics of NOAC initiators.

The median age of NOAC initiators was 74 years (interquartile range 67–82), and the vast majority (86.5%) had a CHA₂DS₂-VASc score ≥ 2 . Overall, 30.1% ($n = 15,256$) had been treated with a VKA prior to NOAC initiation, that is switched from VKA to NOAC. Among individuals initiating a NOAC in the period of 2011–2012, 42.5% were previous VKA users, while this was the case for 29.0% in 2013–2015. Compared to VKA-naïve NOAC initiators, previous users of VKA were older and generally had more comorbid conditions (table 1). Accordingly, they had a higher median CHA₂DS₂-VASc score (4 *versus* 3), were more often started on low-dose NOAC (46.4% *versus* 36.9%) and more frequently had a history of bleeding (19.3% *versus* 9.3%). Patients initiating apixaban had the highest proportion of prior stroke (18.9%), bleeding (14.0%) and chronic renal failure (4.8%), whereas dabigatran initiators were younger and had less comorbid conditions compared to other NOACs (table 1).

VKA-naïve NOAC initiators had higher baseline use of platelet inhibitors (46.9%) compared to previous VKA users (28.7%) (table 1). In both groups, the use of platelet inhibitors was reduced after NOAC initiation, and a similar proportion of the two groups were classified as concomitant users of

Table 1.

Baseline characteristics. Individuals with atrial fibrillation initiating NOAC therapy in Denmark, August 2011–February 2016.

