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Use of Non-Vitamin K Antagonist Oral Anticoagulants 2008–2016: A Danish Nationwide Cohort Study

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Abstract: We aimed to provide detailed utilization data on the total use of non-vitamin K antagonist oral anticoagulants (NOACs) since their introduction in 2008. Using the nationwide Danish National Prescription Registry, we identified all individuals filling prescriptions for NOACs 2008–2016. We reported the development in incident and prevalent users and explored baseline characteristics and treatment persistence according to treatment indication. A total of 126,691 NOAC users were identified within the Danish population of 5.7 million inhabitants. The annual incidence and prevalence increased rapidly reaching 10 and 17 per 1000 individuals in 2016. Patients received NOACs due to atrial fibrillation (AF) (43%), venous thromboembolism (VTE) prophylaxis after arthroplastic surgery (17%), VTE (12%) and no registered indication (28%). The most frequently used NOAC was rivaroxaban (n = 52,431), followed by dabigatran (n = 47,067), apixaban (n = 27,116) and edoxaban (n = 77). The proportion of AF and VTE patients initiating low-dose NOACs were between 23% and 50%. Patients treated with NOAC for VTE primarily received rivaroxaban. We observed a trend towards increased use of apixaban and rivaroxaban at the expense of dabigatran. Treatment persistence was highly dependent on treatment indication. Persistence to NOAC after 3 years was only 62% in AF compared to 28% for VTE. We documented an accelerating increase in the use of all four NOACs in the first 8 years after introduction. We have identified areas requiring further attention, including reasons for missing indications, potential inappropriate dosing and low long-term persistence with NOACs in patients with AF.

Key points

What is already known about this subject?

- In patients with atrial fibrillation or venous thrombosis, NOACs are non-inferior with respect to efficacy but with a similar or lower risk of bleeding compared to vitamin K antagonists (VKA).
- So far, no studies have explored the use of NOACs in Denmark without restricting to a specific patient population.

What this study adds?

- The prevalence of NOAC use increased from 0.058 per 1000 individuals in 2008 to 17.02 in 2016.
- Patients received NOAC due to atrial fibrillation (43%), VTE prophylaxis after arthroplastic surgery (17%), VTE (12%) and no registered indication (28%).
- In general, rivaroxaban was the most frequently prescribed NOAC, in particular for patients with venous thrombosis.

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) directly target specific coagulation factors and include the factor IIa (thrombin) inhibitor dabigatran and the factor Xa inhibitors apixaban, rivaroxaban and edoxaban. The first NOAC was introduced in Europe in 2008 as prophylaxis against venous thromboembolism after arthroplastic surgery. Since then, all NOACs have been approved for stroke prophylaxis in atrial fibrillation (AF) and for treatment of deep venous thromboembolism and pulmonary embolism (collectively 'venous thromboembolism', VTE).

Despite the rapid and extensive uptake of NOACs in Denmark [1,2], the actual clinical use of these drugs remains to be described in full. Description and evaluation of the utilization of NOACs in daily practice are important to, for example, (i) evaluate whether NOACs are used as recommended in clinical guidelines, (ii) describe selective prescribing of NOACs of potential impact to future comparative safety and effectiveness studies and (iii) identify areas of NOAC use requiring further attention.

Previous studies reporting on the utilization patterns of NOACs have mainly focused on the use of NOACs for specific indications, most often AF [3–5], defined by the presence of specific registered diagnoses in healthcare registries serving as proxies for the treatment indication. This method leads to a large number of NOAC users without a registered treatment indication proxy being excluded from these studies [1,3,6], thus, potentially missing important information on a substantial proportion of the population of NOAC users.

The Danish registries provide some of the best sources for observational research in the world due to complete nationwide coverage and the unique civil registration number assigned to all Danish citizens allowing linkage between all

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registries. Using these nationwide Danish health registries, we aimed to provide detailed utilization data on the total use of NOACs since their introduction to the market without restricting to a specific patient group. The objectives of the study were to describe the utilization of NOACs over time as well as potential differences in characteristics of NOAC users according to treatment indication and NOAC type and also to investigate the persistence to NOAC therapy in the context of different indications.

Methods

Design and setting. This was a population-based study describing the complete cohort of Danish NOAC users during the period of March 2008 to the end of 2016, that is, the entire period, NOACs have been available in Denmark.

The total Danish population increased from 5.48 million to 5.75 million during the study period [7].

Data sources. Denmark provides tax-supported health care to all citizens, securing free and equal access to general practitioners and hospitals as well as partial reimbursement for most prescribed medications [8]. To maintain and administer this healthcare system, numerous registries have been established. The civil registration number, a unique 10-digit personal identifier, enables linkage between all registries and thereby allows the conduction of true population-based studies covering all residents in Denmark [9].

Data regarding use of NOACs and other drugs were obtained from the Danish National Prescription Registry, which contains complete information on all prescription drugs dispensed to Danish citizens since 1995; including information on the Anatomical Therapeutic Chemical (ATC) classification code of the dispensed drug, date of purchase, package size in defined daily doses, tablet/capsule strength and civil registration number [10]. Information on duration and indication for treatment is not available in the Prescription Registry. Data used to describe the study population with regard to diagnoses (including proxies for anticoagulant treatment indication) and surgical procedures were obtained from the Danish National Patient Registry, which includes information from Danish hospitals on in- and outpatient diagnoses and surgical procedures with complete nationwide coverage since 1978. Overall, positive predictive values of diagnoses registered in the Patient Register are high. For some conditions, the completeness of the register may, however, be limited by the lack of primary care data [11]. Definitions of drugs, diagnoses, operations and procedures used in this study are detailed in Appendix 1.

Study cohort. The study cohort comprised all patients with a first-time treatment episode of NOAC use. Patients entered the cohort when filling their first (incident) NOAC prescription at a Danish community pharmacy during the study period as registered in the Prescription Registry. The date of the first prescription fill was set as the index date. Patients left the cohort upon discontinuation of NOAC treatment (defined below), death or migration. Thus, only the first treatment episode of NOAC use for each patient was considered.

