Patient Preference and Adherence

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ORIGINAL RESEARCH

# Medication Adherence to Direct Oral Anticoagulants: Extent and Impact of Side Effects

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**Purpose:** Arterial and venous thromboembolism are a leading cause of mortality. Direct oral anticoagulants (DOACs) are highly effective in both stroke prevention and prevention of venous thrombotic events. Medication adherence is a prerequisite for optimal protection against thromboembolic complications. Recent studies have shown that good adherence cannot be taken for granted by DOACs. In this cross-sectional study adherence among DOAC users was investigated and associations between beliefs about medication, perceived side effects and adherence were explored.

**Patients and Methods:** We included 100 randomly selected adult DOAC users visiting one of the two participating Dutch community pharmacies in the summer of 2020. The self-reported adherence (primary outcome) was assessed with the Medication Adherence Rating Scale-5 (MARS-5) using three different cut-off scores. Beliefs about DOACs were assessed with the Beliefs about Medicine Questionnaire Specific (BMQ-S), while side effects and side effect burden were assessed with a self-developed questionnaire based on the Lareb Intensive Monitoring (LIM) system.

**Results:** Of the participants, 9% reported non-adherence on the primary MARS-5 cut-off score <24. For the MARS-5 scores <23 and <25 non-adherence percentages of, respectively, 3 and 33% were calculated. Associations were found between adherence and both side effects and side effect burden, regardless of the MARS-5 cut-off score. Bruising and minor bleeds were the most reported side effects (both 20%). For all patients, the necessity beliefs outweighed the concern beliefs. No associations were found between adherence and either gender, indication, DOAC or dosage.

**Conclusion:** This study confirms that adherence in patients on DOACs cannot be taken for granted. High necessity beliefs do not guarantee good adherence, as side effects impair adherence even in patients having high necessity beliefs. Therefore, we recommend that both physicians and pharmacists evaluate both adherence and side effects with these patients on a regular base.

**Plain Language Summary:**

The issue

Thrombosis affects many people. Complications like stroke and lung embolism are a major cause of health damage, disability and even death. Direct oral anticoagulants (DOACs) are highly effective drugs at preventing these complications. However, patients need to take their medication properly to get the best protection. Recent studies showed that not all patients consistently take their DOACs.

What's new?

In this study, we discovered that patients experiencing bothersome side effect were less likely to stick to their medication schedule. The most common side effects reported were bruising and minor bleeding, by 20% each. There were no differences in how well patients took their medication based on gender, medical condition, type of DOAC or prescribed dosage. Most patients believed their medication was necessary for their health.

Why is this important?

This study shows that side effects hinder patients taking their medication correctly even when they believe their medication is necessary for their health. This means that patients on DOAC therapy who experience side effects may be less protected against stroke and lung embolism. Therefore, we recommend that doctors and pharmacists regularly check in with patients about any side effects they experience and how consistently they take their DOACs.

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What's next?

This study highlights the importance of developing, testing, and implementing practical tools to find and help patients who do not take their DOACs correctly, to ensure they are better protected against blood clots.

**Keywords:** DOACs, compliance, MARS-5, beliefs, BMQ-S

## Introduction

Arterial and venous thromboembolism are estimated to account for 1 in 4 deaths worldwide in 2010 and are a leading cause of mortality.[1] As atrial fibrillation (AF) (with a prevalence of 1–3% in Europe) is associated with an estimated fivefold rise in ischemic stroke risk, it is a major contributor to arterial thrombosis.[2] Diagnosed in 1–2 per 1000 persons per year venous thromboembolism (VTE) including both deep vein thrombosis (DVT) and pulmonary embolism (PE) is the third most common cardiovascular disorder after acute coronary syndrome and ischemic stroke.[3]