Characteristic	All (n = 50,623)	Previous VKA (n = 15,256)	VKA naïve (n = 35,367)	Dabigatran (n = 25,243)	Rivaroxaban (n = 12,627)	Apixaban (n = 12,753)
Female sex	22,822 (45.1%)	6983 (45.8%)	15,839 (44.8%)	10,864 (43.0%)	5894 (46.7%)	6064 (47.5%)
Age (years)						
Median (IQR)	74 (67–82)	76 (68–83)	73 (66–81)	72 (65–80)	75 (68–83)	76 (68–84)
<55	2433 (4.8%)	498 (3.3%)	1935 (5.5%)	1455 (5.8%)	491 (3.9%)	487 (3.8%)
55–64	6859 (13.5%)	1707 (11.2%)	5152 (14.6%)	4031 (16.0%)	1494 (11.8%)	1334 (10.5%)
65–74	16,855 (33.3%)	4732 (31.0%)	12,123 (34.3%)	8907 (35.3%)	4099 (32.5%)	3849 (30.2%)
≥75	24,476 (48.3%)	8319 (54.5%)	16,157 (45.7%)	10,850 (43.0%)	6543 (51.8%)	7083 (55.5%)
CHA ₂ DS ₂ -VASc score						
Median (IQR)	3 (2–4)	4 (3–5)	3 (2–4)	3 (2–4)	3 (2–5)	4 (2–5)
0	2387 (4.7%)	375 (2.5%)	2012 (5.7%)	1494 (5.9%)	448 (3.5%)	445 (3.5%)
1	4470 (8.8%)	911 (6.0%)	3559 (10.1%)	2477 (9.8%)	1086 (8.6%)	907 (7.1%)
≥2	43,766 (86.5%)	13,970 (91.6%)	29,796 (84.2%)	21,272 (84.3%)	11,093 (87.9%)	11,401 (89.4%)
HAS-BLED score						
Median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	3 (2–3)
0–2	26,356 (52.1%)	8022 (52.6%)	18,334 (51.8%)	13,652 (54.1%)	6536 (51.8%)	6168 (48.4%)
≥3	24,267 (47.9%)	7234 (47.4%)	17,033 (48.2%)	11,591 (45.9%)	6091 (48.2%)	6585 (51.6%)
Previous VKA use						
Yes	15,256 (30.1%)	15,256 (100%)	–	8210 (32.5%)	3589 (36.6%)	3013 (23.6%)
No	35,367 (69.9%)	–	35,367 (100%)	17,033 (67.5%)	6222 (63.4%)	9740 (76.4%)
Start dose ¹						
High	30,506 (60.3%)	8176 (53.6%)	22,330 (63.1%)	14,247 (56.4%)	8475 (67.1%)	7784 (61.0%)
Low	20,117 (39.7%)	7080 (46.4%)	13,037 (36.9%)	10,996 (43.6%)	4152 (32.9%)	4969 (39.0%)
Comorbidity						
Alcohol abuse	1871 (3.7%)	640 (4.2%)	1231 (3.5%)	928 (3.7%)	488 (3.9%)	455 (3.6%)
Cancer	4687 (9.3%)	1655 (10.8%)	3032 (8.6%)	2216 (8.8%)	1223 (9.7%)	1248 (9.8%)
Chronic renal failure	1590 (3.1%)	760 (5.0%)	830 (2.3%)	493 (2.0%)	481 (3.8%)	616 (4.8%)
Diabetes	8498 (16.8%)	3135 (20.5%)	5363 (15.2%)	3982 (15.8%)	2196 (17.4%)	2320 (18.2%)
Hypertension	37,281 (73.6%)	12,273 (80.4%)	25,008 (70.7%)	18,370 (72.8%)	9419 (74.6%)	9492 (74.4%)
Ischaemic heart disease	10,450 (20.6%)	4100 (26.9%)	6350 (18.0%)	5136 (20.3%)	2586 (20.5%)	2728 (21.4%)
Liver failure	180 (0.4%)	67 (0.4%)	113 (0.3%)	86 (0.3%)	43 (0.3%)	51 (0.4%)
Peripheral arterial disease	1573 (3.1%)	679 (4.5%)	894 (2.5%)	696 (2.8%)	431 (3.4%)	446 (3.5%)
Previous bleeding, any	6241 (12.3%)	2939 (19.3%)	3302 (9.3%)	2862 (11.3%)	1589 (12.6%)	1790 (14.0%)
Ischaemic stroke/TIA	7878 (15.6%)	2552 (16.7%)	5326 (15.1%)	3538 (14.0%)	1935 (15.3%)	2405 (18.9%)
Baseline medication use						
Platelet inhibitor ²	20,986 (41.5%)	4382 (28.7%)	16,604 (46.9%)	10,484 (41.5%)	5101 (40.4%)	5401 (42.4%)
NSAID	6717 (13.3%)	1547 (10.1%)	5170 (14.6%)	3423 (13.6%)	1661 (13.2%)	1633 (12.8%)
SSRI	4656 (9.2%)	1808 (11.9%)	2848 (8.1%)	2216 (8.8%)	1198 (9.5%)	1242 (9.7%)

¹Low dose: ≤110 mg twice daily for dabigatran, ≤15 mg once daily for rivaroxaban, ≤2.5 mg twice daily for apixaban.²Low-dose aspirin, clopidogrel, ticagrelor, prasugrel.

VKA, Vitamin K antagonist; NOAC, non-vitamin K oral anticoagulant; TIA, transient ischaemic attack; NSAID, non-steroidal anti-inflammatory drug; IQR, interquartile range; SSRI, selective serotonin reuptake inhibitor.

NOAC and platelet inhibitors 180 days after NOAC initiation (16.8% and 16.0%).

Switching from NOAC to VKA.

A total of 10.1% of NOAC initiators had switched to VKA within 1 year of follow-up. After 2 and 3 years, this proportion was 13.6% and 16.5%, respectively (fig. 1). When stratifying by history of VKA use, 13.7% of those with previous use of VKA switched back to VKA within the first year of NOAC treatment (Figure S2a), while the corresponding number was 8.5% for VKA-naïve NOAC initiators (Figure S2b). When stratifying by individual NOACs, we found that 11.8%, 8.5% and 5.7% had switched to VKA within 1 year for users of dabigatran, rivaroxaban and apixaban, respectively (Figure S2c–e).

