Persistence to direct oral anticoagulants for acute venous thromboembolism

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Abstract

Background Currently, direct oral anticoagulants(DOACs) are the treatment of choice for venous thromboembolism (VTE) in the Netherlands. The main advantages of DOACs over vitamin K antagonists (VKAs) are that they are safer than VKA and that neither monitoring nor dose titrations are needed. A main drawback is a potential risk of lower drug persistence, as compared with VKA treatment, which is strictly controlled by anticoagulation clinics in the Netherlands.

Objectives The primary aim of this study was to audit the persistence to DOAC treatment for acute VTE during the first 2 months in daily clinical practice.

Methods Dispensing data from the Dutch Foundation of Pharmaceutical Statistics were used to monitor persistence to DOAC for treatment of VTE from 1 January 2012-1 April 2016. Non-persistence was defined as the cumulative incidence of patients who completely stopped DOAC or VKA treatment. In addition, we estimated the persistence to VKA treatment for VTE in data from the Anticoagulation Clinic Leiden.

Results 1834 patients were selected as DOAC users for the indication VTE. The 2-month cumulative incidence of completely stopping DOAC was 20% (95% confidence interval [CI] 18-24). In the population of 4910 VKA users, 9.1% (95%CI 8.3-9.9) stopped prematurely with VKA.

Conclusion The stopping rate of 20% we found is in line with other cardiovascular treatments. Further research into the reasons and consequences of prematurely stopping DOAC treatment for acute VTE is urgently needed.

Introduction

Direct oral anticoagulants (DOACs) are approved for treatment of venous thromboembolism (VTE), thromboembolic prevention in atrial fibrillation (AF) and thromboprophylaxis. Recently, DOACs have been suggested by international and Dutch guidelines as the treatment of choice for acute VTE[1, 2]. In two meta-analyses based on randomized controlled trials it has been shown that DOACs are overall non-inferior in terms of efficacy (recurrent VTE) but lead to less major bleeding compared with vitamin K antagonists (VKAs) [3, 4]. An important practical advantage of DOACs over VKAs is that neither monitoring nor dose titration is needed. However, a lack of monitoring could decrease drug adherence and persistence [5]. Treatment duration for VTE is recommended to be at least three months [1], as the risk of recurrence is high after prematurely stopping anticoagulation treatment within 1 or 1.5 months after the VTE event compared with longer treatment duration, for a reported Hazard Ratio (HR) of 1.52 (95% confidence interval [CI] 1.1 to 2.0) [6]. In the DOAC trials, the percentage of patients who stopped DOAC treatment prematurely within 6 months ranged from 11 to 15% [7-10]. However, these trials might not be representative for the persistence to DOACs in clinical daily practice since less support for patients to continue their DOAC use will be present as compared with the trial settings. Recently, a Danish registry study in patients treated with DOACs for AF showed that out of 50632 patients, 30% discontinued their initial DOAC treatment within one year: 14% completely stopped DOAC treatment, 10% switched to VKA and 5% switched to another DOAC [11]. Other studies in patients with AF also confirmed a higher non-persistence to DOAC in clinical settings than in trials, with discontinuation rates of 20 to 25% within two years of follow-up [12, 13]. To our knowledge, there are no published data on DOAC persistence in VTE patients in routine clinical practice. In the Netherlands, the first DOAC approved for treatment of VTE was rivaroxaban in 2012, followed by dabigatran and apixaban in 2014 and edoxaban in 2015. Over the last years, the use of DOACs has increased in the Netherlands [14]. The main purpose of the current study was to explore the persistence to DOACs in Dutch patients with acute VTE. A second aim was to assess for potential predictors for stopping DOAC prematurely. Since, to our knowledge, there is

no literature about persistence to VKAs available, this was explored as well. The aim was to compare the two types of treatment, i.e. with monitoring, as provided by anticoagulant clinics in the Netherlands, and without monitoring.

Methods

Definition of persistence

Drug persistence is defined as: continuing treatment for the prescribed duration [15]. The opposite of drug persistence, non-persistence or lower drug persistence can therefore be defined as: prematurely stopping treatment. Because the minimal treatment duration with DOAC for acute VTE is 3 months (also for distal DVT), and many patients will stop shortly before the exact 3 months date, a cut-off point of 2 months treatment duration was chosen as the period in which discontinuation was defined as definitely premature (figure 1).