Given the impact of ischemic stroke and VTE, adequate pharmacotherapy to reduce the incidence and burden of ischemic stroke and VTE is essential. Both direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) are highly effective in stroke prevention (relative risk reduction ≈64%) and prevention of venous thrombotic events (relative risk reduction ≈80%).[3] In most clinical guidelines DOACs are preferred over VKAs due to their simpler fixed dose regime, no need for international normalised ratio (INR) monitoring and fewer intracranial bleedings. Medication adherence is, however, a prerequisite for optimal protection against thromboembolic complications.[4] Paradoxically, no need for INR monitoring for DOACs also means no monitoring of adherence as the INR can be seen as a surrogate marker for proper VKA use.[5]

Recent studies have shown that medication adherence and persistence cannot be taken for granted for patients on DOACs. Various studies demonstrated that both implementation adherence (defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose) and medication persistence (the length of time between initiation and the last dose, which immediately precedes discontinuation) is suboptimal.[4] An international study by Banerjee et al showed that adherence to DOACs does not exceed 55.2%,[5] while according to a Dutch follow-up study by Zielinski et al the non-persistence after 1 year of follow-up was 34%.[6] In an observational study conducted in a primary care setting Capiau et al found that half of the study population did not take their DOAC (mainly non-intentional) on at least 17 cumulative days per year and that 21% were non-adherent.[7] Ruff et al estimated long-term adherence for DOACs to be only in the 40–60% range.[8] One of the findings from the Switching Study conducted by Bartoli-Abdou et al was that after switching from VKA to DOAC 39% of patients had sub-optimal adherence measured by self-report.[9] In contrast, a study by Toorop et al found a clearly higher self-reported adherence of 86%.[10] In a meta-analysis by Ozaki et al, it was calculated that the percentage of patients with good adherence is 69%.[11] Another important finding in this study was that reduced adherence was associated with poorer clinical outcomes.

Medication adherence and persistence are influenced by different factors like medication beliefs, treatment knowledge, patient's self-efficacy and also side effects. For example, a study by Rolfes et al concluded that 9% of DOAC users stopped their DOAC therapy because of side effects.[12,13] Minor bleeding is, according to Toorop et al, an important predictor for non-persistence.[10] Mitrovic et al have also shown that minor bleeds are common among DOAC users and are associated with discontinuation, although no associations were found between minor bleeds and non-adherence, lack of trust or concerns. However, they showed that on an individual basis, there were patients that reported a high burden of minor bleeds.[14–16] Despite two-thirds of DOAC users in the aforementioned study by Capiau et al reported side effects (with easy bleeding (40.2%) being the most common for all DOACs), there was an overall positive attitude towards DOAC use.[7] Bartoli-Abdou et al found that believing that medications in general were overused in healthcare at baseline and that increasing concerns about anticoagulation over time while also having doubts concerning the necessity of the drug treatment were both associated with lower self-reported adherence.[9]

Given the variation between adherence estimates found in the literature, inconclusive findings regarding the role of side effects, their burden and ambiguity regarding the role of specific personal beliefs that can impede good adherence,

this study aims to assess implementation adherence among DOAC users and associations between beliefs about medication, perceived side effects, their burden and implementation adherence.

# Methods

## Study Design and Setting

This cross-sectional study was conducted in the summer of 2020 in two Dutch community pharmacies. The Medical Research Ethics Committee (MREC) of Arnhem-Nijmegen waived official ethical approval and assessed the study as not being subject to the Medical Research Involving Human Subjects Act (WMO). To strengthen the reporting of this study, the STROBE statement has been respected. This study complies with the Declaration of Helsinki.

## Patient Inclusion and Data Collection

### Inclusion Criteria

All adult patients with at least one delivery of a DOAC in the two participating pharmacies in the previous 6 months were eligible for this study. From all the eligible patients, a total of 100 patients were selected with the Excel Randomize tool to be approached for the study. Patients were included after obtaining verbal informed consent.

### Exclusion Criteria

Patients not speaking the Dutch language sufficiently and patients suffering from cognitive impairment and/or receiving supervision of their medication intake were excluded. For this reason, patients using a multidose drug dispensing system and/or living in a nursing home were not eligible.

