Medication adherence to direct oral anticoagulants: extent and impact of side effects

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Abstract

Aim Recent studies have shown that good adherence cannot be taken for granted for patients on direct anticoagulants (DOACs). In this cross-sectional study, adherence among DOAC users was investigated and associations between beliefs about medication, perceived side effects and adherence were investigated. 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). Beliefs about DOACs were assessed with the Beliefs about Medicine Questionnaire Specific (BMQ-S) while side effects 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 MARS-5 (score <24). Associations were found between non-adherence and both reported side effects and side effect burden. Furthermore patients' belief that DOACs have unpleasant side effects was associated with both non-adherence and more side-effects. No associations were found between adherence and either gender, indication, DOAC or dosage. Conclusion This study confirms that non-adherence in patients on DOACs is prevalent. We recommend that both physicians and pharmacists evaluate adherence and side effects with their DOAC patients on a regular base.

Title page

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Principle investigator statement

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 (including the verbal consent procedure) 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. No conflict of interest.

Keywords

Direct anticoagulants, DOACs, adherence, MARS-5, cognition, BMQ-S**,** side effects

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What is already known about this subject

- Arterial and venous thromboembolic conditions are a leading cause of mortality
- Direct oral anticoagulants (DOACs) are highly effective in both stroke prevention and prevention of venous thrombotic events and preferred over vitamin K antagonists (VKAs) in most clinical guidelines these days
- Medication adherence is a prerequisite for optimal protection against thromboembolic complications
- Previous studies have shown that medication adherence cannot be taken for granted for patients on DOACs

What this study adds

- This study confirms that non-adherence in patients on DOACs is prevalent with non-adherence scores of 3-33% depending on the cut-off value for discriminating between adherence and non-adherence
- Having high necessity beliefs does not suffice for good adherence
- Side effects impair adherence even in patients having high necessity beliefs
- We recommend that both physicians and pharmacists evaluate adherence and side effects with their DOAC patients on a regular base

Aim

Recent studies have shown that good adherence cannot be taken for granted for patients on direct anticoagulants (DOACs). In this cross-sectional study, adherence among DOAC users was investigated and associations between beliefs about medication, perceived side effects and adherence were investigated.

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). Beliefs about DOACs were assessed with the Beliefs about Medicine Questionnaire Specific (BMQ-S) while side effects 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 MARS-5 (score <24). Associations were found between non-adherence and both reported side effects and side effect burden. Furthermore patients' belief that DOACs have unpleasant side effects was associated with both non-adherence and more side-effects. No associations were found between adherence and either gender, indication, DOAC or dosage.

Conclusion

This study confirms that non-adherence in patients on DOACs is prevalent. We recommend that both physicians and pharmacists evaluate adherence and side effects with their DOAC patients on a regular base.

Medication adherence to direct oral anticoagulants: extent and impact of side effects Bas J W van de Steeg[1], A

Introduction

Arterial and venous thromboembolic conditions 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 either the 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 (defined as unjustified discontinuation of the drug) is suboptimal. 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 [14,15,16]. 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 (including the verbal consent procedure) 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.

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 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 (e.g. "My health in de future will depend on these medicines") and 5 items about concerns (e.g. "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% accepted margin and a 95% confidence interval, 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. Differences between groups were calculated with Pearson's chi-square test, t-test or regression testing depending on the variables (dichotomous or continuous).

Results

Baseline characteristics

In total, all of the 100 approached 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%).

Table 1. Baseline characteristics

Characteristic	**n=100**
Gender Males Females Unknown	61 34 5
Age – years Mean (SD) Range	73.3 (±7.9) 47-86

Characteristic	n=100
DOAC Apixaban Dabigatran Edoxaban Rivaroxaban	19 14 36 31
DOAC dosage Once a day Twice a day	67 33
Indication Atrial fibrillation Venous thromboembolism Unclear	81 11 8
Renal function (CKD-EPI) – ml/min/1.73m^2 [?]50 30-49 [?]30	89 9 2

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%. For the cut-off value of <23 and <25 the proportion of non-adherent patients was 3% and 33%, respectively (table 2).

