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ORIGINAL ARTICLE

# Self-reported therapy adherence and predictors for nonadherence in patients who switched from vitamin K antagonists to direct oral anticoagulants

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## Abstract

**Background:** Many patients who used vitamin K antagonists (VKAs) for long-term prevention of thromboembolism are now actively switched to a direct oral anticoagulant (DOAC). Strict adherence to a DOAC is crucial for its success. However, therapy adherence and clinical factors that predict nonadherence are currently not well studied among patients who switched from a VKA to a DOAC.

**Methods:** A questionnaire was developed and sent to 2920 former patients of 3 anticoagulation clinics in the Netherlands, who switched from a VKA to a DOAC between January 2016 and December 2017. Questions concerned demographics, treatment persistence, adherence, and the occurrence of bleeding or thromboembolic events on DOACs. To identify predictors for nonadherence, logistic regression models were used to estimate crude and age/sex-adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs).

**Results:** A total of 1399 questionnaires (response rate 48%) were used for analysis. DOAC treatment persistence (94%) and adherence (86%) rates were high. Several predictors of nonadherence were identified, including young age (OR, 5.9; 95% CI, 3.6-9.8 for <60 years compared to >75 years), low consultation frequency with a specialist (OR, 1.6; 95% CI, 1.1-2.2), a history of minor bleeding on DOACs (OR, 1.9; 95% CI, 1.3-2.8), and a twice-daily dosing regimen (OR, 1.9; 95% CI, 1.3-2.6).

**Conclusions:** Self-reported treatment persistence and adherence were high in our study population, and several predictors of nonadherence were identified. Factors that can be influenced (low consult frequency with medical specialist, daily dosing regimen) may be used to improve therapy adherence.

KEYWORDS

anticoagulants, antithrombins, factor Xa inhibitors, medication adherence, patient compliance

**Essentials**

- Strict direct oral anticoagulant (DOAC) adherence is crucial; however, therapy adherence among patients who switched from a vitamin K antagonist (VKA) to a DOAC is not well studied.
- A questionnaire was sent to 2920 former VKA patients who switched to a DOAC.
- Treatment persistence and adherence with DOACs was high in this study.
- Identified predictors for nonadherence could be used to further optimize therapy adherence

## 1 | INTRODUCTION

As direct oral anticoagulants (DOACs) have become available for thromboembolic prophylaxis in atrial fibrillation and for the treatment and prevention of venous thrombosis, vitamin K antagonists (VKAs) may be phased out. Indeed, in the Netherlands, use of VKAs has declined from n = 423 669 users in 2013 to n = 361 169 in 2017, while there has been a steep increase in DOAC use over the same time period (n = 26 501 in 2013 and n = 202 840 in 2017).[1] A similar pattern has been noted in other countries.[2] Many patients who used a VKA for long-term prevention for thromboembolism are now actively switched to a DOAC. The main advantages of DOACs over VKAs are that DOACs can be taken in fixed doses, have less interaction with comedication and food, and do not require routine testing.[3] Although the efficacy of the DOACs is not in doubt,[4] the adherence to DOACs will determine their success.[5] It is for this reason that one not only needs clinical trial data, where adherence of treatment is well monitored, but also observational data on use of DOACs to understand how DOACs are being adopted into clinical practice. Relatively little information is available about which patients are nonadherent to their DOAC. Yet this knowledge is imperative, as it may lead to intervention strategies that could increase the rate of consistent use of DOACs in clinical practice. For example, a history of VKA monitoring might influence patients' perspective on the importance of therapy adherence to DOAC. To our knowledge, patients who switched from a VKA to a DOAC have not been studied previously to determine their adherence to a DOAC.

To study the treatment adherence to DOAC and DOAC adherence in relation to clinical characteristics in patients who switched from a VKA to a DOAC, we sent a questionnaire to former patients of 3 anticoagulation clinics in the Netherlands.

