Original Research

Oral Anticoagulation Therapy for Venous Thromboembolism in Norway: Time Trends and Treatment Patterns

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ABSTRACT

Purpose: Data describing treatment patterns of patients with venous thromboembolism (VTE) patients in Scandinavia are scarce. This study sought to address this scarcity by describing demographic and clinical characteristics, trends in the use of oral anticoagulants (OACs), and treatment patterns in patients treated for VTE in Norway between 2013 and 2017.

Methods: Using data from Norway's nationwide registries, a cohort study included patients newly (after 2008) treated OACs who were diagnosed with VTE between January 2013 and December 2017 and were dispensed an OAC (warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban) within 30 days. Patient characteristics and the percentage of patients with VTE who initiated treatment with each OAC for each calendar year were reported. Initial therapy persistence was assessed using Kaplan-Meier curves and compared between the OAC groups using the log-rank test.

Findings: The comorbidity burden was similar between patients taking warfarin and those taking apixaban but lower among patients taking rivaroxaban. Direct oral anticoagulant (DOAC) use increased from 33.2% to 93.6% during the study period, whereas warfarin use decreased. Persistence was higher in the apixaban cohort compared with the warfarin cohort, with the difference mostly apparent after 6 months, whereas persistence was similar between the patients taking rivaroxaban and those taking warfarin.

Implications: Between 2013 and 2017, DOAC use among patients with VTEs increased markedly in Norway, whereas the use of warfarin decreased. Patients taking apixaban had higher persistence compared with those taking warfarin, whereas patients taking warfarin and those taking rivaroxaban had similar persistence. Further studies with longer follow-up are required to examine the use of extended OAC treatment for VTE. (*Clin Ther.* 2021;43:1179–1193.) © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Keywords: anticoagulant, Norway, pulmonary embolism, venous thromboembolism, venous thrombosis.

INTRODUCTION

Deep vein thrombosis and pulmonary embolism, collectively known as venous thromboembolism (VTE), is

the third most frequent acute cardiovascular syndrome after myocardial infarction and stroke globally.[1] A recent study that used data from the nationwide Norwegian Patient Registry reported the incidence of VTE as 1.38 events per 1000 person-years (95% CI, 1.34–1.41) in 2017.[2] The condition presents as an immediate medical emergency that can result in serious complications, including death. It has been estimated that roughly 1 in 5 patients experiencing VTE will die in the year after an index event.[3] In addition to a high case-fatality rate, recurrence is common, with estimates suggesting a 3-year cumulative incidence rate of 15%.[4]

When a patient experiences a VTE, treatment with an anticoagulant is recommended. Treatment guidelines recommend at least 3 to 6 months of anticoagulation therapy after VTE diagnosis. This treatment is considered sufficient if the patient's first VTE event was provoked by surgery or other transient risk factors for VTE. However, in the absence of transient risk factors and if the patient's risk of bleeding is considered low, extended therapy beyond 6 months could also be recommended.[5] More recently, direct oral anticoagulants (DOACs), indulging apixaban, rivaroxaban, dabigatran, and edoxaban, have been marketed. These medications have established efficacy and tolerability, without the requirement for regular monitoring, unlike more traditional anticoagulants.[6,7]

Real-world data can provide a greater understanding of the current treatment landscape for VTE and are important for furthering our understanding of how anticoagulants are prescribed and used in clinical practice.[8] Real-world studies that have compared the use of DOACs with other anticoagulation therapies in VTE populations have primarily been conducted in Europe[9–12] and North America,[13] with only limited studies in the Scandinavian setting.[14,15] The patient registries in Scandinavia are regarded as valuable sources of real-world data because of their nationwide coverage and high completeness.[16,17] Therefore, our objectives were to describe demographic and clinical characteristics, trends in oral anticoagulant (OAC) use, and anticoagulant treatment patterns of patients with VTE in Norway from 2013 to 2017.
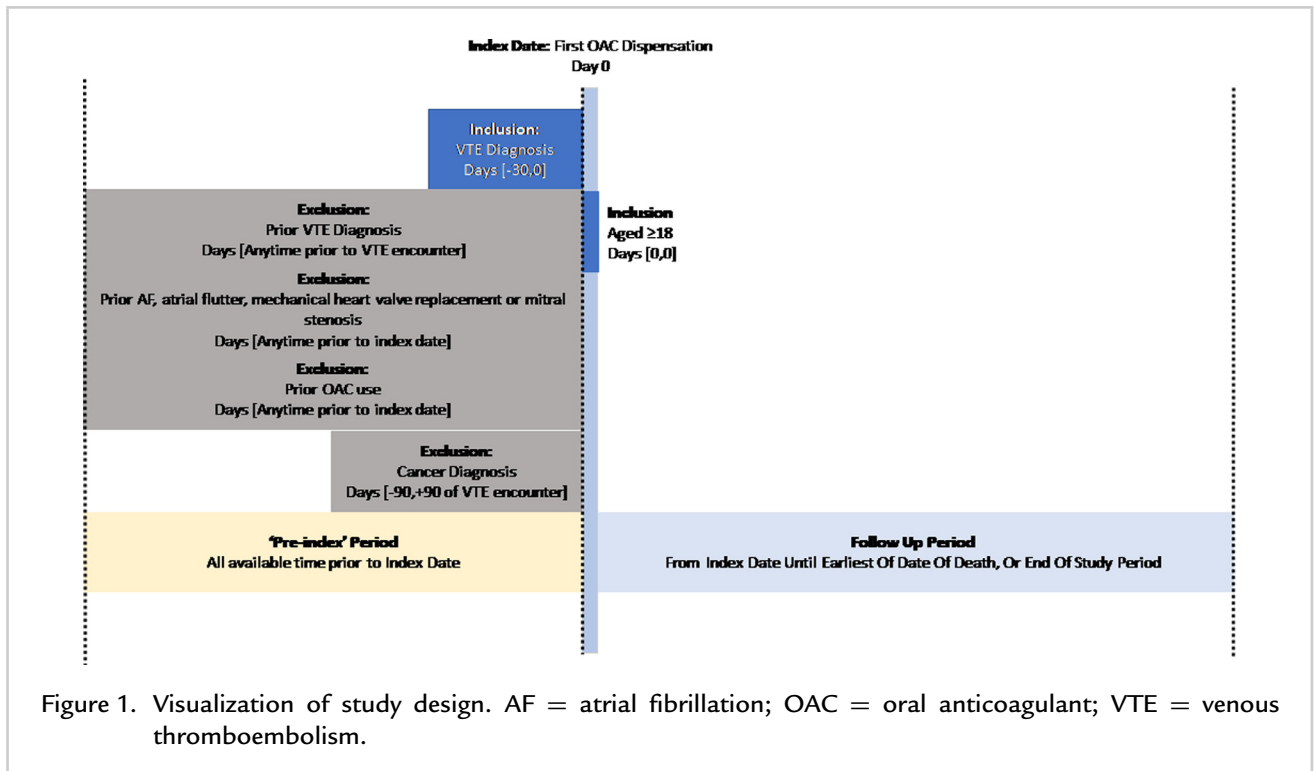
PARTICIPANTS AND METHODS
Data Source
The study included data from 2 nationwide registries in Norway: the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD).