Predictors of switching to VKA within the first year of treatment included young age (<55 years), very low CHA₂DS₂-VASc score (=0), dabigatran use, previous VKA use, chronic renal failure and ischaemic heart disease (table 2). This was similar for individuals with and without prior VKA use (Table S1) as well as for users of the individual NOACs (Table S2).

Switching from NOAC to NOAC.

Within the first year of treatment, 4.8% (n = 1,668) had switched to another NOAC. This proportion increased slightly (6.0%) after 2 years of follow-up (3). Switching to another NOAC within 1 year was more common among VKA-naïve NOAC initiators (5.4%) than among VKA-experienced (3.5%) (Figure S2a–b). For initiators of dabigatran, rivaroxaban and

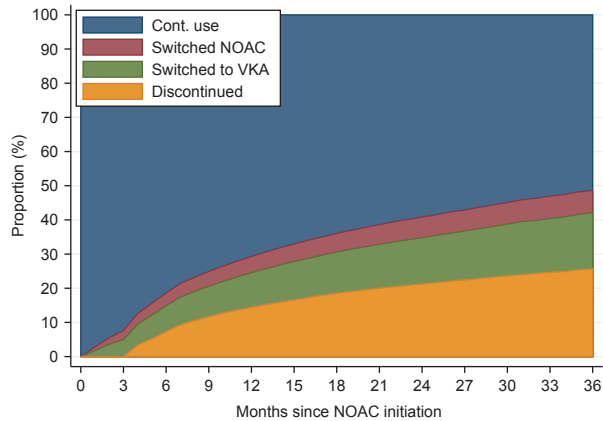


Fig. 1. Treatment changes among all NOAC initiators with atrial fibrillation. Cumulative proportion of NOAC initiators with atrial fibrillation discontinuing treatment, switching to VKA, switching to another NOAC and continuing treatment. Denmark, August 2011–February 2016.

apixaban, the frequency of switching to another NOAC within 1 year was 5.2%, 5.8% and 2.1% (Figure S2c–e).

Discontinuation of anticoagulant treatment.

After 1 year, 14.4% had discontinued NOAC treatment without switching to another anticoagulant agent. The corresponding proportion was 21.3% after 2 years of follow-up and 25.7% after 3 years (fig. 1). Among VKA-naïve NOAC initiators, 15.8% had discontinued treatment within 1 year, whereas this was the case for 11.4% of individuals with prior VKA experience (Figure S2a–b). A total of 15.5% and 13.7% of initiators of dabigatran and rivaroxaban, respectively, had discontinued treatment within 1 year, while this proportion was lower for apixaban (11.4%) (Figure S2c–e).

Predictors of treatment discontinuation within 1 year were overall the same as those for switching, apart from previous VKA use (table 2). Additionally, use of rivaroxaban and NSAIDs increased the risk of discontinuation. Young age (<55 years) and a very low CHA₂DS₂-VASc (=0) score were the strongest predictors for discontinuation of NOAC treatment (table 2). Patients with a high CHA₂DS₂-VASc score (≥2), prior ischaemic stroke/TIA and apixaban use were least likely to discontinue treatment. Neither stratification by prior VKA use (Table S1) nor type of NOAC (Table S3) changed the observed associations.

Discussion

In this large nationwide study on AF patients treated with NOACs, we found treatment changes to be common: 1 of 3 patients starting a NOAC had switched from VKA, and a similar proportion experienced a treatment change during the first year; half of these patients switched to another anticoagulant agent and the other half discontinued anticoagulant treatment. After 3 years, half of all patients were no longer users of the same NOAC, and 1 of 4 patients had discontinued

anticoagulant treatment. The strongest predictor for treatment changes was a low risk of stroke. However, most changes were observed in patients at increased risk of ischaemic stroke based on their CHA₂DS₂-VASc score.