## 2 | METHODS

### 2.1 | Study population

Between May and July 2018, we sent a paper questionnaire to 2920 consecutive patients aged ≥18 years who were switched from a VKA to a DOAC by their treating physician (eg, cardiologist, internist, general practitioner). Patients were enlisted through 3 anticoagulation clinics (locations: Amsterdam, Leiden, the Hague) in the Netherlands, where they had been monitored while using a VKA (phenprocoumon or acenocoumarol) before switching to a DOAC (rivaroxaban, apixaban, dabigatran, or edoxaban) between January 2016 and December 2017.

Relevant patient information (name, home address) was extracted from the computerized patient records of the anticoagulation clinics, after which the paper questionnaire was sent by regular mail to the patient's home address. Patients were asked to return the questionnaire, which was anonymized, as no reference to home address or patient's name was included in the questionnaire. Of note, while this procedure guaranteed anonymity of the participants, it prevented sending reminders. This study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC), the Netherlands.

### 2.2 | Study design

The questionnaire was developed in the LUMC by researchers, and input was requested from medical specialists and the patient interest group Harteraad; a pilot study was conducted among a small group of eligible patients in which the goals were to assess if patients understood the questions, to test whether the questionnaire was too long, and to get an idea about the response rate. Based on the pilot study, the length of the questionnaire seemed to be acceptable, as the majority of the questionnaires were filled in properly. Based on patient feedback, a number of questions were formulated differently. The adjusted questionnaire was then sent to all eligible patients. Patients who were willing to participate returned the survey in a prepaid envelope to the LUMC. All collected data were self-reported.

### 2.3 | Survey components and outcomes

The final survey required demographics; primary anticoagulation indication; information about previous VKA treatment; comorbidity; comedication; DOAC type and dose; educational level; reasons for switching to a DOAC; persistence; adherence; concerns about adverse events, bleeding, and thromboembolic events since switching to a DOAC; and general treatment satisfaction (Appendix S1). Primary outcomes of this study were DOAC treatment persistence and adherence. Persistence was defined as continuing the treatment for the prescribed duration. Adherence was defined as not deviating from the prescribed regimen (ie, never forgetting to take the DOAC as prescribed). To be precise, the question was: "Do you occasionally fail to remember to take your new oral anticoagulant as prescribed?" If the answer was "yes," the patient was considered as nonadherent.

The questions we used to define persistence and adherence, were formulated in such a way that they are easy to use in conversations between physicians and patients when evaluating anticoagulant use. To study determinants of nonadherence, exposures of interest were age, sex, educational level, comorbidity, time on a VKA before switching to a DOAC, frequency of previous International Normalized Ratio (INR) controls while on VKA therapy, frequency of consultation with a medical specialist or general practitioner, the occurrence of minor bleeding events while on DOAC therapy, whether switching to a DOAC was done on the patient's or doctor's initiative, and the number of daily doses. High educational level was defined as having followed a higher professional education or a university education. Comorbidity was defined as suffering from any (chronic) illness that was different from the main anticoagulation indication at the time of filling in the questionnaire. Time on VKA therapy before switching to a DOAC was considered long when it was more than 2 years. Patients were considered stable on a VKA when the frequency of INR controls was less than once per month. Frequency of consultation with a medical specialist regarding anticoagulant treatment was considered low if it occurred less than once per year, as guidelines recommend frequent follow-up.[6–8] Patients treated with rivaroxaban or edoxaban were considered to have a once-daily DOAC dosing, patients treated with apixaban or dabigatran were considered to have a twice-daily DOAC dosing. Bleeding events were classified as minor (eg, superficial skin bleeding, epistaxis) if they did not require hospital admission.[9,10]