Data source

Data from the Foundation of Pharmaceutical Statistics (SFK) were used for selection of patients treated with DOACs. SFK collects pharmacy dispensing data from >95% of community pharmacies in the Netherlands, i.e. information on which drugs were dispensed, including the codes from the Anatomic-Therapeutic-Chemical (ATC) system of the World Health Organization, the prescribed dose and the amount dispensed. For the current study, data collected by SFK from 1538 pharmacies in the Netherlands, which comprise 79% of all community pharmacies in the Netherlands, could be used. All data between January 1st 2012 and April 1st 2016 about type of DOAC (by ATC code), DOAC dose and number of tablets dispensed daily (once or twice), date of dispensing, patient sex, age, concomitant medical therapy and the use of a VKA prior to inclusion or during follow-up were provided. Although SFK does not collect information on the clinical indication for which DOACs are

used, this could be approximated by differences in first dose of DOAC. The first dose of rivaroxaban and apixaban differs between short term prophylaxis (i.e. after orthopaedic surgery), initial treatment of VTE and thromboembolic prevention in atrial fibrillation (Supplementary table 1). DOACs are not registered for treatment of thrombophlebitis in the Netherlands. In case dabigatran is prescribed for acute VTE treatment, this will be preceded by at least 5 days treatment with low-molecular weight heparin (LMWH).

Selection of patients

First, between 1 January 2012 and 1 April 2016, all patients who received one or more dispensings of one of the DOACs rivaroxaban, apixaban or dabigatran according to the data from SFK, were selected. The DOAC edoxaban was not included since it was rarely used in the Netherlands during the studied time period. The aim of this study was to investigate DOAC use for the indication of acute VTE. Records of patients who received rivaroxaban and apixaban doses corresponding with the initial treatment of VTE, or dabigatran preceded by LMWH were selected. From the selected patient group, only patients who received a first prescription of DOAC were included, for which reason patients who received a DOAC prescription between 1 January 2012 and 1 April 2012 were excluded. Since DOAC data were provided until 1 April 2016, patients who started DOACs after 1 February 2016 were excluded because it was unknown whether these patients stopped or continued treatment after 2 months. Specific DOACs were identified by ATC codes: B01AE07 for dabigatran, B01AF01 for rivaroxaban and B01AF02 for apixaban. Patients were also classified for previous use of VKA (ATC code B01AA) or any other concomitant medication (any ATC code) within 0-180 days prior to baseline as provided by SFK.

Outcomes

The primary outcome of this study was the non-persistence to initial DOAC treatment at two months. Non-persistence to DOAC was defined as the cumulative incidence of 'stoppers' in the DOAC group, so patients who stopped DOAC treatment within 2 months without switching to any other oral anticoagulant treatment. They were selected by counting the number of patients who did not register a new prescription of their initial DOAC within 45 days. A secondary outcome of this study was the number of patients who switched from DOAC treatment to another anticoagulant (DOAC or VKA) within 2 months. The cumulative incidence of patients who stopped or switched DOAC was also calculated, together defined as 'discontinuing DOAC'. The cumulative incidence of stopping or switching DOAC within 3 months was calculated as well.

Statistical analysis

Baseline characteristics of the DOAC users are expressed as numbers and percentages, or as means and standard deviations (SD). Observation time was defined as the time between the dates of first DOAC prescription and the end of follow-up, which was restricted to a maximum of 3 months. For stopping with DOAC, follow-up ended at the date that a patient ran out of DOAC tablets. Kaplan-Meier analyses were used to determine the cumulative incidence for the outcome events.

With univariable and multivariable logistic regression analysis we compared the likelihood of non-persistence between the DOAC groups, adjusting for age, sex, and previous VKA use, to get an indication which covariates were related with persistence in DOAC users. Since SFK registers data per pharmacy and not per patient, there is a possibility that patients retrieved their medication from different pharmacies, which could lead to an underestimation in persistence. To adjust for this possibility, we performed a sensitivity analysis for the primary outcome excluding all patients who had the same birth year, sex, postal code and who used the same DOAC.

All statistics were performed using SPSS version 23 (IBM Corp, Armonk, NY).