Switching from NOAC to VKA was less common in our study (10.1% within 1 year) than in a previous Danish study [4], where half of NOAC initiators had switched to VKA within six months. These results were based on a small sample (n = 1,639) of early NOAC users in only one of five Danish regions, which may explain the divergent results. In a more recent and nationwide Danish study [5], 9.4% of VKA-naïve dabigatran initiators switched to warfarin within 1 year, that is a result nearly identical to ours. In the Dresden NOAC registry, only 5% of NOAC initiators (with and without previous VKA use) had switched to VKA within 18 months [9]. This markedly lower switch rate most likely reflects a different attitude towards VKA treatment or motivation for use of NOAC in AF between European countries. In the most recent European AF guidelines, NOAC is preferred over VKA for stroke prophylaxis in AF [1]. In contrast, Danish guidelines [23] consider VKA and NOAC as equal treatment alternatives, as long as 'high-quality VKA treatment' (defined as time in the therapeutic range of INR ≥ 70%) can be expected or demonstrated. Consequently, this may result in differences in the management of NOAC-treated patients between countries.

While the consequences of discontinuation of anticoagulant therapy in AF are well established [7,24], knowledge on the safety implications of switching between anticoagulant agents is sparse. Beyer-Westendorf *et al.* found 30-day rates for bleeding and thromboembolism of 11.6% and 1.1%, respectively, in patients switching from warfarin to NOAC in the Dresden NOAC Registry [6]. However, the corresponding rates for patients continuing warfarin therapy were not presented, thus precluding estimation of relative risks. In a large cohort of Danish AF patients, Larsen *et al.* found similar bleeding rates in warfarin-treated patients switched to dabigatran and in patients persisting to warfarin [25]. Switching from warfarin to dabigatran was, however, associated with a twice as high risk of stroke/TIA in the subgroup of patients with a history of these specific conditions [26]. To the best of our knowledge, the safety of switching from NOAC to VKA has only been assessed in post hoc analyses of randomized clinical trials, in which it was associated with a 3 times increased 30-day risk of both bleeding and thromboembolism [7,8].

Current knowledge on the reasons leading to anticoagulant switching primarily pertains to the switch from VKA to NOAC, which also was the most frequent type of switch in the present study. In the study mentioned above, Beyer-Westendorf *et al.* [6] found 'unstable INR' as the most common reason (58%) for switching from VKA to NOAC among 568 AF patients, and 'bleeding complications' were the second most common reason (18% of patients) [6]. Other studies [27–29] support that unstable INR levels is a major reason for switching from VKA to NOAC. Of note, unstable INR can have several causes including low adherence [30], and it is currently unknown which AF patients with unstable INR values will benefit from being switched to a NOAC [31]. In the

Table 2.

Predictors of early treatment changes. Switching to VKA and discontinuation within 1 year of initiation among NOAC users with atrial fibrillation according to baseline characteristics and adjusted odds ratios¹ for associations between baseline characteristics and treatment changes. Odds ratios were obtained using multivariable logistic regression. Denmark, August 2011–February 2016.