### Outcomes

The primary outcome of this study was self-reported implementation adherence. Beliefs about medication, side effects and burden were secondary outcomes.

## Measurement Instruments

The primary outcome self-reported adherence was assessed with the Medication Adherence Rating Scale-5 (MARS-5).[17] Beliefs about DOACs were assessed with the Beliefs about Medicine Questionnaire specific (BMQ-S).[18] Side effects and side effect burden were assessed with a self-developed questionnaire based on the Lareb Intensive Monitoring (LIM) system.

### Self-Reported (Implementation) Adherence

The MARS-5 consists of 5 items each addressing intentional non-adherence behaviour. All items are rated on a 5-point Likert Scale from 1 (always) to 5 (never), resulting in a sum scale score of 5 to 25. No standard cut-off value is proposed by the scale developers and cut-off values in the literature have ranged from 20 to 25. Because adherence is of utmost importance in DOAC use and given the lack of monitoring and the poorer clinical outcomes associated with non-adherence, a primary cut-off score of <24 to differentiate between non-adherent (score <24) and adherent (score ≥24) patients is used in this study as non-adherence is easily underestimated with the MARS.[9] To evaluate sensitivity of the MARS-5 for assessing adherence to DOACs, all analyses will be performed for the MARS-5 cut-off scores of <23 and <25 as well.[19,20]

### Beliefs About Medicines Questionnaire Specific

The BMQ-S consists of 10 items, with 5 items for beliefs about necessity (eg "My health in the future will depend on these medicines") and 5 items about concerns (eg "Having to take these medicines worries me"). All items are rated on a 5-point Likert Scale from 1 (strongly disagree) to 5 (strongly agree), hence a sum scale score of 5 to 25 for necessity and concern beliefs subscales. The difference between necessity and concern sum scale scores (NC-differential) is between −20 and +20, with a total positive score meaning that advantages of DOAC use outweigh disadvantages. On the basis of the necessity and concern scores, patients are also categorized as accepting (necessity >16, concern ≤13), ambivalent (necessity >16, concern >13), sceptical (necessity ≤16, concern >13) or indifferent (necessity ≤16, concern ≤13).[21] The BMQ consists of one more item that is not used in the shorter BMQ-S for calculating necessity and concern

beliefs scores. Because this item (question 11) is about a concern believe about side effects of DOACs ("These medicines have unpleasant side effects") we have included it as well to compare with results obtained from the side effect burden questionnaire.[17]

### Side Effects

The self-developed side effect burden questionnaire is based on the Lareb Intensive Monitoring (LIM) system and consists of two parts. In part one, patients are asked if they experience side effects that they relate to DOAC use and secondly if they recognize 8 typical side effects attributed to DOAC use. In part two, the side effect burden for every reported side effect was rated on a 5-point Likert Scale from 0 (no burden) to 5 (very high burden). A low side effect burden is defined as either no or only minor burdensome side effects, whereas high burden is defined as moderate to very burdensome side effects. Both the percentage of patients reporting side effects as the sum side effect burden per patient are calculated. The side effect burden questionnaire measures the experiential aspect of side effects whereas BMQ question 11 measures the cognitive aspect of side effects.

## Sample Size and Data Analysis

This study is powered for measuring the primary outcome self-reported adherence. In order to calculate the sample size the Cochran formula was used. Assuming a percentage of patients with good adherence of 69%,[7] a 10% power and an alpha of 5%, the minimal sample size was calculated for 83 patients. Taking into account at least 10% percent non completion of the questionnaire, a convenient sample of 100 patients was strived for.