The NPR includes information on all hospital episodes (inpatient, outpatient, and emergency visits), admission and discharge dates, and hospital procedures since 2008. Diagnoses are recorded using the *International Classification of Diseases, Tenth Revision* (ICD-10) codes. Procedures are coded according to the Nordic Medico-Statistical Committee coding system. The NorPD covers all prescriptions dispensed from nationwide pharmacies from 2004 onward. Each medication is coded using the Anatomical Therapeutic Chemical (ATC) system. Each record also includes information on the date, strength, and quantity of dispensations. These data sets can be linked using unique patient identifiers assigned to each resident in Norway. All directly identifiable information is removed from these datasets by the registry holder before data release. To ensure that patient confidentiality is further protected, the Norwegian registries provide the linked dataset in a restricted format without dates of event occurrences. Instead, so-called difference days are provided, which represent the difference between an event date and a random date. The calendar year of the event date is also available. The random date remains consistent for the same patient, so the number of days among diagnoses, treatment, and other events of interest can be ascertained. Although the difference days from event occurrences are provided, difference days from known event dates, such as the end of study follow-up, are not provided (see the Appendix for further clarification). The study was approved by the Regional Ethics Committee of South-East Norway (2017/1328-9).

Study Design
Patients were identified by their first inpatient or outpatient diagnosis of VTE in NPR that occurred from January 1, 2013, to December 31, 2017. The VTE diagnoses were identified using ICD-10 codes (Appendix) in the primary position only.[18,19] The VTE diagnosis was required to be followed by a pharmacy dispensation for any OAC within 30 days. The index date was the first dispensation of an OAC identified within the study period. Patients were included if they were ≥18 years of age at their index date and were excluded if they had atrial fibrillation, mitral stenosis, mechanical heart valve replacement, or an OAC dispensation any time before the index date (from the January 1, 2008, beginning of the registries' linked data collection). Patients with cancer identified in the 3 months before or after VTE diagnoses were

Figure 1. Visualization of study design. AF = atrial fibrillation; OAC = oral anticoagulant; VTE = venous thromboembolism.

also excluded because traditionally these patients have been excluded from VTE DOAC clinical trials.[20] An illustration of the inclusion and exclusion criteria is provided in Figure 1.

The preindex period included all available time before the index date, whereas follow-up included all available time, including and after the index date, until patient death or the last known date (latest dispensation or diagnostic encounter for each patient) within the data. Patients were classified into treatment groups based on their index dispensation.

Study Measures

The OACs included warfarin and DOACs (apixaban, rivaroxaban, dabigatran, and edoxaban), which were identified using ATC codes from the NorPD. Baseline demographic characteristics, including age and sex, were identified at the index date. Clinical characteristics, such as comorbidities and bleeding history (major, intracranial, gastrointestinal, and clinically relevant nonmajor), were identified using ICD-10 codes in the NPR in the preindex period. The validated weights in the study by Quan et al[21] were used to calculate the Charlson Comorbidity Index score. Transient risk factors for VTE, including any overnight hospital stay, major surgery, fractures, trauma, and estrogen use, were identified using ATC or ICD-10 procedure codes in the 3 months before the index VTE.

The strength of the drug dispensed at the index date was identified in the NorPD. Days of supply were estimated for DOACs using information on the number of dispensations a patient received and on package size and strength, assuming a fixed-dosing schedule that varied, depending on the drug strength (Appendix). Because warfarin dosing varied among patients, the days of supply were estimated by calculating a mean daily dose for each patient who had ≥2 dispensations in the 3 to 12 months after the index date. Daily doses were imputed for all other patients by calculating and applying age-specific (<75–≥75 years) medians of the estimated daily doses.