Study drugs. All four NOACs with market authorization in Denmark, that is dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Lixiana®), were included in the study. Indications, dosing regimens and availability of NOACs including marketing dates for the various indications are provided in tables 1 and 2. Low-dose NOAC treatment was defined as treatment with dabigatran 75 mg or 110 mg, rivaroxaban 2.5 mg, 10 mg or 15 mg and apixaban 2.5 mg. All NOACs are reimbursed by the Danish National Health Service.

Indication for NOAC use. The study cohort of NOAC users was described according to assumed treatment indication. Accordingly, all NOAC initiators were labelled with one of the following major indications: AF, VTE, thromboprophylaxis after knee and hip replacement or no registered indication. Some patients with an indication for anticoagulant treatment, such as patients with valvular heart disease or valvular atrial fibrillation, are not eligible for treatment with NOAC. Rivaroxaban is also registered for use in acute coronary syndromes (ACS), but use for this indication has been very limited in Denmark and thus was not considered in this study.

AF and VTE were defined by relevant diagnoses (see Appendix 1) registered at any time-point before NOAC initiation in the Patient Registry, while also including AF diagnoses registered up to 90 days after NOAC initiation to allow for diagnostic lag [4]. If patients were registered with both a diagnosis of AF and VTE, they were classified as AF, unless the diagnosis of VTE was given within 1 year before NOAC initiation. Patients registered for a hip or knee replacement 2 weeks before or 5 weeks after NOAC initiation were classified as such.

Baseline characteristics of NOAC initiators. Baseline characteristics were assessed at the index date. The following characteristics were included: (i) age and sex; (ii) chronic diseases associated with an increased risk of bleeding and/or thromboembolism (including registration of the following diagnosis within 5 years before index date: alcohol abuse, cancer, chronic renal failure, dialysis, diabetes, hypertension, ischaemic heart disease, liver failure, peripheral arterial disease, any previous bleeding, ischaemic stroke/transient ischaemic attack and chronic heart failure); (iii) prescriptions for platelet inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs) or selective serotonin reuptake inhibitors (SSRIs) filled within 180 days before index date; (iv) previous VKA use defined by having filled one or more prescriptions for VKA within 5 years before index date; (v) type and start dose of NOAC.

Analyses. Firstly, we estimated the annual incidence rate and prevalence proportion of use for all NOACs combined as well as separately for each NOAC. These were calculated as the number of first-ever and current users per 1000 individuals in the Danish population. Calculations were performed with the total Danish population on 1 January in the relevant year as the denominator, as the number of prevalent users is negligible. Patients were considered 'on treatment' for the subsequent number of days corresponding to the number of tablets in a package for rivaroxaban and edoxaban (used once daily) or half the number of tablets for dabigatran and apixaban (used twice daily). Finally, a 60-day grace period was added to account for minor non-compliance and irregular prescription refills. A patient was considered as having discontinued treatment if not filling a new prescription for the same or another NOAC after the estimated prescription duration plus the grace period or upon switching to VKA, defined as filling a prescription for VKA during NOAC therapy.

Secondly, we calculated the sex- and age-specific annual prevalence proportion for the last year of the study period (2016) using the Danish population in relevant age and sex strata as the denominator.

Thirdly, we stratified baseline characteristics of NOAC users on the assumed indication for treatment and according to type of NOAC initially prescribed. Stratified on indication, we also calculated the proportion of patients receiving various NOAC doses.

Fourthly, we calculated the relative distribution between the four included indications for NOAC use for each year throughout the study period. Further, in a post hoc analysis, we calculated the proportion of patients receiving NOAC for one of the four indications and explored the development in this distribution each year throughout the study period.

Fifthly, we calculated the persistence to NOAC use according to indication. For each NOAC user, treatment persistence was assessed

Table 1.

Indications for individual NOACs and dosing recommendations.

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prevention of stroke and systemic embolism in patients with atrial fibrillation	150 mg × 2 daily or 110 mg × daily[1]	20 mg × 1 daily or 15 mg × 1 daily[2]	5 mg × 2 daily or 2.5 mg × 2 daily[3]	60 mg × 1 daily or 30 mg × 1 daily[4]
Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE	150 mg × 2 daily or 110 mg × 2 daily[1] (Preceded by low molecular weight heparin for 5 days)	Initially 15 mg × 2 daily for 3 weeks Hereafter 20 mg × 1 daily	Initially 10 mg × 2 daily for 7 days Hereafter 5 mg × 2 daily for at least 3 months Recurrent VTE: 2.5 mg × 2 daily	60 mg × 1 daily or 30 mg × 1 daily[4] (Preceded by low molecular weight heparin for 5 days)
Venous thromboembolism prophylaxis after knee or hip replacement	Initially 110 mg 1-4 hr after the operation. Hereafter 220 mg × 1 daily for: 10 days after knee replacement 28–35 days after hip replacement	10 mg 6–10 hr after the operation followed by 1 daily for 35 days	Initially 2.5 mg 12–24 hr after the operation followed by 2.5 mg × 2 daily for: 10-14 days after knee replacement 32–38 days after hip replacement	
Secondary prevention of cardiovascular events in patients with acute coronary syndrome		2.5 mg × 2 daily for 12 months		

[1]Age ≥ 80 years, concomitant treatment with verapamil, high risk of bleeding and low risk of thromboembolism and GFR 30–50 ml/min.
[2]GFR 15–49 ml/min.
[3]2/3 criteria fulfilled: age ≥ 80 years, body-weight ≤ 60 kg or GFR 15–29 ml/min.
[4]1/3 criteria fulfilled: GFR 15–50 ml/min., body-weight ≤ 60 kg or concomitant treatment with P-gp inhibitors.

Table 2.

Dates of availability for all approved indications. Information was obtained from the Danish Medicines Agency [34] and the European Commission [35].