Analysis of associations between adherence, medication beliefs and side effects is for explorative purposes only. All data were analysed using STATA version 13. Descriptive statistics were provided using mean (± SD) or median (p25-p75) values depending on the (non-)parametric distribution of measured variables. P-values ≤0.05 were considered statistically significant. The formula that was used for calculating the margin of error and 95% confidence intervals for the main endpoint adherence (calculated as a proportion) was Z*(SQRT (pq/n)) where Z is 1.96 for 95% confidence and q=(1-p). Differences between groups were calculated with Pearson's chi-square test, *t*-test (in case of normal distribution) or regression testing depending on the variables (dichotomous or continuous). We have checked whether assumptions for chi-square tests and t-tests hold and this was the case.

# Results

## Baseline Characteristics

All of the 100 included patients orally consented to participate in this study. For all included patients (mean age 73.3 (SD ±7.9) years, 64% female) the three questionnaires (MARS-5, BMQ-S and side effects) were administered and completed. The baseline characteristics are depicted in Table 1. Most 81% of the patients were on DOAC therapy for the indication atrial fibrillation while edoxaban (36%) and rivaroxaban (31%) were used more often than apixaban (19%) and dabigatran (14%).

## Adherence to DOACs

Mean patients' medication adherence to DOACs as measured with the MARS-5 questionnaire was 24.46 (SD±1.61) while the lowest individual score was 16. The proportion of patients with a MARS-5 score <24 (defined as non-adherence) was 9% (95% CI = 8.94–9.06). For the cut-off value of <23 and <25 the proportion of non-adherent patients was 3% (95% CI = 2.97–3.03) and 33% (95% CI = 32.91–33.09), respectively (Table 2).

## Reported Side Effects and Side Effect Burden Concerning DOACs

Of all patients 35% reported side effects addressed to DOAC use, whereas bruising and (minor) bleedings were the two topmost (both 20%) reported side effects. A high burden was experienced by 13% of the patients (Table 3). Headaches or dizziness reported by 2% of the study subjects were the most invalidating complaints and scored the highest on burden.

**Table 1** Baseline Characteristics

| Characteristic | n=100 |
|---|---|
| Gender | |
| Males | 61 |
| Females | 34 |
| Unknown | 5 |
| Age – years | |
| Mean (SD) | 73.3 (±7.9) |
| Range | 47–86 |
| DOAC | |
| Apixaban | 19 |
| Dabigatran | 14 |
| Edoxaban | 36 |
| Rivaroxaban | 31 |
| DOAC dosage | |
| Once a day | 67 |
| Twice a day | 33 |
| Indication | |
| Atrial fibrillation | 81 |
| Venous thromboembolism | 11 |
| Unclear | 8 |
| Renal function (CKD-EPI) – mL/min/1.73m$^2$ | |
| ≥50 | 89 |
| 30–49 | 9 |
| ≤30 | 2 |

**Table 2** Primary Outcome

| MARS-5 | Mean (SD) | Range |
|---|---|---|
| Item | | |
| I forget to take my medication | 4.61 (0.63) | 2–5 |
| I alter the dose of my medication | 4.98 (0.20) | 3–5 |
| I stop taking my medication for a while | 4.97 (0.22) | 3–5 |
| I decide to miss out a dose of my medication | 4.94 (0.31) | 3–5 |
| I take less of my medication than instructed Total | 4.96 (0.24) | 3–5 |
| Total | 24.46 (1.61) | 14-25 |
| Primary cut-off score <24 | | |
| Non-adherence (n=9) | 21.7 (2.40) | 16–23 |
| Adherence (n=91) | 24.7 (0.44) | 24–25 |
| Cut-off score <23 | | |
| Non-adherence (n=3) | 19 (6.63) | 16–22 |
| Adherence (n=97) | 24.6 (0.44) | 23-25 |
| Cut-off score <25 | | |
| Non-adherence (n=33) | 23.4 (1.60) | 16–24 |
| Adherence (n=67) | 25.0 (0.00) | 25–25 |

