

1 **Persistence to direct oral anticoagulants for acute venous thromboembolism**

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19

1 **Abstract**

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

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

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

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

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

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## 1 Introduction

2 Direct oral anticoagulants (DOACs) are approved for treatment of venous thromboembolism  
3 (VTE), thromboembolic prevention in atrial fibrillation (AF) and thromboprophylaxis. Recently,  
4 DOACs have been suggested by international and Dutch guidelines as the treatment of choice for  
5 acute VTE[1, 2]. In two meta-analyses based on randomized controlled trials it has been shown that  
6 DOACs are overall non-inferior in terms of efficacy (recurrent VTE) but lead to less major bleeding  
7 compared with vitamin K antagonists (VKAs) [3, 4]. An important practical advantage of DOACs over  
8 VKAs is that neither monitoring nor dose titration is needed. However, a lack of monitoring could  
9 decrease drug adherence and persistence [5]. Treatment duration for VTE is recommended to be at  
10 least three months [1], as the risk of recurrence is high after prematurely stopping anticoagulation  
11 treatment within 1 or 1.5 months after the VTE event compared with longer treatment duration, for  
12 a reported Hazard Ratio (HR) of 1.52 (95% confidence interval [CI] 1.1 to 2.0) [6]. In the DOAC trials,  
13 the percentage of patients who stopped DOAC treatment prematurely within 6 months ranged from  
14 11 to 15% [7-10]. However, these trials might not be representative for the persistence to DOACs in  
15 clinical daily practice since less support for patients to continue their DOAC use will be present as  
16 compared with the trial settings. Recently, a Danish registry study in patients treated with DOACs for  
17 AF showed that out of 50632 patients, 30% discontinued their initial DOAC treatment within one  
18 year: 14% completely stopped DOAC treatment, 10% switched to VKA and 5% switched to another  
19 DOAC [11]. Other studies in patients with AF also confirmed a higher non-persistence to DOAC in  
20 clinical settings than in trials, with discontinuation rates of 20 to 25% within two years of follow-up  
21 [12, 13]. To our knowledge, there are no published data on DOAC persistence in VTE patients in  
22 routine clinical practice. In the Netherlands, the first DOAC approved for treatment of VTE was  
23 rivaroxaban in 2012, followed by dabigatran and apixaban in 2014 and edoxaban in 2015. Over the  
24 last years, the use of DOACs has increased in the Netherlands [14]. The main purpose of the current  
25 study was to explore the persistence to DOACs in Dutch patients with acute VTE. A second aim was  
26 to assess for potential predictors for stopping DOAC prematurely. Since, to our knowledge, there is

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

4

## 5 **Methods**

### 6 *Definition of persistence*

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

13

### 14 *Data source*

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

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

7

### 8 *Selection of patients*

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

23

### 24 *Outcomes*

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

10

#### 11 *Statistical analysis*

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

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

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

1

2 *Persistence to VKA therapy*

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

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

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

3

#### 4 *Ethical approval*

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

8

## 9 **Results**

### 10 *Study population*

11 Between January 1<sup>st</sup> 2012 and April 1<sup>st</sup> 2016, 92718 patients initiated DOAC therapy. From this  
12 cohort, 87352 patients who were identified as incident DOAC users were selected (Flow chart, **figure**  
13 **2**). A total of 3427 patients were excluded because the DOAC type or dosage was unknown and 12  
14 patients were excluded because they used (according to SFK) more than 1 DOAC at the same time.  
15 From the remaining 83913 eligible DOAC users, 2048 were identified as DOAC users for acute VTE  
16 treatment, 77333 for AF, and 4532 as DOAC users for thromboprophylaxis. Lastly, from the 2048  
17 patients on DOAC for the indication VTE, 214 patients who started DOAC treatment after 1 February  
18 2016 were excluded, leaving 1834 patients for the primary analysis.

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

22

### 23 *Discontinuation*



1 From 1834 patients, 352 stopped DOAC within 2 months for a cumulative incidence of 20% (95%CI  
2 18 to 24). Additionally, 117 from 1834 patients switched their initial DOAC prescription: 113 to VKA  
3 and 4 to another DOAC for a cumulative incidence of 7% (95%CI 5.7 to 8.1). In total, 469  
4 discontinued DOAC (both 'stoppers' and 'switchers') within 2 months, for a cumulative incidence of  
5 26% (95%CI 24 to 28; Kaplan-Meier curves, **figure 3a**). After 3 months the number of patients that  
6 stopped DOAC increased to 470, for a cumulative incidence of 27% (95%CI 25-29). In addition, 134  
7 patients (8.1% [95%CI 6.7-9.4]) switched to another anticoagulant. In total, 604 patients  
8 discontinued DOAC for a cumulative incidence of 33% (95%CI 31-35). In the sensitivity analysis in  
9 which 52 patients who had the same birth year, sex, postal code and DOAC type were excluded,  
10 discontinuation patterns were comparable: 444 of 1782 patients discontinued for a cumulative  
11 incidence of 26% (95%CI 23 to 27).

