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ORIGINAL REPORT

Use of direct oral anticoagulants in the first year after market entry of edoxaban: A Danish nationwide drug utilization study

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Abstract

Objectives: To describe the early uptake of edoxaban; the fourth direct oral anticoagulant (DOAC) to enter the market.

Methods: Using the Danish nationwide health registries, we identified new users of edoxaban (n = 609) from June 6 (day of marketing) through June 2017. For comparison, we also identified new users of dabigatran (n = 2211), rivaroxaban (n = 19 227), and apixaban (n = 14 736). Users were described regarding indication of use, previous anticoagulant experience, comorbidity, and co-medication.

Results: The rate of edoxaban initiation increased to 2.0 per 100 000 person months in June 2017, compared with 6.3, 37.5, and 27.0 for dabigatran, rivaroxaban, and apixaban. Atrial fibrillation was the most common registered indication for edoxaban (67%) as well as the other DOACs (41–55%). Overall, users of edoxaban were comparable to users of other DOACs (median age 75 vs 72–76 years and 57% vs 53–59% males), except for a generally lower concomitant use of other drugs. Noticeably, 95% of edoxaban users had previously received anticoagulant treatment compared with 31% to 43% for new users of other DOACs, with 77% switching directly from another anticoagulant treatment to edoxaban (45% directly from VKA and 32% directly from DOACs).

Conclusions: While the use of edoxaban is still limited compared with other DOACs, it is increasing. The majority of edoxaban users switch to edoxaban from other anticoagulant treatments. Continued monitoring of the utilization of DOACs, including effectiveness and safety, is considered essential to the safe and rational use of these drugs.

KEYWORDS

anticoagulants, Denmark, direct oral anticoagulants, drug utilization, edoxaban, pharmacoepidemiology

1 | INTRODUCTION

Direct oral anticoagulants (DOAC) have been introduced as alternatives to vitamin K-antagonists (VKA), primarily for stroke prevention in atrial fibrillation[1] and prevention and treatment of venous thromboembolism.[2] The thrombin inhibitor dabigatran etexilate was the first DOAC to receive European approval for use in atrial fibrillation in 2011, and it was soon followed by the two factor Xa inhibitors rivaroxaban and apixaban. Recently, another factor Xa-inhibitor, edoxaban, has been approved as the fourth DOAC in Europe, licensed for use in atrial fibrillation[3] as well as treatment and secondary prevention of pulmonary embolism and deep vein thrombosis.[4]

Dabigatran was adopted very rapidly for the treatment of atrial fibrillation in both Europe[5] and USA.[6,7] After their introduction, rivaroxaban and apixaban also achieved substantial market shares within their first year of availability,[5,7,8] at the expense of dabigatran, which over the years have become a less preferred anticoagulant choice, most likely due to its limited use in renal failure patients and the increased risk of gastrointestinal bleeding.[9,10] The role for edoxaban in a market with 4 similar drugs is not immediately obvious. Using trial data to indirectly compare edoxaban to the other DOACs, it is generally reported to have similar safety and efficacy.[11] Edoxaban holds the advantage of once-daily dosing and an overall low risk of bleeding.[12] However, gastrointestinal bleeding might also be more common among users of edoxaban than at least apixaban.[11]

To understand the use and potential role of this new DOAC, we conducted a drug utilization study to characterize the early uptake of edoxaban. Using Danish nationwide health registries, we quantified the use of edoxaban in the first year after market entry and described the early users with regards to indication of use, previous anticoagulant experience, co-medication, and comorbidity. For comparison, this was also described for new users of dabigatran, rivaroxaban, and apixaban within the same period.

KEY POINTS

What is already known about this subject?

- Edoxaban has recently entered the market as the fourth direct oral anticoagulant (DOAC).
- Overall, edoxaban is considered comparable to the other DOACs regarding safety and efficacy.

What might this study add?

- The early uptake of edoxaban is limited compared with the widespread use of other DOACs.
- Edoxaban is mainly used in patients with atrial fibrillation and, in general, users of edoxaban are similar to patients using other DOACs.
- As an important exception, use of edoxaban is mainly confined to patients with previous anticoagulant experience, with the majority switching to edoxaban directly from other anticoagulant treatment, both vitamin K-antagonists and other DOACs.