Subgroup	n total (n = 34,627)	Switch from NOAC to VKA (n = 3,828)		Discontinuations (n = 7908)	
		Switch frequency	Odds ratio (95% CI)	Discontinuation frequency	Odds ratio (95% CI)
Sex					
Female	15,394	10.3%	1.00 (ref.)	19.9%	1.00 (ref.)
Male	19,233	11.7%	0.97 (0.90–1.04)	25.2%	1.11 (1.05–1.18)
Age (years)					
<55	1807	20.1%	1.56 (1.33–1.82)	51.3%	2.45 (2.16–2.77)
55–64	5195	13.6%	1.03 (0.92–1.16)	29.1%	1.09 (1.00–1.20)
65–74	12,402	11.4%	1.00 (ref.)	20.2%	1.00 (ref.)
≥75	15,223	8.8%	0.85 (0.78–0.94)	19.4%	1.00 (0.93–1.08)
CHA₂DS₂-VASc score					
0	1776	19.8%	1.70 (1.41–2.06)	59.8%	3.98 (3.44–4.61)
1	3360	13.5%	1.18 (1.03–1.35)	28.2%	1.32 (1.19–1.46)
≥2	29,491	10.2%	1.00 (ref.)	20.0%	1.00 (ref.)
HAS-BLED score					
0–2	18,294	12.3%	1.06 (0.94–1.19)	25.8%	0.95 (0.87–1.04)
≥3	16,333	9.6%	1.00 (ref.)	19.5%	1.00 (ref.)
Type of NOAC					
Dabigatran	21,852	13.0%	1.00 (ref.)	25.5%	1.00 (ref.)
Rivaroxaban	6859	9.2%	0.72 (0.65–0.79)	20.4%	0.88 (0.82–0.95)
Apixaban	5916	6.2%	0.50 (0.44–0.56)	15.8%	0.64 (0.58–0.69)
Previous VKA use					
No	23,681	9.2%	1.00 (ref.)	22.9%	1.00 (ref.)
Yes	10,946	15.1%	1.77 (1.64–1.91)	22.7%	0.96 (0.91–1.02)
Start dose²					
High	21,415	12.2%	1.00 (ref.)	23.8%	1.00 (ref.)
Low	13,212	9.2%	0.81 (0.74–0.89)	21.3%	1.11 (1.03–1.18)
Comorbidities³					
Alcohol abuse	1280	8.9%	0.73 (0.60–0.90)	26.1%	1.08 (0.94–1.24)
Cancer	2774	9.5%	0.90 (0.79–1.03)	22.5%	1.10 (1.00–1.21)
Chronic renal failure	870	13.1%	1.58 (1.28–1.96)	25.1%	1.36 (1.16–1.61)
Diabetes	5606	10.0%	0.88 (0.80–0.97)	20.0%	0.94 (0.87–1.01)
Hypertension	25,371	10.8%	1.12 (1.00–1.24)	20.7%	0.96 (0.89–1.04)
Ischaemic heart disease	7094	12.1%	1.25 (1.14–1.37)	23.7%	1.34 (1.26–1.44)
Liver failure	102	11.8%	1.23 (0.66–2.29)	39.2%	2.01 (1.32–3.07)
Peripheral arterial disease	916	8.2%	0.76 (0.60–0.97)	21.4%	1.08 (0.92–1.27)
Previous bleeding, any	4065	10.8%	1.03 (0.91–1.15)	23.2%	1.12 (1.02–1.22)
Ischaemic stroke/TIA	5288	7.9%	0.78 (0.69–0.87)	15.3%	0.68 (0.62–0.74)
Baseline medication use³					
Platelet inhibitor ⁴	14,551	9.6%	0.94 (0.86–1.04)	19.8%	0.81 (0.75–0.87)
NSAID	4627	11.3%	1.08 (0.97–1.20)	24.2%	1.06 (0.98–1.14)
SSRI	2965	8.4%	0.77 (0.67–0.89)	19.1%	0.89 (0.80–0.98)

¹Adjusted for age, sex and baseline characteristics.

²Low dose: ≤110 mg twice daily for dabigatran, ≤15 mg once daily for rivaroxaban, ≤2.5 mg twice daily for apixaban.

³These are variables with binary responses (yes/no), but only the 'yes' is presented here. 'No' serves as reference.

⁴Low-dose aspirin, clopidogrel, ticagrelor, prasugrel.

VKA, Vitamin K antagonist; NOAC, non-vitamin K oral anticoagulant; TIA, transient ischaemic attack; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

present study, information concerning the quality of INR control among patients switched from VKA to NOAC was not available.