**Table 3** Mean (SD) Side Effects and Side Effect Burden Scores

| Patients with Side effects | Frequency (n=100) | Patients with high Side Effect Burden | Frequency (n=100) |
|---|---|---|---|
| Yes | 35 | Yes | 13 |
| No | 65 | No | 87 |
| **Reported side effects** | **Frequency (n=100)** | **Mean burden score (SD)** | **Range burden score** |
| Bruising | 20 | 1.85 (0.75) | 1–3 |
| Bleeding | 20 | 2.35 (1.14) | 2–4 |
| Anemia | 0 | 0 | 0–0 |
| Esophageal complaints | 0 | 0 | 0–0 |
| Gastrointestinal complaints | 2 | 1.5 (1.73) | 3–3 |
| Headaches | 2 | 4.5 (0.71) | 4–5 |
| Dizziness | 2 | 4.5 (0.71) | 4–5 |
| Tiredness | 2 | 3.5 (2.12) | 2–5 |

## Beliefs About DOAC Use

The scores concerning patients' beliefs about DOAC use are shown in Table 4. For all patients, the necessity beliefs outweigh the concern beliefs. As mentioned before, question 11 is not part of the BMQ-S but as it specifically asks for concerns (cognitive level) about side effects related to DOAC use it is displayed as well. Most patients (81%) can be categorized as ambivalent (meaning both necessity and concern beliefs high) while not a single one patient is being sceptical.

## Associations between adherence to DOACs and baseline characteristics, side effects, side effect burden and beliefs about DOAC use

For all MARS-5 scores (irrespective of the cut-off value) an association was found between adherence and both side effects and side effect burden (Table 5, results displayed for primary MARS-5 cut-off value only). Non-adherent patients

**Table 4A** Mean (SD) BMQ-S scores

| BMQ-S | Mean (SD) | Range |
|---|---|---|
| Necessity beliefs about DOAC use | 21.18 (2.73) | 10–25 |
| Concern beliefs about DOAC use | 15.69 (2.50) | 8–20 |
| Question 11: "These medicines give me unpleasant side effects" | 2.89 (0.84) | 1–5 |
| Necessity-concerns differential | 5.49 (2.11) | 1–10 |

**Table 4B** BMQ-S Subtype frequencies

| BMQ-S Subtypes | Frequency (n=100) |
|---|---|
| Accepting | 15 |
| Ambivalent | 81 |
| Sceptical | 0 |
| Indifferent | 4 |

**Table 5** Associations Between Adherence to DOACs and Beliefs About DOAC Use for Primary MARS-5 Cut-off Value

| Variable | Non-Adherence (n=9) | Adherence (n=91) | p-value |
|---|---|---|---|
| Side effects | | | |
| Yes | 7 (77.8%) | 28 (30.8%) | 0.005 |
| No | 2 (22.2%) | 63 (69.2%) | *(Pierson's Chi2 test)* |
| Side effect burden | 3.56 (0.38) | 2.82 (0.08) | 0.006 (t-test) |
| BMQ Necessity | | | |
| Low | 0 (0%) | 4 (4.4%) | 0.521 |
| High | 9 (100%) | 87 (95.6%) | *(Pierson's Chi2 test)* |
| BMQ Concerns | | | |
| Low | 2 (22.2%) | 17 (18.7%) | 0.796 |
| High | 7 (77.8%) | 74 (81.3%) | *(Pierson's Chi2 test)* |
| BMQ Subtype | | | |
| Accepting | 2 | 13 | |
| Ambivalent | 7 | 74 | |
| Sceptical | 0 | 0 | 0.687 |
| Indifferent | 0 | 4 | *(Pierson's Chi2 test)* |
| BMQ NC-differential | 5.44 (0.71) | 5.49 (0.22) | 0.527 (t-test) |
| BMQ Q11 | 3.56 (0.38) | 2.82 (0.08) | 0.012 (t-test) |

reported significantly more side effects and experienced a higher side effect burden regardless of the cut-off value. Furthermore, an association was found between question 11 and adherence: non-adherent patients more often believed that DOACs have unpleasant side effects (Table 5).