Table 2. Primary outcome

MARS-5
Item I forget to take my medication I alter the dose of my medication I stop taking my medication for a while I decide to m
I take less of my medication than instructed Total
Primary cut-off score <24 Non-adherence (n=9) Adherence (n=91)
Cut-off score <23 Non-adherence (n=3) Adherence (n=97)
Cut-off score <25 Non-adherence (n=33) Adherence (n=67)

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 complains and scored the highest on burden.

Table 3. Mean (SD) side effects and side effect burden scores

Patients with side effects	Frequency
Yes No	35 65
Reported side effects	**Frequency**
Bruising Bleeding Anemia Esophageal complaints Gastrointestinal complaints Headaches Dizziness Tiredness	20 20 0 0 2

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.

Table 4. Mean (SD) BMQ scores of patients

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

BMQ-S	Mean (SD)	Range
Question 11: "These medicines give me unpleasant side effects"	2.89 (0.84)	1-5
Necessity-concerns differential	5.49 (2.11)	1-10
Subtypes Accepting (n=15) Ambivalent (n=81) Sceptical (n=0) Indifferent (n=4)	0.04 0.04 0.00 0.02	0.09-0.24 0.72-0.88

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 reported significantly more side effects and experience 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).

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 No	7 (77.8%) 2 (22.2%)	28 (30.8%) 63 (69.2%)	0.005 (*Pierson's Chi2 test)*
Side effect burden	3.56 (0.38)	2.82 (0.08)	0.006 *(t-test)*
BMQ Necessity Low High	0 (0%) 9 (100%)	4 (4.4%) 87 (95.6%)	0.521 (*Pierson's Chi2 test)*
BMQ Concerns Low High	2 (22.2%) 7 (77.8%)	17 (18.7%) 74 (81.3%)	0.796 (*Pierson's Chi2 test)*
BMQ Subtype Accepting Ambivalent Sceptical Indifferent	2 7 0 0	13 74 0 4	0.687 (*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)*

Discussion

This study confirms that non-adherence in patients on DOACs is prevalent 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% (i.e. 31% non-adherence) that was found in the meta-analysis by Ozaki et al. [10] that

we used for our power analysis. We found associations between adherence and both side effects and side effect burden, regardless of the MARS-5 cut-off value. Bruising and minor bleeds were the most reported side effects 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].

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. This is not surprising as 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 el. (21 vs 16 and 16 vs 10, respectively) [6]. 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 could have been overestimated when refill adherence measures were used. 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's 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 is in line with previous studies confirms the robustness of our results

Conclusion

This study confirms that non-adherence in patients on DOACs is prevalent. 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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Appendix 1. Associations between patients' adherence to DOACs and baseline characteristics

Variable	**Non-adherence (n=9)**	**Adherence (n=91)**	**p-value**
Gender Male (n=61) Female (n=34)	6 (66.7%) 3 (33.3%)	55# (60.4%) 31# (34.1%)	0.872 *(Pierson's Chi2 test)*
Indication Atrial fibrillation Venous thromboembolism Other	9 (100%) 0 (0%) 0 (0%)	72 (79.1%) 11 (12.1%) 8 (8.8%)	0.244 *(Pierson's Chi2 test)*
DOAC Apixaban Dabigatran Edoxaban Rivaroxaban	2 (22.2%) 2 (22.2%) 2 (22.2%) 3 (33.3%)	17(18.7%) 12 (13.2%) 34 (37.4%) 28 (30.1%)	0.784 *(Pierson's Chi2 test)*
Dosage Once a day Twice a day	5 (55.6%) 4 (44.4%)	62 (68.1%) 29 (31.9%)	0.444 (*Pierson's Chi2 test)*