Persistence to VKA therapy

Since for VKA therapy the first doses for thromboembolic prevention in AF and treatment of VTE are the same and LMWH is often prescribed when AF is initially diagnosed, it was not possible to distinguish the two indications based on SFK data. Therefore, another database, i.e., the registry of the Anticoagulation Clinic was used to explore the persistence to VKA. In the Netherlands, all patients who use VKA therapy are monitored by the Anticoagulation clinics, which are organized per geographical area. For this study, data from the Anticoagulation Clinic in Leiden were used. Patients are closely monitored by the Anticoagulation Clinic and visit the clinic for INR monitoring at least once per 6 weeks. Patients who seem non-persistent to VKA (i.e. have low INRs) are called or receive letters from the Anticoagulation Clinic. In this VKA only cohort, date of VKA initiation, age at VKA initiation, sex, indication for which the VKA was prescribed (i.e. VTE) and date of VKA discontinuation were provided. From this VKA cohort all patients who started with VKA treatment between 1 January 2004 and 1 January 2012 were included. Patients with an upper extremity deep vein thrombosis (UEDVT) or thrombosis at another infrequent location were excluded, since DOACs were not prescribed for these indications in the studied period.

We chose for the time period between 2004 and 2012 because in this period only VKA was available as oral anticoagulant drug, since DOACs were not registered for the indication VTE. Therefore, these patients could not discontinue their drug due to a switch to a DOAC (as was possible from 2012 onwards). Using this time period for VKA allowed us to estimate the expected non-persistence rate in an unselected group of patients with VTE who were prescribed oral anticoagulant treatment at an anticoagulation clinic where this treatment is rigorously monitored. Non-persistence to VKA was defined as the cumulative incidence of patients who stopped VKA treatment within 2 months after initiation. For treatment duration the time between the start and discontinuation of VKA according to the data from the Anticoagulation Clinic Leiden was calculated. Kaplan-Meier analyses were used

to determine the cumulative incidence for stopping with VKA within 2 months. Cumulative incidence of stopping VKA within 3 months was calculated as well.

Ethical approval

The data from SFK and the Anticoagulation Clinic Leiden were anonymised prior to analysis. For use of retrospective observational registry data for a descriptive study no approval from the medical ethical committee was needed according to Directive 2001/20/EC and Dutch legislation.

Results

Study population

Between January 1st 2012 and April 1st 2016, 92718 patients initiated DOAC therapy. From this cohort, 87352 patients who were identified as incident DOAC users were selected (Flow chart, **figure 2**). A total of 3427 patients were excluded because the DOAC type or dosage was unknown and 12 patients were excluded because they used (according to SFK) more than 1 DOAC at the same time. From the remaining 83913 eligible DOAC users, 2048 were identified as DOAC users for acute VTE treatment, 77333 for AF, and 4532 as DOAC users for thromboprophylaxis. Lastly, from the 2048 patients on DOAC for the indication VTE, 214 patients who started DOAC treatment after 1 February 2016 were excluded, leaving 1834 patients for the primary analysis.

Baseline characteristics from the included DOAC users are shown in **Table 1**. Most patients used rivaroxaban (n=1429), followed by dabigatran (n=311) and apixaban (n=94). A small proportion of DOAC patients (7%) had used VKA previously.

Discontinuation

From 1834 patients, 352 stopped DOAC within 2 months for a cumulative incidence of 20% (95%CI 18 to 24). Additionally, 117 from 1834 patients switched their initial DOAC prescription: 113 to VKA and 4 to another DOAC for a cumulative incidence of 7% (95%CI 5.7 to 8.1). In total, 469 discontinued DOAC (both 'stoppers' and 'switchers') within 2 months, for a cumulative incidence of 26% (95%CI 24 to 28; Kaplan-Meier curves, **figure 3a**). After 3 months the number of patients that stopped DOAC increased to 470, for a cumulative incidence of 27% (95%CI 25-29). In addition, 134 patients (8.1% [95%CI 6.7-9.4]) switched to another anticoagulant. In total, 604 patients discontinued DOAC for a cumulative incidence of 33% (95%CI 31-35). In the sensitivity analysis in which 52 patients who had the same birth year, sex, postal code and DOAC type were excluded, discontinuation patterns were comparable: 444 of 1782 patients discontinued for a cumulative incidence of 26% (95%CI 23 to 27).