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Introduction to the Danish market	02/06/2008	30/09/2008	13/06/2011	06/06/2016
Available for thromboprophylaxis after knee and hip replacement	02/06/2008	30/09/2008	18/05/2011	Not approved for this indication in Europe
Available for atrial fibrillation	22/08/2011	06/02/2012	10/12/2012	06/06/2016
Available for venous thromboembolism	06/06/2014	06/02/2012	28/07/2014	19/06/2015
Available for acute coronary syndrome	Not approved for this indication in Europe	24/05/2013	Not approved for this indication in Europe	Not approved for this indication in Europe

from the day of the first prescription fill. NOAC treatment was considered as discontinued according to the definition above. Switching between NOACs was allowed. A drug survival curve (Kaplan–Meier plot) showing treatment persistence stratified on the three major indications, and no registered indication was produced. Further, a sensitivity analysis was performed with a grace period of 90 days.

Ethics

According to Danish law, ethical approval is not required for register-based studies [8].

Results

Incidence and prevalence of NOAC use.

We identified a total of 126,691 individuals initiating NOAC therapy from 2008 to the end of 2016. The most frequently used NOAC over the entire period was rivaroxaban (n = 52,431), followed by dabigatran (n = 47,067), apixaban (n = 27,116) and, finally, edoxaban (n = 77). The number of incident users per 1000 individuals increased from 0.06 to 10 during the study period (fig. 1A). This was accompanied by a close to 300-fold increase in the prevalence proportion from 0.06 to 17 per 1000 individuals (fig. 1B). The annual number of dabigatran users increased until 2014 (n = 21,907; 48% of all NOAC users in 2014) followed by a decline in the subsequent years (n = 18,838; 24% of all NOAC users in 2016). Until 2012, the use of rivaroxaban was limited. However, after 2012, use of rivaroxaban increased steadily each year reaching a total of 30,966 users in 2016, hereby accounting for 40% of all NOAC use. Similarly, we observed an increase in apixaban use from 17,931 users in 2015 to 27,312 users in 2016 accounting for 35% of incident NOAC users in 2016

(fig. 1A). The use of edoxaban (n = 77) was too limited to be distinguishable in fig. 1A,B.

Baseline characteristics.

Tables 3 and 4 present baseline characteristics of the study cohort stratified by assumed treatment indication and type of NOAC. A greater proportion of patients using NOAC for VTE prophylaxis related to arthroplastic surgery had recently filled a prescription for NSAID (65%) and PPIs (45%) when compared to other indications. The prevalence of previous VKA use was highest among patients using NOACs for AF and VTE (34% and 31%, respectively, *versus* 3–15% for other indications) and likewise for edoxaban users. Baseline characteristics for patients with no registered indication were similar to those of the patients receiving NOAC due to AF, except that substantially more patients with AF had previously received VKA and that more patients with AF were treated with dabigatran (43% *versus* 30%).

Overall, 55.116 individuals (44% of all NOAC users) received NOAC due to AF. Of these, most individuals received dabigatran (43%), followed by apixaban (29%) and rivaroxaban (28%). Nearly, all individuals initiating NOACs as VTE prophylaxis related to arthroplastic surgery (21,531, 17% of all NOAC users) received either dabigatran or rivaroxaban (55% and 45%), whereas individuals with VTE (14,828; 12% of all NOAC users) primarily received rivaroxaban (77%). Approximately half of the individuals filling a prescription for dabigatran, apixaban or edoxaban could be classified as having AF compared to one-third of rivaroxaban users (table 4). In general, there were minor differences in the prevalence of comorbidities and concomitant medication between users of the various NOACs, although apixaban users had a higher prevalence of previous bleeding, stroke and chronic heart failure (13%, 17% and 17%, respectively) than users of the other NOACs. For all four NOACS, more male than female users were observed.

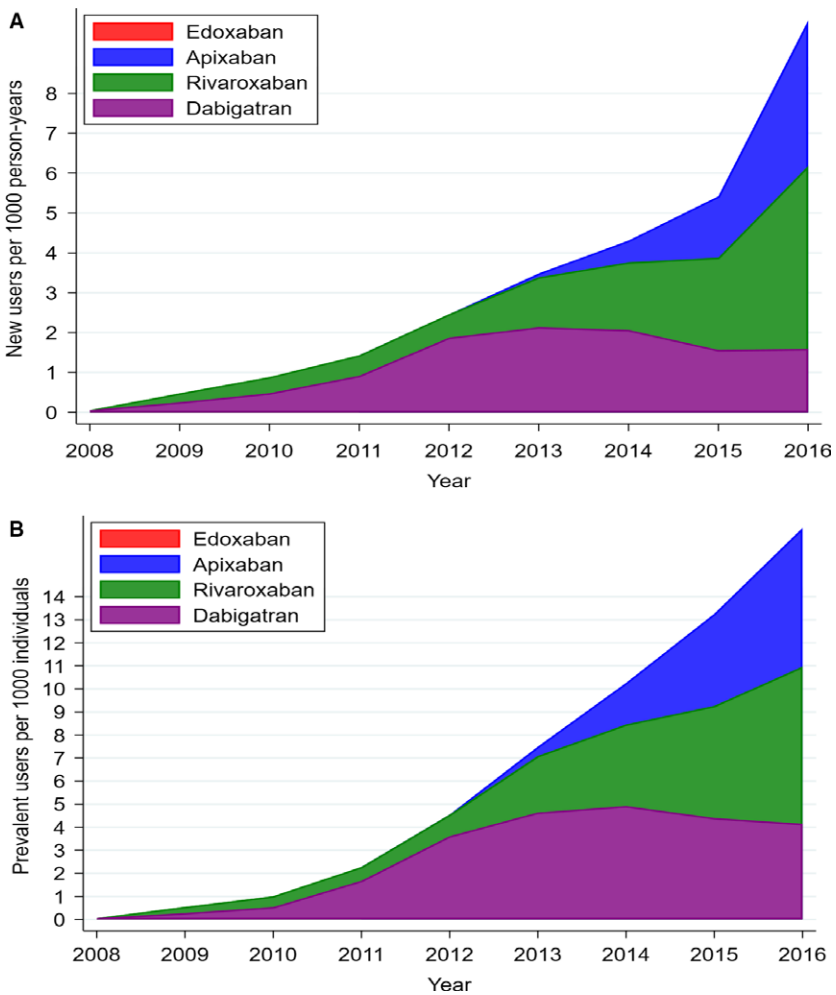

Fig. 1. (A) Annual incidence of NOAC use.
The annual incidence of NOAC users in the entire study period from 2008 to 2016 displayed as new users per 1000 person-years and stratified on type of NOAC.
(B) Prevalence proportion of NOAC use.
The annual prevalence of NOAC users in the entire study period from 2008 to 2016 displayed as prevalent users per 1000 person-years and stratified on type of NOAC.