Treatment persistence was defined as evidence of a repeat prescription that allowed for a 30-day gap (grace period) after the end of the days' supply of each prescription. If patients discontinued treatment or switched to another therapy, then they were regarded as being nonpersistent with treatment. Patients were followed up until their deaths or their last known follow-up dates (latest dispensation or diagnostic encounter for each patient).

Statistical Analysis

Baseline characteristics were summarized by index treatment and compared. For each calendar year, the distribution of patients undergoing VTE and newly initiating treatments was described. Kaplan-Meier methods were used to describe the time on their initial therapy. Patients were censored at death or their last known follow-up date.

RESULTS

During the 5-year study period, 12,585 patients with a first diagnosis of VTE were identified, which included 3557 treated with warfarin, 3088 with apixaban, 5828 with rivaroxaban, 87 with dabigatran, and 1 with edoxaban. Because of low numbers of patients using dabigatran and edoxaban, characteristics of those patients were not described any further, leaving a total population of 12,473 patients taking OAC. The demographic and clinical characteristics of patients are provided in Table I. These patients had a median age of 63 years (interquartile range [IQR], 50–74 years), and 45.7% were female. Comorbidities with the highest prevalence in all OAC treatment groups were hypertension (44.3%), chronic obstructive pulmonary disease (COPD) and/or asthma (20.6%), ischemic heart disease (12.1%), and rheumatic disease (9.3%). The most common prior bleeding type was clinically relevant nonmajor (9.7%), and the most common transient risk factor for VTE, identified in the 3 months before diagnosis, was at least 1 overnight hospital stay (18.4%).

Patients initiating warfarin therapy were younger than those initiating apixaban therapy (median age, 64 [IQR, 50–76] vs 66 [IQR, 52–76] years) but older than those initiating rivaroxaban therapy (median, 61 years; IQR, 48–72 years). The median follow-up time was longest in the warfarin patient group (45.6 months; IQR, 31–54 months) followed by the rivaroxaban patient group (29.1 months; IQR, 15–42 months) and then the apixaban patient group (12.4 months; IQR, 6–21 months). However, these estimates are a reflection of the calendar year in which patients in each of the OAC groups initiated their first treatment (Table II and Figure 2).

The prevalence of comorbidities in the apixaban and warfarin treatment groups was similar for most comorbidities at baseline, with minor differences for myocardial infarction (warfarin, 8.3%; apixaban, 5.5%), renal disease (warfarin, 7.6%; apixaban,

5.2%), and ischemic heart disease (warfarin, 15.6%; apixaban, 13.7%). For each comorbidity, patients taking warfarin had the higher prevalence. Greater differences in comorbidity prevalence were found when patients taking warfarin were compared with patients taking rivaroxaban, with the patients taking warfarin generally having the highest prevalence of these comorbidities. The greatest differences were for hypertension (warfarin, 48.8%; rivaroxaban, 40.0%), ischemic heart disease (warfarin, 15.6%; rivaroxaban, 9.1%), and renal disease (warfarin, 7.6%; rivaroxaban, 2.2%) (Table II).

Warfarin versus apixaban users had a similar history of bleeding for all bleeding types (major, 3.2% vs 2.8%; intracranial, 1.0% vs. 0.8%; gastrointestinal, 3.4% vs 3.3%; and clinically relevant nonmajor, 9.9% vs 10.6%), whereas rivaroxaban users had a somewhat lower prevalence of major bleeding (2.0%) but a similar prevalence of the other bleeding types when compared with warfarin users. Warfarin, apixaban, and rivaroxaban users had a similar prevalence of transient risk factors for VTE in the 3 months before the index date, except for the prevalence of prior overnight hospital stay that was higher in warfarin users (warfarin, 21.9%; apixaban, 17.3%; rivaroxaban, 16.9%).

Trends in OAC Use Over Time

The percentage of patients with VTE initiating treatment with DOACs after an incident VTE increased from 33.2% in 2013 to 93.6% in 2017, and consequently, the use of warfarin decreased from 66.8% to 6.3%. In 2017, patients with incident VTE most commonly initiated OAC treatment with apixaban (53.9%), followed by rivaroxaban (38.4%), warfarin (6.3%), dabigatran (1.3%), and edoxaban (0.04%) (Figure 2).

Treatment Patterns

The strength of the index drug was 2.5 mg for all warfarin dispensations, 5 mg for most apixaban dispensations (94.3%), and 15 mg alone (31.9%) or 15 and 20 mg (62.6%) for rivaroxaban dispensations (the latter strength presumed to be initiated 21 days after completion of the former). The median time receiving initial therapy was just >6 months in all treatment cohorts (warfarin: 6.3 [interquartile range, 3.4–10.6] months; apixaban: 6.4 [interquartile range, 3.7–15.9] months, rivaroxaban: 6.0 [interquartile range, 3.9–

Table I. Baseline characteristics of patients with VTE initiating OAC therapy between 2013 and 2017, overall and by index OAC group.