Predictors for premature discontinuation

In univariable analysis, predictors for discontinuing DOAC (stopping DOAC or switching to alternative treatment) were: no previous use of VKA (OR 1.67; 95%CI 1.05 to 2.65), the use of no other drugs (concomitant drug use) (OR 1.57; 95%CI 1.25 to 1.98) and female sex (OR 1.32; 95%CI 1.07 to 1.63). After multivariable analysis, no concomitant drug use (OR 1.86; 95%CI 1.45 to 2.39), and female sex (OR 1.38; 95%CI 1.11 to 1.72) remained predictors of premature discontinuation of DOAC treatment **(Table 2)**.

Rivaroxaban and dabigatran were associated with higher discontinuation rates than apixaban with odds ratios of 2.45 (95%CI 1.29 to 4.64) and 4.01 (95%CI 2.05 to 7.85; Table 2) compared with apixaban respectively. After multivariable analysis these odds ratios were: 2.19 (95%CI 1.15 to 4.20) and 4.16 (95%CI 2.12 to 8.18) respectively.

Persistence to VKA therapy

5237 patients started VKA between January 1st 2004 and January 1st 2012 for the indication VTE. From this patient group, 327 patients who used VKA for upper extremity DVT (UEDVT) or thrombosis at another infrequent location were excluded, leaving 4910 patients for the analysis. Mean age was 60 years (95% CI 59-60), and 48% of patients were men. Within 2 months 449 of 4910 stopped VKA for a cumulative incidence of 9.1% (95%CI 8.3 to 9.9; **figure 3b**). After 3 months 800 patients stopped with VKA, for a cumulative incidence of 18% (95%CI 17-19).

Discussion

This study, based on Dutch pharmacy dispensing and anticoagulation clinics registry data, showed that the cumulative incidence of premature discontinuation of DOAC treatment for the indication VTE in daily clinical practice within the first 2 months was 20% (95%CI 18 to 24) and an additional 7% (95%CI 5.7 to 8.1) switched to another anticoagulant treatment. The cumulative incidence of discontinuation (stopping or switching) DOAC was 26% (95%CI 24 to 28). This discontinuation rate is higher than was reported in the phase 3 DOAC trials, i.e., 11 to 15% within 6 months [7-10]. Furthermore, we showed that the cumulative incidence of stopping VKA within the first 2 months was 9.1% (95% CI 8.3-9.9).

To our knowledge, there are only a few observational studies in small numbers of patients on discontinuation rates in DOAC use. One systematic review in patients with acute VTE included 7 VKA studies and 3 conference abstracts about DOAC persistence. Stratifying the results from this systematic review into patients with VTE who used VKA and who used DOAC, discontinuation rates within 3 months ranged between 6% to 28% for VKA (average 18%) and 6% to 36% in patients on DOAC (average 13%) [16].This study therefore shows the opposite from our study: a lower discontinuation rate in DOACs compared with VKA. However, the systematic review only included 203 patients with acute VTE who were treated with DOAC, which is in stark contrast to our large

population based registry of patients with acute VTE who were treated with a DOAC (n=1834). Another recent study used the Dresden registry to analyse the persistence to Rivaroxaban in 418 patients with VTE. After 6 months 58.3% of patients were still taking rivaroxaban, 28.2% had a scheduled end of treatment, 7.2% were switched to other anticoagulants, 1.7% had withdrawn their consent and the remaining 3.6% of patients had unplanned complete discontinuation of anticoagulation. However, in contrast to our study, patients were contacted by phone during follow-up which could have positively altered the persistence rate [17]. Recently, a study based on RIETE registry data also reported that adequate treatment with DOACs for VTE is challenging in clinical practice [18]. This study showed that a high proportion of VTE patients who were prescribed DOACs did not receive the recommended daily dosings, i.e. once daily dosing of apixaban instead of twice daily. For the initial therapy, 50% (22 of 44) of apixaban users and 18% (287 of 1591) of rivaroxaban did not receive the recommended dosing, resulting in a higher VTE recurrence rate (HR 10.5, 95%CI 1.28-85.9); discontinuation rates of DOAC during follow-up were not reported in this study.