Discontinuation of anticoagulant therapy is a well-known consequence of both major and minor bleeding events [9,32,33], although recent studies [34,35] have questioned the appropriateness of this. In our study, a high HAS-BLED score (≥3) at baseline was not a predictor of discontinuation, which

may reflect use of the low NOAC doses in these patients [26]. Presumed lack of indication of anticoagulant therapy may also be an important determinant of discontinuation, indicated by the finding of stable sinus rhythm (41%) as the most common cause of discontinuation among 32 dabigatran users in the Dresden NOAC Registry [36] and by the high prevalence of discontinuation among patients with CHA₂DS₂-VASc score=0 in the present study.

Users of apixaban showed better persistence than users of dabigatran and rivaroxaban. This is in accordance with other observational studies based on 'real-life' patients [10], but contrasts with phase III trials, where users of the three NOACs showed similar persistence [37–39]. Although apixaban may be better tolerated than other NOACs, the finding may reflect selection bias. As shown in the present and other studies [2,10], apixaban is preferred in AF patients with a high thromboembolic risk, that is the patients most likely to persist to treatment [5]. Moreover, physicians were already experienced with the selection and management of NOAC treated patients when apixaban entered the market in late 2012. However, as users of apixaban also had better persistence in the analysis adjusting for these factors, this difference in persistence should be further explored.

The principal strength of the present study is the nationwide analyses, including all Danes registered with AF and initiating a NOAC since the date of marketing of the first NOAC in Denmark to the beginning of 2016. Other strengths include the completeness of the registries employed [14,16] as well as the high validity of the AF diagnosis [18,19]. There are limitations as well. In the restriction to patients with a known AF diagnosis, an approach commonly used in studies on NOAC use in AF patients [2,5,25], we excluded 22.9% of all NOAC initiators as they did not have a hospital diagnosis compatible with any approved indication of NOAC use. A substantial but unknown proportion of these patients are likely to receive NOAC treatment because of unregistered AF (e.g. cases of AF handled in primary care alone). This may be a source of selection bias, if treatment patterns among these patients are different from the study population. Further, although pharmacy dispensing information is generally considered a valid measure of drug exposure [40], misclassification remains possible [41]. Finally, although the majority of diagnoses used to identify comorbidity and clinical events in the study have been validated with acceptable results [15], the validity of some of the used diagnoses remains unknown.

In conclusion, we found switching from VKA to NOAC, and to a lesser extent from NOAC to VKA, to be common, as were treatment discontinuation. Young age and low CHA₂DS₂-VASc score were the strongest predictors of switching from NOAC to VKA and discontinuation. However, based on their CHA₂DS₂-VASc score, the majority of patients experiencing a treatment change had an increased risk of ischaemic stroke. The extent and patterns of treatment changes found in this study call for further exploration of the risks and benefits associated with changes in oral anticoagulant therapy.

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Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer and has participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim and Bristol-Myers Squibb. SH has received speaker honoraria from and participated in advisory board for Boehringer Ingelheim, AstraZeneca, Pfizer, Bristol-Myers Squibb and Bayer. SPJ has received speaker honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer and has participated in advisory board meetings for Bayer, Bristol-Myers Squibb and Pfizer. AP, LR and JH have participated in projects funded by Boehringer Ingelheim, with funds paid to the institution where they were employed.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Predictors of early treatment changes, stratified on prior use of VKA.

Table S2. Predictors of early switching to VKA, stratified on NOAC type.

Table S3. Predictors of early discontinuation, stratified on NOAC type.

Fig. S1. Inclusion of NOAC initiators with atrial fibrillation.

Fig. S2a. Treatment changes among VKA experienced NOAC initiators with atrial fibrillation.

Fig. S2b. Treatment changes among VKA naïve NOAC initiators with atrial fibrillation.

Fig. S2c. Treatment changes among initiators of dabigatran with atrial fibrillation.

Fig. S2d. Treatment changes among initiators of rivaroxaban with atrial fibrillation.

Fig. S2e. Treatment changes among initiators of apixaban with atrial fibrillation.

Appendix S1. Data sources.

Appendix S2. Definitions of drugs, diseases, operations, and procedures.

Appendix S3. Definitions of risk scores.