Characteristic	Overall (N = 12,473)	Warfarin (n = 3557)	Apixaban (n = 3088)	Rivaroxaban (n = 5828)
Age at index date, median (IQR), y	63 (50–74)	64 (50–76)	66 (52–76)	61 (48–72)[a]
Female, No. (%)	5,697 (45.7)	1,726 (48.5)	1,423 (46.4)	2,539 (43.6)[a]
Follow-up time,[b] median (IQR), mo	–	45.6 (31–54)	12.4 (6–21)	29.1 (15–42)
Comorbidities, No. (%)				
Myocardial infarction	701 (5.6)	296 (8.3)	171 (5.5)[a]	234 (4.0)[a]
Congestive heart failure	1,022 (8.2)	366 (10.3)	263 (8.5)	393 (6.7)[a]
Peripheral vascular disease	653 (5.2)	228 (6.4)	194 (6.3)	231 (4.0)[a]
Cerebrovascular disease	688 (5.5)	238 (6.7)	203 (6.6)	247 (4.2)[a]
Chronic pulmonary disease	2,565 (20.6)	730 (20.5)	692 (22.4)	1,143 (19.6)
Rheumatic disease	1,164 (9.3)	372 (10.5)	341 (11.0)	451 (7.7)[a]
Peptic ulcer disease	461 (3.7)	164 (4.6)	148 (4.8)	149 (2.6)[a]
Mild liver disease	248 (2.0)	56 (1.6)	66 (2.1)	126 (2.2)
Diabetes without chronic complications	651 (5.2)	193 (5.4)	190 (6.2)	268 (4.6)
Diabetes with chronic complications	248 (2.0)	92 (2.6)	69 (2.2)	87 (1.5)
Renal disease	559 (4.5)	271 (7.6)	160 (5.2)[a]	128 (2.2)[a]
Malignant tumors	654 (5.2)	181 (5.1)	207 (6.7)	266 (4.6)
Ischemic heart disease	1,510 (12.1)	556 (15.6)	422 (13.7)	532 (9.1)[a]
Hypertension	5,520 (44.3)	1,736 (48.8)	1,450 (47.0)	2,334 (40.0)[a]
Pulmonary hypertension	89 (0.7)	21 (0.6)	38 (1.2)	30 (0.5)
Severe obesity[c]	420 (3.4)	143 (4.0)	96 (3.1)	181 (3.1)
Charlson score, No. (%)				
0	7,628 (61.2)	2,043 (57.4)	1,774 (57.4)	3,811 (65.4)[a]
1	2,386 (19.1)	720 (20.2)	613 (19.9)	1,053 (18.1)[a]
2	1,305 (10.5)	410 (11.5)	356 (11.5)	539 (9.2)[a]
3	659 (5.3)	219 (6.2)	187 (6.1)	253 (4.3)[a]
≥4	495 (4.0)	165 (4.6)	158 (5.1)	172 (3.0)[a]
Bleeding history, No. (%)				
Major bleeding	315 (2.5)	113 (3.2)	88 (2.8)	114 (2.0)
Intracranial bleeding	82 (0.7)	34 (1.0)	24 (0.8)	24 (0.4)
Gastrointestinal bleeding	380 (3.0)	121 (3.4)	101 (3.3)	158 (2.7)
CRNM bleeding	1209 (9.7)	353 (9.9)	328 (10.6)	528 (9.1)
Transient risk factors for VTE (in the 3 mo before index VTE), No. (%)	3610 (28.9)	1138 (32.0)	818 (26.4)	1656 (28.4)
Major surgery	295 (2.4)	87 (2.4)	76 (2.5)	132 (2.3)
Any overnight hospitalization	2296 (18.4)	779 (21.9)	534 (17.3)[a]	983 (16.9)[a]
Fracture	767 (6.1)	202 (5.7)	178 (5.8)	387 (6.6)
Trauma	372 (3.0)	104 (2.9)	82 (2.7)	186 (3.2)
Estrogen use	992 (8.0)	272 (7.6)	213 (6.9)	507 (8.7)

CRNM = clinically relevant nonmajor; IQR, interquartile range; OAC = oral anticoagulant; VTE = venous thromboembolism.

[a] P <0.0001 compared with warfarin.

[b] Because of data limitations, follow-up time was derived as: the latest of the last diagnostic encounter or prescription during 2017 or 365 days after the last diagnostic encounter or prescription up to 2016.

[c] Severe obesity is identified using the *International Classification of Diseases, Tenth Revision* (ICD-10) code E66 because body mass index data are not available in the registries.

Table II. Treatment patterns of patients with VTE initiating use of OACs between 2013 and 2017, overall and by index OAC group.

Treatment pattern	Warfarin (n = 3557)	Apixaban (n = 3088)	Rivaroxaban (n = 5828)
Tablet strength of index dose,[a] No. (%)			
2.5 mg	3557 (100.0)	156 (5.1)	–
2.5 mg, 5 mg	–	19 (0.6)	–
5 mg	–	2913 (94.3)	–
10 mg	–	–	23 (0.4)
10 mg, 15 mg	–	–	5 (0.09)
10 mg, 20 mg	–	–	4 (0.07)
15 mg	–	–	1861 (31.9)
15 mg, 20 mg	–	–	3646 (62.6)
20 mg	–	–	289 (5.0)
Kaplan-Meier estimates			
Time receiving therapy, median (IQR), mo	6.3 (3.4–10.6)	6.4 (3.7–15.7)	6.0 (3.9–9.2)
Patients persistent in each of the following periods, % (95% CI)			
0–3 mo	79.7 (78.3–81.0)	83.7 (82.3–85.0)	87.4 (86.5–88.2)
0–6 mo	53.1 (51.4–54.7)	53.9 (51.9–55.8)	49.7 (48.4–51.1)
0–9 mo	30.3 (28.8–31.8)	36.5 (34.5–38.4)	25.4 (24.3–26.6)
0–12 mo	21.9 (20.6–23.4)	30.8 (28.8–32.8)	19.2 (18.2–20.3)

IQR = interquartile range; OAC = oral anticoagulant; VTE = venous thromboembolism.