2 | METHODS

We identified all Danish users of edoxaban via the Danish National Prescription Registry. Using descriptive statistics and data from the Prescription Registry and the Danish National Patient Registry, we characterized these users regarding treatment indication, previous anticoagulant experience, co-medication, and comorbidity.

2.1 | Setting and data sources

The Danish National Health Service provides tax-supported health care, guaranteeing free and equal access to medical care by general practitioners and hospitals as well as partial reimbursement for prescribed medications.[13] For administration and maintenance of this health care system, numerous administrative and health registries have been established. These registries allow population-based studies covering all residents in Denmark (approximately 5.7 million). We obtained data from the National Prescription Registry,[14] the National Patient Registry,[15] and the Danish Civil Registration System.[16,17] All data sources were linked using the unique civil registry number assigned to all Danish residents.[16]

The National Prescription Registry[14] contains data on all prescription drugs filled by Danish residents since 1995. The data include the type of drug, date of filling, and quantity, whereas the dosing information and the indication for prescribing are not available. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index,[18] and the quantity dispensed for each prescription is described by the number and strength of the pharmaceutical entities (eg, tablets). The Danish National Patient Registry[15] contains nationwide data on all non-psychiatric hospital admissions since 1977 and on outpatient hospital contacts and psychiatric admissions since 1995. Discharge/contact diagnoses have been coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994. The Danish Civil Registration System[16,17] contains data on addresses, migrations, and dates of death.

All codes and definitions applied within these data sources are provided in Appendix A and B.

2.2 | Study cohort

We identified all patients filling a prescription for edoxaban between June 6, 2016 (day of marketing in Denmark) and June 30, 2017. For comparison, we also included patients initiating (first ever prescription) dabigatran, rivaroxaban, or apixaban within the same period.

During the study period, Danish national guidelines considered the 4 different NOACs as equal treatment alternatives in atrial fibrillation, whereas edoxaban was only included in the national guidelines on VTE treatment from May 2017. All NOACs are reimbursed independently of treatment indication by the Danish National Health Service, and there were only minor differences in prices between NOACs during the study period.

2.3 | Treatment indication

We considered 3 potential indications for DOAC use: atrial fibrillation, venous thromboembolism (including deep vein thrombosis and pulmonary embolism), and thromboprophylaxis after knee and hip replacement, although the latter is not an approved indication for edoxaban in Europe. Atrial fibrillation and venous thromboembolism were defined by relevant diagnoses registered at any time prior to DOAC initiation in the Patient Registry, while also including atrial fibrillation up to 90 days after DOAC initiation to allow for diagnostic lag.[5] Patients registered with both conditions were classified as atrial fibrillation unless the diagnosis of venous thromboembolism had been registered less than 1 year prior to DOAC initiation. All patients fulfilling the criteria for a recent knee or hip replacement was classified as such (a relevant procedure code registered in the period from 2 weeks before to 5 weeks after DOAC initiation).

2.4 | Previous anticoagulant experience

We assessed new DOAC users with respect to previous use of anticoagulants. Based on the time between the date of filling the index (cohort defining) DOAC prescription and the date of the most recent previous prescription filled for any oral anticoagulant (VKA or DOAC), patients were classified into current (<120 days), recent (120 days to 2 years), distant (>2 years), and never-use of oral anticoagulants at the day of cohort entry. For patients in the "current" category, ie,

patients seemingly switching to edoxaban from active anticoagulant treatment, we also registered which anticoagulant was the last one filled prior to switching.

2.5 | Co-medication and comorbidity

We included chronic diseases associated with an increased risk of bleeding and/or thromboembolism as registered in the Patient Registry (including both inpatient and outpatient diagnoses) within 5 years prior to the date of inclusion: cancer, chronic renal failure, diabetes, hypertension, myocardial infarction, peripheral arterial disease, any previous bleeding, previous gastrointestinal bleeding, and ischaemic stroke/transient ischaemic attack. Comorbidity was also described by the Charlson Comorbidity Score.[19,20] We further included medication filled within 120 days prior to inclusion: proton pump inhibitors, low-dose aspirin, $P2Y_{12}$ antagonists (clopidogrel, ticagrelor and prasugrel), and non-steroidal anti-inflammatory drugs (NSAIDs). Lastly, for patients with atrial fibrillation, we estimated the CHA_2DS_2-VASc-score[21] (based on age, sex, presence of heart failure, hypertension, diabetes, vascular disease, and history of stroke/transient ischaemic attack/systemic arterial embolism) and HAS-BLED-score[22] (based on age, consumption of platelet inhibitors/alcohol abuse, presence of hypertension and/or abnormal renal/liver function, history of stroke, and bleeding; no information on international normalized ratio was available). Definitions of single constituents of the CHA_2DS_2-VASc and HAS-BLED risk scores are provided in Appendix B.