#### 12 *Predictors for premature discontinuation*

13 In univariable analysis, predictors for discontinuing DOAC (stopping DOAC or switching to alternative  
14 treatment) were: no previous use of VKA (OR 1.67; 95%CI 1.05 to 2.65), the use of no other drugs  
15 (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).  
16 After multivariable analysis, no concomitant drug use (OR 1.86; 95%CI 1.45 to 2.39), and female sex  
17 (OR 1.38; 95%CI 1.11 to 1.72) remained predictors of premature discontinuation of DOAC treatment  
18 **(Table 2)**.

19 Rivaroxaban and dabigatran were associated with higher discontinuation rates than apixaban with  
20 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  
21 apixaban respectively. After multivariable analysis these odds ratios were: 2.19 (95%CI 1.15 to 4.20)  
22 and 4.16 (95%CI 2.12 to 8.18) respectively.

#### 23 *Persistence to VKA therapy*

1 5237 patients started VKA between January 1<sup>st</sup> 2004 and January 1<sup>st</sup> 2012 for the indication VTE.  
2 From this patient group, 327 patients who used VKA for upper extremity DVT (UEDVT) or thrombosis  
3 at another infrequent location were excluded, leaving 4910 patients for the analysis. Mean age was  
4 60 years (95% CI 59-60), and 48% of patients were men. Within 2 months 449 of 4910 stopped VKA  
5 for a cumulative incidence of 9.1% (95%CI 8.3 to 9.9; **figure 3b**). After 3 months 800 patients  
6 stopped with VKA, for a cumulative incidence of 18% (95%CI 17-19).

7

## 8 **Discussion**

9 This study, based on Dutch pharmacy dispensing and anticoagulation clinics registry data, showed  
10 that the cumulative incidence of premature discontinuation of DOAC treatment for the indication  
11 VTE in daily clinical practice within the first 2 months was 20% (95%CI 18 to 24) and an additional 7%  
12 (95%CI 5.7 to 8.1) switched to another anticoagulant treatment. The cumulative incidence of  
13 discontinuation (stopping or switching) DOAC was 26% (95%CI 24 to 28). This discontinuation rate is  
14 higher than was reported in the phase 3 DOAC trials, i.e., 11 to 15% within 6 months [7-10].  
15 Furthermore, we showed that the cumulative incidence of stopping VKA within the first 2 months  
16 was 9.1% (95% CI 8.3-9.9).

17 To our knowledge, there are only a few observational studies in small numbers of patients  
18 on discontinuation rates in DOAC use. One systematic review in patients with acute VTE included 7  
19 VKA studies and 3 conference abstracts about DOAC persistence. Stratifying the results from this  
20 systematic review into patients with VTE who used VKA and who used DOAC, discontinuation rates  
21 within 3 months ranged between 6% to 28% for VKA (average 18%) and 6% to 36% in patients on  
22 DOAC (average 13%) [16]. This study therefore shows the opposite from our study: a lower  
23 discontinuation rate in DOACs compared with VKA. However, the systematic review only included  
24 203 patients with acute VTE who were treated with DOAC, which is in stark contrast to our large

1 population based registry of patients with acute VTE who were treated with a DOAC (n=1834).  
2 Another recent study used the Dresden registry to analyse the persistence to Rivaroxaban in 418  
3 patients with VTE. After 6 months 58.3% of patients were still taking rivaroxaban, 28.2% had a  
4 scheduled end of treatment, 7.2% were switched to other [anticoagulants](#), 1.7% had withdrawn their  
5 consent and the remaining 3.6% of patients had unplanned complete discontinuation of  
6 anticoagulation. However, in contrast to our study, patients were contacted by phone during follow-  
7 up which could have positively altered the persistence rate [17]. Recently, a study based on RIETE  
8 registry data also reported that adequate treatment with DOACs for VTE is challenging in clinical  
9 practice [18]. This study showed that a high proportion of VTE patients who were prescribed DOACs  
10 did not receive the recommended daily dosings, i.e. once daily dosing of apixaban instead of twice  
11 daily. For the initial therapy, 50% (22 of 44) of apixaban users and 18% (287 of 1591) of rivaroxaban  
12 did not receive the recommended dosing, resulting in a higher VTE recurrence rate (HR 10.5, 95%CI  
13 1.28-85.9); discontinuation rates of DOAC during follow-up were not reported in this study.

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

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

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

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

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

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

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

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

13 In conclusion, in this study, based on Dutch pharmacy registry data, in patients who were  
14 selected as DOAC users for acute VTE, the cumulative incidence of stopping DOAC treatment within  
15 2 months after initiation was 20%, which is in line with use of other cardiovascular medications.  
16 Since the primary outcome of this study is based on Dutch registry data with corresponding  
17 limitations and may be not representative for other countries, our results should be mainly  
18 interpreted as hypothesis generating and as a warning that further investigation on the incidence  
19 and consequences of non-persistence in DOAC patients is urgently needed.

20

21 **Contributors:**

22 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  
23 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  
24 manuscript. M.T., F.J.M.vdM, F.A.K. and S.C.C. critically revised the paper for important intellectual  
25 content.

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1 **Figure 1: Definition of persistence to DOACs**

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

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**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 ≤ 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