Table 5 further explores NOAC dosing according to indication. Patients classified with AF receiving low-dose NOAC as defined above accounted for 35% overall and for 40%, 26% and 35% of users of the individual NOACs in AF patients.

Age and sex distribution.

The full age spectrum for prevalence in 2016 stratified by gender is provided in fig. 2, showing a more frequent use with increasing age and for all ages a greater proportion of male users, for example, 3% of men aged 65 years compared to 11% of men aged 85 years.

Distribution among indications.

Figure 3 shows that, the first 3 years after NOAC was introduced, they were mainly used for the only registered indication: VTE prophylaxis after hip or knee surgery (86–90%). From 2010 to 2015, this proportion dropped from 89% to 2%. Figure 3 also shows a shift in the distribution from 2011 to the end of the study period towards an increased proportion of AF patients. Further, the proportion of patients receiving NOACs for no registered indication increased each year from 9% in 2009 to 35% in 2016.

Treatment persistence.

Figure 4 shows that persistence with NOAC use was largely dependent on indication. After 1.5 years, 72% of individuals with AF were still on continuous treatment with a NOAC compared to 55% for no registered indication and 36% for VTE. Treatment persistence for VTE prophylaxis after hip and knee replacement dropped to 5% after 120 days.

Treatment persistence among patients with AF continued to drop, and after 3 years, 38% of AF patients had discontinued NOAC therapy. When changing the grace period to either 30

Table 3.

Baseline characteristics of NOAC users stratified by indication.

	Atrial fibrillation (n = 55,116)	VTE (n = 14,828)	VTE prophylaxis after knee and hip replacement (n = 21,531)	No registered indication (n = 35,200)
Type of NOAC (%)				
Dabigatran	23,682 (43.0)	1109 (7.5)	11,767 (54.7)	10,509 (29.9)
Rivaroxaban	15,522 (28.2)	11,370 (76.7)	9642 (44.8)	15,897 (45.2)
Apixaban	15,876 (28.8)	2346 (15.8)	124 (0.6)	8770 (24.9)
Edoxaban	46 (0.1)	(n < 5)	–	27 (0.1)
Age at index date				
Median (IQR)	73 (66–81)	68 (55–78)	68 (61–74)	74 (64–82)
0–17 (%)	(n < 5)	45 (0.3)	–	78 (0.2)
18–39 (%)	234 (0.4)	1130 (7.6)	175 (0.8)	1454 (4.1)
40–59 (%)	5725 (10.4)	3582 (24.2)	4459 (20.7)	4896 (13.9)
60–89 (%)	46,277 (84.0)	9365 (63.2)	16,739 (77.7)	26,305 (74.7)
≥90 (%)	2877 (5.2)	706 (4.8)	158 (0.7)	2467 (7.0)
Sex (%)				
Men	30,809 (55.9)	7590 (51.2)	8929 (41.5)	18,859 (53.6)
Women	24,307 (44.1)	7238 (48.8)	12,602 (58.5)	16,341 (46.4)
Comorbidity (%)				
Alcohol abuse	1390 (2.5)	605 (4.1)	311 (1.4)	882 (2.5)
Cancer	6688 (12.1)	2063 (13.9)	1665 (7.7)	4383 (12.5)
Chronic renal failure	1661 (3.0)	451 (3.0)	235 (1.1)	1108 (3.1)
Dialysis	33 (0.1)	20 (0.1)	(n < 5)	30 (0.1)
Diabetes	9005 (16.3)	1766 (11.9)	2206 (10.2)	5613 (15.9)
Hypertension	39,712 (72.1)	7489 (50.5)	12,115 (56.3)	23,462 (66.7)
Ischaemic heart disease	8455 (15.3)	1344 (9.1)	954 (4.4)	4913 (14.0)
Liver failure	200 (0.4)	71 (0.5)	48 (0.2)	125 (0.4)
Peripheral arterial disease	1554 (2.8)	383 (2.6)	223 (1.0)	1034 (2.9)
Previous bleeding	6617 (12.0)	1582 (10.7)	1300 (6.0)	3538 (10.1)
Stroke	6856 (12.4)	976 (6.6)	523 (2.4)	5759 (16.4)
Chronic heart failure	8477 (15.4)	1072 (7.2)	409 (1.9)	4360 (12.4)
Concomitant medication (%)				
Platelet inhibitors	21,126 (38.3)	3167 (21.4)	4966 (23.1)	13,666 (38.8)
NSAIDs	7296 (13.2)	2590 (17.5)	13,949 (64.8)	6698 (19.0)
PPIs	13,477 (24.5)	4087 (27.6)	9752 (45.3)	9466 (26.9)
SSRIs	4439 (8.1)	1526 (10.3)	1544 (7.2)	3355 (9.5)
Glucocorticoids	4565 (8.3)	1618 (10.9)	1476 (6.9)	3041 (8.6)
Previous VKA (%)				
>5 years	18,918 (34.8)	4652 (31.5)	574 (2.7)	5384 (15.1)

NOAC, non-vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors; VKA, vitamin K antagonist.