2.6 | Analysis

Using descriptive statistics, we estimated the incidence rate of new use of edoxaban (among all adult Danes) and characterized these new users regarding age, sex, prescribed strength, and the parameters outlined previously (indication, anticoagulant experience, co-medication, and comorbidity). Results are presented overall and stratified by treatment indication. For comparison, we provided similar baseline characteristics for patients initiating dabigatran, rivaroxaban, and apixaban within the study period.

2.7 | Other

All analyses were performed using STATA Release 14.2 (StataCorp, College Station, TX, USA). The Danish Health Data Authority approved the study. According to Danish law, ethical approval is not required for registry-based studies.

3 | RESULTS

We identified 609 users of edoxaban and 2211, 19 227, and 14 736 users of dabigatran, rivaroxaban, and apixaban during the study period (June 2016 through June 2017). The monthly rate of new use of edoxaban among all Danish adults increased from zero to 2.0 per 100 000 person months in June 2017 (Figure 1, left panel). Comparable rates for dabigatran, rivaroxaban, and apixaban were 6.3, 37.5, and 27.0 in June 2017 (Figure 1, right panel).

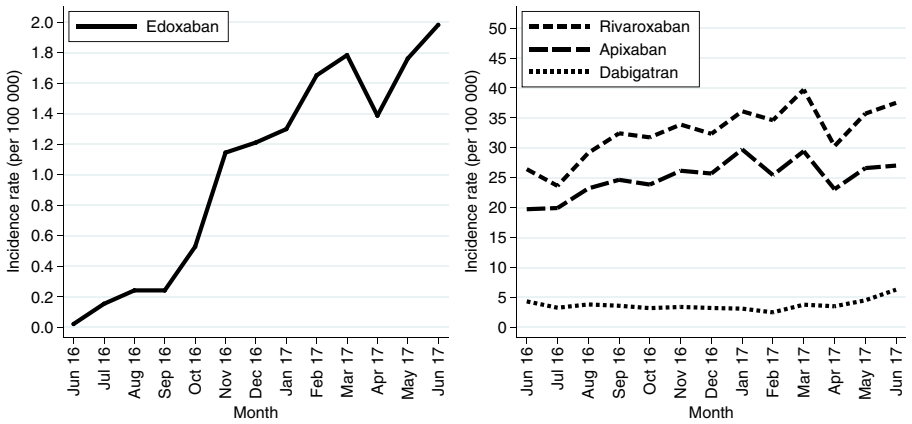

FIGURE 1 The monthly rate of new adult users of edoxaban (per 100 000 person-months) and, for comparison, dabigatran, rivaroxaban, and apixaban from June 2016 to June 2017

TABLE 1 Indication for use of direct oral antagonists (DOACs) initiated between June 2016 and June 2017, based on registry-based hospital discharge diagnoses

	Edoxaban	Dabigatran	Rivaroxaban	Apixaban
	(*n* = 609)	(*n* = 2211)	(*n* = 19 227)	(*n* = 14 736)
Atrial fibrillation	405 (66.5%)	1220 (55.2%)	7841 (40.8%)	7877 (53.5%)
Venous thromboembolism	17 (2.8%)	69 (3.1%)	3737 (19.4%)	1143 (7.8%)
Knee or hip surgery[a]	-	18 (0.8%)	544 (2.8%)	71 (0.5%)
Not classified	187 (30.7%)	904 (40.9%)	7105 (37.0%)	5645 (38.3%)

[a]Edoxaban is not approved for use in relation to knee and hip surgery in Europe.