For the primary cut-off MARS value, no associations were found between patients' beliefs about DOAC use and adherence for both necessity scores, concern scores, differential and subtypes. Interestingly, all non-adherent patients scored high on necessity.

Patients that believe DOACs have unpleasant side effects (BMQ question 11) reported, as was to be expected, significantly more side effects and experienced a higher side effect burden. Using a regression model to check for correlations between side effects and beliefs, we found an association between bleedings and a negative attitude towards DOAC use.

For the primary MARS-5 cut-off value no associations were found between patients' adherence to DOACs and either gender, DOAC or dosing regimen (once or twice a day intake). Interestingly, although there is no statistical significance, all non-adherent patients (9%) used their DOAC for the indication atrial fibrillation (see Appendix 1).

## Discussion

This study confirms that non-adherence in patients on DOACs cannot be taken for granted with non-adherence scores of 9% (range 3–33% depending on the used cut-off value for discriminating between adherence and non-adherence). The non-adherence score of 33% for the cut-off value of <25 seems to be even higher than the 21% found in the study by Capiau et al using the same <25 cut-off score[7] and being comparable with the estimated adherence of 69% (ie 31% non-adherence) that was found in the meta-analysis by Ozaki et al[10] that we used for our power analysis. In contrast, a study by Toorop et al found a clearly higher self-reported adherence of 86% (ie 14% non-adherence). Although a different measurement tool was used consisting of only one question one would expect the found adherence score to be comparable to our adherence score for the <25 cut-off value. Possible reasons for the different findings between Toorop and our study is a higher chance for desirability bias (as adherence in Toorop's study is just questioned with

one question instead of the validated MARS in our study) and difference in inclusion-exclusion criteria between both studies as other than that patients receiving supervision of their medication intake and/or using a multidose drug dispensing system were excluded in our study as adherence among these patients is expected to be optimal. It is unclear whether or not these patients were excluded in the study by Toorop et al.

We found associations between adherence and both side effects and side effect burden, regardless of the MARS-5 cut-off value. Hayat et al on the other hand found that the occurrence of minor bleeding complications was not associated with a lower degree of adherence for any of the studied DOACs.[22] Bruising and minor bleeds were the most reported side effects in our study by far. This is in line with the results reported in the cited studies in the introduction of Toorop et al and Mitrovic et al.[8,12,13] However, this finding contrasts with the most reported side effects in the Lareb Intensive Monitoring (LIM) study conducted by Rolfes et al where dizziness, tiredness and headaches made up the top three.[13]

Results from the MARS-5 for assessing adherence to DOACs are not absolute. Low MARS-scores are just an indication for an adherence issues. In our opinion, a deviating score is a cue to have a conversation with the patient to explore and address possible adherence problems. In choosing a higher cut-off value, we lose some sensitivity meaning that non-adherence according to the MARS-5 could be a false-positive result. As proper adherence is a prerequisite for optimal protection against thromboembolism and patient counselling is an accessible intervention we think using a higher cut-off score is justified because a lower cut-off score will lead to more false-negative results.

Although previous studies demonstrated that high BMQ-necessity and low BMQ-concern beliefs are considered to be associated with medication adherence, this study did not found an association between patient's beliefs about DOACs and adherence. Capiau et al concluded in their study that the BMQ demonstrated a positive attitude towards DOAC therapy in general, where necessity beliefs outweigh the concerns.[6] We have come to exactly the same conclusion. That we could not find an association between patients' beliefs about DOAC and adherence could mean that side effects impair adherence regardless of patient's beliefs or because our power was insufficient to differentiate between adherent and non-adherent patients. We have not made distinctions between intentional and unintentional non-adherence. One could assume that intentional non-adherence is more closely related to patient's beliefs about DOACs than unintentional non-adherence. In the Capiau et al study unintentional (mainly forgetfulness) was reported most frequently.[6] Apart from this, all included patients showed higher necessity scores compared to other studies, resulting in less contrast in the study population. We found both a higher mean BMQ-necessity score and a higher BMQ-concerns score compared to Capiau et al (21 vs 16 and 16 vs 10, respectively).[6]

Capiau et al demonstrated that patients with a history of thromboembolic or major bleeding events had significantly higher BMQ-necessity but comparable BMQ-concerns scores compared with patients without a history of those events.[6] As we did not have access to the full medical records in the pharmacy databases we could not check for differences between patients with or without previous thromboembolic or major bleedings events unfortunately.