We found a high incidence of stopping DOACs within 2 months after initiation. Although we cannot directly compare this finding to previous studies in patients with acute VTE who used DOACs, this non-persistence percentage is in line with other treatment regimens for cardiovascular conditions that are strongly recommended according to clinical guidelines. For example, oral antiplatelet (OAP) treatment after acute coronary syndrome (ACS) is recommended to be used for at least one year. Nevertheless, a study based on prescription register data from Finland showed that only 49% of patients received OAP treatment after hospital discharge and approximately 20% of patients stopped OAP within 90 days [19]. Other studies showed similar results in treatment with antiplatelet therapy after acute coronary syndrome and percutaneous coronary intervention (PCI) [20, 21]. Also, the percentage of stopping chronic medication after acute myocardial infarction as beta blockers or aspirin is close to 20-30% within one year [22]. This percentage is also described for preventive drugs after hospitalization for stroke. A large American registry study in 2589 patients showed that 25% of

patients reported stopping 1 or more of their prescribed regimen of secondary prevention medications within 3 months after acute stroke [23].

Clearly, the stopping rates that we found for DOACs are in line with those of other cardiovascular medications and therefore seem to be part of a general problem of low persistence to medication [24]. The fact that the stopping rate in VKA users is lower suggests that the strict monitoring by an anticoagulation clinic improves adherence compared to the routine use of other medications. A previous study that focussed on adherence to dabigatran for the indication of AF showed that monitoring by phone calls or follow-up visits performed by pharmacists resulted in higher adherence [25]. Such a strategy is also followed by anticoagulation clinics in the Netherlands for patients who use VKA and this clearly contrasts with the current clinical practice where patients on DOAC are not mandatorily monitored on their drug persistence. In contrast, one study in AF patients reported a higher persistence to DOACs (79.2) compared with VKA (63.6%) after one year[13]. This was assumed to be the result of the more simple treatment with DOAC, without food interactions and monitoring compared with VKA. In countries where VKA monitoring is not as well organized as in the Netherlands, the difference in persistence to DOAC and VKA may be less pronounced.

Nevertheless, reasons for discontinuing DOAC in particular can be speculated on. Reasons for discontinuing reported in the DOAC trials were diverse and included bleeding events, withdrew of consent, loss to follow-up, death or other non-specified reasons [7, 9, 10]. A small part of the 20% stopping rate could be explained by death. In addition, cancer could also be a reason to stop DOAC treatment, in a Dutch study, the incidence of cancer diagnosis shortly after VTE was 3.5% [26].

With respect to adverse events, it may well be that patients could have discontinued DOAC because of bleeding complications. Although it has been shown that DOACs have a lower risk of major bleeding compared with VKA, the percentage of patients with a major or clinically relevant bleeding in the several DOAC trials still ranged from 4-10% within 3 months of follow-up. However,

this is no explanation for the discrepancy with the VKA group [7, 9, 10]. We showed that female sex was a predictor of premature discontinuation of DOAC. This result is in line with a meta-analysis including 8 studies comprising 9417 patients that showed that women suffer from more bleeding complications than men when using DOACs for VTE treatment [27]. Part of this higher bleeding risk in women may be due to increased uterine bleeds when using a DOAC, as suggested by a recent study that showed that the occurrence of uterine bleeds was higher in women treated with rivaroxaban or apixaban compared with warfarin [28, 29]. Another study showed that abnormal menstrual bleeding also occurred more frequently with rivaroxaban treatment than with enoxaparin/VKA, for a HR 2.13 (95%CI 1.57-2.89) [29]. In a survey among clinicians, 15% replied to consider (temporally) stopping DOAC treatment in patients with abnormal menstrual bleeding [30].

The main strength of our study is that we investigated the persistence to DOAC for the indication of VTE in a large population of unselected DOAC users. For the interpretation of our study some limitations should be mentioned. First, we do not know why patients were non-persistent. We tested a few predictors by multivariate analysis as concomitant drug use, age and sex, but could not study other potentially relevant predictors as socioeconomic class or level of education. Our results indicate that studies focusing on the reason *why* patients with acute VTE stop using their DOAC should be conducted. A second limitation of this study is that SFK does not provide the exact indication and planned treatment duration for DOAC treatment. However, we could have missed patients who used DOAC for VTE in our study, for example because they received the wrong initial dosing. Another potential limitation is that SFK was only able to provide data of 79% of all pharmacies in the Netherlands. However, reasons for not including pharmacies were completely at random, so could not have introduced selection bias. The first reason was that pharmacies which went out of business during the study period could not provide follow-up data from the moment that they closed. In addition, merging pharmacies received new pharmacy numbers by SFK, and from that moment onwards it was unclear from which patient follow-up was provided. Furthermore, pharmacies who switched to another computer system during the study period could not be used