Atrial fibrillation was the most common registered indication for use of all four DOACs, including edoxaban (Table 1). The majority of patients with venous thromboembolism as well as knee and hip surgery received rivaroxaban, followed by apixaban. Baseline characteristics for users of the individual DOACs are presented in Table 2. Overall, users of edoxaban were comparable with users of other DOACs with regards to age, sex, and comorbidities. As a noticeable exception, almost all users of edoxaban had received previous anticoagulant treatment (95%), compared with 43% for dabigatran, 31% for rivaroxaban, and 39% for apixaban. Among edoxaban users, 77% switched directly from active anticoagulant treatment to edoxaban treatment; 45% from VKA and 32% from another DOAC. Further, users of edoxaban had a lower proportion of concomitant use of drugs, most notably antiplatelet drugs (13% vs 18–23% for low-dose aspirin and 4% vs 8–11% for $P2Y_{12}$-inhibitors). Characteristics of edoxaban users stratified by indication is presented in Table 3. Similar stratifications for the other DOACs are presented in Supplementary Tables 1 to 3. Lastly, edoxaban users with atrial fibrillation had comparable median CHA_2DS_2-VASc and HAS-BLED scores to users of other DOACs (Table 4).

TABLE 2 Baseline characteristics of direct oral antagonist (DOAC) users between June 2016 and June 2017

	Edoxaban	Dabigatran	Rivaroxaban	Apixaban
	(*n* = 609)	(*n* = 2211)	(*n* = 19 227)	(*n* = 14 736)
Age, median (IQR)	75 (69–83)	72 (64–79)	72 (63–80)	76 (69–84)
Male sex	347 (57.0%)	1306 (59.1%)	10 606 (55.2%)	7756 (52.6%)
Previous AC experience[a]				
Current	468 (76.8%)	704 (31.8%)	3669 (19.1%)	3704 (25.1%)
Switch from warfarin	272 (44.7%)	427 (19.3%)	2875 (15.0%)	2298 (15.6%)
Switch from dabigatran	73 (12.0%)	–	473 (2.5%)	614 (4.2%)
Switch from rivaroxaban	70 (11.5%)	158 (7.1%)	–	777 (5.3%)
Switch from apixaban	53 (8.7%)	114 (5.2%)	305 (1.6%)	–
Recent	79 (13.0%)	145 (6.6%)	834 (4.3%)	838 (5.7%)
Distant	33 (5.4%)	113 (5.1%)	1541 (8.0%)	1139 (7.7%)
Never-use	29 (4.8%)	1249 (56.5%)	13 183 (68.6%)	9055 (61.4%)
Dose[b]				
High	421 (69.1%)	1298 (58.7%)	11 192 (58.2%)	9438 (64.0%)
Low	188 (30.9%)	844 (38.2%)	6369 (33.1%)	5298 (36.0%)
Very low	–	69 (3.1%)	1591 (8.3%)	–
Charlson comorbidity score				
Median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
0	224 (36.8%)	1036 (46.9%)	8604 (44.7%)	4899 (33.2%)
1	139 (22.8%)	525 (23.7%)	4606 (24.0%)	3764 (25.5%)
2+	246 (40.4%)	650 (29.4%)	6017 (31.3%)	6073 (41.2%)
Co-morbidity				
Cancer	60 (9.9%)	245 (11.1%)	2062 (10.7%)	1640 (11.1%)
Chronic renal failure	41 (6.7%)	40 (1.8%)	562 (2.9%)	791 (5.4%)
Diabetes	71 (11.7%)	200 (9.0%)	1878 (9.8%)	1863 (12.6%)
Hypertension	460 (75.5%)	1451 (65.6%)	12 044 (62.6%)	10 658 (72.3%)
Myocardial infarction	52 (8.5%)	172 (7.8%)	1355 (7.0%)	1248 (8.5%)
Peripheral arterial disease	20 (3.3%)	46 (2.1%)	438 (2.3%)	471 (3.2%)
Previous bleeding	92 (15.1%)	258 (11.7%)	1944 (10.1%)	2074 (14.1%)
Previous GI bleeding	26 (4.3%)	100 (4.5%)	729 (3.8%)	817 (5.5%)
Ischaemic stroke / TIA	62 (10.2%)	238 (10.8%)	1712 (8.9%)	2169 (14.7%)
Co-medication				
Proton pump inhibitors	154 (25.3%)	522 (23.6%)	4879 (25.4%)	4232 (28.7%)
Low-dose aspirin	78 (12.8%)	396 (17.9%)	3541 (18.4%)	3341 (22.7%)
P2Y12-antagonists	24 (3.9%)	161 (7.3%)	1635 (8.5%)	1691 (11.5%)
Non-aspirin NSAID	57 (9.4%)	279 (12.6%)	2735 (14.2%)	1427 (9.7%)

Abbreviations: AC, oral anticoagulant; GI, gastrointestinal; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; P2Y12-antagonists, clopidogrel, ticagrelor, and prasugrel; TIA, transient ischaemic attack.