Table 4.
Baseline characteristics of NOAC users stratified by type of NOAC.

	Dabigatran (n = 47,067)	Rivaroxaban (n = 52,431)	Apixaban (n = 27,116)	Edoxaban (n = 77)
Indication (%)				
AF	23,682 (50.0)	15,079 (28.8)	15,354 (56.6)	46 (59.7)
VTE	1109 (2.4)	11,309 (21.6)	2348 (8.7)	(n < 5)
VTE prophylaxis after knee and hip replacement	11,767 (25.0)	9637 (18.4)	124 (0.5)	NA
No registered indication	10,509 (22.6)	16,406 (31.3)	9290 (34.3)	27 (35.1)
Age at index date				
Median (IQR)	71 (64–79)	70 (60–79)	76 (68–84)	74 (70–83)
0–17 (%)	12 (0.0)	110 (0.2)	(n < 5)	–
18–39 (%)	409 (0.9)	2328 (4.4)	256 (0.9)	(n < 5)
40–59 (%)	6235 (13.2)	10,220 (19.5)	2206 (8.1)	(n < 5)
60–89 (%)	38,853 (82.5)	37,550 (71.6)	22,227 (82.0)	68 (88.3)
≥90 (%)	1558 (3.3)	2223 (4.2)	2423 (8.9)	(n < 5)
Sex (%)				
Men	25,040 (53.2)	26,841 (51.2)	14,270 (52.6)	43 (55.4)
Women	22,027 (46.8)	25,590 (48.8)	12,846 (47.4)	34 (44.6)
Comorbidity (%)				
Alcohol abuse	1034 (2.2)	1430 (2.7)	722 (2.7)	(n < 5)
Cancer	5005 (10.6)	6115 (11.7)	3670 (13.5)	11 (14.3)
Chronic renal failure	777 (1.7)	1334 (2.5)	1339 (4.9)	6 (7.8)
Dialysis	16 (0.0)	29 (0.1)	41 (0.2)	–
Diabetes	6774 (14.4)	6950 (13.3)	4853 (17.9)	15 (19.5)
Hypertension	31,895 (67.8)	31,038 (59.2)	19,798 (73.0)	59 (76.6)
Ischaemic heart disease	6042 (12.8)	5215 (9.9)	4399 (16.2)	12 (15.6)
Liver failure	131 (0.3)	194 (0.4)	118 (0.4)	(n < 5)
Peripheral arterial disease	1106 (2.3)	1152 (2.2)	934 (3.4)	(n < 5)
Previous bleeding	4518 (9.6)	4878 (9.3)	3634 (13.4)	9 (11.7)
Stroke	5081 (10.8)	4372 (8.3)	4655 (17.2)	9 (11.7)
Chronic heart failure	5192 (11.0)	4619 (8.8)	4499 (16.6)	11 (14.3)
Concomitant medication (%)				
Platelet inhibitors	17,304 (36.8)	14,567 (27.8)	11,044 (40.7)	16 (20.8)
NSAIDs	13,257 (28.2)	13,719 (26.2)	3557 (13.1)	(n < 5)
PPIs	13,834 (29.4)	15,036 (28.7)	7899 (29.1)	18 (23.4)
SSRIs	3947 (8.4)	4346 (8.3)	2571 (9.5)	(n < 5)
Glucocorticoids	3728 (7.9)	4409 (8.4)	2559 (9.4)	9 (11.7)
Previous VKA (%)				
>5 years	12,155 (25.8)	10,760 (20.5)	6558 (24.2)	58 (75.3)

NOAC, non-vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors; VKA, vitamin K antagonist.

or 90 days, the treatment persistence for AF patients changed to 47% and 69% after 3 years (see Appendix 2).

Discussion

This study showed a rapid increase in the use of NOAC since their introduction in 2008 reaching a prevalence of 17 per 1000 individuals (2%) in Denmark by the end of 2016. We documented an increase in both incident and prevalent users of all four NOACs, although use of edoxaban was limited. The prevalence of NOAC use increased with higher age, with a prevalence >10% among men aged 85 years or older. The main indication for NOAC treatment was AF. Patients with AF presented with higher age and more comorbidity, such as stroke and chronic heart failure comprising a patient group at higher risk compared to patients with VTE. Lastly, this study found that continuous long-term treatment with NOACs in AF patients was limited. Patients with VTE were primarily treated with rivaroxaban. Contrary to AF, treatment persistence for VTE was more in alignment with treatment recommendations.

A total of 11,767 individuals (accounting for 25% of all dabigatran users) initiated dabigatran for VTE prophylaxis in relation to knee and hip replacement. Dabigatran was approved for treatment of AF in Denmark in 2011 followed by a rapid increase in its use (fig. 1A) [4]. This increase most likely reflects that the total number and fraction of AF patients initiating OAC treatment have increased in Denmark during the last years [16]. Later, a drop in the use of dabigatran was observed, which could be explained by the change in regional guideline recommendations during the study period favouring mainly rivaroxaban and apixaban.

Venous thromboembolism prophylaxis in relation to arthroplastic surgery was the first approved indication for NOAC use. In the wake of studies comparing dabigatran and rivaroxaban to enoxaparin (Dabigatran Etexilate in Extended Venous Thromboembolism Prevention After Hip Replacement Surgery

Table 5.
Specification of all incident NOAC prescriptions by type and dose stratified by assumed treatment indication.