for a similar reason. A fourth limitation is that we cannot ascertain whether the DOACs dispensed by the pharmacies were actually taken by the patients. Notably, not having taken the medication would have led to an even higher discontinuation rate than we have found. For example, even clinical trials report that the percentage of the prescribed doses of medication actually taken by the patient ranges between 43-78% [24]. A final limitation of our study is that we used different time periods for the DOAC and VKA databases. As mentioned, we did this on purpose in order to investigate the persistence to VKA in a period in which it was not possible to switch to another oral anticoagulant, to create a representative reference population for the persistence to oral anticoagulants in general. However, there was a slight possibility to switch to low molecular weight heparin (LMWH) as therapeutic anticoagulation treatment in that time period. Although the incidence of switching from VKA to LMWH is expected to be low, we have no data about this available. Even so, this could have led to an overestimation of the persistence in the VKA group.

In conclusion, in this study, based on Dutch pharmacy registry data, in patients who were selected as DOAC users for acute VTE, the cumulative incidence of stopping DOAC treatment within 2 months after initiation was 20%, which is in line with use of other cardiovascular medications. Since the primary outcome of this study is based on Dutch registry data with corresponding limitations and may be not representative for other countries, our results should be mainly interpreted as hypothesis generating and as a warning that further investigation on the incidence and consequences of non-persistence in DOAC patients is urgently needed.

Contributors:

C.E.A.D. , W.M.L., F.A.K., S.C.C. and M.V.H. designed the research. W.M.L and F.J.M.vd M. collected the data. C.E.A.D., W.M.L and M.T. analysed the data. C.E.A.D., W.M.L., and M.V.H. wrote the manuscript. M.T., F.J.M.vdM, F.A.K. and S.C.C. critically revised the paper for important intellectual content.

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The authors declare no competing financial interests

References

[1] C. Kearon, E.A. Akl, J. Ornelas, A. Blaivas, D. Jimenez, H. Bounameaux, M. Huisman, C.S. King, T.A. Morris, N. Sood, S.M. Stevens, J.R. Vintch, P. Wells, S.C. Woller, L. Moores, Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, Chest 149(2) (2016) 315-52.

[2] Richtlijn Antitrombotisch Beleid, Nederlandse Internisten Verenging (2015).

[3] T. van der Hulle, J. Kooiman, P.L. den Exter, O.M. Dekkers, F.A. Klok, M.V. Huisman, Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis, J. Thromb. Haemost. 12(3) (2014) 320-8.

[4] N. van Es, M. Coppens, S. Schulman, S. Middeldorp, H.R. Buller, Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials, Blood 124(12) (2014) 1968-75.

[5] J.K. Abdou, V. Auyeung, J.P. Patel, R. Arya, Adherence to long-term anticoagulation treatment, what is known and what the future might hold, Br. J. Haematol. 174(1) (2016) 30-42.

[6] F. Boutitie, L. Pinede, S. Schulman, G. Agnelli, G. Raskob, J. Julian, J. Hirsh, C. Kearon, Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials, BMJ 342 (2011) d3036.

[7] G. Agnelli, H.R. Buller, A. Cohen, M. Curto, A.S. Gallus, M. Johnson, U. Masiukiewicz, R. Pak, J. Thompson, G.E. Raskob, J.I. Weitz, Oral apixaban for the treatment of acute venous thromboembolism, N. Engl. J. Med. 369(9) (2013) 799-808.

[8] H.R. Buller, H. Decousus, M.A. Grosso, M. Mercuri, S. Middeldorp, M.H. Prins, G.E. Raskob, S.M. Schellong, L. Schwocho, A. Segers, M. Shi, P. Verhamme, P. Wells, Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism, N. Engl. J. Med. 369(15) (2013) 1406-15.

[9] H.R. Buller, M.H. Prins, A.W. Lensin, H. Decousus, B.F. Jacobson, E. Minar, J. Chlumsky, P. Verhamme, P. Wells, G. Agnelli, A. Cohen, S.D. Berkowitz, H. Bounameaux, B.L. Davidson, F. Misselwitz, A.S. Gallus, G.E. Raskob, S. Schellong, A. Segers, Oral rivaroxaban for the treatment of symptomatic pulmonary embolism, N. Engl. J. Med. 366(14) (2012) 1287-97.