[a]Defined as the time from inclusion (index prescription) to the recent prescription for any oral anticoagulant (VKA or DOAC): current (<120 days), recent (120 days to 2 years), distant (>2 years), and never-use.

[b]Dose is based on the prescribed capsule or tablet strength, divided as high (60-mg edoxaban; 150-mg dabigatran; 20-mg rivaroxaban; 5-mg apixaban), low (30-mg edoxaban; 110-mg dabigatran; 10 to 15-mg rivaroxaban; 2.5-mg apixaban), or very low (15-mg edoxaban; 75-mg dabigatran; 2.5-mg rivaroxaban).

TABLE 3 Baseline characteristics of new users of edoxaban between June 2016 and June 2017, stratified by indication for use

	Overall	Atrial Fibrillation	Venous Thromboembolism	Not Classified
	(*n* = 609)	(*n* = 405)	(*n* = 17)	(*n* = 187)
Age, median (IQR)	75 (69–83)	75 (69–82)	72 (68–82)	75 (70–83)
Male sex	347 (57.0%)	233 (57.5%)	9 (52.9%)	105 (56.1%)
Previous AC experience[a]				
Current	468 (76.8%)	313 (77.3%)	15 (88.2%)	140 (74.9%)
Switch from warfarin	272 (44.7%)	178 (44.0%)	6 (35.3%)	88 (47.1%)
Switch from dabigatran	73 (12.0%)	51 (12.6%)	(*n* < 5)	21 (11.2%)
Switch from rivaroxaban	70 (11.5%)	42 (10.4%)	8 (47.1%)	20 (10.7%)
Switch from apixaban	53 (8.7%)	42 (10.4%)	–	11 (5.9%)
Recent	79 (13.0%)	55 (13.6%)	–	24 (12.8%)
Distant	33 (5.4%)	23 (5.7%)	(n < 5)	9 (4.8%)
Never use	29 (4.8%)	14 (3.5%)	(n < 5)	14 (7.5%)
Dose[b]				
60 mg	421 (69.1%)	281 (69.4%)	12 (70.6%)	128 (68.4%)
30 mg	188 (30.9%)	124 (30.6%)	5 (29.4%)	59 (31.6%)
15 mg	–	–	–	–
Charlson comorbidity score				
Median (IQR)	1 (0–2)	1 (0–2)	0 (0–1)	1 (0–2)
0	224 (36.8%)	147 (36.3%)	9 (52.9%)	68 (36.4%)
1	139 (22.8%)	96 (23.7%)	5 (29.4%)	38 (20.3%)
2+	246 (40.4%)	162 (40.0%)	(n < 5)	81 (43.3%)
Comorbidity				
Cancer	60 (9.9%)	39 (9.6%)	(n < 5)	20 (10.7%)
Chronic renal failure	41 (6.7%)	28 (6.9%)	(n < 5)	12 (6.4%)
Diabetes	71 (11.7%)	48 (11.9%)	–	23 (12.3%)
Hypertension	460 (75.5%)	309 (76.3%)	8 (47.1%)	143 (76.5%)
Myocardial infarction	52 (8.5%)	37 (9.1%)	–	15 (8.0%)
Peripheral arterial disease	20 (3.3%)	13 (3.2%)	–	7 (3.7%)
Previous bleeding	92 (15.1%)	65 (16.0%)	–	27 (14.4%)
Previous GI bleeding	26 (4.3%)	17 (4.2%)	–	9 (4.8%)
Ischaemic stroke / TIA	62 (10.2%)	38 (9.4%)	(n < 5)	23 (12.3%)
Co-medication				
Proton pump inhibitors	154 (25.3%)	104 (25.7%)	(n < 5)	47 (25.1%)
Low-dose aspirin	78 (12.8%)	47 (11.6%)	(n < 5)	29 (15.5%)
P2Y12-antagonists	24 (3.9%)	17 (4.2%)	–	7 (3.7%)
Non-aspirin NSAID	57 (9.4%)	44 (10.9%)	(n < 5)	12 (6.4%)

Abbreviations: AC, oral anticoagulant; GI, gastrointestinal; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; P2Y12-antagonists, clopidogrel, ticagrelor, and prasugrel; TIA, transient ischaemic attack.