[a] If patients had >1 dispensation of different strengths of the same OAC at index, then both strengths were described.
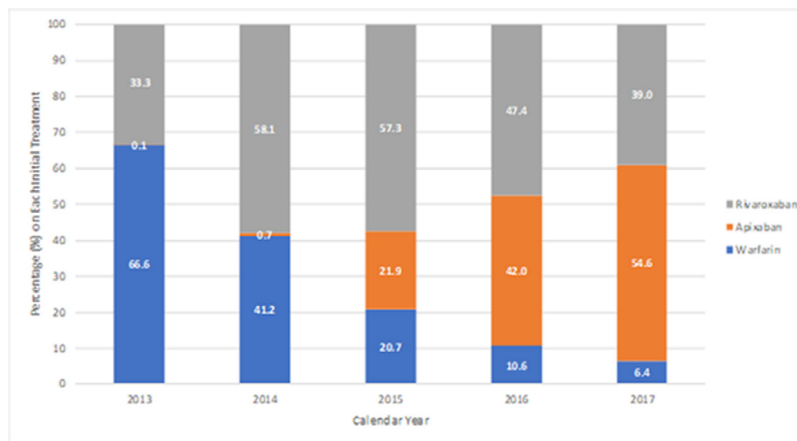

Figure 2. Distribution of oral anticoagulants (OACs) used among the newly treated incident venous thromboembolism (VTE) population in Norway. The percentage of those that initiate treatment after their VTE diagnosis in Norway in each calendar year is given. The denominator is the total number of patients with VTE who use OACs in Norway.
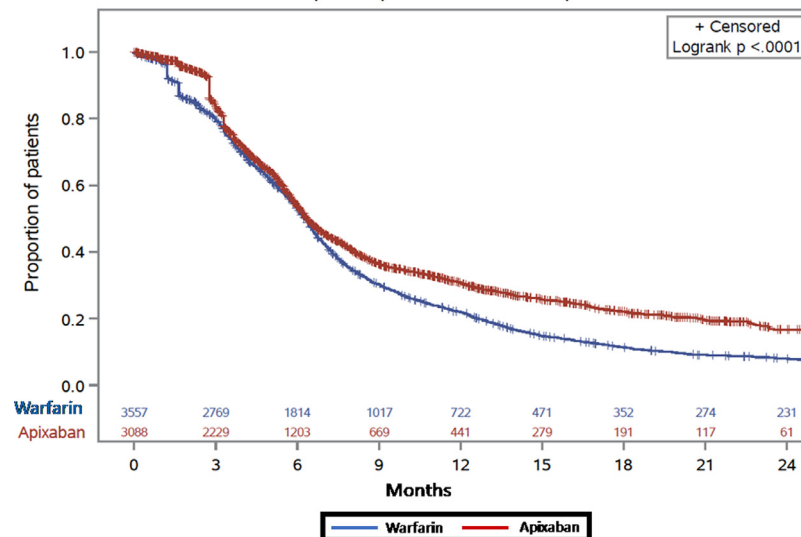
Figure 3. Proportion of patients persistent with their initial therapy of warfarin versus apixaban. The data are the proportion of patients discounting their initial therapy of those who first initiated apixaban therapy compared with warfarin therapy. Persistent patients are defined as patients who did not discontinue treatment (including switches) within 30 days of the end of the days' supply of the previous dispensation.

9.2] months) (Table II). At 3 months, more than three-quarters of patients in all treatment groups were persistent with their initial treatment; at 6 months, this number had decreased to approximately half of patients in all groups (Table II). At 12 months, a slightly higher percentage of patients taking apixaban was persistent with their initial treatment (30.8%; 95% CI, 28.8%–32.8%) compared with patients taking warfarin (21.9%; 95% CI, 20.6%–23.4%). The percentage of patients taking rivaroxaban who were persistent was similar to that among patients taking warfarin (19.2%; 95% CI, 18.2%–20.3%). The proportion of patients persistent with treatment can be seen in Figures 3 and 4.

DISCUSSION
In this study of patients diagnosed with VTE who were newly (after 2008) treated with OACs, nearly half of patients had prior hypertension, one-fifth had COPD and/or asthma, and approximately one-tenth had ischemic heart disease or rheumatic disease. The characteristics of the patients taking apixaban and those taking warfarin were similar for most comorbidities, with a slightly higher prevalence of history of myocardial infarction, ischemic heart disease, and renal disease among warfarin users. The differences in comorbidity prevalence were greater when comparing rivaroxaban and warfarin users, with warfarin users having a higher prevalence of hypertension, ischemic heart disease, and renal disease. During the study period (2013–2017), DOAC use increased markedly, whereas warfarin use decreased. Patients treated with apixaban had higher treatment persistence compared with patients treated with warfarin; rivaroxaban and warfarin users had similar persistence.