For the primary cut-off value, all patients in the non-adherence group scored high on necessity beliefs, meaning that patients' knowing of the importance of proper DOAC use (knowledge) does not suffice for good adherence (behavior).

We found that non-adherent patients, patients reporting side effects related to their DOAC use and patients experiencing a high side effect burden all more often believed that DOACs have unpleasant side effects (BMQ question 11). Side effects were associated with non-adherence even in patients having high necessity beliefs. This means that both the occurrence of side effects, the side effect burden (experiential aspect) and concern beliefs about side effects (cognitive aspect) are associated with non-adherence.

No associations were found between adherence and either gender, indication, DOAC and dosage. It is noteworthy however that for the primary cut-off score all non-adherent patients were on DOAC therapy for the indication atrial fibrillation. One could speculate that patients with atrial fibrillation without a history of ischemic stroke that need to use a DOAC to prevent future thromboembolic events are less motivated for and prone to proper adherence than people that have suffered from deep vein thrombosis and pulmonary embolism.

## Strengths and Limitations

This study was powered for assessing the extent of self-reported adherence. Nevertheless, the found associations between adherence and both side effects and side effect burden were significant regardless of the chosen MARS-5 cut-off value.

A limitation of this study is the use of only one subjective instrument (MARS-5) to measure implementation adherence. The combination of a self-reported method to assess medication adherence and an objective method is often recommended, however due to automatic repeat prescription services in the participating pharmacies, medication adherence would have been overestimated when pharmacy refill adherence (for instance the Medication Possession Rate, MRP) measures were used. However, our results are in line with the adherence scores found in a recent study by Hayat et al using a different medication adherence questionnaire, the Morisky Medication Adherence Scale (MMA-8).[22] In situations where using the refill rate is not suitable, a Medication Event Monitoring System (MEMS) could be a valuable way to measure adherence objectively.

Another limitation of this study is the risk of patients giving socially desirable answers while being interviewed, but one could assume this would rather lead to underestimation of adherence problems than the other way around. That is why the primary MARS-5 cut-off value of <24 seems justified, all the more because even with the higher cut-off value of <25 differences between non-adherent and adherent patients regarding side effects and burden remain statistically significant. One more limitation is that this study was conducted in only two Dutch community pharmacies, which might hamper the generalization of the results. However, the fact that the results of our study are in line with previous studies confirms the robustness of our results. Furthermore, in order to improve the generalisability of our results, it is recommendable to repeat this study in more diverse populations (eg with more diverse ethnical background and health literacy) and settings."

## Conclusion

This study confirms that non-adherence in patients on DOACs cannot be taken for granted. Of the participants, 9% reported non-adherence on the MARS-5 (score <24). We found associations between non-adherence and both reported side effects and side effect burden. We also found that patients' belief that DOACs have unpleasant side effects was associated with both non-adherence and more side-effects.

As previous research has already shown that the occurrence of side effects in patients on DOACs could also lead to non-persistence,[8] we recommend that both physicians and pharmacists evaluate side effects with their DOAC patients on a regular base. If patients report side effects, the possibility of adherence problems should be considered and taken care of as well. Both by assessing the side effect burden and by challenging and reframing concern beliefs, especially those about side effects. Monitoring long-term persistence in these patients is recommended as well. This study emphasizes the need for developing, testing and implementing practical tools to identify and coach non-adherent DOAC patients to optimize protection against thromboembolic complications.

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## Disclosure

The authors report no conflicts of interest in this work.

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