### 2.4 | Comparison with data from the Foundation for Pharmaceutical Statistics

To study the generalizability and to assess the influence of a potential selection bias of our study results, we compared our results with data on DOAC use from the Dutch Foundation for Pharmaceutical Statistics (SFK), of which the methods and several results were published previously.[11] In brief, SFK gathers pharmacy dispensing data from >95% of community pharmacies in the Netherlands. Relevant variables (age, sex, DOAC type, prior VKA use, and use of comedication) of patients who were treated with DOACs (rivaroxaban, apixaban, dabigatran) for stroke prevention in atrial fibrillation between January 1, 2012, and April 1, 2016, were extracted from the SFK and used for analysis. Primary study outcomes were patient persistence and adherence to the DOAC at 1 year of follow-up for patients with a history of VKA use. Persistence was defined as the cumulative incidence of patients who had continued initial DOAC treatment at 12 months, without switching to any other oral anticoagulant treatment. Patient adherence to the DOAC was measured as a dichotomous variable for the proportion of days covered (PDC) of at least 80%. This PDC cutoff is consistent with published research.[12]

### 2.5 | Statistical analysis

Baseline characteristics are presented as numbers and percentages, or as overall means (± standard deviation [SD]), and stratified by DOAC type. The observation time was defined as the number of days between switching to a DOAC and the time that the questionnaire was completed or when DOAC therapy was ceased, whichever came first. DOAC persistence and adherence were measured as dichotomous variables for the total follow-up period and calculated as proportions. An additional analysis concerning therapy adherence was performed after stratification of patients with a follow-up of <12 months and >12 months.

To identify potential predictors of treatment nonadherence, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were estimated using univariable and multivariable logistic regression analysis, adjusting for age and sex where applicable. For all patients with atrial fibrillation, the frequency of consultation with a medical specialist or a primary care physician was also included as a predictor of nonadherence. In the case of a missing value, the variable was excluded from analysis. All statistical analyses were performed with SPSS for Windows, release 24.0 (IBM, Armonk, NY, USA).

## 3 | RESULTS

### 3.1 | MONDOAC study population

A total of 2920 eligible patients were identified through 3 anticoagulation clinics. Overall, 112 questionnaires were returned without being filled out (n = 91 due to a change in address that was not known from electronic patients records of the anticoagulation clinics; n = 29 patients died before receiving the questionnaire). A total of 1399 questionnaires were returned and were used for analysis, which led to a response rate of 48%.

The mean age of patients was 74 years (SD, 10), 816 were male (60%), the mean time on DOAC therapy was 504 days (SD, 260), and atrial fibrillation was the primary indication for anticoagulant therapy in 1068 patients (76%) (Table 1). There were 288 patients who switched to a DOAC on their own initiative (22%), and 1027 patients (78%) switched on their doctors' initiative. The duration of VKA therapy before switching to a DOAC was longer than 2 years for 959 patients (70%), 1 to 2 years for 204 patients (15%), 6 months to 1 year for 82 patients (6%), and <6 months for 124 patients (9%). Comorbidity, defined as the presence of any illness (eg, diabetes, hypertension) that was different from the anticoagulation indication, was present in 997 patients (75%), 207 patients (15%) had diabetes, and 590 patients (42%) had hypertension. A total of 465 patients (34%) had a high educational level. Intervals of INR control during previous VKA treatment were weekly for 300 patients (23%) and monthly or less frequent for 542 patients (41%). Minor bleeding events had occurred in 292 patients (21%). DOAC-related consultation with a medical specialist occurred once or more per year for 535 patients (44%; and in 438 (48%) of patients with