Previous real-world studies have also reported a high prevalence of cardiovascular conditions, particularly hypertension, in groups of VTE patients.[13–15,22–26] The high prevalence of hypertension is likely because this is an elderly patient population,[27] and the high prevalence of cardiovascular disease is likely because these conditions share similar underlying risk factors with VTE.[28] Other studies describing characteristics of patients with VTE have also reported a high prevalence of COPD and/or asthma in this patient population,[10,29] which has previously been attributed to the fact that patients with COPD and/or asthma are at higher risk of VTE.[30]
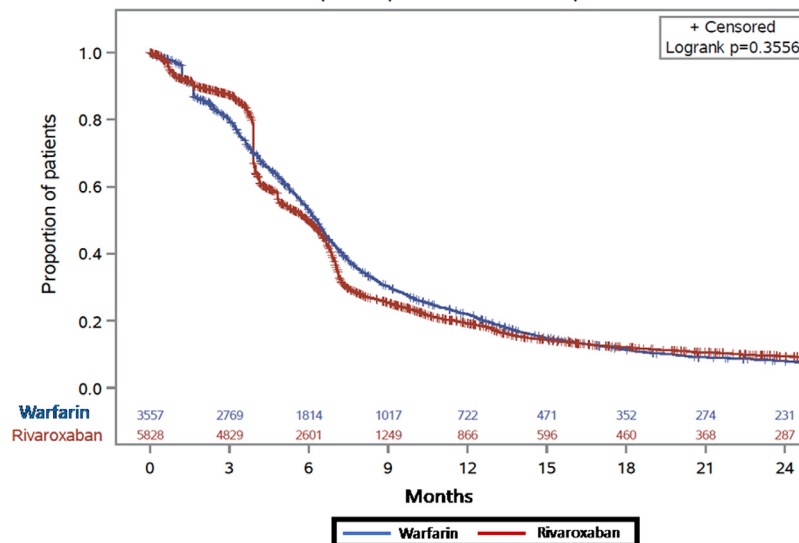
Figure 4. Proportion of patients persistent with warfarin versus rivaroxaban therapy. The data are the proportion of patients discounting their initial therapy of those who first initiated apixaban compared with warfarin. Persistent patients are defined as patients who did not discontinue treatment (including switches) within 30 days of the end of the days' supply of the previous dispensation.

A number of real-world studies have also compared comorbidity prevalence between DOAC and warfarin users.[13,23–25] These studies mostly report a higher prevalence of almost all comorbidities in warfarin users compared with apixaban and rivaroxaban users,[13,23,24] except for one nationwide study in Denmark that reported a higher prevalence of most comorbidities in apixaban users when compared with warfarin and rivaroxaban.[25] The present study, as well as previous studies, have consistently reported a higher prevalence of renal disease in warfarin users when compared with DOAC users.[13,23–25] To investigate this further, we conducted a sensitivity analyses to describe the characteristics of warfarin users by calendar year (Appendix). This analysis found that the prevalence of renal disease in warfarin users increased over time. The high prevalence in this patient group is likely because DOACs are contraindicated in patients with a glomerular filtration rate <15.[31,32] Other previous real-world studies,[13,23,24] except for the aforementioned Danish study,[25] also reported a higher prevalence of cardiovascular conditions in warfarin users when compared with apixaban or rivaroxaban users. However, the reason for the higher prevalence in this patient group is less clear. Nonetheless, the high heterogeneity in comorbidity prevalence between these patient groups highlights the importance of adjusting for these comorbidities in comparative analyses.

Previous real-world studies across the globe have also reported a similar trend of increasing DOAC and decreasing warfarin use in patients with VTE in recent years.[11,15,25,33] The same trends have also been seen for OAC use in patients with atrial fibrillation.[34–37] A 2019 Swedish study that used administrative data to describe the uptake of anticoagulants in Stockholm reported that an increasing number of DOACs were prescribed to patients with VTE in more recent years.[15] The higher DOAC use in recent years likely reflects physicians' confidence in DOACs and changes in treatment guidelines during this period. Warfarin is still recommended in a few patients with VTE with specific characteristics, including very obese patients[38] or those with renal disease,[31,32] because there is a lack of clinical evidence for DOACs in these patient populations. This finding is reflected in the sensitivity analyses conducted in the present study (Appendix) that found an annually increasing prevalence of obesity and renal disease during the study period.

Previous real-world studies have also assessed persistence in VTE anticoagulation users.[9,10,26,39–41] Some of the older publications[10,26,42] describe warfarin treatment patterns and the duration of treatment ranging from 2[26] to 6[42] months. The higher estimate is in line with the present study; however, this range likely reflects regional differences and the different methods used to estimate treatment duration. Three recent real-world studies compared persistence between DOAC and warfarin users.[9,39,41] One study, published in 2018, that used data from Clinical Practice Research Datalink linked to Hospital Episode Statistics reported treatment persistence similar to the present study. At 3 months, 81.4% of warfarin, 81.0% of apixaban, and 59.0% of rivaroxaban users were persistent with treatment, and by 6 months, there were more patients taking apixaban who were persistent with treatment compared with warfarin and rivaroxaban users (apixaban, 54.7%, 95% CI, 45.3%–63.2%; warfarin, 47.1%; 95% CI, 44.8%–49.4%; rivaroxaban, 41.2%; 95% CI, 37.8%–44.6%).[9] Another study reported higher persistence in DOAC versus non-DOAC groups.[39] However, specific treatments were not identified.

Current guidelines recommend treatment for at least 3 to 6 months for all patients who had a VTE provoked by transient risk factors. However, in patients without transient risk factors and for whom the risk of bleeding is low, extended treatment is recommended beyond 6 months.[5,43,44] The findings of the present study agree with these recommendations because there is a sharp increase in nonpersistence seen at 6 months in all the treatment groups. In addition, some patients are continuing their therapy beyond 6 months, and more often, these patients are those taking apixaban. The differences in persistence between the OAC groups are interesting and could be explained by the possibility that clinicians may be considering apixaban over other OACs when patients' risk profiles deem them suitable for extended therapy, although in the present study there did not appear to be a difference in transient risk factors at baseline across the OAC groups. The recently published National Institute for Health and Care Excellence guidelines in the United Kingdom suggests that apixaban may be more cost-effective than the other NOACs for extended treatment. However, further research is required to fully assess the clinical impact of switching DOACs.