[10] S. Schulman, A.K. Kakkar, S.Z. Goldhaber, S. Schellong, H. Eriksson, P. Mismetti, A.V. Christiansen, J. Friedman, F. Le Maulf, N. Peter, C. Kearon, Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis, Circulation 129(7) (2014) 764-72.

[11] M. Hellfritzsch, S.E. Husted, E.L. Grove, L. Rasmussen, B.K. Poulsen, S.P. Johnsen, J. Hallas, A. Pottegard, Treatment Changes among Users of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation, Basic Clin. Pharmacol. Toxicol. 120(2) (2017) 187-194.

[12] T. Forslund, B. Wettermark, P. Hjemdahl, Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation, Eur. J. Clin. Pharmacol. 72(3) (2016) 329-38.

[13] C. Martinez, A. Katholing, C. Wallenhorst, S.B. Freedman, Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study, Thromb. Haemost. 115(1) (2016) 31-9.

[14] S. Hanemaaijer, F. Sodihardjo, A. Horikx, M. Wensing, P.A. De Smet, M.L. Bouvy, M. Teichert, Trends in antithrombotic drug use and adherence to non-vitamin K oral anticoagulants in the Netherlands, Int. J. Clin. Pharm. 37(6) (2015) 1128-35.

[15] J.A. Cramer, A. Roy, A. Burrell, C.J. Fairchild, M.J. Fuldeore, D.A. Ollendorf, P.K. Wong, Medication compliance and persistence: terminology and definitions, Value Health 11(1) (2008) 44-7.

[16] P. Vora, M. Soriano-Gabarro, K. Suzart, G. Persson Brobert, Limited evidence on persistence with anticoagulants, and its effect on the risk of recurrence of venous thromboembolism: a systematic review of observational studies, Patient Prefer. Adherence. 10 (2016) 1657-65.

[17] L. Keller, S. Marten, J. Hecker, K. Sahin, L. Tittl, J. Beyer-Westendorf, Venous thromboembolism therapy with rivaroxaban in daily-care patients: Results from the Dresden NOAC registry, Int. J. Cardiol. 257 (2018) 276-282.
[18] J. Trujillo-Santos, P. Di Micco, F. Dentali, J. Douketis, J.A. Diaz-Peromingo, M.J. Nunez, I. Canas, D. Mastroiacovo, M. Saraiva de Sousa, M. Monreal, Real-life treatment of venous thromboembolism with direct oral anticoagulants: The influence of recommended dosing and regimens, Thromb. Haemost. 117(2) (2017) 382-389.
[19] T. Prami, H. Khanfir, A. Deleskog, P. Hasvold, V. Kyto, E. Reissell, J. Airaksinen, Clinical factors associated with initiation of and persistence with ADP receptor-inhibiting oral antiplatelet treatment after acute coronary syndrome: a nationwide cohort study from Finland, BMJ Open 6(11) (2016) e012604.
[20] P. Latry, K. Martin-Latry, M. Lafitte, C. Peter, T. Couffinhal, Dual antiplatelet therapy after myocardial infarction and percutaneous coronary intervention: analysis of patient adherence using a French health insurance reimbursement database, EuroIntervention 7(12) (2012) 1413-9.
[21] M.J. Claeys, C. Beauloye, S. Pourbaix, P.R. Sinnaeve, Real world insights on the initiation and treatment duration of oral antiplatelets in acute coronary syndromes: a retrospective cohort study, Eur Heart J Cardiovasc Pharmacother 3(4) (2017) 189-197.
[22] E. Simpson, C. Beck, H. Richard, M.J. Eisenberg, L. Pilote, Drug prescriptions after acute myocardial infarction: dosage, compliance, and persistence, Am. Heart J. 145(3) (2003) 438-44.
[23] C.D. Bushnell, L.O. Zimmer, W. Pan, D.M. Olson, X. Zhao, T. Meteleva, L. Schwamm, B. Ovbiagele, L. Williams, K.A. Labresh, E.D. Peterson, Persistence with stroke prevention medications 3 months after hospitalization, Arch. Neurol. 67(12) (2010) 1456-63.
[24] L. Osterberg, T. Blaschke, Adherence to medication, N. Engl. J. Med. 353(5) (2005) 487-97.
[25] S. Shore, P.M. Ho, A. Lambert-Kerzner, T.J. Glorioso, E.P. Carey, F. Cunningham, L. Longo, C. Jackevicius, A. Rose, M.P. Turakhia, Site-level variation in and practices associated with dabigatran adherence, JAMA 313(14) (2015) 1443-50.
[26] F.F. Van Doormaal, W. Terpstra, R. Van Der Griend, M.H. Prins, M.R. Nijziel, M.A. Van De Ree, H.R. Buller, J.C. Dutilh, A. ten Cate-Hoek, S.M. Van Den Heiligenberg, J. Van Der Meer, J.M. Otten, Is extensive screening for cancer in idiopathic venous thromboembolism warranted?, J. Thromb. Haemost. 9(1) (2011) 79-84.
[27] G.S. Alotaibi, H. Almodaimegh, M.S. McMurtry, C. Wu, Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis, Thromb. Res. 132(2) (2013) 185-9.
[28] M.P. Brekelmans, L.J. Scheres, S.M. Bleker, B.A. Hutten, A. Timmermans, H.R. Buller, S. Middeldorp, Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin, Thromb. Haemost. 117(4) (2017) 809-815.
[29] I. Martinelli, A.W. Lensing, S. Middeldorp, M. Levi, J. Beyer-Westendorf, B. van Bellen, H. Bounameaux, T.A. Brighton, A.T. Cohen, M. Trajanovic, M. Gebel, P. Lam, P.S. Wells, M.H. Prins, Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use, Blood 127(11) (2016) 1417-25.
[30] F.A. Klok, K. Schreiber, K. Stach, W. Ageno, S. Middeldorp, S. Eichinger, A. Delluc, M. Blondon, C. Ay, Oral contraception and menstrual bleeding during treatment of venous thromboembolism: Expert opinion versus current practice: Combined results of a systematic review, expert panel opinion and an international survey, Thromb. Res. 153 (2017) 101-107.