**TABLE 1** Baseline characteristics of questionnaire responders (n = 1399)

| | Total | Rivaroxaban | Apixaban | Dabigatran | Edoxaban |
|---|---|---|---|---|---|
| Men | 816 (60) | 247 (58) | 221 (61) | 248 (63) | 87 (53) |
| Age | 74 (10) | 72 (11) | 74 (9) | 75 (9) | 75 (10) |
| Atrial fibrillation | 1068 (76) | 285 (66) | 305 (81) | 330 (82) | 137 (84) |
| Venous thromboembolism | 227 (16) | 121 (28) | 40 (11) | 39 (10) | 22 (13) |
| Other indications | 129 (10) | 29 (7) | 27 (8) | 33 (9) | 15 (9) |
| Comorbidity | 997 (75) | 292 (69) | 279 (76) | 294 (76) | 129 (80) |
| Diabetes | 207 (15) | 63 (15) | 55 (15) | 58 (15) | 26 (16) |
| Hypertension | 590 (42) | 166 (39) | 164 (44) | 183 (47) | 71 (44) |
| Days on DOAC therapy | 504 (260) | 530 (274) | 499 (275) | 531 (248) | 382 (169) |
| Time on VKA therapy ≥ 2 y | 959 (70) | 296 (69) | 256 (69) | 274 (70) | 123 (76) |
| High educational level | 465 (34) | 149 (35) | 117 (32) | 154 (39) | 42 (26) |
| Interval INR control – weekly | 300 (23) | 101 (24) | 79 (21) | 84 (22) | 30 (20) |
| Interval INR control – monthly or less | 542 (41) | 165 (40) | 150 (40) | 162 (42) | 60 (39) |
| Minor bleeding events | 292 (21) | 100 (23) | 76s (20) | 70 (17) | 40 (24) |
| Consultation with MS ≥ once/y | 535 (44) | 164 (41) | 135 (44) | 147 (43) | 85 (54) |
| Consultation with MS < once/y | 687 (56) | 233 (59) | 175 (57) | 196 (57) | 72 (46) |
| Switching, own initiative | 288 (22) | 91 (22) | 67 (19) | 102 (27) | 28 (18) |
| Switching, doctor's initiative | 1027 (78) | 320 (78) | 289 (81) | 283 (73) | 127 (82) |

*Note:* Continuous variable denoted as mean (standard deviation), categorical variables as number (percentage).
DOAC, direct oral anticoagulant; INR, International Normalized Ratio; MS, medical specialist; VKA, vitamin K antagonist.

atrial fibrillation) and less than once per year for 687 patients (56%; and in 479 [52%] of patients with atrial fibrillation).

## 3.2 | Persistence and adherence—MONDOAC

The majority of patients (n = 1265) were persistent to their DOAC at the time of participation in our study (94%). 51 patients (4%) did not report persistence (did not fill in the question of interest). Complete DOAC adherence was identified for 1173 (86%) of patients. Thirty-seven patients (3%) did not report adherence (did not fill in the question of interest). Adherence rates remained similar after stratification for time on DOAC therapy (87% for patients <1 year on DOAC vs 85% for patients >1 year on DOAC) (Table 2).

**TABLE 2** DOAC persistence and adherence

| | |
|---|---|
| **Persistence** | |
| Still uses DOAC | 1265 (94) |
| Stopped using all OACs | 25 (2) |
| Switched to PAI | 31 (2) |
| Switched to different DOAC | 29 (2) |
| Switched back to VKA | 17 (1) |
| **Adherence questions** | |
| Occasionally forgets to take DOAC | 189 (14) |
| Stopped using DOAC because of side effects | 31 (2) |
| Stopped using DOAC because disease symptoms were absent | 7 (1) |
| Did not take DOAC day before filling out questionnaire | 28 (2) |
| Difficulty following treatment plan | 113 (9) |
| **Adherence follow up** | |
| Adherence first 1 y of follow-up | 296 (87) |
| Adherence after 1 y of follow-up | 564 (85) |

*Note:* Continuous variable denoted as mean (standard deviation), categorical variables as number (percentage).
DOAC, direct oral anticoagulant; OAC, oral anticoagulant; PAI, platelet aggregation inhibitor; VKA, vitamin K antagonist.