Strengths and Limitations

One of the biggest strengths of the study is that the data from the Norwegian registries are nationwide and therefore representative and generalizable to the Norwegian population; however, these data are also likely applicable to other European countries. This is also the first study to characterize the use of OACs for VTE in Norway and, as such, addresses an important gap in the current literature.

However, there are some limitations to the study. First, the registries have limited clinical information; therefore, some transient risk factors for VTE and the reasons for discontinuation could not be identified. Second, this research excluded patients with cancer; therefore, the results might not be representative of a patient population with VTE and cancer. Third, treatment dosing is estimated based on the available information within the prescription registry and guideline dosing recommendations for VTE. Therefore, some inaccuracies are expected when estimating the duration of supply, particularly for patients taking warfarin, where the dose can vary significantly, depending on the patients' international normalized ratio. Fourth, because patients taking apixaban mainly initiated treatment in the later years of the study period, our ability to assess long-term trends in treatment duration was limited. Further studies, with longer follow-up, are required to study the extended use of OAC treatment for VTE.

CONCLUSIONS

Important differences were found in the characteristics of patients receiving different OACs, which emphasizes the importance of adjusting for potential confounding by indication in analyses of comparative effectiveness and tolerability. As found in other real-world studies, the use of DOACs for the treatment of acute VTE has increased considerably during the past decade in Norway. In 2017, the most commonly prescribed OAC was apixaban. Treatment patterns indicate that most patients were persistent with OAC treatment for approximately 6 months. By 12 months, a higher percentage of patients taking apixaban persisted with treatment compared with patients taking warfarin. Additional research using longer follow-up periods to further characterize the extended use of treatment for patients with VTE is required.

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APPENDIX

Description of restrictions in Norwegian registry data

In Norway, due to strict patient confidentiality laws, the Norwegian registries deliver data without dates. Instead, each variable is provided with the calendar year that the event occurred as well as derived days from a date randomly assigned by the registry holders (Figure S.1).

Although all relative days are provided for clinical events and prescriptions, relative days to or from known calendar dates are not provided. In particular, the registries do not release relative days between a

patient's index date and the end of data availability. This impacted our ability to censor patients at the end of data availability, and patients were instead censored at their last known follow-up date. This was derived as the latest date of the last diagnostic or prescription encounter in 2017, or 365 days after the last diagnostic or prescription encounter in all other calendar years. Although this approach allowed us to impute the latest known follow-up date, it was not possible for patients who initiated treatment in 2017. This could have led to an underestimation of follow-up time for this year.

Table S1. VTE ICD-10 Codes

ICD-10 codes for VTE	Description
Pulmonary embolism	
I26.0	Pulmonary embolism with mention of acute cor pulmonale
I26.9	Pulmonary embolism without mention of acute cor pulmonale
Deep vein thrombosis	
I80.1	Phlebitis and thrombophlebitis of femoral vein
I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
I81	Portal vein thrombosis
I82.3	Embolism and thrombosis of renal vein
I82.8	Embolism and thrombosis of other specified veins

ICD-10: International Classification of Diseases, 10th Revision; VTE: venous thromboembolism

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Day 0. Randomly assigned date created by registry holders and unknown to external researchers

Day 523: Patient was admitted to hospital: VTE diagnosis

Day 525: Patient was discharged from hospital

Day 542: Warfarin dispensation = index date

Day 575: Major bleeding

Time from randomly assigned date to first hospital admission: 523 days

Hospital length of stay: 2 days

Dispensation within 17 days of discharge

Time to first major bleed: 33 days from index date

Bold text: dates provided by the registry
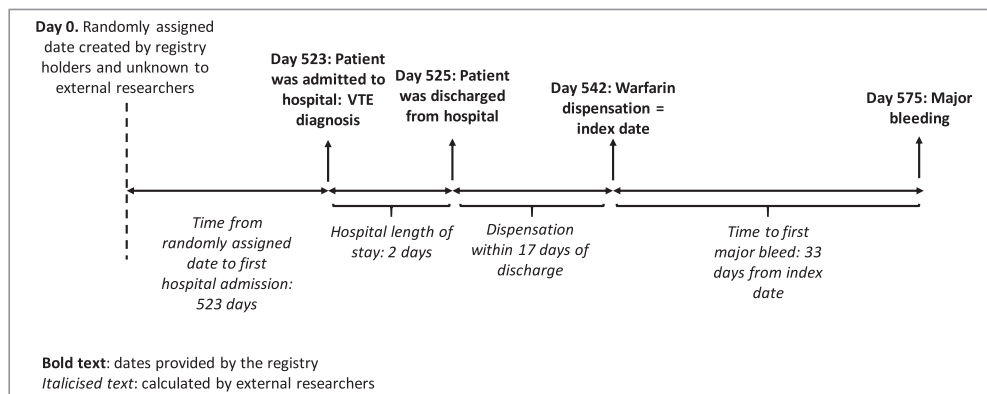*Italicised text*: calculated by external researchers

Figure S1. Example of data delivered from the Norwegian registries
VTE: venous thromboembolism.
Note: This is hypothetical data for visualization purposes only.