Type of NOAC and start dose	Atrial fibrillation (n = 54,021) (%)	VTE (n = 14,771) (%)	VTE prophylaxis after knee and hip replacement (n = 21,533) (%)	No registered Indication (n = 36,347) (%)
Dabigatran	**23,682 (100)**	**1109 (100)**	**11,767 (100)**	**10,509 (100)**
Dabigatran 75 mg	488 (2.1)	66 (6.0)	2768 (23.5)	422 (4.0)
Dabigatran 110 mg	8980 (37.9)	559 (50.4)	8931 (75.9)	5779 (54.7)
Dabigatran 150 mg	14,214 (60.0)	484 (43.6)	68 (0.6)	4308 (41.3)
Rivaroxaban	**15,522 (100)**	**11,370 (100)**	**9642 (100)**	**15,897 (100)**
Rivaroxaban 2.5 mg	31 (0.2)	12 (0.1)	–	54 (0.3)
Rivaroxaban 10 mg	436 (2.8)	422 (3.7)	9399 (97.5)	4259 (26.8)
Rivaroxaban 15 mg	3603 (23.2)	6769 (59.5)	92 (1.0)	4761 (29.9)
Rivaroxaban 20 mg	11,452 (73.8)	4167 (36.7)	151 (1.5)	6823 (42.9)
Apixaban	**15,876 (100)**	**2346 (100)**	**124 (100)**	**8770 (100)**
Apixaban 2.5 mg	5493 (34.6)	759 (32.4)	56 (45.2)	3873 (44.2)
Apixaban 5 mg	10,383 (65.4)	1587 (67.6)	68 (54.8)	4896 (55.8)
Edoxaban	**46 (100)**	**(n < 5)**	**–**	**27 (100)**
Edoxaban 15 mg	–	–	–	–
Edoxaban 30 mg	14 (30.4)	(n < 5)	–	9 (33.3)
Edoxaban 60 mg	32 (69.6)	(n < 5)	–	18 (66.6)

NOAC, non-vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism. The bold lines represent 100% of each of the four drugs.

(RE-NOVATE) [12] and Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism (RECORD) [13]), a change in treatment regimens and clinical guidelines for VTE prophylaxis in relation to arthroplastic surgery followed, as both NOACs were non-inferior in terms of efficacy and with no need for monitoring [14]. Accordingly, our study showed that 21,531 individuals (accounting for 17% of total NOAC users) filled a NOAC prescription for this indication. Most of these patients were treated with either dabigatran or rivaroxaban. Apixaban is also approved for this indication (May 2011). However, a very limited use was observed in our study (1%), although studies show a favourable safety profile [15,16].

Rivaroxaban and apixaban were approved for stroke prophylaxis in patients with AF in February and December 2012. We observed a large increase in the total use of these NOACs from 2014 to 2016. Several factors may have contributed to the difference in initial uptake among NOACs, such as different branding strategies from the pharmaceutical companies upon introduction and changes in guidelines for anticoagulant treatment in AF patients recommending NOAC rather than VKA [17]. Individuals receiving apixaban for AF had a higher percentage of previous bleeding, stroke and chronic heart failure. This might be explained by selective prescribing due to the low risk of bleeding with apixaban [18–20], especially in the elderly [21].

Rivaroxaban was the first NOAC to be approved for treatment of VTE, and throughout our study period, it has been the preferred NOAC for this indication, accounting for 77% of

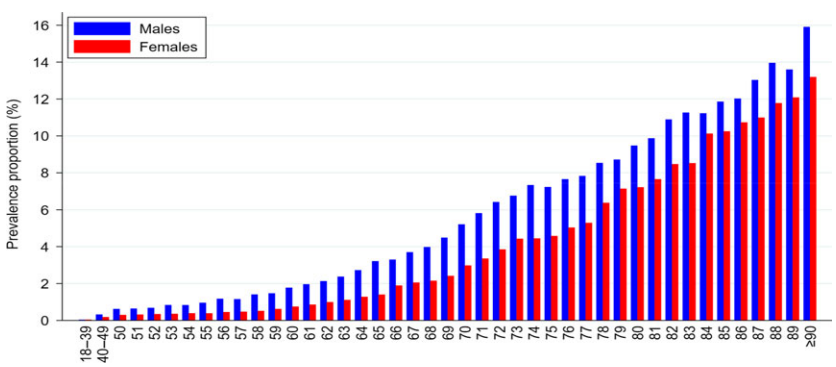

Fig. 2. Sex and age-specific annual prevalence proportion of NOAC user in 2016.

The sex and age distribution of all NOAC users in 2016 displayed as annual prevalence proportion, showing an increasing prevalence with increasing age and for all ages a higher prevalence for males.

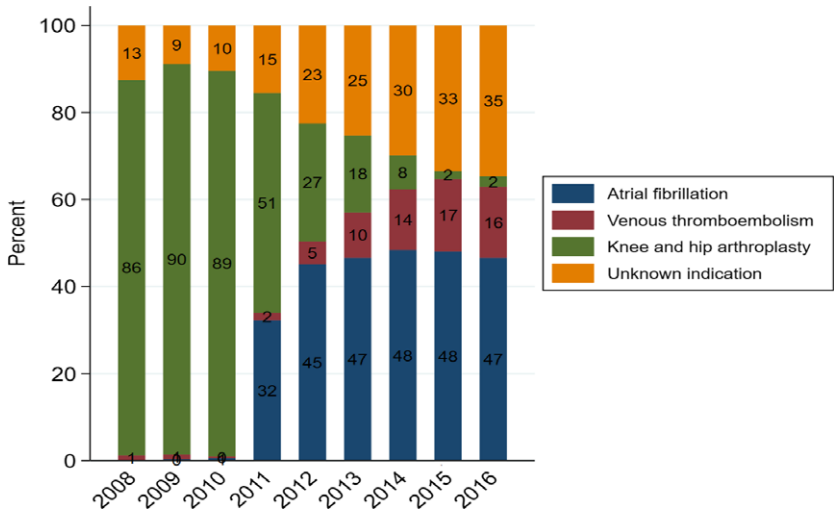

Fig. 3. Proportions of patients receiving NOAC according to indications each year 2008–2016.

The relative distribution of the first filled prescription between the four included indications for NOAC use for each year throughout the study period (2008–2016).