## 3.3 | Predictors of therapy nonadherence—MONDOAC

Predictors of DOAC nonadherence included young age, male sex, high education, no comorbidity, previous INR controls once or more per week (Table 3). Duration of treatment with a VKA before switching to a DOAC <2 years increased the risk of nonadherence 1.4-fold (95% CI, 1.0-2.0) (Table 3). Other predictors of nonadherence were consultation frequency with a medical specialist less than once per year (OR, 1.5; 95% CI, 1.1-2.1), the experience of minor bleeding events on DOAC therapy (OR, 1.4; 95% CI, 1.0-2.0), and twice-daily dosing of DOACs (OR, 1.6; 95% CI, 1.2-2.2). For patients with atrial fibrillation who indicated that they were not followed regularly (less than once per year) by their specialist or

**TABLE 3** Predictors of therapy nonadherence in MONDOAC

| | Adherent | Nonadherent | OR (95% CI) | OR[a] (95% CI) |
|---|---|---|---|---|
| >75 y | 568 (92) | 46 (8) | Reference | Reference |
| 60-75 y | 507 (83) | 107 (17) | 2.6 (1.8-3.8) | 2.5 (1.8-3.7) |
| <60 y | 74 (67) | 36 (33) | 6.0 (3.7-9.9) | 5.9 (3.6-9.8) |
| Female | 471 (90) | 55 (10) | Reference | Reference |
| Male | 667 (83) | 133 (17) | 1.7 (1.2-2.4) | 1.7 (1.2-2.4) |
| Low education | 480 (93) | 37 (7) | Reference | Reference |
| High education | 356 (78) | 102 (22) | 3.7 (2.5-5.6) | 2.9 (1.9-4.4) |
| Time on VKA before switch ≥2 y | 823 (87) | 119 (13) | Reference | Reference |
| Time on VKA before switch <2 y | 328 (83) | 68 (17) | 1.4 (1.0-2.0) | 1.26 (0.9-1.7) |
| INR control ≤ monthly | 459 (87) | 71 (13) | Reference | Reference |
| INR control ≥ weekly | 235 (81) | 55 (19) | 1.5 (1.0-2.2) | 1.5 (1.0-2.2) |
| Comorbidity | 881 (88) | 116 (12) | Reference | Reference |
| No comorbidity | 263 (79) | 68 (21) | 2.0 (1.4-2.7) | 1.5 (1.1-2.2) |
| Consultation with MS ≥ once/year | 465 (88) | 61 (12) | Reference | Reference |
| Consultation with MS < once/year | 563 (83) | 113 (17) | 1.5 (1.1-2.1) | 1.6 (1.1-2.2) |
| No history of minor bleeding events on DOAC | 940 (87) | 140 (13) | Reference | Reference |
| History of minor bleeding events on DOAC | 233 (83) | 49 (17) | 1.4 (1.0-2.0) | 1.9 (1.3-2.8) |
| Switching own initiative | 246 (86) | 39 (14) | Reference | Reference |
| Switching advice of physician | 857 (86) | 144 (14) | 1.1 (0.7-1.6) | 1.1 (0.7-1.6) |
| DOAC once daily | 534 (89) | 65 (11) | Reference | Reference |
| DOAC twice daily | 634 (84) | 124 (16) | 1.6 (1.2-2.2) | 1.9 (1.3-2.6) |

*Note:* Continuous variable denoted as mean (standard deviation), categorical variables as number (percentage).

DOAC, direct oral anticoagulant; INR, International Normalized Ratio; MONDOAC, Monitoring of direct oral anti-coagulant; MS, medical specialist; VKA, vitamin K antagonist.

[a]Adjusted for age and sex (where applicable).

primary care physician on their anticoagulation use (n = 376), the unadjusted OR for nonadhering to a DOAC was 1.5 (95% CI, 1.0-2.2) (adjusted OR, 1.5; 95% CI, 1.0-2.2) compared with those who were followed at least once per year by their specialist or primary care physician.

### 3.4 | SFK treatment persistence and adherence data compared to the MONDOAC study

As was recently published by Zielinksi et al,[11] the mean age of oral anticoagulant naïve patients (n = 70 977) in SFK was 70 years (SD, 11), 38 995 were male (55%), and 60 028 used comedication (85%). For patients in SFK who switched from VKA to DOAC (n = 6356) the mean age was 70 years (SD, 11), 3667 were male (58%), and 6323 used comedication (99%) (Table 4). In SFK data, persistence rates among patients with atrial fibrillation after 1 year of follow-up was 77% for patients who switched from a VKA to a DOAC, while in the Monitoring of direct oral anti-coagulant (MONDOAC) study the persistence rate was 94% for patients with atrial fibrillation (Table 5).[11] In SFK data, the adherence rate for DOAC after 1 year of follow-up was 88% for patients who switched from a VKA to a DOAC, this was also 88% for patients with atrial fibrillation in the MONDOAC study.