[a]Defined as the time from inclusion (index prescription) to the recent prescription for any oral anticoagulant (VKA or DOAC): current (<120 days), recent (120 days to 2 years), distant (>2 years), and never-use.

[b]Dose is based on the prescribed tablet strength.

4 | DISCUSSION

We have documented a slow but increasing initial uptake of edoxaban and have described the characteristics of early edoxaban users in Denmark within the first year following market entry. Edoxaban is primarily used in atrial fibrillation and appears to be used in patients that are generally similar to those using other DOACs, with the important exception that the majority of new users are switched to edoxaban from other oral anticoagulant therapies.

Compared with the study population in ENGAGE AF trial,[3] "real-life" users of edoxaban with AF had a similar median age (75 years in the present study vs 72 in the trial) but at the same time lower frequencies of comorbid conditions, such as prior stroke/TIA (9% vs 28% in the trial), diabetes (11% vs 36%), and aspirin use (14% vs 29%). Despite the lower frequency of comorbidity in patients initiating edoxaban, the proportion of patients using a reduced dose in our population (31%) was higher than the proportion fulfilling the criteria for dose reduction in the ENGAGE AF trial (25%). Although assessment of the appropriateness of dosing was not possible in the present study, this may indicate underdosing with edoxaban in some patients. Physicians withholding[23,24] or underdosing[25,26] anticoagulation in order to avoid bleeding have previously been reported in real-life studies on

TABLE 4 CHA_2DS_2-VASc and HAS-BLED scores among users of edoxaban, dabigatran, rivaroxaban, and apixaban, restricted to those with atrial fibrillation

	Edoxaban	Dabigatran	Rivaroxaban	Apixaban
	(*n* = 405)	(*n* = 1220)	(*n* = 7841)	(*n* = 7877)
CHA_2DS_2-VASc				
Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
0–1	38 (9.4%)	255 (20.9%)	1178 (15.0%)	903 (11.5%)
2	80 (19.8%)	281 (23.0%)	1623 (20.7%)	1294 (16.4%)
3+	287 (70.9%)	684 (56.1%)	5040 (64.3%)	5680 (72.1%)
HAS-BLED				
Median (IQR)	3 (2–3)	2 (2–3)	3 (2–3)	3 (2–3)
0–1	40 (9.9%)	204 (16.7%)	1106 (14.1%)	847 (10.8%)
2	119 (29.4%)	407 (33.4%)	2431 (31.0%)	2208 (28.0%)
3+	246 (60.7%)	609 (49.9%)	4304 (54.9%)	4822 (61.2%)

patients treated with DOACs. Importantly, low-dose edoxaban was inferior to warfarin with regards to prevention of ischaemic stroke in the ENGAGE AF trial.[3]

Concomitant use of antiplatelet agents and NSAIDs was less common in new users of edoxaban compared with new users of other DOACs. This may be explained by the higher proportion of prevalent users of oral anticoagulants (ie, switchers) in the edoxaban group. As demonstrated in a recent Danish study,[27] use of both platelet inhibitors and NSAIDs was markedly more common in anticoagulant naïve initiators of DOACs compared with those switching from another oral anticoagulant. However, this difference was reduced during the 6-month period following DOAC initiation, reflecting that antiplatelet therapy is often discontinued at the time of initiation of an oral anticoagulant, as recommended by international guidelines.[1] Another potential explanation for the lower concomitant medication use in the edoxaban group is selective prescribing, ie, the channeling of edoxaban away from individuals at increased risk of gastrointestinal bleeding, as this is an important safety concern related to edoxaban.[12] Regardless of the underlying cause, these differences in patient characteristics between users of different DOACs must be kept in mind when conducting and interpreting observational studies assessing the comparative effectiveness and safety of DOACs.[28,29]