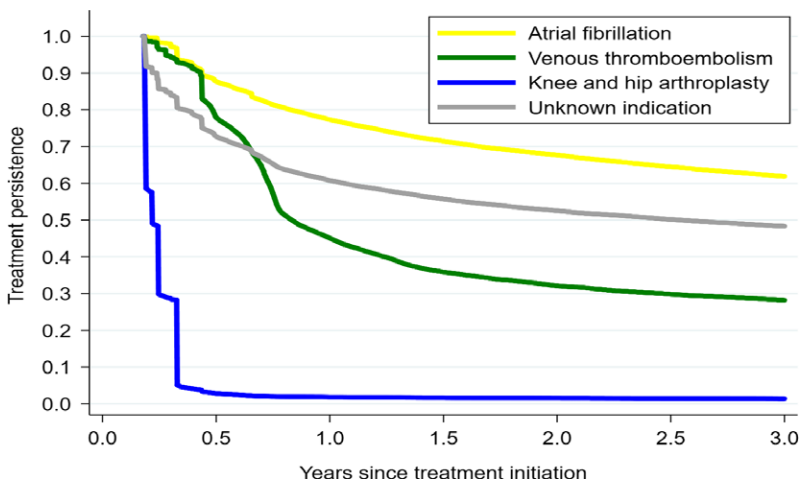

Fig. 4. Treatment persistence for separate indications for anticoagulant treatment.

Treatment persistence 3 years forward from treatment initiation for each indication to NOAC, defined as number of days corresponding to the number of tablets in a package for rivaroxaban and edoxaban (used once daily) or half the number of tablets for dabigatran and apixaban (used twice daily) plus a 60-day grace period.

all users for this indication. This is likely explained by the recommendations in Danish guidelines [22] along with the regional pricing of NOAC favouring rivaroxaban. Apart from the once-daily dosing, rivaroxaban (and apixaban) are the only NOACs providing a single oral drug strategy with no need for heparin lead-in. Similar to our findings, Urbaniak *et al.* [23] also found rivaroxaban to be the preferred NOAC for VTE patients in Norway.

The development in edoxaban use is difficult to investigate in this study due to the low number of users, but the use of edoxaban has recently been explored in more detail [6] documenting a slow but increasing use of edoxaban. The study also showed that edoxaban is primarily used in patients with AF. The baseline characteristics for edoxaban users are generally similar to users of other NOACs, except that the vast majority have switched from other previous OAC treatment.

In the present study, we found 36,347 individuals (28%) receiving NOACs with no identifiable indication according to available ICD codes. In 2009, the share of NOAC initiators where no apparent indication could be identified was 9%. This share increased to 38% in 2016. Drug users without a registered indication may reflect additional time lag between diagnosis and registration of the indication than accounted for in

our study [4], under-reporting (i.e. suboptimal specificity) in healthcare registries, off-label use (e.g. use for cerebral venous thrombosis [24] and heparin-induced thrombocytopenia [25]) or that some patients with indications for NOACs are for some reason not 'selected' for hospital management of their condition, hence never receiving a hospital diagnosis, for example AF. Patients solely treated in primary care may contribute to this, but as we did not have access to information regarding prescriber type, we could not explore this in the present study. As individuals with no registered indication are most often excluded in studies on NOACs [1,4], this patient group should be further explored. In our study, baseline characteristics of these patients were similar to patients with AF (table 3).

The proportion of AF and VTE patients initiating the lower dose of dabigatran (110 mg) was 38% and 50% of all dabigatran initiators, respectively. This dose is recommended for individuals aged ≥80 years, patients with concomitant treatment with verapamil, high risk of bleeding and low risk of thromboembolism or GFR 30–50 ml/min. [26]. A Danish study by Nielsen *et al.* [27] on reduced NOAC doses in AF explored patients initiating a reduced dose with regard to age and chronic kidney disease. Based on their results, it is suspected that a considerable number of patients are inappropriately underdosed, that is, receiving the lower dose without fulfilling the criteria for this (table 1). The same concern applies for rivaroxaban and apixaban. In this study, we documented that 23% and 35% of AF patients receiving rivaroxaban or apixaban received the low dose (15 and 2.5 mg). Previous studies have reported underdosing of NOACs among physicians due to fear of bleeding risk [28]. As most studies supporting the use of NOACs over warfarin were conducted with the standard NOAC dose, patients not treated according to current guidelines may not benefit as well as expected.

During our study, rivaroxaban 2.5 mg bid was only approved for ACS. One hundred patients were treated with this dose (table 5). However, half of these were classified as patients with either AF or VTE. This may reflect physicians not registering an ACS diagnosis for patients hospitalized for AF or VTE. Presuming that rivaroxaban 2.5 mg is dispensed correctly in daily clinical practice, our study finds that rivaroxaban is only rarely used in patients with ACS.

Treatment persistence with NOACs was highly dependent on indication. Guideline recommendations for the duration of anticoagulant treatment in patients with VTE vary between 3 and 12 months depending on patient characteristics and the presumed balance between the risk of recurrence and bleeding [29]. Our results likely reflect this variation, as treatment persistence for VTE steadily dropped within a year of treatment. As anticoagulant treatment for AF is considered to be lifelong, it is remarkable that our results suggest that only 63% are still on continuous NOAC treatment after 3 years, that is, have had no break between periods covered by a prescription exceeding 60 days. An Australian study conducted by Simons *et al.* [30] found treatment persistence for any NOAC to be 48% after 2.5 years. Importantly, we employed a definition of persistence requiring uninterrupted use of NOACs with a grace period of no more than 60 days. This was chosen due to very short half-lives of all NOACS and the consequences of breaks and discontinuation of OAC treatment with even short treatment breaks potentially leading to increased stroke risk [31,32]. Our findings suggest that more research on both persistence and adherence to NOAC treatment among AF patients is needed in order to explore the prognosis in patients with AF stopping anticoagulant treatment and to identify predictors of low adherence.

A major strength of our study is the inclusion of all NOAC users in the study period from Danish national registries covering the entire Danish population including high-quality data on prescription records [11]. A limitation is the lack of information on clinical data such as body-weight and creatinine clearance, which influence the choice and dosing of NOACs [33]. Further, indications for NOACs were defined according to hospital diagnoses. As discussed previously, these definitions may be subject to limitations such as greater diagnostic lag [4] or patients treated outside hospital care, for example patients treated in primary care.