**TABLE 4** Baseline characteristics of SFK data compared to questionnaire data

| | VKA to DOAC switchers in SFK (n = 6356) | Questionnaire (AF only) (n = 1068) |
|---|---|---|
| Age | 70 (11) | 75 (8) |
| Male | 3667 (58) | 647 (62) |
| Comedication use | 6323 (99) | 984 (94) |

*Note:* Continuous variable denoted as mean (standard deviation), categorical variables as number (percentage).

AF, atrial fibrillation; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; SFK, Foundation of Pharmaceutical Statistics; VKA, vitamin K antagonist.

## 4 | DISCUSSION

In this study among patients who recently switched from a VKA to a DOAC, DOAC treatment persistence (94%) and adherence (86%) rates were high. Those who were nonadherent were more likely to be of young age and male sex, have a high educational level, have no comorbidity, have a low consultation frequency with a medical specialist, have more frequent INR controls during VKA therapy, and

**TABLE 5** Persistence and adherence in patients from SFK database compared to questionnaire data

| | VKA to DOAC switchers in SFK | Questionnaire (AF only) |
|---|---|---|
| Persistence | 77 | 94 |
| Adherence | 88 | 88 |

*Note:* Variables as percentages according to previously mentioned definitions.

AF, atrial fibrillation; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; SFK: Foundation of Pharmaceutical Statistics; VKA, vitamin K antagonist.

have a history of minor bleeding while using DOACs. Also, those who had a twice-daily dosing regimen were more likely to be nonadherent. To our knowledge, most predictors of DOAC nonadherence that we studied have not been studied before. We identified young age as a predictor, which is in line with earlier studies.[13] Other predictors (male sex, twice-daily dosing regimen) were studied before, but results are inconsistent.[14]

Several observational studies have described DOAC adherence over recent years. DOAC adherence rates are variable between studies (38%-99%), with large differences between studies likely depending on setting and definition of adherence.[8] Our findings of high adherence are in line with some earlier studies that evaluated DOAC use in daily care. In a study by van den Heuvel et al,[15] prescription data of pharmacies in the Netherlands showed a high proportion (88%) of patients with a PDC ≥80%. Other studies have also shown high median adherence to DOACs (94%-99%).[5,16,17] In contrast, poor DOAC adherence is reported as well. In a New Zealand–based pharmaceutical database study by Harper et al,[13] full adherence (PDC = 100%) to dabigatran in patients with atrial fibrillation was around 30% over a 2-year follow-up period. In a large retrospective cohort study in the United States, only 48% of DOAC-treated patients had a PDC ≥80% over a 1-year follow-up period.[18] The discrepancy between the low DOAC adherence rates in these studies and our study results can be explained by a number of reasons. First, differences in study design or definitions of adherence are likely to contribute. Second, our study specifically focused on patients who switched from a VKA to a DOAC, whereas in other observational studies only oral anticoagulant (OAC)-naïve patients or a combination of OAC-naïve and OAC-experienced patients were included. We also found a high anticoagulant adherence rate among VKA-experienced patients in the SFK database, which was also described in other studies.[19,20] This might be caused by a higher awareness of the importance of therapy adherence in patients with a history of anticoagulant monitoring. Third, our specific VKA-experienced patient group may also be a selective group, as patients with the highest risk of poor persistence may already have discontinued VKA therapy prematurely before they had the chance to switch to a DOAC. A fourth possible reason for higher adherence among switchers is that switching from a VKA to a DOAC might be initiated when patients need to visit the hospital or their medical specialist in case of sickness.[21] Patients who recently met with their doctor or experienced an adverse event might pay extra attention to adequate use of their anticoagulants afterwards.