We have shown that the uptake of edoxaban has been considerably slower than what was seen for the other DOACS, especially dabigatran, which was the first DOAC entering the market.[5] The rapid uptake of dabigatran was likely explained by the novel availability of a supposedly safer anticoagulant treatment option with no need for monitoring and less interactions with food and co-medication. This is further supported by the substantially larger proportion of patients without current anticoagulant use who initiated treatment with dabigatran during the first 4 months following market entry of dabigatran compared with the first edoxaban initiators (59% vs 23%).[30] Thus, dabigatran was initially used both in patients newly diagnosed with an indication for anticoagulant therapy,[31] in patients previously found unsuitable for VKA therapy,[23] and in switchers from other anticoagulants.[32] By contrast, the early uptake of edoxaban has almost exclusively been in the latter group of patients (ie, switchers), which is consistent with prior findings on the utilization patterns of newly introduced drugs.[33] Incidentally, the ENGAGE AF trial is the only DOAC trial in AF reporting previous VKA experience to modify the effect of edoxaban treatment.[34] For patients with previous VKA use, the advantageous effect of high-dose edoxaban compared with VKA was attenuated, while low-dose edoxaban was inferior to warfarin among those with previous VKA use.[35]

Considering the availability of four relatively similar drugs, one may speculate on the role for the fourth DOAC to enter the market. In terms of preventing stroke and systemic embolism, subgroup analyses of the ENGAGE AF trial have reported edoxaban to be at least as effective as warfarin in patients with a history of ischaemic stroke or transient ischaemic attack,[36] patients with heart failure (NYHA III/IV),[37] East Asian patients,[38] and the elderly,[39] thus suggesting a broad applicability of edoxaban. Network meta-analyses have inherent limitations, but most publications conclude that in comparison with other DOACs, edoxaban has an overall similar efficacy with the 60-mg dose, whereas the 30-mg dose may be less effective than twice-daily apixaban and twice-daily dabigatran 150 mg.[40,41] With respect to safety, edoxaban 60 mg may have a lower bleeding risk than rivaroxaban and dabigatran, and edoxaban 30 mg has a favorable bleeding risk compared with all other DOACs.[40,41] Overall, edoxaban thus holds the advantage of once-daily dosing and has a predictable, dose-dependent pharmacology with similar efficacy compared with warfarin and a potentially lower risk of major bleeding compared with other DOACs. Among patients with AF, edoxaban seems as a valid alternative to warfarin, especially the elderly or other patients at increased bleeding risk. Importantly, recent data on the use of edoxaban 60 mg in patients with creatinine clearance >95 mL/min has reported a signal of higher thromboembolic rates with edoxaban compared with warfarin.[42]

The primary strength of our study is the use of high-quality data on prescription records[14] and inpatient diagnoses[15] and the timely analysis with only a few months lag in the reporting of edoxaban uptake. Further, the use of data on prescription fills, as opposed to prescriptions issued, increases the likelihood that we are in fact describing patients that ultimately uses the drug in question.[43] The main limitation of our study is the limited data on indications for use, and consequently a large proportion of patients (31%–41% across DOACs) was denoted with unknown indication for treatment. As these patients were more commonly new anticoagulant users, the missing indications

for DOAC therapy may be explained by lag time between diagnosis and registration of the indication, as shown in prior studies.[5] Further, some patients might be managed solely in primary care, thus never receiving a hospital diagnosis (ie, the basis of our classification). More likely, the lack of diagnoses is a product of suboptimal coding practices within the hospitals. Importantly, these DOAC users without a registered indication were older, more frequently had a history of ischaemic stroke, and more often received low-dose DOAC compared with DOAC users with a registered indication. Therefore, the exclusion of DOAC users without a registered indication may constitute an important selection bias in observational studies based on the Danish health care registries, as pointed out previously.[5,27]

In conclusion, we have documented the initial uptake of edoxaban. While early users are generally similar to new users of other DOACs in the same time-period, edoxaban users typically switch to edoxaban directly from other anticoagulant treatment. Continued monitoring of the utilization of DOACs, including studies of comparative effectiveness and safety, is essential to the safe and rational use of these drugs.

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CONFLICT OF INTEREST

Anton Pottegård reports participation in research projects funded by Boehringer-Ingelheim with funds paid to the institution where he was employed (no personal fees). Erik L. Grove has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, and Pfizer and has previously participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. Maja Hellfritzsch reports speaker honorarium from Bristol-Myers Squibb and Pfizer.

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SUPPORTING INFORMATION

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

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