Table S2. Assumed dosing schedules for DOACs, based on EMA product licenses*,†

Drug	Strength	Dosing plan
Apixaban	5 mg	Twice daily
	2.5 mg	Twice daily
Rivaroxaban	15 mg	Twice daily
	20 mg	Once daily
Dabigatran	N/A	None [injectable/subcutaneous ACs]
	150mg	Twice daily
Edoxaban	N/A	None [injectable/subcutaneous ACs]
	60mg	Once daily

AC: Anticoagulant; EMA: European Medicines Agency; DOAC: direct oral anticoagulant
* Electronic Medicines Compendium (EMC). Published: Datapharm, 2019. Accessed 18 Nov 2019.
Eliquis 2.5 mg film-coated tablets. https://www.medicines.org.uk/emc/product/4756/smpc.
Eliquis 5 mg film-coated tablets. https://www.medicines.org.uk/emc/product/2878/smpc.
Xarelto 15mg film-coated tablets. https://www.medicines.org.uk/emc/product/2794/smpc.
Xarelto 20mg film-coated tablets. https://www.medicines.org.uk/emc/product/2793/smpc.
Pradaxa 110 mg hard capsules. https://www.medicines.org.uk/emc/product/6229/smpc.
Pradaxa 150 mg hard capsules. https://www.medicines.org.uk/emc/product/4703/smpc.
http://Lixiana 60mg Film-Coated Tablets. https://www.medicines.org.uk/emc/product/6905/smpc.
† European Medicines Agency (EMA). Accessed 18 Nov 2019.
Eliquis, INN-apixaban. Annex 1: Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf.

Table S3. A sensitivity analyses to assess warfarin characteristics over the study period

Characteristics	2013	2014	2015	2016	2017
Age at index (years), median (Q1–Q3)	63 (50–74)	66 (52–77)	68 (51–79)	65 (49–77)	62 (47–77)
Female, N (%)	783 (47.4)	465 (48.4)	263 (52.2)	133 (49.1)	82 (48.0)
Comorbidities, N (%)					
Myocardial infarction	129 (7.8)	76 (7.9)	49 (9.7)	35 (12.9)	7 (4.1)
Congestive heart failure	144 (8.7)	107 (11.1)	62 (12.3)	39 (14.4)	14 (8.2)
Peripheral vascular disease	95 (5.8)	64 (6.7)	34 (6.7)	23 (8.5)	12 (7.0)
Cerebrovascular disease	98 (5.9)	58 (6.0)	45 (8.9)	22 (8.1)	15 (8.8)
Chronic pulmonary disease	319 (19.3)	211 (22.0)	104 (20.6)	57 (21.0)	39 (22.8)
Rheumatic disease	133 (8.1)	118 (12.3)	68 (13.5)	32 (11.8)	21 (12.3)
Peptic ulcer disease	58 (3.5)	49 (5.1)	33 (6.5)	17 (6.3)	7 (4.1)
Mild liver disease	17 (1.0)	23 (2.4)	7 (1.4)	4 (1.5)	5 (2.9)
Diabetes without chronic complications	97 (5.9)	47 (4.9)	21 (4.2)	16 (5.9)	12 (7.0)
Diabetes with chronic complications	26 (1.6)	27 (2.8)	16 (3.2)	16 (5.9)	7 (4.1)
Renal disease	77 (4.7)	69 (7.2)	54 (10.7)	44 (16.2)	27 (15.8)
Malignancy	75 (4.5)	54 (5.6)	22 (4.4)	17 (6.3)	13 (7.6)
Ischemic heart disease	226 (13.7)	147 (15.3)	103 (20.4)	56 (20.7)	24 (14.0)
Hypertension	738 (44.7)	482 (50.2)	274 (54.4)	156 (57.6)	86 (50.3)
Pulmonary hypertension	6 (0.4)	5 (0.5)	6 (1.2)	2 (0.7)	2 (1.2)
Severe obesity*	46 (2.8)	30 (3.1)	26 (5.2)	24 (8.9)	17 (9.9)
Charlson score, N (%)					
0	1042 (63.1)	538 (56.0)	254 (50.4)	128 (47.2)	81 (47.4)
1	293 (17.7)	187 (19.5)	131 (26.0)	63 (23.2)	46 (26.9)
2	170 (10.3)	116 (12.1)	62 (12.3)	39 (14.4)	23 (13.5)
3	93 (5.6)	69 (7.2)	28 (5.6)	19 (7.0)	10 (5.8)
≥4	53 (3.2)	50 (5.2)	29 (5.8)	22 (8.1)	11 (6.4)
Bleeding history, N (%)					
Major bleeding	45 (2.7)	28 (2.9)	18 (3.6)	14 (5.2)	8 (4.7)
Intracranial bleeding	17 (1.0)	6 (0.6)	6 (1.2)	4 (1.5)	1 (0.6)
GI bleeding	43 (2.6)	30 (3.1)	24 (4.8)	15 (5.5)	9 (5.3)
CRNM bleeding	135 (8.2)	86 (9.0)	79 (15.7)	30 (11.1)	23 (13.5)
Transient risk factors for VTE (in 3 months prior to index VTE), N (%)	524 31.7)	291 (30.3)	160 (31.7)	97 (35.8)	66 (38.6)
Major surgery	42 (2.5)	24 (2.5)	10 (2.0)	6 (2.2)	5 (2.9)
Any overnight hospitalization	348 (21.1)	193 (20.1)	115 (22.8)	72 (26.6)	51 (29.8)
Fracture	112 (6.8)	46 (4.8)	20 (4.0)	14 (5.2)	10 (5.8)
Trauma	52 (3.1)	28 (2.9)	14 (2.8)	7 (2.6)	3 (1.8)
Estrogen use	135 (8.2)	74 (7.7)	32 (6.3)	19 (7.0)	12 (7.0)

CRNM: clinically relevant non-major; GI: gastrointestinal; Q1–Q3: first to third quartile; VTE: venous thromboembolism.
* Severe obesity is identified using the ICD-10 code E66 as the registries do not include data on body mass index.