Conclusion

This study documents a rapid increase in the use of all four NOACs in the first 8 years after NOACs were introduced in Denmark. Importantly, we have identified areas requiring further attention, such as the reasons for missing indications in a large proportion of patients, low long-term persistence with NOACs in AF patients and potential inappropriate dosing. Exploring these areas in more detail may guide clinicians to safer and more rational use of NOACs.

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Conflict of Interest

The authors report the following general conflict of interests. SH has no conflict to report. MH reports personal fees from Bristol-Myers Squibb and Pfizer and travel expenses covered by LEO Pharma. LH and AP report an institutional grant from Boehringer Ingelheim. ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD and Roche.

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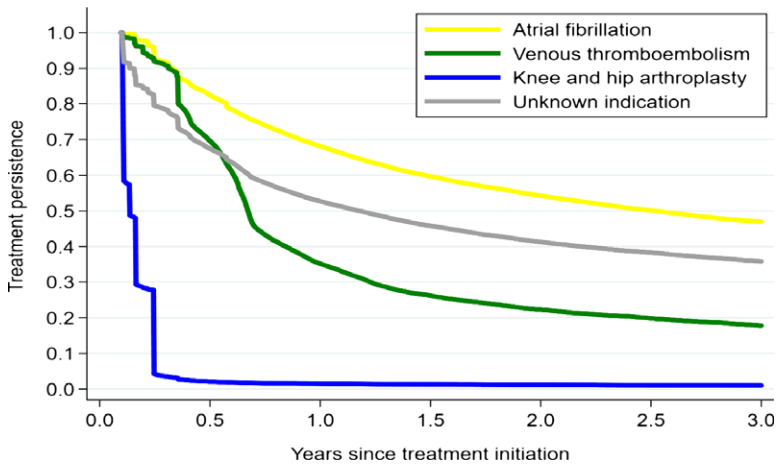
Appendix 1 Definitions of drugs, diseases and procedures

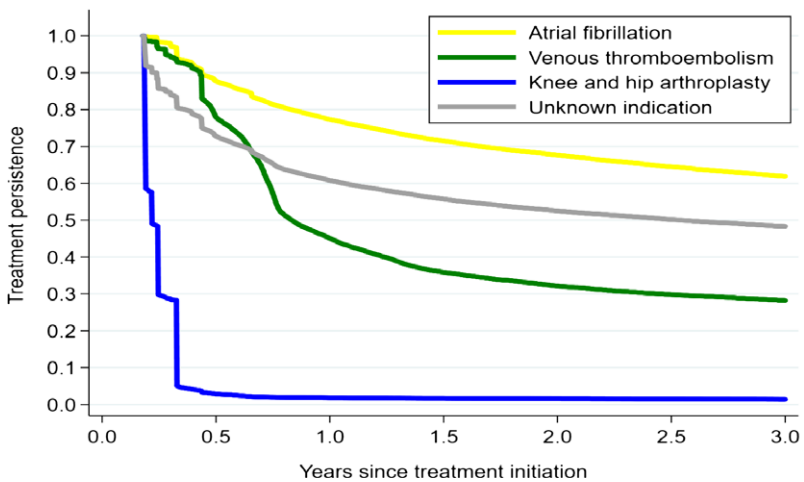
Oral anticoagulants (ATC code)	
Vitamin K antagonists (warfarin and phenprocoumon)	B01AA03, B01AA04
Dabigatran	B01AE07
Rivaroxaban	B01AF01
Apixaban	B01AF02
Edoxaban	B01AF03
Other drugs (ATC code)	
Proton pump inhibitors	A02BC
Low-dose aspirin	B01AC06, B01AC30
$P2Y_{12}$ antagonists	B01AC04, B01AC22, B01AC24
NSAID	M01A (÷M01AX05), N02BA01
SSRI	N06AB
Glucocorticoids	H02AB
Diseases (ICD-10, unless specified otherwise)	
Alcohol abuse	E244 E529A F10 G312A G312B G312C G312D G312E G621 G721 I426 K292 K70 K860 O354 P043 T519 Z502 Z714 Z721 ATC: N07BB
Atrial fibrillation	I48
Previous bleeding	D62 I60-62 I690 I691 J942 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K298A K625 K638C K920-2 N02 N93 R04 R31 S064-S066
Previous GI bleeding	K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K298A K625 K638C K920-2
Cancer (except non-melanoma skin cancer)	C00-C97 (÷C44)
Diabetes	E10-14 G590 G632 H280 H360 N083 O240 O241 O242 O243 ATC: A10
Hypertension	ATC: C03A, C08CA, C08DB01, C09A-D
Ischaemic heart disease	I200 I21 I23 I24 I25
Ischaemic stroke/TIA	G458 G459 I63 I64 I693
Liver failure	D684C I850 I859 I982 K701 K703 K704 K720 K721 K729 K746 K767
Peripheral arterial disease	I700 I702 I708 I709
Renal failure, chronic	E102 E112 E122 E132 E142 I12 (÷I129) N01 N03 N083 N085 N118C N14 N150 N16 (÷ N160) N18 (÷N181) N19 N26 P960 Q601 Q602 Z992
Chronic heart failure	DI50 DI099A DI509 DI971A DO754C DO291A DO742A DO754D DO891A DI130 DZ035EA
Venous thromboembolism (deep venous thrombosis and pulmonary embolism)	I26 I801 I802 I803 I808 I809
Operations/procedures (NOMESCO classification)	
Arthroplastic surgery (knee or hip)	KNFB, KNFC, KNGB, KNGC
Dialysis	BJDF DZ992 DN185

Appendix 2. Sensitivity analyses of treatment persistence

Treatment persistence when the grace period was defined as 30 days



Treatment persistence when the grace period was defined as 60 days



Treatment persistence when the grace period was defined as 90 days