This study has strengths and limitations. A strength of our study is the unique study design, in which only patients who switched from a VKA to a DOAC were included. Despite the clinical relevance of this group of patients at a time when VKA use is rapidly declining due to the large number of people switching to a DOAC, very few studies evaluated DOAC use in this specific patient group.[22] Another strength is that many predictors that were identified in this study have not been studied before for the purpose of DOAC adherence. For instance, 41% of patients with atrial fibrillation indicated that they were not followed by their physician or primary care physician on their yearly bleeding risk while on DOAC. The odds ratio of these patients for non-adhering to DOAC was 1.5 (95%CI 1.1-2.2) compared with those who were followed at least once per year by their physician. This result shows that even though frequency of consultation with a medical specialist or primary care physician for blood sampling (hemoglobin, renal and liver function) is considered by guidelines to take place at least once a year and review of anticoagulant treatment is considered to take place at frequent intervals,[6–8] these principles of informed decision making are not always met (as also in other medical disciplines),[23] which can have harmful consequences.[5]

However, strong conclusions about this and other results from our study should be handled with caution due to a number of potential limitations. First, the response rate of our questionnaire was 48%. This is an acceptable response rate for questionnaires in social sciences,[24] but it may have affected our study results as nonresponse bias cannot be excluded. For example, the high number of responders with a self-reported academic background (34%, while in the Netherlands <20% of individuals have such an educational background) suggests that patients with low educational status were underrepresented. Also, patients who are not adherent to treatments might also not be adherent to questionnaire requests. However, adherence rates in our study were comparable with studies in similar patient populations,[20] including SFK, where adherence rates in those who switched from a VKA to a DOAC were similar to our study results. To establish the generalizability of our results, we recommend confirmation of our study also because there are currently very few studies that look into this matter.[22]

Second, all information was self-reported (paper questionnaire), which could have led to an overestimation of treatment adherence or persistence. Third, we did not compare our results with VKA treated patients, as these patients are expected to be different from patients who are eligible for DOAC therapy (ie, confounding by indication).[25] Fourth, our definition of treatment adherence in the questionnaire study was not optimal. Within the questions we used to test for treatment adherence (Table 2), not deviating from the prescribed regimen seemed most useful in clinical practice. A selection of other tested variables are shown in the paper but left out of account for the predictor analyses, as numbers were small. Due to the study design, we were not able to calculate the more commonly used PDC. Finally, we did not use a validated questionnaire

on adherence to anticoagulant treatment[26] but used our own expertise, together with those of patient organization Harteraad to define self-reported adherence and markers for adherence. For instance, a measure like "consultation frequency with a medical specialist" (in our study related with self-reported adherence) is a question that has not been validated. That our questionnaire is not validated stresses the importance that our novel findings need to be validated in other studies.

In conclusion, high therapy adherence and persistence rates were shown in patients who switched from a VKA to a DOAC. Important predictors for nonadherence were young age, male sex, history of minor bleeding, low consultation frequency with a medical specialist, and a twice-daily dosing regimen. Confirmation of our results is necessary and could increase generalizability when performed in a more heterogenous population, which could be done relatively easily and with a low study budget.

## RELATIONSHIP DISCLOSURE

MMAT, NvR, FJMvdM, MCN, HWV, SCC, and WML have nothing to disclose. MVH reports grants from ZonMW Dutch Healthcare Fund, grants and personal fees from Boehringer-Ingelheim, Pfizer-BMS, Bayer Health Care, Aspen, and Daiichi-Sankyo, outside the submitted work.

## AUTHOR CONTRIBUTIONS

MMAT, SCC, and WML designed the research. MMAT, FJMvdM, MCN, HWV, and WML collected the data. MMAT and WML analyzed the data. MMAT, and WML wrote the manuscript. MMAT, NvR, FJMvdM, MCN, HWV, MVH, SCC and WML revised the paper for important intellectual content.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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