Figure 1: Definition of persistence to DOACs

Figure 2: Flow chart selecting DOAC users for the indication VTE

Figure 3 Cumulative incidence of stopping or switching DOAC within 3 months and cumulative incidence of stopping VKA

Table 1. Baseline characteristics

	DOAC use		Apixaban use		Rivaroxaban use		Dabigatran use	
Venous thrombosis patients								
Any dose, n	1834		94		1429		311	
Mean age, years (SD)	60	(16)	68	(12)	58	(16)	67	(13)
Men, n (%)	990	(54)	59	(61)	778	(54)	153	(49)
Concomitant drug use, n (%)	1370	(75)	80	(85)	989	(69)	301	(97)
Previous use of VKA, n (%)	131	(7)	11	(12)	98	(7)	22	(7)

DOAC denotes direct oral anticoagulant; SD, standard deviation; VKA, vitamin K antagonist; NA not available

Table 2. Predictors for discontinuing DOAC treatment within 2 months according to clinical characteristics

	Discontinued	Continued	Odds ratio (95% CI)		Odds ratio (95% CI)*	
Apixaban	11	83	1	(reference)	1	(reference)
Rivaroxaban	350	1079	2.45	(1.29-4.64)	2.19	(1.15-4.20)
Dabigatran	108	203	4.01	(2.05-7.85)	4.16	(2.12-8.18)
Previous use of VKA	23	108	1	(reference)	1	(reference)
No previous use of VKA	446	1257	1.67	(1.05-2.65)	1.37	(0.85-2.20)
Concomitant drug use	319	1051	1	(reference)	1	(reference)
No concomitant drug use	150	314	1.57	(1.25-1.98)	1.86	(1.45-2.39)
Age $\leq$ 60 years	205	640	1	(reference)	1	(reference)
Age 60-75 years	179	475	1.18	(0.93-1.49)	1.19	(0.93-1.52)
Age >75 years	85	250	1.06	(0.79-1.42)	1.04	(0.77-1.41)
Men	229	761	1	(reference)	1	(reference)
Women	240	604	1.32	(1.07-1.63)	1.38	(1.11-1.72)

*Multivariable adjusted for each other